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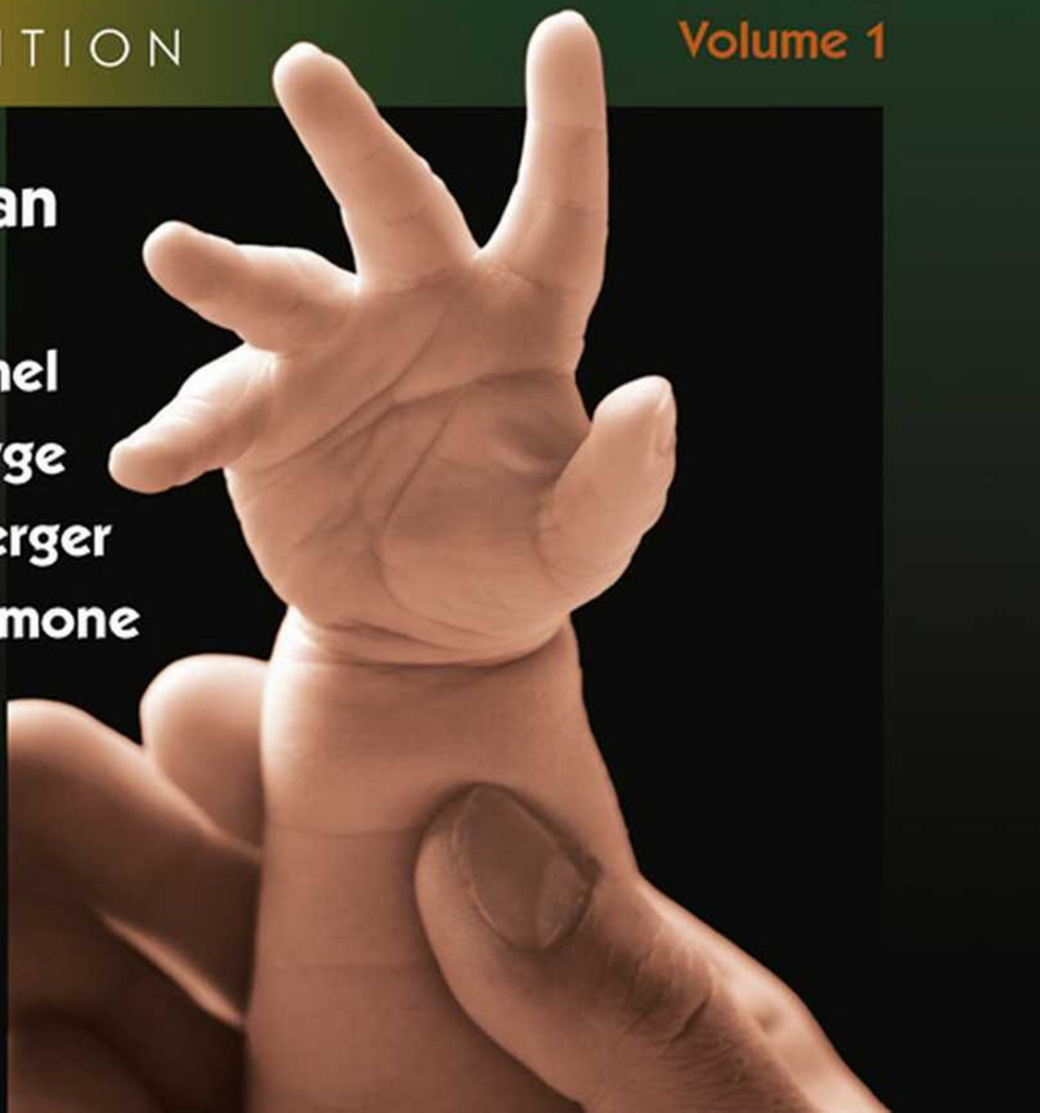
# PEDIATRIC SURGERY

SEVENTH EDITION

Volume 1



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Robert C. Shamberger
Anthony A. Caldamone

Emeritus Editors
Jay L. Grosfeld
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SEVENTH EDITION

**VOLUME ONE**

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**N. SCOTT ADZICK, MD,** has served as the Surgeon-in-Chief and Director of The Center for Fetal Diagnosis and Treatment at The Children's Hospital of Philadelphia since 1995. He is the C. Everett Koop Professor of Pediatric Surgery at the University of Pennsylvania School of Medicine. Dr. Adzick was raised in St. Louis, received his undergraduate and medical degrees from Harvard, and has a Master of Medical Management degree from Carnegie Mellon University. He was a surgical resident at the Massachusetts General Hospital and a pediatric surgery fellow at Boston Children's Hospital. His pediatric surgical expertise is centered on neonatal general and thoracic surgery, with a particular focus on clinical applications of fetal diagnosis and therapy. He has received grant support from the National Institutes of Health for more than 20 years and has authored more than 550 publications. He was elected to the Institute of Medicine of the National Academy of Science in 1998. Scott and Sandy Adzick have one son.

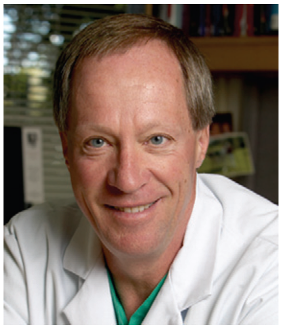
**ANTHONY A. CALDAMONE, MD,** graduated from Brown University and Brown School of Medicine. He was the first graduate of the medical school to become full professor at the institution. He did his residency at the University of Rochester and completed his fellowship under Dr. John W. Duckett at The Children's Hospital of Philadelphia. He is currently Professor of Surgery (Urology) and Pediatrics and Program Director for the Urology Residency at Brown University School of Medicine and Chief of Pediatric Urology at Hasbro Children's Hospital in Providence.

Dr. Caldamone has served as President of the New England Section of the American Urological Association (AUA). He has also served as Secretary-Treasurer and President of the Society for Pediatric Urology. He has been on several committees of the AUA including the Socio-Economic Committee, Publications Committee, and Nominating Committee. He is currently Executive Secretary of the Pediatric Urology Advisory Council. Locally he has served as President of the Rhode Island Urological Society, as President of the Brown Medical Alumni Association, as Chairman of the Board of Directors of Komedyplast Foundation, and as a member of the Board of Regents of La Salle Academy.

Dr. Caldamone has been on several medical missions to the Middle East, South America, and Bangladesh and has been on the Board of Directors of Physicians for Peace.

He was one of the editors of the sixth edition of *Pediatric Surgery*. He is currently an Editor for the *Journal of Pediatric Urology* and is Editor in Chief of the *Dialogues in Pediatric Urology*.

Dr. Caldamone is married to Barbara Caldamone and has two children, Amy and Matthew.



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**JEAN-MARTIN LABERGE, MD**, is Professor of Surgery at McGill University and surgeon at the Montreal Children's Hospital of the McGill University Health Centre. He was the Director of Pediatric Surgery at the Montreal Children's Hospital from 1996 to 2008 and Program Director from 1994 to 2008. He is editorial consultant for the *Journal of Pediatric Surgery* and *Pediatric Surgery International* and was guest editor of two issues of *Seminars in Pediatric Surgery.* He has contributed chapters to several textbooks, including previous editions of *Pediatric Surgery,* Holcomb and Murphy's *Ashcraft's Pediatric Surgery,* Taussig and Landau's *Pediatric Respiratory Medicine,* and *Paediatric Surgery: A Comprehensive Text for Africa.* His research has focused on the effects of fetal tracheal occlusion to promote lung growth. His clinical interests include fetal diagnosis and treatment, congenital lung lesions, and anorectal malformations. He was President of the International Fetal Medicine and Surgery Society and is the immediate past President of the Canadian Association of Paediatric Surgeons (2009–2011). He has been married to Louise Caouette-Laberge, a pediatric plastic surgeon, for 34 years and has four children and three grandchildren.

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# Preface

In June 1959, a group of five distinguished pediatric surgeons from the United States and Canada formed an editorial board to investigate the possibility of writing an authoritative, comprehensive textbook of pediatric surgery. The five individuals assembled were Kenneth Welch, who served as chairman of the board from Boston Children's Hospital (the original name); Mark Ravitch from The Johns Hopkins Hospital; Clifford Benson from Detroit Children's Hospital (the original name); William Snyder from Los Angeles Children's Hospital; and William Mustard from The Hospital for Sick Children in Toronto, Canada. From 1953 to 1962, the most comprehensive textbook of pediatric surgery was *The Surgery of Infancy and Childhood* by Robert E. Gross. At that time, Dr. Gross had no plans to write a second edition of his book. He was the sole author of the first edition of his book and did not wish to carry out such a monumental task with a second edition. The five editors thought that an updated textbook of pediatric surgery was needed. The first edition was published in 1962 and quickly became recognized as the most definitive and comprehensive textbook in the field. Between 1962 and 2006, six editions of the book were published. During this period, this textbook has been considered the bible of pediatric surgery. The editors and authors have changed during the 44 years that elapsed from the first to the sixth editions. In most cases, the editorial board changed gradually with the deletion and addition of two to three pediatric surgeons with each edition. The editors of the fifth edition also continued as the editors of the sixth edition. In the current seventh edition, the editorial board has been replaced except for Arnold Coran, who has functioned as the Chief Editor of this edition, and Anthony Caldamone, who continues to be the editor for the urology section. A new generation of pediatric surgical leaders has emerged since the last edition, and the editorial board reflects that change. Robert Shamberger from Children's Hospital Boston, Scott Adzick from The Children's Hospital of Philadelphia, Thomas Krummel from the Lucile Packard Children's Hospital and Stanford University Medical Center, and Jean-Martin Laberge from the Montreal Children's Hospital of the McGill University Health Centre represent the new members of the editorial board.

The seventh edition continues its international representation, with authors from several countries contributing chapters. Most of the previous chapters have been retained, but, in several cases, new authors have been assigned to these chapters. Of special interest is the addition of a new chapter (Chapter 16) on patient- and family-centered pediatric surgical care, a relatively new concept in the management of the pediatric surgical patient. Two chapters from the sixth edition, "Bone and Joint Infections" and "Congenital Defects of Skin, Connective Tissues, Muscles, Tendons, and Joints," have been deleted because currently, most pediatric surgeons do not deal with these problems. A few of the urology chapters have been merged, but all the material from the previous edition is included in these chapters. The chapter "Congenital Heart Disease and Anomalies of the Great Vessels" (Chapter 127) was kept comprehensive because so many of these patients have co-existent pediatric surgical problems or have surgical problems after cardiac surgery. Overall, there are 131 chapters in this edition, all of which are written by experts in the field and represent a comprehensive treatise of the subject with an exhaustive bibliography. In addition, each chapter provides a complete discussion of both open and closed techniques, when appropriate, for the management of the surgical problem.

One of the remarkable things about this edition is that not a single sheet of paper was used by the authors or editors in the creation of the book. Everything from the writing of the chapter to its editing was done electronically. This entire process was overseen by Lisa Barnes, the developmental editor at Elsevier. All the editors wish to thank her for her patience, availability, and efficiency in completing this textbook. Finally, we want to thank all the authors for their outstanding chapters, which will provide definitive and comprehensive information on the various pediatric surgical problems to pediatric surgeons throughout the world and thus improve the surgical care of infants and children worldwide.

The Editors

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# Part I

# GENERAL

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CHAPTER 1

# History of Pediatric Surgery: A Brief Overview

Jay L. Grosfeld and James A. O'Neill, Jr.

The history of pediatric surgery is rich, but only the major contributions and accounts of the leaders in the field can be summarized here.

## Early Years

The development of pediatric surgery has been tightly bound to that of surgery in adults, and in general, surgical information was based on simple observations of obvious deformities, such as cleft lip and palate, skeletal deformities, and imperforate anus. The only basic science of the 2nd through 16th centuries, until the 19th, was anatomy, mostly developed by surgeons; so, technical care was based on this, regardless of the patient's age. The fate of affected infants with a defect was frequently related to the cultural and societal attitudes of the time, and most did not survive long. A better understanding of the human body was influenced by Galen's study of muscles, nerves, and blood vessels in the 2nd century.[1] Albucacis described circumcision, use of urethral sounds, and cleft lip in Cordoba in the 9th century.[2] Little progress was made during the Middle Ages. In the 15th and 16th centuries, Da Vinci provided anatomic drawings; Vesalius touched on physiology; and Ambrose Paré, better known for his expertise in war injuries, wrote about club foot and described an omphalocele and conjoined twins.[3] The 17th and 18th centuries were the era of the barber surgeon. Johannes Fatio, a surgeon in Basel, was the first to systematically study and treat surgical conditions in children, and he attempted separation of conjoined twins in 1689.[4] Other congenital malformations were identified as a result of autopsy studies, including descriptions of esophageal atresia in one of thoracopagus conjoined twins by Durston in 1670,[5] intestinal atresia by Goeller in 1674,[6] an instance of probable megacolon by Ruysch in 1691,[7] and a more precise description of esophageal atresia by Gibson in 1697,[8] but there were no attempts at operative correction. Surgery for children was usually limited to orthopedic procedures, management of wounds, ritual circumcision, and drainage of superficial abscesses. In 1793, Calder[9] was the first to describe duodenal atresia. In France, Duret[10] performed the initial colostomy for a baby with imperforate anus in 1793, Amussat[11] performed the first formal perineal anoplasty in 1834, and in the United States, Jacobi[12] performed the first colostomy for probable megacolon in 1869. Up to this point, no surgeon devoted his practice exclusively to children. Despite this fact, a movement began to develop hospitals for children, led mainly by women in various communities, who felt that adult hospitals were inappropriate environments for children.

In Europe, the major landmark in the development of children's hospitals was the establishment of the Hôpital des Enfants Malades in Paris in 1802, which provided treatment for children with both medical and surgical disorders.[13] Children younger than 7 years of age were not admitted to other hospitals in Paris. Subsequently, similar children's hospitals were established in major European cities, including Princess Lovisa Hospital in Stockholm in 1854, and other facilities followed in St. Petersburg, Budapest, East London, and Great Ormond Street, London.[14] Children's hospitals in the United States opened in Philadelphia (1855), Boston (1869), Washington, DC (1870), Chicago (1882), and Columbus, Ohio (1892).[15] The Hospital for Sick Children in Toronto was established in 1885. Some of these facilities started out as foundling homes and then mainly cared for orthopedic problems and medical illnesses. Few had full-time staff, because it was difficult to earn a living caring for children exclusively.

Major advances in the 19th century that would eventually influence surgical care were William T.G. Morton's introduction of anesthesia in 1864, antisepsis using carbolic acid championed by Joseph Lister and Ignaz Semelweiss in 1865, and Wilhelm Roentgen's discovery of the x-ray in 1895. Harald Hirschsprung of Copenhagen wrote a classical treatise on two infants with congenital megacolon in 1886,[16] and Max Wilms, then in Leipzig, described eight children with renal tumors in 1899.[17] Fockens accomplished the first successful anastomosis for intestinal atresia in 1911[18]; Pierre Fredet (1907)[19] and Conrad Ramstedt (1912)[20] documented effective operative procedures (pyloromyotomy) for hypertrophic pyloric stenosis; and N.P. Ernst did the first successful repair of duodenal atresia in 1914, which was published 2 years later.[21]

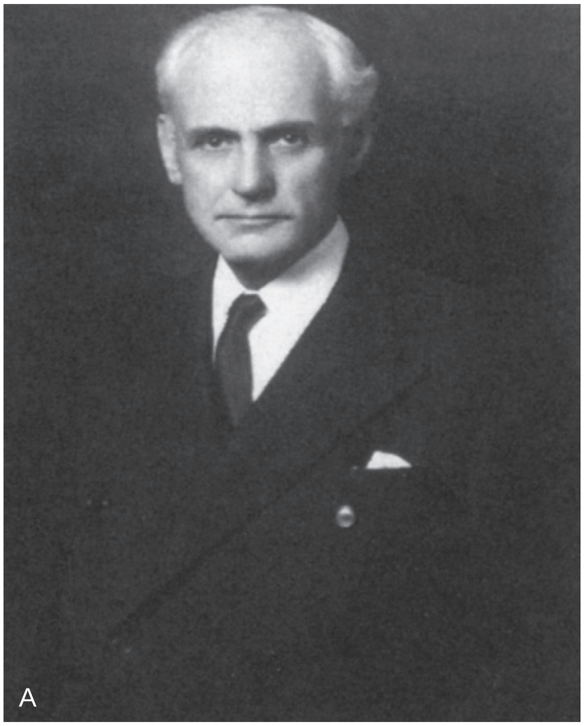
# 20th Century: The Formative Years

## UNITED STATES

There was little further progress in the early 20th century because of World War I and the Great Depression. It was during this time that a few individuals emerged who would devote their total attention to the surgical care of children. William E. Ladd of Boston, Herbert Coe of Seattle, and Oswald S. Wyatt of Minneapolis, the pioneers, set the stage for the future of pediatric surgery in the United States.[14,15,22]

Ladd, a Harvard medical graduate in 1906, trained in general surgery and gynecology and was on the visiting staff at the Boston Children's Hospital. After World War I, he spent more time there and subsequently devoted his career to the surgical care of infants and children and became surgeon-in-chief in 1927. His staff included Thomas Lanman, who attempted repair of esophageal atresia in more than 30 patients unsuccessfully, but the report of his experience set the stage for further success. Ladd recruited Robert E. Gross, first as a resident and then as a colleague. Ladd developed techniques for management of intussusception, pyloric stenosis, and bowel atresia; did the first successful repair of a correctable form of biliary atresia in 1928; and described the Ladd procedure for intestinal malrotation in 1936 (Fig. 1-1, *A* and *B*).[23–26] While Ladd was out of Boston, and against his wishes, Gross, then 33 years old and still a resident, performed the first ligation of a patent ductus arteriosus in 1938. One can imagine how this influenced their relationship. Nonetheless, in 1941, Ladd and Gross published their seminal textbook, *Abdominal Surgery of Infants and Children.*[27] 1941 was of importance not only because of the entry of the United States into WW II, but that was the year that Cameron Haight,[28] a thoracic surgeon in Ann Arbor, Michigan, and Rollin Daniel, in Nashville, Tennessee, independently performed the first successful primary repairs of esophageal atresia.

In addition to his landmark ductus procedure, Gross' surgical innovations, involving the great vessels around the heart, coarctation of the aorta, management of vascular ring deformities, and early use of allografts for aortic replacement, were major contributions to the development of vascular surgery (Fig. 1-2).[14] The training program in Boston grew and recruited future standouts in the field, such as Alexander Bill, Orvar Swenson, Tague Chisholm, and H. William Clatworthy. Ladd retired in 1945 and was succeeded by Gross as surgeon-in-chief. Gross was a very skillful pediatric surgeon and cardiovascular surgical pioneer who continued to attract bright young trainees to his department. In 1946, C. Everett Koop and Willis Potts spent a few months observing at the Boston Children's Hospital and then returned to the Children's Hospital of Philadelphia and Children's Memorial Hospital in Chicago, respectively. Luther Longino, Judson Randolph, Morton Wooley, Daniel Hays, Thomas Holder, W. Hardy Hendren, Lester Martin, Theodore Jewett, Ide Smith, Samuel Schuster, Arnold Colodny, Robert Filler, Arvin Phillipart, and Arnold Coran were just a few of the outstanding individuals attracted to the Boston program. Many became leaders in the field, developed their own training programs and, like disciples, spread the new gospel of pediatric surgery across the country. After Gross retired, Judah Folkman, a brilliant surgeon-scientist, became the third surgeon-in-chief in Boston in 1968. W. Hardy Hendren, Moritz Ziegler, and, currently, Robert Shamberger followed in the leadership role at the Children's Hospital, Boston.[15,25]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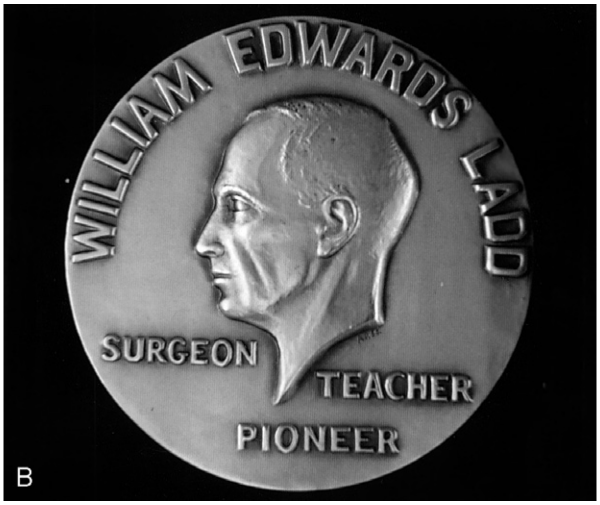

B

**FIGURE 1-1** **A,** William E. Ladd. **B,** To honor Dr. Ladd's pioneering achievements, the Ladd Medal was established by the Surgical Section of the American Academy of Pediatrics to award individuals for outstanding achievement in pediatric surgery.

**FIGURE 1-2** Robert E. Gross.

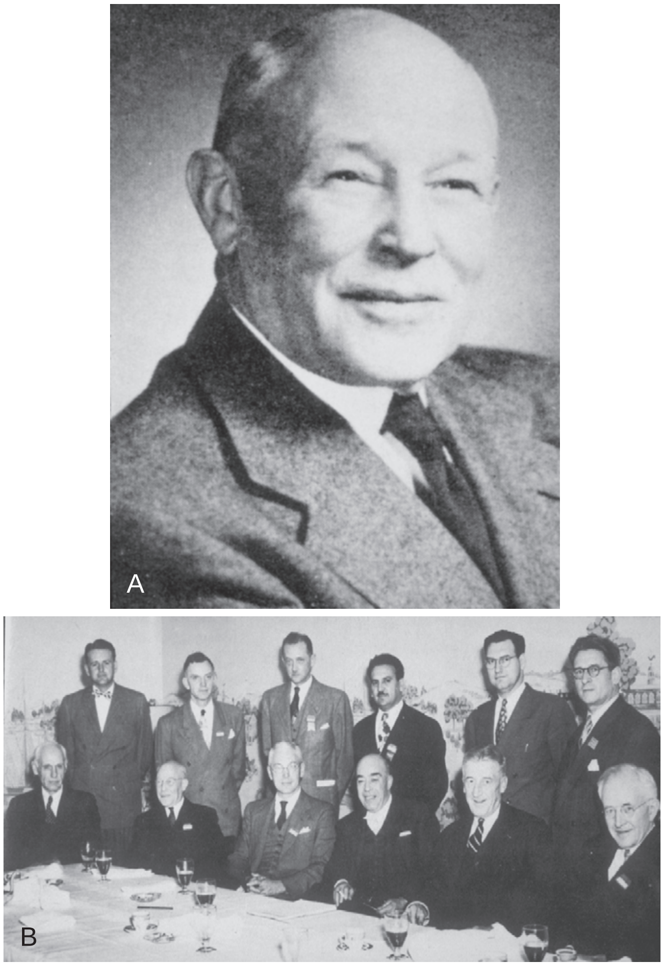

**FIGURE 1-3** **A,** Herbert Coe, Seattle, Washington. **B,** Photograph of the first meeting of the Section on Surgery, American Academy of Pediatrics, November 12, 1948. Seated, from *left to right,* are Drs. William E. Ladd, Herbert Coe, Frank Ingraham, Oswald Wyatt, Thomas Lanman, and Clifford Sweet. Standing, from *left to right,* are Drs. Henry Swan, J. Robert Bowman, Willis Potts, Jesus Lozoya-Solis (of Mexico), C. Everett Koop, and Professor Fontana.

Herbert Coe was raised in Seattle, Washington, and attended medical school at the University of Michigan. After training in general surgery, he returned to Seattle in 1908 and was on staff at the Children's Orthopedic Hospital. After WWI, he spent time at the Boston Children's Hospital as an observer, gaining experience in pediatric surgical care. When he returned to Seattle in 1919, he was the first to exclusively limit his practice to pediatric surgery. He initiated the first children's outpatient surgical program in the country. He was a strong advocate for children and, in 1948, helped to persuade the leadership of the American Academy of Pediatrics (AAP) to form its surgery section, which he saw as a forum for pediatric surgeons to gather, share knowledge, and gain recognition for their new specialty (Fig. 1-3). Alexander Bill joined Coe in practice following his training in Boston and subsequently became surgeon-in-chief at the Children's Orthopedic Hospital.[14,15]

Oswald Wyatt, a Canadian by birth, attended both undergraduate school and medical school at the University of Minnesota. He trained in general surgery in Minneapolis. After serving in the military in WWI, Wyatt returned to Minneapolis and entered surgical practice. In 1927, he spent time with Edwin Miller at the Children's Memorial Hospital in Chicago. When he returned to Minneapolis, he then limited his surgical practice to children. When Tague Chishom completed his training with Ladd and Gross in 1946, he joined Wyatt's practice. Together they developed one of the largest and most successful pediatric surgery community practice groups in the country.[14,15]

In 1948, C. Everett Koop became the first surgeon-in-chief at the Children's Hospital in Philadelphia and served until 1981. He was followed by James A. O'Neill and subsequently Scott Adzick. Prominent trainees from this program include William Kiesewetter, Louise Schnaufer, Dale Johnson, John Campbell, Hugh Lynn, Judah Folkman, Howard Filston, John Templeton, Moritz Ziegler, Don Nakayama, Ron Hirschl, and others. Dr. Koop was the second president of the American Pediatric Surgical Association (APSA) and also served as Surgeon General of the United States from 1981 to 1989 (Fig. 1-4).

Also in 1948, Orvar Swenson performed the first successful rectosigmoidectomy operation for Hirschsprung disease at Boston Children's Hospital (Fig. 1-5).[29] In 1950, he became surgeon-in-chief of the Boston Floating Hospital and subsequently succeeded Potts as surgeon-in-chief at the Children's Memorial Hospital in Chicago.

H. William Clatworthy, the last resident trained by Ladd and Gross' first resident, continued his distinguished career as surgeon-in-chief at the Columbus Children's Hospital, (now Nationwide Children's Hospital) at Ohio State University in 1950 (Fig. 1-6). Clatworthy was a gifted teacher and developed a high-quality training program that produced numerous graduates who became leaders in the field and professors of pediatric surgery at major universities, including

**FIGURE 1-4** C. Everett Koop.

**FIGURE 1-5** Orvar Swenson.

**FIGURE 1-6** H. William Clatworthy, Jr.

Peter Kottmeier (Brooklyn), Jacques Ducharme (Montreal,) Lloyd Schulz (Omaha), James Allen (Buffalo), Beimann Othersen (Charleston), Dick Ellis (Ft. Worth), Alfred de Lorimier (San Francisco), Eric Fonkalsrud (Los Angeles), Marc Rowe (Miami and Pittsburgh), James A. O'Neill (New Orleans, Nashville, and Philadelphia), Jay Grosfeld (Indianapolis), Neil Feins (Boston), Arnold Leonard (Minneapolis), and Medad Schiller (Jerusalem).[25] E. Thomas Boles succeeded Dr. Clatworthy as surgeon-in-chief in 1970.

## EDUCATION, ORGANIZATIONAL CHANGES, AND RELATED ACTIVITIES

Following World War II, a glut of military physicians returned to civilian life and sought specialty training. A spirit of academic renewal and adventure then pervaded an environment influenced by the advent of antibiotics, designation of anesthesia as a specialty, and the start of structured residency training programs in general surgery across the country. By 1950, one could acquire training in children's surgery as a preceptor or as a 1- or 2-year fellow at Boston Children's Hospital (Gross), Children's Memorial Hospital in Chicago (Potts), Children's Hospital of Philadelphia (Koop), Boston Floating Hospital (Swenson), Babies' Hospital in New York (Thomas Santulli), or the Children's Hospital of Los Angeles (William Snyder). There were two established Canadian programs in Toronto and Montreal. The training program at the Columbus Children's Hospital (Clatworthy) started in 1952. Other programs followed in Detroit (C. Benson), Cincinnati (L. Martin), Pittsburgh (Kiesewetter), and Washington, DC (Randolph). The output of training programs was sporadic, and some graduates had varied experience in cardiac surgery and urology, but all had broad experience in general and thoracic pediatric surgery. Gross published his renowned textbook, *The Surgery of Infancy and Childhood*, in 1953.[30] This extraordinary text, the "Bible" of the fledgling field, described in detail the experience at Boston Children's Hospital in general pediatric surgery, cardiothoracic

surgery, and urology and became the major reference source for all involved in the care of children. The successor to this book, *Pediatric Surgery,* originally edited by Clifford Benson, William Mustard, Mark Ravitch, William Snyder, and Kenneth Welch was first published in two volumes in 1962 and has now gone through seven editions. It continues to be international and encyclopedic in scope, covering virtually every aspect of children's surgery. Over time, Judson Randolph, E. Aberdeen, James O'Neill, Marc Rowe, Eric Fonkalsrud, Jay Grosfeld, and Arnold Coran were added as editors through the sixth edition. As the field has grown, several other excellent texts have been published, adding to the rich literature in pediatric surgery and its subspecialties.

The 1950s saw an increasing number of children's surgeons graduating from a variety of training programs in the United States and Canada. Many entered community practice. A number of children's hospitals sought trained pediatric surgeons to direct their surgical departments, and medical schools began to recognize the importance of adding trained pediatric surgeons to their faculties. In 1965, Clatworthy requested that the surgical section of the AAP form an education committee whose mandate was to evaluate existing training programs and make recommendations for the essential requirements for educating pediatric surgeons. Originally, 11 programs in the United States and 2 in Canada met the standards set forth by the Clatworthy committee. In short order, additional training programs, which had been carefully evaluated by the committee, implemented a standard curriculum for pediatric surgical education.[14,15,31,32]

In the 1960s, a number of important events occurred that influenced the recognition of pediatric surgery as a bona fide specialty in North America.[33] Lawrence Pickett, then secretary of the AAP Surgical Section, and Stephen Gans were strong proponents of the concept that the specialty needed its own journal. Gans was instrumental in starting the *Journal of Pediatric Surgery* in 1966, with Koop serving as the first editor-in-chief.[34] Eleven years later, Gans succeeded Koop as editor-in-chief, a position he held until his death in 1994. Jay Grosfeld then assumed the role and continues to serve as editor-in-chief of the *Journal of Pediatric Surgery* and the *Seminars of Pediatric Surgery,* which was started in 1992.

Lucian Leape, Thomas Boles, and Robert Izant promoted the concept of a new independent surgical society, in addition to the surgical section of the AAP. The idea was quickly embraced by the pediatric surgical community, and the American Pediatric Surgical Association (APSA) was launched in 1970, with Gross serving as its first president.[35,36]

In the 1950s and 1960s, three requests to the American Board of Surgery (ABS) to establish a separate board in Pediatric Surgery were unsuccessful. However, with the backing of a new independent surgical organization, established training programs, a journal devoted to the specialty, and inclusion of children's surgery into the curricula of medical schools and general surgical residency programs, another attempt was made to approach the Board for certification.[35] Harvey Beardmore of Montreal (Fig. 1-7), a congenial, diplomatic, and persuasive individual, was chosen as spokesperson. He succeeded where others had failed. In 1973, the ABS approved a new Certificate of Special Competence in Pediatric Surgery to be awarded to all qualified applicants. There was no grandfathering of certification, because all applicants for the certificate had to pass a secured examination administered by the ABS. The first examination was given in 1975 and, for the first time in any specialty, diplomats were required to recertify every 10 years. The accreditation of training programs was moved from the Clatworthy Committee of the AAP, initially, to the APSA Education Committee, and, following Board approval of certification for the specialty, to the Accreditation Council for Graduate Medical Education (ACGME) Residency Review Committee (RRC) for Surgery in 1977.

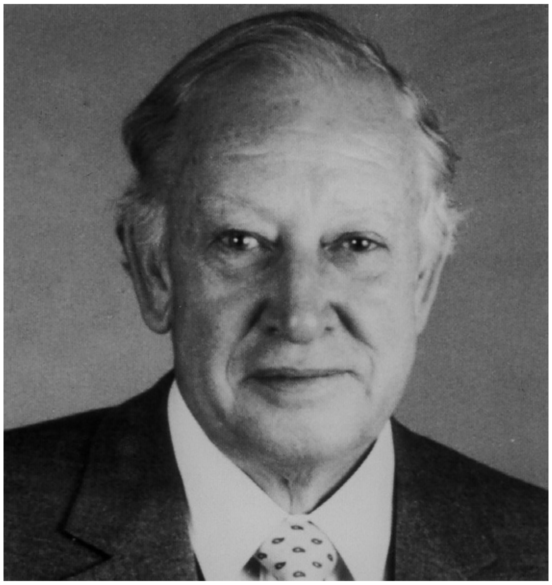

**FIGURE 1-7** Harvey Beardmore, distinguished Canadian pediatric surgeon from Montreal.

In 1989, the Association of Pediatric Surgery Training Program Directors was formed and developed as a liaison group with the RRC. Prospective residents applied for postgraduate training in pediatric surgery, initially through a matching process overseen by APSA and, in 1992, through the National Residency Matching Program (NRMP). In 1992, the ABS developed an in-training examination to be given annually to all pediatric surgical residents. In 2000, the ABS approved a separate pediatric surgery sub-board to govern the certification process. By 2010, there were 49 accredited training programs in the United States and Canada. The American College of Surgeons (ACS) recognized pediatric surgery as a separate specialty and developed focused programs at its annual congress devoted to the specialty, including a pediatric surgery research forum. Pediatric surgeons have an advisory committee at the College and have served in leadership positions on numerous committees, the Board of Governors, Board of Regents and as vice-president and president of the College (Kathryn Anderson). At this point pediatric surgery had come of age in North America and the world.

## Research

Early research in pediatric surgery was clinical in nature and involved clinical advances in the 1930s and 1940s.[14] Ladd's operation for malrotation in 1936 was a signal event based on anatomical studies.[26] In addition to Gross' work on patent ductus arteriosus and coarctation, Alfred Blalock's systemic-to-pulmonary shunt for babies with tetralogy of Fallot was another landmark. Potts' direct aortic-to-pulmonary artery shunt accomplished similar physiologic results but required

a special clamp. When Potts and Smith developed a clamp with many delicate teeth to gently hold a pulsatile vessel securely, they implemented a major technical advance that enabled the development of vascular surgery.[14] To bridge the gap in long, narrow coarctations of the aorta, Gross devised the use of freeze-dried, radiated aortic allografts and demonstrated their initial effectiveness, further promoting the use of interposition grafts in vascular surgery.[14]

Research in surgical physiology affecting adult surgical patients began to be integrated with research adapted to children. Studies of body composition in injured and postoperative patients by Francis D. Moore in adults were adapted to infants by Rowe in the United States, Peter Rickham and Andrew Wilkinson in the United Kingdom, and Ola Knutrud in Norway. Curtis Artz, John Moncrief, and Basil Pruitt were leaders in adult burn care management, and they stimulated O'Neill's interest in burn and injury research, in children.[14] In 1965, Stanley Dudrick and Douglas Wilmore, working with Jonathan Rhodes in Philadelphia, introduced the use of total parenteral nutrition, first studied in dogs, to sustain surgical patients chronically unable to tolerate enteral feedings, saving countless patients of all ages.[37] Shortly thereafter, Ola Knutrud and colleagues in Norway introduced the use of intravenous lipids. In the 1960s following extensive laboratory studies, Robert Bartlett and Alan Gazzaniga instituted extracorporeal membrane oxygenation (ECMO) for infants with temporarily inadequate heart and lung function, including those with congenital diaphragmatic hernia, certain congenital heart anomalies, meconium aspiration, and sepsis.[38] The technique was subsequently expanded for use in older children and adults. ECMO has been used successfully in thousands of infants and children worldwide.

The field of organ transplantation led by Joseph Murray, Thomas E. Starzl, and Norman Shumway in the United States, Peter Morris and Roy Y. Calne in the United Kingdom, Henri Bismuth and Yann Revillion in France, Jean-Bernard Otte in Belgium, as well as others, provided new options for the treatment of end-stage organ failure in patients of all ages. Renal, liver, and bowel transplantation have significantly altered the outcomes of infants with uncorrectable biliary atresia, end-stage renal disease, short bowel syndrome, and intestinal pseudo-obstruction. The use of split liver grafts and living-related donors to offset the problems with organ shortage, has added to the availability of kidneys, liver, and bowel for transplantation, but shortages still exist. Joseph Vacanti and colleagues in Boston and Anthony Atala in Winston Salem have laid the preliminary groundwork for the development of the field of tissue engineering. Using a matrix for select stem cells to grow into various organs, these investigators have successfully grown skin, bone, bladder, and some other tubular organs.

Ben Jackson of Richmond, J. Alex Haller in Baltimore, and Alfred de Lorimier in San Francisco, began experimenting with fetal surgery in the late 1960s and early 1970s.[15] De Lorimier's young associate, Michael Harrison and his colleagues (Scott Adzick, Alan Flake, and others) have provided new insights into fetal physiology and prenatal diagnosis and pursued clinical investigations into the practicalities of intrauterine surgery. Fetal intervention has been attempted for obstructive uropathy related to urethral valves, repair of congenital diaphragmatic hernia, twin–twin transfusion syndrome, arteriovenous shunting for sacrococcygeal teratoma, cystic lung disease, a few cardiac defects, large tumors of the neck, and myelomeningocele repair. Some of these initiatives have been abandoned, but limited protocol-driven investigation continues for fetal myelomeningocele repair in Nashville, Philadelphia, and San Francisco, and fetoscopically placed balloon tracheal occlusion in selected fetuses with diaphragmatic hernia in San Francisco, Providence, and Leuven, Belgium in an attempt to avoid pulmonary hypoplasia.

Patricia Donohoe has carried out fundamental fetal research investigating growth factors that influence embryologic development. Her seminal work defined müllerian inhibitory substance, which influences sexual development and tumor induction. Judah Folkman's discovery of the new field of angiogenesis and antiangiogenesis led him to postulate and search for antiangiogenic agents for use as cancer inhibitors. Antiangiogenic agents are currently being used clinically in a number of cancer protocols for breast and colon cancer, neuroblastoma, gastrointestinal stromal tumors, and others.

### Clinical Advances Related to Research

Although many clinical and research accomplishments have occurred in the United States, many related ones have occurred in other parts of the world as more collaborations have developed. However, the United States got a head start on many of these researches, because medical developments were not as hampered during WWII in the United States as in Europe and Asia.

In the late 1960s and early 1970s, the advent of neonatal intensive care units (NICUs) and the evolving subspecialty of neonatology had a major impact on the survival of premature infants and the activities of pediatric surgeons. The first pediatric surgical ICU was established at Children's Hospital of Philadelphia in 1962. Prior to the availability of infant ventilators, monitoring systems, other life support technologies, and microtechniques, most premature infants succumbed. Most infants weighing greater than 1000 g and 75% to 80% weighing greater than 750 g now survive with satisfactory outcomes. With these advances came new challenges in dealing with premature and micropremature surgical patients with immature physiology and conditions previously rarely encountered, such as necrotizing enterocolitis. This led to a universal emphasis on pediatric surgical critical care.

Sophisticated advances in imaging, including computerized tomography (CT), and use of prenatal ultrasound and magnetic resonance imaging to detect anomalies prior to birth and portable sonography for evaluation of cardiac defects, renal abnormalities, and intracranial hemorrhage in the NICU advanced patient care and survival.

The introduction of nitric oxide, surfactant, and newer ventilator technologies, such as oscillating and jet ventilators, have markedly diminished complications and improved outcomes for infants with respiratory distress. Exogenous administration of indomethacin to induce ductus closure and reduce the need for operative intervention has also enhanced survival.

The evolution of comprehensive children's hospitals capable of providing tertiary care to high-risk patients enabled the activities of pediatric surgeons, and this was further amplified by the expansion of specialists in the critical support services of pediatric anesthesia, pathology, and radiology. Other surgical disciplines began to focus their efforts on children, which eventually led to pediatric subspecialization in orthopedics, urology, plastic surgery, otolaryngology, ophthalmology, cardiac surgery, and neurosurgery.

Because it was recognized that trauma was the leading cause of death in children, trauma systems, including prehospital care, emergency transport, and development of assessment and management protocols, were developed by J. Alex Haller, Martin Eichelberger, James O'Neill, Joseph Tepas, and others, dramatically improving the survival of injured children. The implementation of the Glasgow Coma and Pediatric Injury Severity scores aided in triage and outcome research studies. After the initial favorable experience with nonoperative management of splenic injury in children reported by James Simpson and colleagues in Toronto in the 1970s,[39] nonoperative management protocols were applied to blunt injuries of other solid organs, and the availability of modern ultrasound and CT imaging dramatically changed the paradigm of clinical care. A national pediatric trauma database was subsequently developed, which has provided a vital data research base that has influenced trauma care. Criteria for accreditation of level 1 pediatric trauma centers were established through the Committee on Trauma of the ACS to standardize trauma systems and ideal methods of management.

Pediatric surgeons have been intimately involved in collaborative multidisciplinary cancer care for children with solid tumors since the early 1960s. Cooperative cancer studies in children antedated similar efforts in adults by more than 2 decades. In the United States, the National Wilms' Tumor Study, Intergroup Rhabdomyosarcoma Study, Children's Cancer Group, Pediatric Oncology Group and, more recently, Children's Oncology Group are examples. Tremendous strides have been achieved by having access to many children with a specific tumor managed with a standard protocol on a national basis. C. Everett Koop, Judson Randolph, H. William Clatworthy, Alfred de Lorimier, Daniel Hays, Phillip Exelby, Robert Filler, Jay Grosfeld, Gerald Haase, Beimann Othersen, Eugene Weiner, Richard Andrassy, and others represented pediatric surgery on many of the early solid tumor committees. They influenced the concepts of delayed primary resection, second-look procedures, primary reexcision, selective metastectomy, staging procedures, and organ-sparing procedures. Antonio Gentils-Martins in Portugal and Denis Cozzi in Rome have been the leading proponents of renal-sparing surgery for Wilms' tumors.[40] Currently, 80% of children with cancer now survive. The elucidation of the human genome has led to an understanding of genetic alterations in cancer cells and has changed the paradigm of care. Individualized risk-based management, depending on the molecular biology and genetic information obtained from tumor tissue, often determines the treatment protocol and the intensity of treatment for children with cancer.

In addition to the accomplishments noted above, major advances in clinical pediatric surgery, education, and research continue to unfold, and some of these contributions have been extended to adult surgery as well. Examples include the nonoperative management of blunt abdominal trauma, Clatwothy's mesocaval (Clatworthy-Marion) shunt for portal hypertension, and Lester Martin's successful sphincter-saving pull-through procedures for children with ulcerative colitis and polyposis in 1978, all techniques which have been adapted to adults. Jan Louw of Cape Town clarified the etiology of jejunoileal atresia and its management in 1955, and Morio Kasai of Sendai revolutionized the care of babies with biliary atresia by implementing hepatoportoenterostomy in 1955. The latter procedure was implemented in the United States by John Lilly and Peter Altman and in the United Kingdom by Edward Howard, Mark Davenport, and Mark Stringer. Samuel Schuster's introduction of temporary prosthetic coverage for abdominal wall defects; Donald Nuss' minimally invasive repair of pectus excavatum; Hardy Hendren's contributions in managing obstructive uropathy and repair of patients with complex cloaca; Barry O'Donnell and Prem Puri's endoscopic treatment (sting procedure) for vesicoureteral reflux; Mitrofanoff's use of the appendix as a continent catheterizable stoma for the bladder; Joseph Cohen's ureteral reimplantation technique; Malone's institution of the antegrade continent enema (MACE procedure) for fecal incontinence; Douglas Stephen's introduction of the sacroabdominal perineal pull-through for imperforate anus in 1953; Alberto Peña and DeVries' posterior sagittal anorectoplasty in the 1970s; Luis de la Torre's introduction of the transanal pull-through for Hirschsprung disease in the 1990s; laparoscopic-assisted pull-through for Hirschsprung disease and anorectal malformations by Keith Georgeson, Jacob Langer, Craig Albanese, Atsayuki Yamataka, and others; the longitudinal intestinal lengthening procedure by Adrian Bianchi and introduction of the serial transverse enteroplasty (STEP) procedure by H. B. Kim and Tom Jaksic for infants with short bowel syndrome; and use of the gastric pull up for esophageal replacement by Spitz and later Arnold Coran all represent some of the innovative advances in the specialty that have improved the care of children. Early use of peritoneoscopy by Stephen Gans and thoracoscopy by Bradley Rodgers in the 1970s influenced the development of minimally invasive surgery (MIS) in children. Bax, George Holcomb, Craig Albanese, Thom Lobe, Frederick Rescorla, Azad Najmaldin, Gordon MacKinlay, Keith Georgeson, Steven Rothenberg, C. K. Yeung, Jean-Luc Alain, Jean-Stephane Valla, Nguyen Thanh Liem, Felix Schier, Benno Ure, Marcelo Martinez-Ferro, and others have been the early international leaders in pediatric MIS.

## CANADA

As events in children's surgery were unfolding in the United States, Canadian pediatric surgery was experiencing a parallel evolution. References have already been made above to some of the clinical and research contributions made in Canada. Alexander Forbes, an orthopedic surgeon, played a leading role at the Montreal Children's Hospital from 1904 to 1929. Dudley Ross was chief-of-surgery at Montreal Children's Hospital from 1937 to 1954 and established the first modern children's surgical unit in Quebec. In 1948, he performed the first successful repair of esophageal atresia in Canada.[41] David Murphy served as chief of pediatric surgery and director of the pediatric surgical training program from 1954 to 1974. He was assisted by Herbert Owen and Gordon Karn, and his first trainee in 1954 was Harvey Beardmore.[42] Beardmore served as chief-of-surgery from 1974 to 1981 and was followed by Frank Guttman from 1981 to 1994 and Jean-Martin Laberge after that. The Sainte-Justine Hospital in Montreal, was founded in 1907. The hospital was combined with the Francophone Obstetrical Unit of Montreal, creating one of the largest maternal/child care centers in North America. Pierre-Paul Collin arrived at the hospital in 1954 after training in thoracic surgery in St. Louis, bringing a commitment to child care. He recruited Jacques Ducharme, who had trained in pediatric surgery in Columbus, Ohio, to join him in 1960. They trained a number of leaders in pediatric surgery in

Canada, including Frank Guttman, Hervé Blanchard, Salam Yazbeck, Jean-Martin Laberge, and Dickens St.-Vil. Jean Desjardins became chief in 1986.

The Hospital for Sick Children in Toronto was established in 1875 by Mrs. Samuel McMaster, whose husband founded McMaster University in Ontario.[42] As was the case in the United States, adult surgeons operated on children in Toronto at the end of the 19th and beginning of the 20th centuries. Clarence Starr, an orthopedic surgeon, was the first chief-of-surgery from 1913 to 1921. W. Edward Gallie served as chief surgeon at the Hospital for Sick Children from 1921 to 1929 and was named chair of surgery at the University of Toronto, where he established the Gallie surgical training program. The Gallie School of Surgery in Canada was compared with that of Halsted at Johns Hopkins in the United States.[42] Because of increasing responsibilities as chair, Gallie relinquished his role as chief of pediatric surgery to Donald Robertson, a thoracic surgeon who held the post until 1944. Arthur Lemesurer, a plastic and orthopedic surgeon became chief and in 1949 began a general pediatric surgical training program that produced Clinton Stephens, James Simpson, Robert Salter, Phillip Ashmore, Donald Marshall, and Stanley Mercer, to name some of the illustrious graduates who became leaders in the field of pediatric surgery in Canada.[14,42] In 1956, Alfred Farmer became surgeon-in-chief at the Hospital for Sick Children and developed several specialty surgical divisions, including one for general pediatric surgery. This allowed for separate specialty leadership under direction of Stewart Thomson from 1956 to 1966. Clinton Stephens was chief from 1966 to 1976 and was ably supported by James Simpson and Barry Shandling. During these 2 decades there was an impressive roster of graduates, including Phillip Ashmore, Gordon Cameron, Samuel Kling, Russell Marshall, Geoffrey Seagram, and Sigmund Ein. The tradition of excellence in pediatric surgery was continued with the appointment of Robert Filler, who arrived from Boston in 1977. Jacob Langer is the current chief of pediatric surgery in Toronto. From the latter three key surgical centers, leadership and progress in pediatric surgery spread across the Canadian provinces with the same comprehensive effect seen in the United States. Colin Ferguson, who trained with Gross in Boston, became chief-of-surgery in Winnipeg. Stanley Mercer began the pediatric surgery effort in Ottawa; there was also Samuel Kling, in Edmonton, where he was joined by Gordon Lees and James Fischer, and Geoffrey Seagram in Calgary. In 1957, Phillip Ashmore was the first trained pediatric surgeon in Vancouver, and he was joined by Marshall and Kliman, who trained at Great Ormond Street. In 1967, Graham Fraser, who also trained at Great Ormond Street joined the Vancouver group and became director of the training program. He was succeeded by Geoffrey Blair. Alexander Gillis trained with Potts and Swenson in Chicago and, in 1961, was the first pediatric surgeon in Halifax, Nova Scotia. He started the training program there in 1988. Gordon Cameron, a Toronto graduate, was the first chief of pediatric surgery at McMasters University in Hamilton. Currently, Peter Fitzgerald is head of the training program in Hamilton, which was approved in 2008.[42] The Canadian Association of Pediatric Surgeons (CAPS) was formed in 1967, three years before APSA, with Beardmore serving as the first president and Barry Shandling as secretary.[43] There are currently eight accredited pediatric surgery training programs in Canada: Halifax, Montreal Children's Hospital, Sainte-Justine Hospital in Montreal, Children's Hospital of Eastern Ontario in Ottawa, Hospital for Sick Children in Toronto, Hamilton, Calgary, Alberta, and Vancouver. All these programs are approved by the Royal College of Surgeons of Canada, and candidates for training match along with the U.S. programs through the NRMP.

## UNITED KINGDOM AND IRELAND

In 1852, the Hospital for Sick Children at Great Ormond Street (HSC) opened its doors in a converted house in London.[44] The hospital was the brainchild of Charles West, whose philosophy was that children with medical diseases required special facilities and attention, but those with surgical disorders at the time, mostly trauma related, could be treated in general hospitals.[44] West opposed the appointment of a surgeon to the staff, but the board disagreed and appointed G.D. Pollock. Pollock soon resigned and was replaced by Athol Johnson in 1853. T. Holmes, who followed Johnson, published his 37-chapter book, *Surgical Treatment of the Diseases of Infancy and Childhood,* in 1868.[45] Pediatric care in the 19th century either followed the pattern established in Paris, where all children were treated in hospitals specially oriented toward child care, or the Charles West approach, common in Britain,[46] such as those in Birmingham and Edinburgh, established to provide medical treatment but not surgery for children. In contrast, the Board at the Royal Hospital for Sick Children in Glasgow (RHSC) appointed equal numbers of medical and surgical specialists.[14,47] A major expansion in children's surgery in the latter part of the 19th century followed the development of ether and chloroform anesthesia and the gradual acceptance of antiseptic surgery. Joseph Lister provided the main impetus for antiseptic surgery, which he developed in Glasgow before moving to Edinburgh and then to King's College, London. One of Lister's young assistants in Glasgow was William Macewen, known as the father of neurosurgery, and one of the original surgeons appointed to the RHSC.[14] In Scotland, where pediatric care was generally ahead of the rest of Britain, the Royal Edinburgh Hospital for Sick Children (REHSC) opened in 1860 but did not provide a surgical unit until 1887. The sewing room was used as an operating theater.[48] Joseph Bell, President of the Royal College of Surgeons of Edinburgh, Harold Styles, John Fraser, and James J. Mason Brown, also a president of the Royal College of Surgeons of Edinburgh were the senior surgeons from 1887 to 1964. Gertrude Hertzfeld held a surgical appointment at the REHSC from 1919 to 1947, one of the few women surgeons of that era.[46] In the 19th century, training in pediatric surgery, independent of general surgery in the United Kingdom, occurred in Glasgow. Soon after these hospitals opened, their boards recognized the need for developing dispensaries or outpatient departments. In Manchester, the dispensary actually preceded the hospital. Dispensaries handled many surgical patients, and much of the pediatric surgery of the day was done there. One of the outstanding surgeons of that generation was James Nicoll, who reported 10 years of his work in 1909,[49] one of more than 100 of his publications. He was the "father of day surgery," although only part of his time was devoted to children's surgery because he had a substantial adult practice.[50] He performed pyloromyotomy with success in the late 19th century in a somewhat different fashion from Ramstedt. The Board of the RHSC decided that both physicians or surgeons appointed to the hospital must devote all their professional time to the

treatment of children. In 1919, the University of Glasgow received funding to establish both medical and surgical lectureships, the first academic appointments in Britain. Alex MacLennan was appointed Barclay lecturer in surgical and orthopedic diseases of children at the University of Glasgow from 1919 to 1938. His successor, Matthew White, the Barclay lecturer in 1938, was a thoracic and abdominal surgeon. Mr. Wallace Dennison and Dan Young were among the other surgeons who later filled these posts. In Edinburgh, the children's surgical services and the adult services remained closely associated until Mason Brown became the chief.[14]

Modern pediatric surgery was a development that had to wait until after World War II. Introduction of the National Health Service in Britain, which provided access to care for all citizens, the development of the plastics industry, and many other technical innovations in the mid-20th century, allowed great strides, particularly in neonatal surgery and critical care.[14] In London, and elsewhere in England, general surgeons who were interested in pediatric surgery carried on their pediatric practices in conjunction with their adult practices. Financial considerations influenced their activities, because few were able to earn a living in pediatric surgical practice alone. However, further developments in the specialty were closely related to committed individuals.

Denis Browne, an Australian who stayed in London after serving in WWI, was appointed to the HSC in London in 1924. Browne was the first surgeon in London to confine his practice to pediatric surgery, and he is recognized as the pioneer of the specialty in the United Kingdom.[51–53] He was a tall impressive figure with a somewhat domineering, authoritative manner (Fig. 1-8). Browne's longtime colleague James Crooks called him an "intellectual adventurer, a rebel and a cynic."[51] After World War II, many surgeons from overseas spent time in the United Kingdom; the majority visited the HSC, where they were influenced by Browne. Some subsequently established internationally recognized centers such as Louw in South Africa, and Stephens and Smith in Australia. Browne's major interest was structural orthopedic anomalies, and as an original thinker, he achieved widespread recognition for promoting intrauterine position and pressure as a cause of these deformities.[53] He developed instruments, retractors, and splints to assist in his work, all named after himself. His early contemporaries were L. Barrington-Ward and T. Twistington Higgins, surgeons of considerable stature. It was Higgins who initially held discussions in London that led to the formation of the British Association of Pediatric Surgeons (BAPS) in 1953. Browne became the association's first and longest-serving president. The Denis Browne Gold Medal, an award given by the BAPS, remains a symbol of his presence and demonstrates his views (Fig. 1-9). In his later years in the National Health Service, his colleagues included George McNab, introducer of the Holter valve for hydrocephalus; David Waterston, an early pediatric cardiothoracic surgeon; and David Innes Williams, doyen pediatric urologist of Britain.[14] Each of these outstanding men made major contributions to the development of pediatric surgery. Many young surgeons continued to flock to HSC in London for training in pediatric surgery, including Nate Myers, Barry O'Donnell, H.H. Nixon and others. Andrew Wilkinson replaced Browne as surgeon-in-chief. Many other developments were also taking place. Wilkinson in London and Knutrud in Oslo were studying infant metabolism. Isabella Forshall, later joined by Peter Rickham, established an excellent clinical service in Liverpool. She was one of the few female pediatric surgeons of the time and was president of the BAPS in 1959. Pediatric surgery services were established in Sheffield by Robert Zachary, and in Manchester, Newcastle, Birmingham, Southampton, Bristol, Nottingham, and Leeds. Lewis Spitz from South Africa trained at Alder Hey Hospital in Liverpool with Peter Rickham in 1970. After a brief stay in Johannesburg, he immigrated to the United Kingdom to work with Zachary in Sheffield in 1974. He was then named the Nuffield Professor and head at Great Ormond Street, London and provided excellent leadership and strong surgical discipline at the HSC, leading by example for many years, until 2004 when he retired. His main areas of expertise included esophageal surgery, congenital hyperinsulinism, and separation of conjoined twins.[54,55] His colleagues included Kiely, Brereton, Drake, and Pierro. The latter established a strong research base at the institution and succeeded Spitz as the Nuffield Professor.

**FIGURE 1-8** Sir Denis Browne, London, United Kingdom.

## IRELAND

In 1922, Ireland was divided into six northern counties under British rule and 26 southern counties that became the Republic of Ireland. The first children's hospital in Ireland was in the south, the National Children's Hospital, opening on Harcourt Street in Dublin in 1821.[56] The Children's University Hospital in Dublin was founded on Temple Street in 1872. John Shanley, a general surgeon, was appointed to the Temple Street facility and devoted all his surgical activities to children. Another general surgeon, Stanley McCollum, worked at the National Hospital and did pediatric surgery at the Rotunda at the Maternity Hospital. A third children's hospital, Our Lady's Hospital for


**FIGURE 1-9** Denis Browne Gold Medal. **A,** Front of the medal. **B,** Back of the medal, which reads, "The aim of paediatric surgery is to set a standard not to seek a monopoly."

Sick Children, managed by the Daughters of Charity of St. Vincent De Paul, opened in 1956 in Crumlin. Barry O'Donnell was the first full-time, fully trained pediatric surgeon at this facility. Each of the children's hospitals had an academic affiliation, the National Hospital with Trinity College, and Temple Street and Our Lady's with The Royal College of Surgeons University College. Edward Guiney was added to the consultant staff of Our Lady's in 1966 and also was appointed to Temple Street and assisted McCollum at the National Children's Hospital, Dublin. From 1979 to 1993, Ray Fitzgerald, Prem Puri, and Martin Corbally were added as consultant pediatric surgeons. Following Barry O'Donnell's retirement in 1991 and Guiney stepping down in 1993, Fergal Quinn was eventually named to replace him. The Children's Research Center was developed in 1971, with Guiney appointed as director in 1976. He was replaced by Prem Puri, who has mentored numerous overseas research fellows and provided outstanding research concerning many neonatal and childhood conditions. O'Donnell conceived and Puri developed the innovative sting procedure to endoscopically treat vesicoureteral reflux, initially by Teflon injection and subsequently with Deflux. O'Donnell, Guiney, and Fitzgerald have served as presidents of the BAPS. Both O'Donnell and Puri are Denis Browne Gold Medal recipients and achieved international stature. Fitzgerald was president of European Pediatric Surgeons Association (EUPSA) and IPSO, and O'Donnell was president of the Royal College of Surgeons of Ireland. Puri served as president of EUPSA and the WOFAPS (World Federation of Associations of Pediatric Surgeons)

Pediatric surgery in Northern Ireland developed more slowly. Brian Smyth, who trained at Great Ormond Street and Alder Hey Hospitals, was appointed the first specialist pediatric surgeon consultant in 1959. He was joined by a Scotsman, William Cochran, who trained in Edinburgh. Following training in Newcastle and Cape Town, Victor Boston was added as a pediatric surgery consultant in 1975. Political unrest and economic constraints placed some limitations on growth in the north. Cochran returned to Scotland, and in 1995, McCallion was added as a consultant. Today they have similar standards to the southern centers in Ireland.

## EUROPE

Europe served as the cradle of pediatric surgery, but because of space limitations, only the major developments and leading figures can be discussed. In France, the Hôpital des Enfants Malades has a long and storied history, starting with the contributions of Guersant, Giraldes, and de Saint-Germain from 1840 to 1898.[57] Most of their work involved orthopedic conditions and the management of infectious problems. Kirmisson, also well-versed in orthopedic disorders, was appointed the first professor of pediatric surgery in 1899 and published a pediatric surgical textbook in 1906 that contained radiologic information and discussed osteomyelitis and some congenital anomalies. In 1914, Broca described the management of intussusception, instances of megacolon, and experience with Ramstedt's operation for pyloric stenosis. He was succeeded by Ombredanne, a self-taught pediatric surgeon whose works were published by Fevre in 1944.[58] Petit performed the first successful repair of type C esophageal atresia in France in 1949. Because of two world wars, intervals of foreign occupation, and long periods of recovery in all of Europe, it was some time after WWII before modern pediatric surgery could develop in this part of the world. Following WWII, Bernard Duhamel was at the Hôpital des Enfantes Malades but moved to St. Denis, where he devised the retrorectal pull-through for Hirschsprung disease, an alternative procedure to the Swenson operation in 1956 (Fig. 1-10).[59] He was the first editor of *Chirurgie Pediatrique,* started in 1960. Denys Pellerin became chief-of-surgery at the Hôpital des Enfantes Malades and developed a strong department at the institution until he retired in 1990. His successor was Claire Nihoul-Fekete, the first female professor of pediatric surgery in France. Fekete was recognized for her stylish demeanor and expertise in intersex surgery, esophageal anomalies, and congenital hyperinsulinism. She was succeeded by Yann Revillion, an international leader in intestinal transplantation. Yves Aigran plays a leadership role as well. Elsewhere, Michel Carcassone, who developed pediatric surgery in Marseille, had expertise in treating portal hypertension and was an early advocate of a primary pull-through procedure for Hirschsprung disease. He also served as the

**FIGURE 1-10** Bernard Duhamel, Paris, France.

editor-for-Europe for the *Journal of Pediatric Surgery*. J.M. Guys is currently chief in Marseilles. Prevot was the first leader in Nancy. The Société Francaise de Chirurgie Infantile was established in 1959, with Fevre as the first president. The group changed its name to the French Society of Pediatric Surgery in 1983. A strong pediatric oncology presence has existed in Villejuif for many years, initially under the direction of Mme. Odile Schwiesgut.

Pediatric surgical development in Scandinavia also has a rich history. In Sweden, The Princess Lovisa Hospital in Stockholm opened in 1854, but it was not until 1885 that a surgical unit was added under the direction of a general surgeon.[60,61] The first pediatric surgery unit was actually started at the Karolinska Hospital in 1952 and was transferred to St. Gorans Hospital in 1982. In 1998, all pediatric surgery in Stockholm was moved to the newly constructed Astrid Lindgren Children's Hospital at Karolinska University. Three other major pediatric surgery centers were developed in Gothenberg, Uppsala, and Lund. Philip Sandblom was appointed chief-of-surgery at Lovisa from 1945 to 1950, and then he moved to Lund and, later, Lausanne as chief-of-surgery. He was succeeded by Theodor Ehrenpreis, who moved to the Karolinska Pediatric Clinic in 1952. He had a strong interest in research in Hirschsprung disease. Gunnar Ekstrom took his place, and he was succeeded by Nils Ericsson, whose major interest was pediatric urology. Bjorn Thomasson became chief at St. Gorans in 1976. Tomas Wester is the current chief in Stockholm. Gustav Peterson was the initial chief of pediatric surgery in Gothenberg. Ludvig Okmian became the chief of pediatric surgery in Lund in 1969 and helped develop the infant variant of the Engstrom ventilator, and along with Livaditis, employed circular myotomy for long gap esophageal atresia. In 1960, Gunnar Grotte was appointed the first chief of pediatric surgery in Uppsala. He was joined by Leif Olsen, and their major interests included pediatric urology, Hirschsprung disease, and metabolism. The Swedish Pediatric Surgical Association was formed in 1952, and Swedes also participate in the Scandinavian Association of Pediatric Surgeons, founded in 1964.

In Finland, pediatric surgery developed after WWII. Mattie Sulamaa, the pioneer in Finland, was the first to work in the new children's hospital in Helsinki, which opened in 1946. He was instrumental in introducing pediatric anesthesiology. He trained young students, who later started programs at children's hospitals in Turku and Oulu, and university centers in Tampere and Kuopio. He retired in 1973 and was succeeded by Ilmo Louhimo, who specialized in cardiothoracic surgery. He trained Harry Lindahl and Risto Rintala. Rintala is the current chief at Helsinki Children's Hospital and is well recognized for his expertise in pediatric colorectal surgery. Lindahl is a leader in upper gastrointestinal surgery, endoscopy, and the management of esophageal atresia.

There were no children's hospitals in Norway. However, pediatric surgery was strongly influenced by Ola Knutrud of Oslo, beginning in 1962 when he was appointed chief of pediatric surgery at the University Rikshospital. He was an early leader in the field, with interest in pediatric fluid and electrolyte balance, metabolism, fat nutrition, and congenital diaphragmatic hernia. In 1975, Torbjorn Kufaas was named chief of pediatric surgery at the University Hospital in Trondheim.

In Denmark, the first children's hospital opened in1850 and moved to a new facility named after Queen Louise in 1879, with Harald Hirschsprung, a pediatrician appointed as chief physician. Hirschsprung's interests centered on surgical problems, including esophageal atresia, intussusception, ileal atresia, pyloric stenosis, and congenital megacolon.[62] C. Winkel Smith and Tyge Gertz initiated pediatric surgery at University Hospital in Copenhagen, with the latter performing the first successful repair of esophageal atresia in Denmark in 1949. Smith mysteriously disappeared in 1962 but was not declared deceased until 1968.[63] Knud Mauritzen was named his successor as director of pediatric surgery in Copenhagen. Ole Nielsen, a urologic surgeon, succeeded him. Carl Madsen became consultant surgeon at Odense University Hospital; however, there is no department of pediatric surgery there or in Arhus, where pediatric urology and children's surgery are performed in the Department of Urology or Surgery. The only Danish department of pediatric surgery exists in Copenhagen. Although the Danish governmental specialty rules listed pediatric surgery as a specialty in 1958, this was rescinded in 1971 and has not been restored.[63]

Modern pediatric surgery in Switzerland starts with the pioneer in that country, Max Grob. A native of Zurich, he trained in general surgery with Clairmont in Zurich in 1936 and then spent 6 months in Paris at the Hôpital des Enfantes Malades under Ombredanne. He returned to Zurich and entered private practice. It was during WWII that he was appointed to replace Monnier, a general surgeon in charge at the Children's Hospital, whom he met during training. His pediatric surgical practice was quite varied and included plastic surgery and cardiac surgery.[64] He modified Duhamel's operation for Hirschsprung disease and did the first hiatal hernia repair in a child in Switzerland. He trained a new generation of pediatric surgeons in Zurich, including Marcel Bettex, Noel Genton, and Margrit Stockman. The Swiss Society of Pediatric Surgery was formed in 1969, with Grob as its first president.[65] Peter Paul Rickham moved from Liverpool to succeed Grob in Zurich in 1971. Marcel Bettex

developed a separate department of pediatric surgery in Bern, as did Noel Genton in Lausanne, Alois Scharli in Luzern, Anton Cuendet in Geneva, and Nicole in Basel. Urs Stauffer replaced Professor Rickham as chief in Zurich in 1983. Martin Meuli is the current chief in Zurich. Claude Lecoutre succeeded Cuendet in Geneva. The current chief there is Barbara Wildhaber. Peter Herzog is presently chief in Basel, Marcus Schwoebel in Lausanne, and Zachariah Zachariou in Bern. Alois Scharli began the journal *Pediatric Surgery International* in 1985 and served as editor-in-chief for 18 years, followed by Puri and Coran as the current co–editors-in-chief.

In Germany, pediatric care began with the development of children's hospital facilities in various cities across the country, most notably, in Munich, Cologne, and Berlin. Early contributions from Max Wilms in Liepzig and Conrad Ramstedt in Münster have been previously noted.[17,20] Progress was somewhat hampered by war, political and social unrest, and the separation of the country into East Germany and West Germany during the occupation following WW II. Children's surgical units developed either in university settings within adult hospitals or in independent children's hospitals. The contributions of Anton Oberniedermayr and Waldemar Hecker in Munich, who was the first professor of pediatric surgery in the Federal Republic of Germany, Fritz Rehbein in Bremen, and Wolfgang Maier in Kahrlsruhe are well recognized.[66] Fritz Rehbein's clinic in Bremen attracted many young men to train there. He was a thoughtful and resourceful pediatric surgical leader who contributed much to patient care, including the Rehbein strut for pectus excavatum, modifications in esophageal surgery, low pelvic anterior resection for Hirschsprung disease (the Rehbein procedure),[67,68] and a sacral approach with rectomucosectomy of the atretic rectum with abdominoperineal pull-through for high imperforate anus (Fig. 1-11). He was a founding editor of *Zeitschrift Kinderchirurgie* in 1964, which was the precursor of the *European Journal of Pediatric Surgery* following merger with the French journal *Chirurgie Pedaitrique* in 1990. Alex Holschneider was editor from 1980 to 2007, and Benno Ure of Hannover has been the editor-in-chief since 2007. Many of Rehbein's trainees went on to leadership roles in other European cities, including Michael Hoellwarth (Graz), Alex Holschneider (Cologne), Pepe Boix-Ochoa (Barcelona), and others. He was recognized throughout Europe as a leader in the field and was a recipient of the Denis Browne Gold Medal from the BAPS and many other awards. His contributions to European pediatric surgery are recognized by the establishment of the Rehbein Medal, awarded each year by the EUPSA, representing 28 countries in Europe. In West Germany, pediatric surgery was not recognized as an independent specialty until 1984. Following the fall of the Berlin Wall and the reunification of Germany in 1990, the 33 East German pediatric surgery programs joined those of the West from the Federal Republic of Germany and formed a joint German Society of Pediatric Surgery.

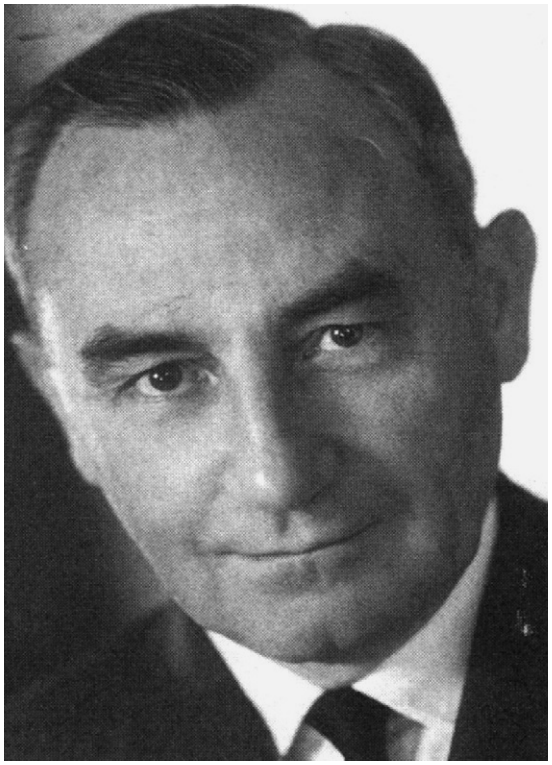

**FIGURE 1-11** Fritz Rehbein, Bremen, Germany.

In Italy, early evidence of a hospital devoted to children dates back to the 15th century with the Hospital of the Innocents in Florence, which was more of a foundling home than a hospital. Other facilities for sick children were documented in the 1800s in many Italian cities. The first hospital dedicated to children's surgery was in Naples in 1880. In Milan in 1897, Formiggini was the surgeon-in-charge, and he eventually started the first Italian pediatric surgical journal, *Archivio di Chirurgia Infantile,* in 1934. It was a short-lived effort, however. Once again WW II delayed progress. Carlo Montagnani spent 18 months in Boston in 1949 and returned to Florence, where he translated Gross' textbook into Italian. He had a productive career as a pioneer pediatric surgeon. He organized the Italian Society of Pediatric Surgery in 1964, with Pasquale Romualdi of Rome serving as the first president. That was the same year Franco Soave of Genoa described the endorectal pull-through for Hirschsprung disease (Fig. 1-12). In 1992, the Italian journal ceased to publish, and the *European Journal of Pediatric Surgery* became the official journal of the Italian Society. Major advances in the management of neonatal conditions, childhood tumors, Hirschsprung disease, esophageal disorders, and pediatric urology have emanated from Italy in the past 2 decades from centers in Rome, Milan, Genoa, Naples, Pavia, Florence, Bologna, Turin, and others.

In the Netherlands, the first children's hospital was opened in Rotterdam in 1863, with eight beds located in a first-floor apartment. The children's hospital in Amsterdam followed in 1865 in an old orphanage. In 1899, the name of the facility was changed to Emma Children's Hospital, after the Queen. Volunteer adult surgeons did whatever children's surgical work that presented. Throughout the rest of the 19th century, additional children's facilities sprung up in other cities. R.J. Harrenstein was the first full-time surgeon appointed at the Emma Children's Hospital. In the 1970s, Born at The Hague and David Vervat in Rotterdam dedicated themselves to children's care. Vervat was also an early editorial consultant for the *Journal of Pediatric Surgery.* Jan Molenaar trained with Vervat and eventually replaced him at Erasmus University in Rotterdam in 1972. Molenaar served as the editor-for-Europe for the *Journal of Pediatric Surgery.* Franz Hazebroeck replaced Molenaar as chief in 1998, and Klaas Bax subsequently succeeded Hazebroeck. The Rotterdam school focused on basic

**FIGURE 1-12** Franco Soave, Genoa, Italy.

science research and a high level of clinical care. Anton Vos spent time in Boston with Gross and Folkman and later returned to Amsterdam as an associate of Professor Mak Schoorl. In 1991, he was appointed professor of pediatric surgery at the University of Amsterdam with a strong focus on pediatric oncology. Hugo Heij succeeded Vos as chief in 1999. Currently there are five pediatric surgery training programs in the Netherlands located in Rotterdam, Amsterdam, Utrecht, Nijmegen, and Groningen. Trainees are certified by the European Board of Pediatric Surgery (EBPS), sponsored by the Union of European Medical Specialties (EUMS).

In Spain, the modern day pioneers included Julio Monoreo, who was appointed the first head of pediatric surgery at the Hospital of the University of La Paz, Madrid in 1965. Pepe Boix-Ochoa filled the same role at Hospital Valle de Hebron in Barcelona. Juan Tovar succeeded Monoreo after his passing. In the 1970s and 1980s, major regional pediatric surgical centers were located in numerous cities around the country. The Spanish Pediatric Surgical Association was formed as an independent group for pediatrics in 1984. Tovar is the current editor-for-Europe for the *Journal of Pediatric Surgery* and served as president of EUPSA.

Other leaders in Europe included Aurel Koos, Imre Pilaszanovich, and Andras Pinter in Hungary; Petropoulos, Voyatzis, Moutsouris Pappis, and Keramidis in Greece; Kafka, Tosovsky, and Skaba in the Czech Republic; Kossakowski, Kalicinski, Lodzinski, and Czernik in Poland; and Ivan Fattorini in Croatia. In Austria, the leaders in the field included Sauer and Hoellwarth in Graz, Rokitansky and Horcher in Vienna, Menardi in Innsbruck, Oesch in Salzburg, and Brandesky in Klangenfurt. In Turkey, Ihsan Numanoglu developed the first pediatric surgery service in Izmir in 1961. Akgun Hiksonmez started the program at Hacettepe University in Ankara in 1963. Acun Gokdemir was an early pediatric urologist in Istanbul. Daver Yeker, Cenk Buyukunal, Nebil Buyukpamukcu, and Tolga Dagli are major contributors to contemporary Turkish pediatric surgery and urology. The Turkish Association of Pediatric Surgeons (TAPS) formed in 1977, with Hicsonmez elected the first president.

## AUSTRALIA AND NEW ZEALAND

The first children's hospital opened in Melbourne, Australia in 1870.[69] In 1897, Clubbe performed a successful bowel resection for intussusception in Sydney. In 1899, Russell published the method of high ligation of an inguinal hernia sac. Hipsley described successful saline enema reduction of intussusception in 1927. As was the case elsewhere, pediatric surgery did not experience significant growth until after WW II. Howard performed the first successful repair of esophageal atresia in Melbourne in 1949. He was joined there by F. Douglas Stephens, who had spent time with Denis Browne in London, and he directed the research program at the Royal Melbourne Children's Hospital for many years. Bob Fowler and Durham Smith later joined the Melbourne group. They set a standard for investigation of malformations of the urinary tract and anorectum. Stephens developed the sacroperineal pull-through operation for high anorectal malformations. The pediatric surgery staff in Melbourne was exemplary and added Nate Myers, Peter Jones, Alex Auldist, Justin Kelley, Helen Noblett, and Max Kent to the group. Archie Middleton, Douglas Cohen, and Toby Bowring led the way in Sydney, Geoff Wylie in Adelaide, Alastair MacKellar in Perth, and Fred Leditschke in Brisbane.

Pediatric surgical contributions from Australia were considerable. Myers was an expert in esophageal atresia and provided the first long-term outcome studies.[70] Noblett promoted nonoperative gastrografin enema for simple meconium ileus and devised the first forceps for submucosal rectal biopsy for Hirschsprung disease.[71,72] Jones spearheaded the nonoperative management of torticollis and management of surgical infections. Fowler devised the long-loop vas operation for high undescended testis[73]; MacKellar instituted the first trauma prevention program; Kelly developed a scoring system for fecal incontinence and total repair of bladder exstrophy; and Smith and Stephens developed the Wingspread classification for anorectal malformations. Hutson's studies on the influence of hormones and the genitofemoral nerve on testicular descent and colonic motility, Cass' insights into the genetics of Hirschsprung disease, and Borzi and Tan's leadership in pediatric MIS are more recent examples of Australian contributions to the field. Pediatric surgery in New Zealand took longer to develop. There are now four major training centers in Auckland, Hamilton, and Wellington on the North Island and Christchurch on the South Island. Leaders include Morreau in Auckland, supported by Stuart Ferguson and others; Brown in Hamilton; Pringle in Wellington; and Beasley in Christchurch. A significant outreach program for the islands of the South Pacific is in place.

## ASIA

There have been significant contributions to pediatric surgery from Japan, China, Taiwan, and other Asian countries following WW II. In China, Jin-Zhe Zhang in Beijing survived war,

national turmoil, and the Cultural Revolution to emerge as that nation's father figure in children's surgery. Other early leaders included She Yan-Xiong and Ma in Shanghai and Tong in Wuhan. The latter was the first editor of the *Chinese Journal of Pediatric Surgery*. The first pediatric surgery congress in China was held in 1980, and the China Society of Pediatric Surgeons was formed in 1987. There is a new generation of pediatric surgeons, including Long Li, G-D Wang, and others. Major children's hospitals are now located in Beijing, Shanghai, Fudan, Shenyang, Wuhan, and many other mainland cities. The use of saline enemas under ultrasound guidance, as well as the introduction of the air-enema for reduction of intussusception, are examples of significant Chinese contributions. Paul Yue started the first pediatric surgery unit in Hong Kong in 1967. H. Thut Saing was appointed the first chair of pediatric surgery at the University of Hong Kong in 1979.[74] Paul Tam and CK Yeung trained with Saing and went on to have very productive careers. Tam spent time at Oxford in the United Kingdom and returned to become chair of pediatric surgery at the University of Hong Kong in 1996. Yeung succeeded Kelvin Liu as chief of pediatric surgery at the Chinese University Prince of Wales Hospital. Both Tam and Yeung provided pediatric surgery leadership in Hong Kong and have been productive in the study of the genetic implications of many surgical disorders, including Hirschsprung disease and neuroblastoma (Tam) and application of MIS, particularly in pediatric urology (Yeung).

V.T. Joseph was the first director of pediatric surgery in Singapore in 1981. Following his departure, Anette Jacobsen has been influential in further developing the specialty and providing strong leadership in children's surgery in Singapore.[74] Sootiporn Chittmittrapap, Sriwongse Havananda, and Niramis have been strong advocates in establishing a high level of pediatric surgical care in Thailand. In Vietnam, years of political strife and conflict delayed progress in children's surgery. Nguyen Thanh Liem has emerged as a leading contributor from Hanoi, with extensive experience in the use of MIS for managing a myriad of pediatric surgical conditions. There are now 13 pediatric surgical centers in Vietnam.[74]

In Japan, the first generation of pediatric surgeons appeared in the early 1950s: Ueda in Osaka, Suruga at Juntendo University in Tokyo, Kasai at Tohoku University in Sendai, and Ikeda at Kyushu University in Fukuoka. Suruga performed the first operation for intestinal atresia in 1952. Kasai performed the first hepatoportoenterostomy for uncorrectable biliary atresia in 1955 (Fig. 1-13), and Ueda performed the first successful repair of esophageal atresia in 1959.[14] The first children's hospital in the country was the National Children's Hospital in Tokyo, opened in 1965. The first department of pediatric surgery was established at Juntendo University in Tokyo in 1968 by Suruga (Fig. 1-14); today, training programs exist in nearly all the major university centers. The Japanese Society of Pediatric Surgeons and its journal were established in 1964, paralleling developments in other parts of the world. The second generation of pediatric surgeons include Okamoto and Okada in Osaka; Nakajo, Akiyama, Tsuchida, and Miyano in Tokyo; Ohi and Nio in Sendai; Suita in Fukuoka and Ken Kimura in Kobe and later in Iowa and Honolulu. These individuals made seminal contributions in the fields of nutrition, biliary and pancreatic disease, management of choledochal cyst, oncology, and intestinal disorders, including Hirschsprung disease, esophageal atresia, duodenal atresia, and tracheal reconstruction. In recent decades, laboratories and clinical centers in Asia, particularly in Japan and Hong Kong, have generated exciting new information in the clinical and basic biological sciences that continues to enrich the field of children's surgery.

**FIGURE 1-13** Morio Kasai, Sendai, Japan.

**FIGURE 1-14** Keijiro Suruga, Tokyo, Japan.

## DEVELOPING COUNTRIES

Nowhere in the world is the global burden of surgical disease more evident than in Africa. Pediatric surgery in underdeveloped areas of the world suffers from a lack of infrastructure, financial resources, and governmental support. In Africa, hepatitis B, malaria, malnutrition, human immunodeficiency virus–acquired immune deficiency virus (HIV-AIDS), and the ravages of political unrest and conflict play a major role in the higher childhood mortality noted on the continent. There are some exceptions, such as South Africa, where pediatric surgery is an established specialty with major children's centers in Cape Town, Johannesburg, Durban, Pretoria, and Bloemfontein; in Egypt with centers in Cairo and Alexandria; and in Nairobi, Kenya. The pioneer pediatric surgeon in South Africa was Jan Louw of Cape Town (Fig. 1-15). Collaborating with Christian Barnard in 1955, they demonstrated, in a fetal dog model, that most jejunoileal atresias were related to late intrauterine vascular accidents to the bowel and/or mesentery. Sidney Cywes succeeded Louw at the Red Cross Memorial Children's Hospital in 1975. He was the first surgeon in the country to limit his practice to children.

Cywes was joined in Cape Town by Michael Davies, Heinz Rode, Alastair Millar, Rob Brown, and Sam Moore. Millar is the current surgeon-in-chief. Michael Dinner was the first professor of pediatric surgery at Witwatersrand University in Johannesburg. Derksen and Jacobs started the pediatric surgery service in Pretoria and were succeeded by Jan Becker in 1980. R. Mikel was the first professor of pediatric surgery at the University of Natal in Durban; he was succeeded by Larry Hadley. The South African Association of Pediatric Surgeons was formed in 1975, with Louw serving as its first president.[75] Major contributions to pediatric surgical care from South Africa include management of intersex, separation of conjoined twins, childhood burn care, pediatric surgical oncology, treatment of jejunoileal atresia, caustic esophageal injury, Hirschsprung disease, and liver transplantation. In 1994 in Nairobi, where pediatric surgery was pioneered by Julius Kyambi, the Pan African Pediatric Surgical Association (PAPSA) was established with pediatric surgeons from all the nations on the continent joining as members.

**FIGURE 1-15** Professor Jan Louw, Cape Town, South Africa.

In India, the Association of Indian Surgeons first recognized pediatric surgery as a separate section in 1964. This organization subsequently became independent as the Indian Association of Pediatric Surgeons (IAPS) and met for the first time in New Delhi in 1966. Facilities for pediatric surgical care were limited to a few centers in metropolitan areas. Early leaders in the field included S. Chatterjee, R.K. Ghandi, P. Upadhaya, R.M. Ramakrishnan, V. Talwalker, and S. Dalal. Ms. Mridula Rohatgi was the first female professor of pediatric surgery. Professor Ghandi served as president of the WOFAPS, and presently, Professor Devendra Gupta of New Delhi is the president-elect of that organization. There are currently 24 pediatric surgery teaching centers in the country, all located in major cities. Rural care is still less than desirable, and there are only 710 pediatric surgeons to care for a population of 1.2 billion people.

Space limitations prevent individual mention of some other countries and deserving physicians who have made contributions to the field of pediatric surgery.

The discipline of pediatric surgery around the world is mature at this point and as sophisticated as any medical field. It has become a science-based enterprise in a high-technology environment. In the developed world, children with surgical problems have never been as fortunate as now. Pediatric surgery has truly become internationalized, with various countries developing national societies and striving to improve the surgical care of infants and children. The availability of the Internet to rapidly disseminate information has provided a method to share knowledge and information regarding patient care. The World Federation of Associations of Pediatric Surgeons (WOFAPS), which originated in 1974 and under the leadership of Professor Boix-Ochoa, the organization's secretary general, has grown and matured as an organization that now comprises more than 100 national associations.[76] It is an international voice for the specialty and sponsors a world congress of pediatric surgery every 3 years in a host country and provides education, support, and assistance to underdeveloped countries to improve the surgical care of infants and children. With children representing a higher percentage of the population in the developing world, this becomes an increasingly important factor in enhancing the global effort to provide better surgical care for children.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 2

# Molecular Clinical Genetics and Gene Therapy

Alan W. Flake

The topics of this chapter are broad in scope and outside the realm of a classic core education in pediatric surgery. However both molecular genetics and gene therapy will be of increasing clinical importance in all medical specialties, including pediatric surgery, in the near future. A few conservative predictions include improvements in the diagnostic accuracy and prediction of phenotype, the development of new therapeutic options for many disorders, and the optimization of pharmacotherapy based on patient genotype, but there are many other possible uses. The goal here is to provide an overview of recent developments that are relevant or potentially relevant to pediatric surgery.

## Molecular Clinical Genetics

Although hereditary disease has been recognized for centuries, only relatively recently has heredity become the prevailing explanation for numerous human diseases. Before the 1970s, physicians considered genetic diseases to be relatively rare and irrelevant to clinical care. With the advent of rapid advances in molecular genetics, we currently recognize that genes are critical factors in virtually all human diseases. Although an incomplete indicator, McKusick's *Mendelian Inheritance in Man* has grown from about 1500 entries in 1965[1] to 12,000 in 2010, documenting the acceleration of knowledge of human genetics. Even disorders that were once considered to be purely acquired, such as infectious diseases, are now recognized to be influenced by genetic mechanisms of inherent vulnerability and genetically driven immune system responses.

Despite this phenomenal increase in genetic information and the associated insight into human disease, until recently there was a wide gap between the identification of genotypic abnormalities that are linked to phenotypic manifestations in humans and any practical application to patient treatment. With the notable exceptions of genetic counseling and prenatal diagnosis, molecular genetics had little impact on the daily practice of medicine or more specifically on the practice of pediatric surgery. The promise of molecular genetics cannot be denied however. Identifying the fundamental basis of human disorders and of individual responses to environmental, pharmacologic, and disease-induced perturbations is the first step toward understanding the downstream pathways that may have a profound impact on clinical therapy. The ultimate application of genetics would be the correction of germline defects for affected individuals and their progeny. Although germline correction remains a future fantasy fraught with ethical controversy,[2] there is no question that molecular genetics will begin to impact clinical practice in myriad ways within the next decade. A comprehensive discussion of the field of molecular genetics is beyond the scope of this chapter, and there are many sources of information on the clinical genetics of pediatric surgical disorders.

### HUMAN MOLECULAR GENETICS AND PEDIATRIC SURGICAL DISEASE

The rapid identification of genes associated with human disease has revolutionized the field of medical genetics, providing more accurate diagnostic, prognostic, and potentially therapeutic tools. However, increased knowledge is always associated with increased complexity. The classic model assumed that the spread of certain traits in families is associated with the transmission of a single molecular defect, with individual alleles segregating into families according to Mendel's laws, whereas today's model recognizes that very few phenotypes can be satisfactorily explained by a mutation at a single gene locus. The phenotypic diversity recognized in disorders that were once considered monogenic has led to a reconceptualization of genetic disease. Although mendelian models are useful for identifying the primary cause of familial disorders, they appear to be incomplete as models of the true physiologic and cellular nature of defects.[3–5] Numerous disorders that were initially characterized as monogenic are proving to be either caused or modulated by the action of a small number of loci. These disorders are described as oligogenic disorders, an evolving concept that encompasses a large spectrum of phenotypes that are neither monogenic nor polygenic. In contrast to polygenic or complex traits, which are thought to result from poorly understood interactions between many genes and the environment, oligogenic disorders are primarily genetic in cause but require the synergistic action of mutant alleles at

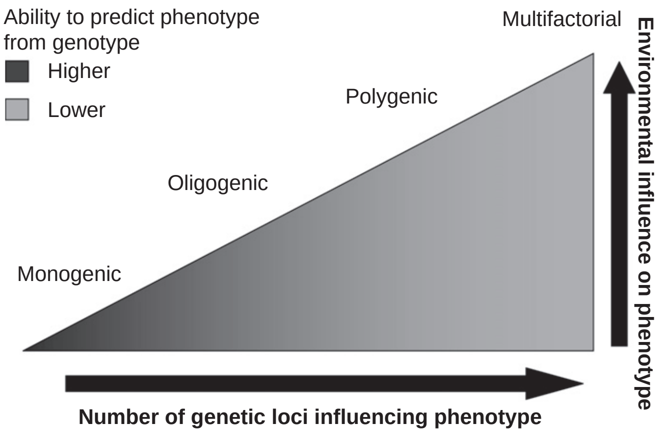


FIGURE 2-1 Conceptual continuum of modern molecular genetics. The genetic characterization of a disorder depends on (1) whether a major locus makes a dominant contribution to the phenotype, (2) the number of loci that influence the phenotype, and (3) the presence and extent of environmental influence on phenotype. The farther toward the right a disorder lies, the greater the complexity of the genetic analysis and the less predictive genotype is of phenotype.

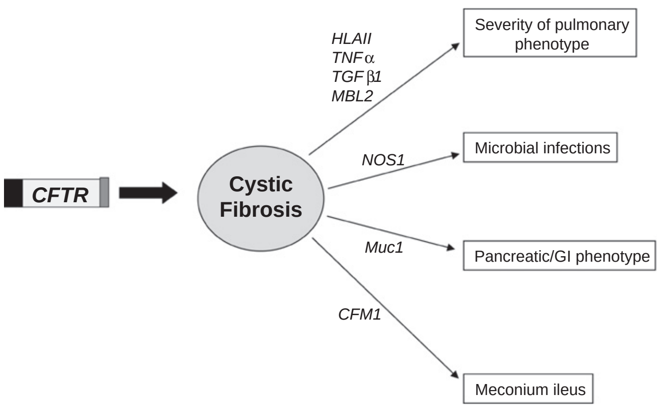


FIGURE 2-2 Complexity in monogenic diseases. Mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) almost always cause the cystic fibrosis (CF) phenotype. Owing to modification effects by other genetic factors, the presence and nature of mutations at the *CFTR* locus cannot predict the phenotypic manifestation of the disease. Therefore, although CF is considered a mendelian recessive disease, the phenotype in each patient depends on a discrete number of alleles at different loci. *CFM1*, cystic fibrosis modifier 1; GI, gastrointestinal; HLAII, major histocompatibility complex class II antigen; *MBL2*, mannose-binding lectin (protein C) 2; *Muc1*, mucin 1; *NOS1*, nitric oxide synthase 1; *TGFB1*, transforming growth factor-β1; *TNF*, tumor necrosis factor encoding gene.

a small number of loci. One can look at modern molecular genetics as a conceptual continuum between classic mendelian and complex traits (Fig. 2-1). The position of any given disorder along this continuum depends on three main variables: (1) whether a major locus makes a dominant contribution to the phenotype, (2) the number of loci that influence the phenotype, and (3) the presence and extent of environmental influence on the phenotype.

## DISEASE-SPECIFIC EXAMPLES OF CHANGING CONCEPTS IN MOLECULAR GENETICS

### Monogenic Disorders

Cystic fibrosis (CF) is an example of a disorder close to the monogenic end of the continuum, but it also illustrates the complexity of the genetics of some disorders, even when a mutation of a major locus is the primary determinant of phenotype. On the basis of the observed autosomal recessive inheritance in families, the gene *CFTR* (cystic fibrosis transmembrane conductance regulator) was first mapped in humans to chromosome 7q31.2.[6] Once the *CFTR* gene was cloned,[7] it was widely anticipated that mutation analyses might be sufficient to predict the clinical outcome of patients. However analyses of *CFTR* mutations in large and ethnically diverse cohorts indicated that this assumption was an oversimplification of the true genetic nature of this phenotype, particularly with respect to the substantial phenotypic variability observed in some patients with CF. For instance, although *CFTR* mutations show a degree of correlation with the severity of pancreatic disease, the severity of the pulmonary phenotype, which is the main cause of mortality, is difficult to predict.[8–10] Realization of the limitations of a pure monogenic model prompted an evaluation of more complex inheritance schemes. This led to the mapping of a modifier locus for the intestinal component of CF in both human and mouse.[11,12] Further phenotypic analysis led to the discovery of several other loci linked to phenotype, including (1) the association of low-expressing mannose-binding lectin (*MBL2*; previously known as *MBL*) alleles, human leukocyte antigen (HLA) class II polymorphisms, and variants in tumor necrosis factor-α (*TNFA*) and transforming growth factor-β1 (*TGFB1*) with pulmonary aspects of the disease;[13–16] (2) the correlation of intronic nitric oxide synthase 1 (*NOS1*) polymorphisms with variability in the frequency and severity of microbial infections[17]; and (3) the contribution of mucin 1 (*Muc1*) to the gastrointestinal aspects of the CF phenotype in mice (Fig. 2-2).[18] Further layers of complexity have been discovered for both *CFTR* and its associated phenotype. First, heterozygous CF mutations have been associated with susceptibility to rhinosinusitis, an established polygenic trait.[19] Second, and perhaps more surprising, a study group reported that some patients with a milder CF phenotype do not have any mutations in *CFTR*. This indicates that the hypothesis that *CFTR* gene dysfunction is a requisite for the development of CF might not be true.[20] Identification of these and many other gene modifiers and appreciation of their importance in this and other diseases is a major step forward. Although at the present time, the effects of these polymorphisms are incompletely understood, such findings could lead to potential therapeutic targets for CF or identification of risk factors early in life.

### Oligogenic Disorders

Recent developments in defining the molecular genetics of Hirschsprung disease (HD) exemplify a relatively new concept in genetics—the oligogenic disorder. Although mathematic analyses of oligogenicity are beyond the scope of this discussion,[21,22] it is important to recognize that modifications of traditional linkage approaches are useful tools for the study of oligogenic diseases, especially if a major locus that contributes greatly to the phenotype is known. In the case of HD, two main phenotypic groups can be distinguished on the basis of the extent of aganglionosis: short-segment HD (S-HD) and the more severe long-segment HD (L-HD). Autosomal dominant inheritance with incomplete penetrance has been proposed for L-HD, whereas complex inheritance that involves

an autosomal recessive trait has been observed in S-HD. Oligogenicity has been established in both HD variants by virtue of several factors: a recurrence risk that varies from 3% to 25%, depending on the length of aganglionosis and the sex of the patient; heritability values close to 100%, which indicates an exclusively genetic basis; significant clinical variability and reduced penetrance; and nonrandom association of hypomorphic changes in the endothelin receptor type B (*EDNRB*) with rearranged during transfection (*RET*) polymorphisms and HD.[23,24] So far a combination of linkage, positional cloning studies, and functional candidate gene analyses has identified eight HD genes (Table 2-1),[25] of which the proto-oncogene *RET* is thought to be the main predisposing locus,[26,27] particularly in families with a high incidence of L-HD.[28]

The non-mendelian transmission of HD has hindered the identification of predisposing modifier loci by conventional linkage approaches. When these approaches (parametric and nonparametric linkage studies) were carried out on a group of 12 L-HD families, very weak linkage was observed on chromosome 9q31. However based on the hypothesis that only milder *RET* mutations could be associated with another locus, families were categorized according to the *RET* mutational data. Significant linkage on chromosome 9q31 was detected when families with potentially weak *RET* mutations were analyzed independently,[27] indicating that mild *RET* alleles, in conjunction with alleles at an unknown gene on chromosome 9, might be required for pathogenesis. The mode of inheritance in S-HD has proved to be more complex than that in L-HD, requiring further adjustments to the linkage strategies. Recently the application of model-free linkage, without assumptions about the number and inheritance mode of segregating factors, showed that a three-locus segregation was both necessary and sufficient to manifest S-HD, with *RET* being the main locus, and that the transmission of susceptibility alleles was additive.[28]

The inheritance patterns observed in disorders such as HD illustrate the power of both expanded models of disease inheritance that account for reduced penetrance and phenotypic variability and the ability of these models to genetically map loci involved in oligogenic diseases, which is a first step toward identifying their underlying genes. More important, the establishment of non-mendelian models caused a change of perception in human genetics, which in turn accelerated the discovery of oligogenic traits.

## Polygenic or Complex Disorders

Polygenic or complex disorders are thought to result from poorly understood interactions between many genes and the environment. An example of a polygenic disorder relevant to pediatric surgery is hypertrophic pyloric stenosis (HPS). The genetic cause of HPS has long been recognized, with frequent familial aggregation, a concordance rate of 25% to 40% in monogenetic twins, a recurrence rate of 10% for males and 2% for females born after an affected child, and a ratio of risk of 18 for first-degree relatives compared with the general population.[29] However this risk is considerably less than would be predicted based on mendelian patterns of inheritance.[30] In addition, HPS has been reported as an associated feature in multiple defined genetic syndromes[31–35] and chromosomal abnormalities[36–40] and anecdotally with many other defects,[41–45] suggesting a polygenic basis. Although the molecular genetic basis of HPS remains poorly defined, a likely common final pathway causing the disorder is altered expression of neural nitric oxide synthase (*NOS1*) within the pyloric muscle.[46] A detailed analysis of the molecular mechanisms of this alteration has been published, describing a reduction of messenger RNA (mRNA) expression of *NOS1* exon 1c, with a compensatory up-regulation of *NOS1* exon 1f variant mRNA in HPS.[46] DNA samples of 16 HPS patients and 81 controls were analyzed for *NOS1* exon 1c promoter mutations and single nucleotide polymorphism (SNP). Sequencing of the 5′-flanking region of exon 1c revealed mutations in 3 of 16 HPS tissues, whereas 81 controls showed the wild-type sequence exclusively. Carriers of the A allele of a previously

**TABLE 2-1**

**Genes Associated with Hirschsprung Disease and Relationship to Associated Anomalies**

| *Gene* | *Gene Locus* | *Gene Product* | *Inheritance* | *Population Frequency (%)* | *Associated Anomalies* | *Incidence in Gene HD (%)* |
|---|---|---|---|---|---|---|
| *RET* | 10q11.2 | Coreceptor for *GDNF* | AD | 17-38 (S-HD)<br>70-80 (L-HD)<br>50 (familial)<br>15-35 (sporadic) | CCHS<br>MEN2A<br>MEN2B | 1.8-1.9<br>2.5-5.0<br>Unknown |
| *GDNF* | 5p12-13.1 | Ligand for *RET* and *GFRα-1* | AD | <1* | CCHS | 1.8-1.9 |
| *NRTN* | 19p13.3 | Ligand for *RET* and *GFRα-2* | AD | <1* | Unknown | — |
| *GFRA1* | 10q26 | Coreceptor for *GDNF* | Unknown | † | Unknown | — |
| *EDNRB* | 13q22 | Receptor for *EDN3* | AD/AR | 3-7 | Waardenburg syndrome | Unknown |
| *EDN3* | 20q13.2-13.3 | Ligand for *EDNRB* | AD/AR | 5 | CCHS<br>Waardenburg syndrome | 1.8-1.9<br>Unknown |
| *ECE1* | 1p36.1 | *EDN3* processing gene | AD | <1 | Unknown | — |
| *SOX10* | 22q13.1 | Transcription factor | AD | <1 | Waardenburg syndrome type 4 | Unknown |

*Limited data available.
†No mutations detected thus far in humans, but associated with HD in mice.
AD, autosomal dominant; AR, autosomal recessive; CCHS, congenital central hypoventilation syndrome (Ondine's curse); *ECE1*, endothelin-converting enzyme-1; *EDNRB*, endothelin receptor type B; *EDN3*, endothelin 3; *GDNF*, glial cell line–derived neurotrophic factor; *GFRA1*, GDNF family receptor α-1; HD, Hirschsprung disease; L-HD, long-segment HD; MEN, multiple endocrine neoplasia; *NRTN*, neurturin; RET, rearranged during transfection; S-HD, short-segment HD; SOX, SRY (sex determining region Y)-box 10.

uncharacterized *NOS1* exon 1c promoter SNP (-84G/A SNP) had an increased risk of HPS developing (odds ratio, 8.0; 95% confidence interval, 2.5 to 25.6), which could indicate that the -84G/A promoter SNP alters expression of *NOS1* exon 1c or is in linkage dysequilibrium with a functionally important sequence variant elsewhere in the *NOS1* transcription unit and therefore may serve as an informative marker for a functionally important genetic alteration. The observed correlation of the -84G/A SNP with an increased risk for the development of HPS is consistent with a report showing a strong correlation of a microsatellite polymorphism in the *NOS1* gene with a familial form of HPS.[47] However the -84G/A SNP does not account for all HPS cases; therefore other components of the nitric oxide–dependent signal transduction pathway or additional mechanisms and genes may be involved in the pathogenesis of HPS. This is in accordance with other observations suggesting a multifactorial cause of HPS.[29] In summary, genetic alterations in the *NOS1* exon 1c regulatory region influence expression of the *NOS1* gene and may contribute to the pathogenesis of HPS, but there are likely numerous other genes that contribute to the development of HPS as well as predispose to environmental influences in this disorder.

These examples provide insight into the complexity of current models of molecular genetics and illustrate the inadequacy of current methods of analysis to fully define genetic causes of disease, particularly polygenic disorders. The majority of pediatric surgical disorders currently fall into the category of undefined multifactorial inheritance, which is even less well understood than the genetic categories described. In these disorders, no causative, predisposing, or influencing gene loci have been identified. Isolated regional malformations are presumed to result from interactions between the environment and the actions of multiple genes. Multifactorial inheritance is characterized by the presence of a greater number of risk genes within a family. The presumption of a genetic basis for the anomalies is based on recurrence risk. The recurrence risks in multifactorial inheritance disorders, although generally low, are higher than in the general population; they are increased further if more than one family member is affected, if there are more severe malformations in the proband, or if the parents are closely related. Beyond these generalizations, genetics can provide little specific information about this category of disorder.

## UTILITY OF MOLECULAR GENETICS IN CLINICAL PEDIATRIC SURGERY

### Genetic Counseling and Prenatal Diagnosis

As mentioned earlier there is still a gap between genotypic understanding of a disorder and direct application to clinical treatment. The exceptions are in the areas of genetic counseling and prenatal diagnosis. Pediatric surgeons are likely to require some knowledge of molecular genetics as their role in prenatal counseling of parents continues to increase. Molecular genetics can supply specific information about an affected fetus by providing genotypic confirmation of a phenotypic abnormality, a phenotypic correlate for a confirmed genotype, and in many instances the recurrence risk for subsequent pregnancies and the need for concern (or lack thereof) about other family members. Once again HD is an example of how molecular genetics can be valuable in genetic counseling.[48,49] The generalized risk to siblings is 4% and increases as the length of involved segment increases. In HD associated with known syndromes, genetic counseling may focus more on prognosis related to the syndrome than on recurrence risk. In isolated HD a more precise risk table can be created. Risk of recurrence of the disease is greater in relatives of an affected female than of an affected male. Risk of recurrence is also greater in relatives of an individual with long-segment compared with short-segment disease. For example the recurrence risk in a sibling of a female with aganglionosis beginning proximal to the splenic flexure is approximately 23% for a male and 18% for a female, whereas the recurrence risk in a sibling of a male with aganglionosis beginning proximal to the splenic flexure is approximately 11% for a male and 8% for a female. These risks fall to 6% and lower for siblings of an individual with short-segment disease. Prenatal diagnosis is possible if the mutation within the family is known. However because the penetrance of single gene mutations is low (except for *SOX10* mutations in Waardenburg syndrome), the clinical usefulness of prenatal diagnosis is limited.

More commonly, a general knowledge of genetics can allow accurate counseling of recurrence risk and reassurance for parents of an affected fetus diagnosed with a multifactorial inheritance defect, the most common circumstance involving prenatal consultation with a pediatric surgeon. Pediatric surgeons should also be aware of the value of genetic evaluation of abortus tissue in cases of multiple anomalies when after counseling the parents choose to terminate the pregnancy. It is a disservice to the family not to send the fetus to an appropriate center for a detailed gross examination and a state-of-the-art molecular genetic assessment when appropriate.

As molecular genetics increasingly characterizes the genes responsible for specific disorders, their predisposing and modifier loci, and other genetic interactions, a better ability to predict the presence and severity of specific phenotypes will inevitably follow. This will allow prenatal counseling to be tailored to the specific fetus and lead to improved prognostic accuracy, giving parents the opportunity to make more informed prenatal choices.

### Postnatal Treatment

In the future molecular genetics will allow specific therapies to be optimized for individual patients. This may range from specific pharmacologic treatments for individual patients based on genotype and predicted pharmacologic response to anticipation of propensities for specific postoperative complications, such as infection or postoperative stress response. Of course the ultimate treatment for an affected individual and his or her progeny would be to correct the germline genetic alteration responsible for a specific phenotype. Although there are many scientific and ethical obstacles to overcome before considering such therapy, it is conceivable that a combination of molecular genetics and gene transfer technologies could correct a germline mutation, replacing an abnormal gene by the integration of a normal gene and providing the ultimate preventive therapy. Although the state of gene transfer technology is far from this level of sophistication, progress in the past 3 decades can only be described as astounding. The next section provides an overview of the current state of gene transfer and its potential application for therapy.

# Gene Therapy

Gene therapy remains controversial; however its tremendous potential cannot be denied, and significant strides in safety have been made in the past few years. The year 2000 brought the first clinical gene therapy success—treatment of X-linked severe combined immune deficiency (XSCID)[50]—only to have this dramatic achievement undermined by the induction of leukemia by a mechanism of insertional oncogenesis in four of the nine successfully treated patients.[51] This and other adverse events[52,53] threatened to overshadow the substantial progress made in gene transfer technology in recent years. The adversity has accelerated progress in our understanding of the mechanisms of insertional oncogenesis and in the design of vectors with much lower propensity to induce malignancies.[54] Methods for gene transfer are being developed that have greater safety, specificity, and efficacy than ever before. With improved understanding of the risks and better vector design, several recent trials of gene therapy for immunodeficiency disorders[55] and for ocular disease[56] have demonstrated early success. The technology of gene transfer can be divided into viral vector–based gene transfer and nonviral gene transfer. Because of the limited scope of this chapter and the limited efficiency of nonviral-based gene transfer thus far, only the current state of viral-based gene transfer is reviewed.

## VIRAL VECTORS FOR GENE TRANSFER

Viruses are highly evolved biologic machines that efficiently penetrate hostile host cells and exploit the host's cellular machinery to facilitate their replication. Ideally viral vectors harness the viral infection pathway but avoid the subsequent replicative expression of viral genes that causes toxicity. This is traditionally achieved by deleting some or all of the coding regions from the viral genome but leaving intact those sequences that are needed for the vector function, such as elements required for the packaging of viral DNA into virus capsid or the integration of vector DNA into host chromatin. The chosen expression cassette is then cloned into the viral backbone in place of those sequences that were deleted. The deleted genes encoding proteins involved in replication or capsid or envelope proteins are included in a separate packaging construct. The vector genome and packaging construct are then cotransfected into packaging cells to produce recombinant vector particles (Fig. 2-3).

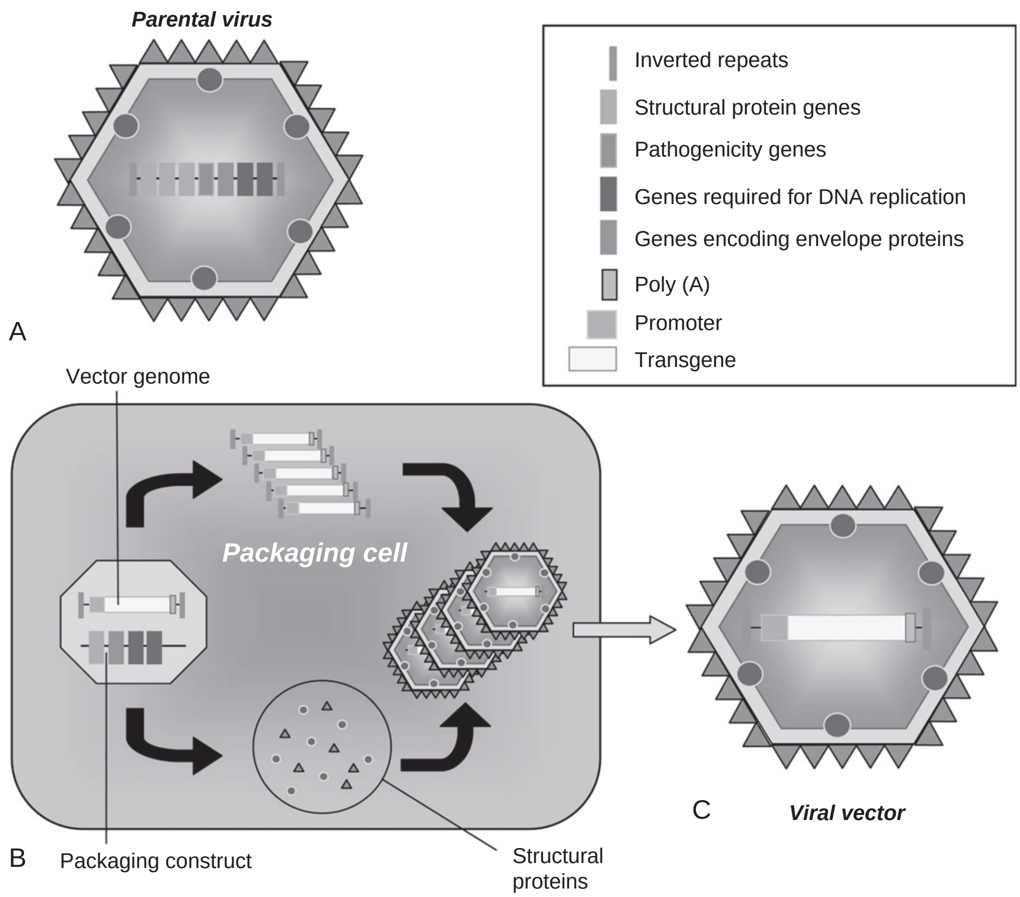


**FIGURE 2-3** Requirements for the creation of a generic viral vector. **A,** The basic machinery of a chosen parental virus is used, including genes encoding specific structural protein genes, envelope proteins, and proteins required for DNA replication, but not genes encoding proteins conferring pathogenicity. **B,** The vector is assembled in a packaging cell. A packaging (helper) construct, containing genes derived from the parent virus, can be delivered as a plasmid or helper virus or stably integrated into the chromatin of the packaging cell. Pathogenicity functions and sequences required for encapsidation are eliminated from the helper construct so that it cannot be packaged into a viral particle. In contrast, the vector genome contains the transgenic expression cassette flanked by inverted terminal repeats and *cis*-acting sequences that are required for genome encapsidation. Viral structural proteins and proteins required for replication of the vector DNA are expressed from the packaging construct, and the replicated vector genomes are packaged into the virus particles. **C,** The viral vector particles are released from the packaging cell and contain only the vector genome.

**TABLE 2-2**
**Five Main Viral Vector Groups**

| *Vector* | *Coding* | *Packaging Capacity (kb)* | *Tissue Tropism* | *Vector Genome* | *Type Advantages* | *Material Disadvantages* |
|---|---|---|---|---|---|---|
| Retrovirus | RNA | 8 | Dividing cells only | Integrated | Persistent gene transfer in dividing cells | Requires cell division; may induce oncogenesis |
| Lentivirus | RNA | 8 | Broad, including stem cells | Integrated | Integrates into nondividing cells; persistent gene transfer | Potential for oncogenesis |
| HSV-1 | dsDNA | 40 | Neural | Episomal | Inflammatory response; limited tropism | Large packaging capacity; strong tropism for neurons |
| AAV | ssDNA | <5 | Broad | Episomal (90%) Integrated (<10%) | Noninflammatory; nonpathogenic | Small packaging capacity |
| Adenovirus | dsDNA | 8 30* | Broad | Episomal | Extremely efficient gene transfer in most tissues | Capsid-mediated potent immune response; transient expression in dividing cells |

*Helper dependent.
AAV, adeno-associated vector; ds, double-strand; HSV-1; herpes simplex virus-1; ss, single-strand.

Given the diversity of therapeutic strategies and disease targets involving gene transfer, it is not surprising that a large number of vector systems have been devised. Although there is no single vector suitable for all applications, certain characteristics are desirable for all vectors if they are to be clinically useful: (1) the ability to be reproducibly and stably propagated, (2) the ability to be purified to high titers, (3) the ability to mediate targeted delivery (i.e., to avoid widespread vector dissemination), and (4) the ability to achieve gene delivery and expression without harmful side effects. There are currently five main classes of vectors that, at least under specific circumstances, satisfy these requirements: oncoretroviruses, lentiviruses, adeno-associated viruses (AAVs), adenoviruses, and herpesviruses. Table 2-2 compares the general characteristics of these vectors.

Oncoretroviruses and lentiviruses are "integrating," that is, they insert their genomes into the host cellular chromatin. Thus they share the advantage of persistent gene expression. Nonintegrating viruses can achieve persistent gene expression in nondividing cells, but integrating vectors are the tools of choice if stable genetic alteration must be maintained in dividing cells. It is important to note, however, that stable transcription is not guaranteed by integration and that transgene expression from integrated viral genomes can be silenced over time.[57] Oncoretroviruses and lentiviruses differ in their ability to penetrate an intact nuclear membrane. Retroviruses can transduce only dividing cells, whereas lentiviruses can naturally penetrate nuclear membranes and can transduce nondividing cells, making them particularly useful for stem cell targeting applications.[58,59] Because of this difference, lentivirus vectors are superseding retrovirus vectors for most applications. Because of their ability to integrate, both types of vector share the potential hazard of alteration of the host cell genome. This could lead to the undesirable complications of human germline alteration or insertional mutagenesis, particularly important considerations for pediatric or fetal gene therapy.[2] Nevertheless these vectors have proved most efficient for long-term gene transfer into cells in rapidly proliferative tissues and for stem cell directed gene transfer.

Nonintegrating vectors include adenovirus, AAV, and herpesvirus vectors. Adenovirus vectors have the advantages of broad tropism, moderate packaging capacity, and high efficiency, but they carry the usually undesirable properties of high immunogenicity and consequent short duration of gene expression. Modifications of adenovirus vectors to reduce immunogenicity and further increase the transgene capacity have consisted primarily of deletion of "early" (E1-E4) viral genes that encode immunogenic viral proteins responsible for the cytotoxic immune response.[60,61] The most important advance, however, has been the development of helper-dependent adenoviruses (HD-Ads) from which all viral genes are deleted, thus eliminating the immune response to adenoviral-associated proteins.[62] These vectors may ultimately be most valuable for long-term gene transfer in tissues with very low rates of cell division, such as muscle or brain. AAV is a helper-dependent parvovirus that in the presence of adenovirus or herpesvirus infection undergoes a productive replication cycle. AAV vectors are single-strand DNA vectors and represent one of the most promising vector systems for safe long-term gene transfer and expression in nonproliferating tissues. AAV is the only vector system for which the wild-type virus has no known human pathogenicity, adding to its safety profile. In addition the small size and simplicity of the vector particle make systemic administration of high doses of vector possible without eliciting an acute inflammatory response or other toxicity. Although the majority of the AAV vector genome after transduction remains episomal, an approximately 10% rate of integration has been observed.[63] There are two primary limitations of AAV vectors. The first is the need to convert a single-strand DNA genome into a double strand, limiting the efficiency of transduction. This obstacle has been overcome by the development of double-strand vectors that exploit a hairpin intermediate of the AAV replication cycle.[64] Although these vectors can mediate a 10- to 100-fold increase in transgene expression in vitro and in vivo, they can package only 2.4 kb of double-strand DNA, limiting their therapeutic usefulness. This relates to the second primary limitation of AAV vectors, which is limited packaging capacity (4.8 kb of single-strand DNA). One approach to address this limitation is to split the expression cassette across two vectors, exploiting the in vivo concatemerization of rAAV genomes. This results in reconstitution of a functional cassette after concatemerization in the cell nucleus.[65,66] Finally, an approach that has become common for enhancing or redirecting the

tissue tropism of AAV vectors is to pseudotype the vectors with capsid proteins from alternative serotypes of AAV.[67] Although most rAAV vectors have been derived from AAV2, nine distinct AAV serotypes have been identified thus far, all of which differ in efficiency for transduction of specific cell types. AAV vectors have proved particularly useful for muscle, liver, and central nervous system directed gene transfer.

Herpes simplex virus (HSV-1) vectors are the largest and most complex of all currently used vector systems. Their primary advantages are a very large packaging capacity (up to 40 kb) and their strong neurotropism, allowing lifelong expression in sensory neurons. This has made neuropathologic disorders a primary target for HSV-1–mediated gene transfer.

## CLINICALLY RELEVANT CHALLENGES IN GENE TRANSFER

The adverse events described previously demonstrate the potential for disaster when using vector-based gene transfer. Major initiatives must be undertaken to delineate the potential complications of gene transfer with specific vectors to convince physicians and the public of their safety for future clinical trials. Nevertheless because of the potential benefit, continued efforts to develop safe and efficacious strategies for clinical gene transfer are warranted.

One of the primary obstacles to successful gene therapy continues to be the host immune response. The intact immune system is highly capable of activation against viral vectors using the same defense systems that combat wild-type infections. Viral products or new transgene encoded proteins are recognized as foreign and are capable of activating an immune response of variable intensity. Adenovirus vectors are the most immunogenic of all the viral vector types and induce multiple components of the immune response, including cytotoxic T-lymphocyte responses, humoral virus-neutralizing responses, and potent cytokine-mediated inflammatory responses.[68] Great progress has been made in reducing T-cell responses against adenoviral antigens by the development of HD-Ad vectors from which all adenoviral genes are deleted. These vectors have demonstrated reduced immunogenicity with long-term phenotypic correction of mouse models and negligible toxicity.[69,70] However even HD-Ad vectors or less immunogenic vector systems such as AAV or lentivirus vectors can induce an immunologic response to capsid proteins[71] or to novel transgene encoded proteins,[72] a potentially limiting problem in a large number of human protein deficiency disorders caused by a null mutation. Thus the application of gene transfer technology to many human disorders may require the development of effective and nontoxic strategies for tolerance induction.[73]

Another major area of interest that may improve the safety profile of future viral vector–based gene transfer is specific targeting to affected tissues or organs. Wild-type virus infections are generally restricted to those tissues that are accessible through the route of transmission, whereas recombinant vectors are not subject to the same physical limitations. The promiscuity of viral vectors is a significant liability, because systemic or even local administration of a vector may lead to unwanted vector uptake by many different cell types in multiple organs. For instance, lack of adenovirus vector specificity was directly linked to the induction of a massive systemic immune response that resulted in a gene therapy–related death in 1999.[68] Because many of the toxic effects of viral vector–based gene transfer are directly related to dose, increasing the efficiency with which viral vectors infect specific cell populations should reduce viral load and improve safety.

There are a variety of promising methods to achieve the targeting of viral vectors for specific organs or cell types. Perhaps the simplest approach is vector pseudotyping, which has been performed for retrovirus, lentivirus, and AAV vectors. By changing the capsid envelope proteins to alternative viral types or serotypes, a portfolio of vectors with different tropisms can be generated.[74] Another approach is the conjugation of capsid proteins to molecular adapters such as bispecific antibodies with specific receptor binding properties.[75,76] A third approach is to genetically engineer the capsid proteins themselves to alter their receptor binding (i.e., to abolish their normal receptor binding) or to encode a small peptide ligand for an alternative receptor.[77] These and other approaches, when combined with the appropriate use of tissue-specific promoters, may significantly reduce the likelihood of toxicity from viral-based gene therapy.

Another important obstacle to human gene therapy—particularly fetal gene therapy—is the potential for insertional mutagenesis when using integrating vectors. Until recently this risk was considered extremely low to negligible, based on the assumption that oncogenesis requires multiple genetic lesions and the fact that induced cancer had not been observed in any of the hundreds of patients treated with retrovirus vectors in the many gene therapy trials. However in two trials of retroviral gene therapy for XSCID[50,78] leukemia developed in 5 of 20 patients treated.[51,79] Evidence suggests that this was caused by retroviral genome insertion in or near the oncogene *LM02*. These concerns have been further heightened by evidence that retroviral genes are not randomly inserted, as previously believed; rather, they preferentially integrate into transcriptionally active genes.[80] Although such events may be more likely to occur under the unique selective influences of XSCID, it is clear that the risk of insertional mutagenesis can no longer be ignored. Approaches designed to neutralize cells expressing transgene if and when an adverse event occurs, such as engineering suicide genes into the vector, are one option, but this would also neutralize any therapeutic effect. More exciting approaches are based on site-specific integration—for instance, taking advantage of site-integration machinery of bacteriophage $\phi$X31.[81] This is undoubtedly only one of many approaches that will use site-specific integration in the future and should, if successful, negate the risk of insertional mutagenesis. Even without site-specific integration, vector design, such as inclusion of a self-inactivating long terminal repeat in lentiviral vector design, can markedly reduce the likelihood of insertional mutagenesis.[54]

Finally, a critical issue for in vivo gene transfer with integrating vectors in individuals of reproductive age is the potential for germline transmission, with alteration of the human genome. The risk of this event is poorly defined at present and is most likely extremely low, although in some circumstances (e.g., fetal gene transfer), it could be increased.[2] Although still not technically possible, the intentional site-specific correction of defects in the germline would be the ultimate in gene therapy. However even if the technology becomes available, the intentional alteration of the human genome raises profound ethical and societal questions that

will need to be thoroughly addressed before its application. The considerations are similar to those for insertional mutagenesis, so many of the approaches mentioned earlier for gene targeting and reduction of the potential for insertional mutagenesis are applicable here as well.

## OVERVIEW OF THE CURRENT STATUS OF GENE TRANSFER

At present it is clear that viral vectors are the best available vehicle for efficient gene transfer into most tissues. Several gene therapy applications have shown promise in early-phase clinical trials. Although the adverse events noted in the XSCID trial have dampened enthusiasm, this still represents the first successful treatment of a disease by gene therapy. The treatment of hemophilia B using rAAV is promising,[82] as are the successful trials for ocular disease[56] and adenosine deaminase SCID[55] mentioned previously. The next few years are likely to bring advances in the treatment of certain types of cancer using conditionally replicating oncolytic viruses and in the treatment of vascular and coronary artery disease using viral vectors that express angiogenic factors. In the future new disease targets are likely to become approachable through the fusion of viral vector–mediated gene transfer with other technologies such as RNA interference, a powerful tool to achieve gene silencing. Such vectors could be useful in developing therapy for a range of diseases, such as dominantly inherited genetic disorders, infectious diseases, and cancer. Advances in the understanding of viral vector technology and DNA entry into cells and nuclei will likely lead to the development of more efficient nonviral vector systems that may rival viral vectors in efficiency and have superior safety. Gene vector systems of the future may be very different from those in use today and will ultimately provide efficient delivery of target-specific regulated transgene expression for an appropriate length of time.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 3

# Impact of Tissue Engineering in Pediatric Surgery

Howard I. Pryor II, David M. Hoganson, and Joseph P. Vacanti

Tissue engineering is a rapidly developing interdisciplinary field at the intersection of clinical medicine, cellular biology, and engineering. The goal of tissue engineering is to create living replacement organs and tissues to provide, restore, maintain, or improve lost or congenitally absent function.[1] Early attempts by surgeons to restore function include various wooden and metal prostheses mentioned in the Talmud and a description of a rhinoplasty using a forehead flap detailed in the *Sushruta Samhita* from around 6 BC. Modern medicine has embraced both the use of manufactured substitutes (such as Dacron aortic grafts) to repair abdominal aortic aneurysms and the approach of redirecting autologous tissue for a new function, as in the transfer of a toe to replace a finger. In the past half-century, the development of immunosuppressive medication has allowed for allogeneic substitution of tissues, as in organ transplantation, demonstrating that functional replacement can be lifesaving.

Unfortunately, all these approaches have significant limitations. In pediatric surgery, prosthetic material poses several problems, including material failure, increased rates of infection, and immunodestruction of foreign material. In addition, nonliving material does not grow with the patient nor does it adapt to changing circumstances, so pediatric patients may need to undergo multiple operations with increasing levels of complexity. Native substitutions of tissue are limited by the dilemma of prioritizing the value of various tissues and accepting the functional tradeoff that must be made when redirecting tissue to new functions. The effectiveness of organ transplantation is limited by a short supply of donor organs and a long list of associated morbidities related to lifelong immunosuppression. None of these approaches has permanently solved the need to replace composite tissues.

The field of tissue engineering evolved from the collaboration of Dr. Joseph Vacanti, a pediatric surgeon, and Robert Langer, Ph.D., a chemical engineer, in the laboratory of Dr. Judah Folkman at Children's Hospital Boston as a response to the need for replacement composite tissues. In a white paper published by the National Science Foundation, it was observed that "most lead authors in Tissue Engineering have worked at least once with Langer and Vacanti."[2] Tissue engineering is considered specifically applicable to pediatric surgery because the durability of surgical therapy must be greatest in children. The outcome may be measured over decades, and the surgical reconstruction is subjected to higher levels of growth and physiologic change. This can be especially challenging for congenital defects in which the amount of available donor tissue may be insufficient and prosthetic material may not approximate the functional, cosmetic, and growth requirements of the missing tissue. Satisfying this ongoing medical need is the focus of tissue engineering.

## Interdisciplinary Approach

Engineering is fundamentally different from science. The goal of science is to understand and define natural relationships. In contrast, the goal of engineering is to take advantage of relationships defined by science to address problems with solutions that do not exist in nature.[3] Engineering has been defined as the creative application of "scientific principles to design or develop structures, machines, apparatus, or processes" to solve a specific problem.[4] An engineer's invention must be communicated in concrete terms, and it must have defined geometry, dimensions, and characteristics. Engineers usually do not have all the information needed for their designs, and they are typically limited by insufficient scientific knowledge.[3] Traditionally, engineering has been based on physics, chemistry, and mathematics and their extensions into *materials science*, solid and *fluid mechanics*, thermodynamics, transfer phenomena, and systems analysis.[5] Tissue engineering is an approach that attempts to combine these traditional engineering principles with the biologic sciences to produce viable structures that replace diseased or deficient native structures.[6] As of 2004, aggregate development costs in tissue engineering exceeded $4.5 billion, and the field has encountered the kinds of challenges converting bench-top science into clinically marketable tools that were experienced during the development of other breakthrough medical technologies.[7]

Unlike biologic scientists, tissue engineers are not free to select the problems that interest them. Instead, tissue engineers must tackle the problems that present clinical

dilemmas. Frequently, the solutions must satisfy conflicting requirements; for instance, safety improvements increase complexity, but increased efficiency increases costs.[5] Problem solving is common to all engineering work. Although the problems may vary in scope and complexity, a common engineering design approach is applicable (Fig. 3-1). First, the problem is thoroughly analyzed, and a preliminary solution is selected. The preliminary solution is further subdefined by the identification of design variables that must be addressed. The preliminary solution is then refined by accounting for as many variables as possible and creatively synthesizing a new preliminary design. The preliminary design is checked for accuracy and adequacy. Finally, the results are interpreted in terms of the original problem. If the results are satisfactory, the engineering design process is complete. If the results do not adequately resolve the original problem, the design is analyzed for failure points, and the process is repeated until the original problem is solved.[5]

The short history of tissue engineering is replete with examples of this approach. For instance, monolayer cell culture has been used in the biologic sciences for decades, but this culture system typically supports only small numbers of cells in poorly organized sheets. Early attempts to organize these sheets into more clinically relevant constructs focused on the addition of an underlying support or scaffold for the cells as a substitute for the extracellular matrix (ECM).[8–11] Although these innovative approaches improved the handling characteristics and achievable cell mass of these constructs, new problems were identified in terms of poor clinical function, and the iterative process was begun anew, leading to the development of bioreactors. Early bioreactors were dynamic tissue culture devices with simple mechanical designs meant to provide oxygen exchange, defined nutrient flow rates, and electrical and mechanical stimulation that more closely approximated physiologic conditions. The results of these studies revealed further improvements in cell morphologic features, growth characteristics, and metabolic activity.[12–14] As the field of tissue engineering matures, the design variables that must be addressed for each construct will be expanded and refined accordingly.

Several fundamental biology-limited design variables of tissue engineering have been identified, including cell source, ECM, co-culture cell populations, and culture environment (Fig. 3-2). Many initial studies focused on the use of

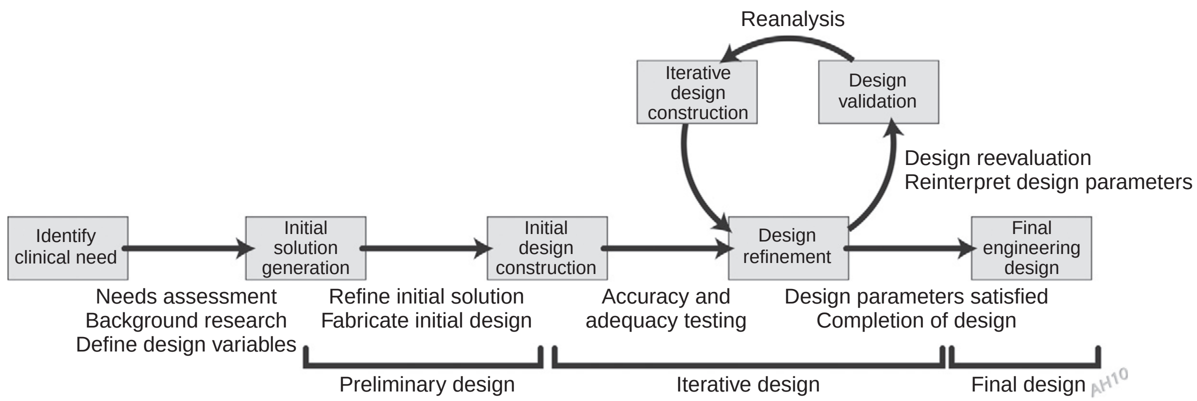


**FIGURE 3-1** The iterative engineering design process. The engineering design process begins with the identification of a problem. The problem is analyzed to assess the minimum solution requirements, research the background of previous work, and define the variables that must be addressed. The preliminary design phase begins with an initial solution design and ends when the preliminary design is constructed. The iterative design phase begins with testing of the preliminary design and proceeds through design refinement, validation, and creation of subsequent designs. If a secondary design fails to satisfy initial requirements, the iterative process is undertaken repeatedly until the criteria are met. The final design phase is characterized by the formal definition of the satisfactory design through mathematic equations, drawings, and operating parameters.

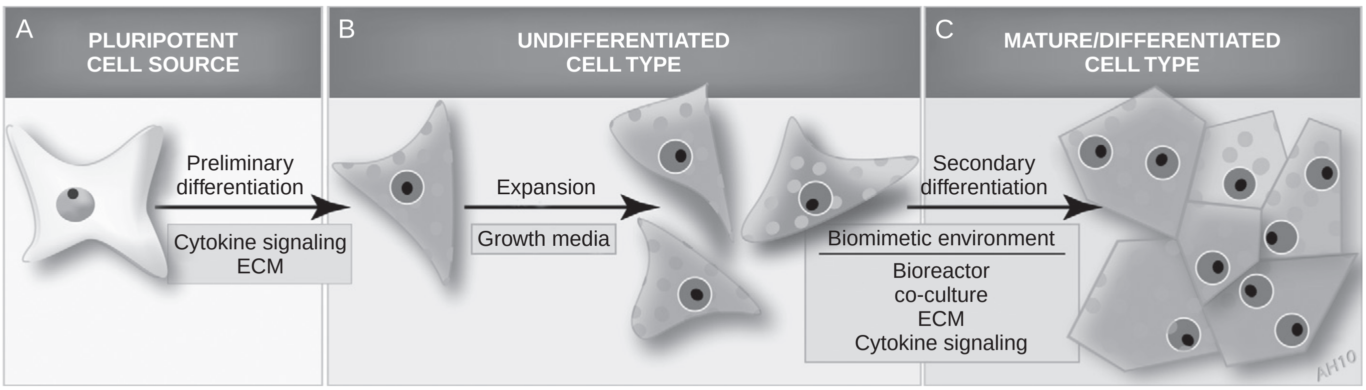


**FIGURE 3-2** Multipotent cell differentiation. Pluripotent cell populations have the ability to expand in culture and differentiate into a variety of mature cell types. **A,** The process begins with expansion of the pluripotent cell type in the presence of ECM and cytokines that preserve their expandability while focusing their differentiation down the desired lineage. **B,** The partially differentiated cells are then expanded in growth media to clinically significant quantities. **C,** Using biomimetic culture techniques—including ECM, cytokine signaling, co-culture, and bioreactors—the cells are differentiated into the desired mature cell type.

autologous organ-derived, fully differentiated parenchymal, or primary, cells. Because primary cells are typically in short supply and do not naturally replicate in large quantities, several other cell sources have been investigated, including autologous bone marrow and adipose-derived mesenchymal stem cells, umbilical cord blood cells, Wharton jelly–derived cells, amniotic fluid cells, and allogeneic embryonic stem cells.[15–21] These cell populations have the ability to expand in culture and have demonstrated adequate plasticity to differentiate into a variety of cells, including the epithelium of liver, lung, and gut, as well as the cells of both hematopoietic and endothelial systems.[16,17,22–25] As the differentiation scheme for each of these cellular populations becomes clarified, it has been suggested that cell banks for tissue-engineering applications be developed to respond more rapidly to the clinical need for tissue-engineered constructs.[26]

As more immature cell populations have been investigated, the essential role of ECM in differentiation and maintenance of organ structure has become apparent. For structural tissue constructs such as bone, merely providing the cell population with a polymer scaffold with properties similar to type I collagen has proved less satisfactory than adding elements commonly found in forming bone, such as hydroxyapatite or calcium phosphate.[26–29] Similarly, in liver tissue constructs that use collagen, Matrigel and PuraMatrix hydrogel sandwiches have resulted in greater hepatocyte longevity.[30,31] Work in liver tissue engineering also demonstrated the benefit of co-culturing primary cells with tissue-specific supporting cells.[32] The adult liver requires many complex cell-cell interactions for coordinated organ function, and in vitro investigations have shown that co-cultured hepatocytes and nonparenchymal cells were more tolerant of the culture environment.[33] Co-culture of embryonic stem cells with adipose-derived mesenchymal stem cells (ADSCs) or fibroblasts resulted in enhanced culture viability and formation of vascular tubelike structures.[12,22,34] Even with the correct combinations of cells and ECM, the culture environment must mimic the in vivo environment for the tissue construct to demonstrate clinical function. A fundamental limitation of the field to date has been the adequate mass transfer of nutrients and oxygen to meet the metabolic needs of tissue constructs. The driving force for mass transfer is a concentration gradient that must be kept in perfect balance with the supply of depleted resources precisely as they are used, perpetuating the net transfer of mass from an area of high concentration to an area of low concentration.[35] In addition to a precisely tuned nutrient supply, the mechanical and anatomic in vivo environment must also be mimicked. For cardiac tissue engineering, this has been shown to be important, because constructs cultured without electrical and mechanical stimulation fail to meet critical design criteria when compared with constructs in a biomimetic environment.[6] Highly complex flow bioreactors have been designed to systematically quantify the independent and coupled effects of cyclic flexure, stretch, and flow on engineered heart valve tissue formation in vitro.[36] Researchers have evaluated tissue-engineered heart valves using a bioreactor that automatically controls mean pressure, mean flow rate, beat frequency (heart rate), stroke volume, and the shape of the driving pressure waveform.[37] In addition, researchers studying the liver have developed a biomimetic flat-plate bioreactor system housing phenotypically stabilized hepatocyte-fibroblast co-cultures in an effort to recapture the zonal features of the liver.[38]

However, the nascent field of biomimetic bioreactors has only recently begun to bring the entire weight of the field of engineering to bear. Three critical advancements that the broad field of engineering will lend to the field of tissue engineering are computational fluid dynamics, advanced modeling, and real-time culture monitoring. Computational fluid dynamics is a technique of design analysis that allows for the accurate prediction of shear stress, culture medium dynamic velocity, and mass transfer of nutrients and oxygen.[36] This technique can be applied as a modeling method in which a virtual design is created and tested by simulation. The virtual design can then be refined and retested several times before the expense of building a real prototype.[6,36,37] This modeling strategy has been applied in a few instances to predict the production of collagenous ECM in engineered tissues, to accurately reproduce scaffold mechanical properties, and to mathematically model oxygen transport in a bioreactor.[6,36,38,39] This type of modeling in the field of tissue engineering will allow for the development of theoretical frameworks to model complex biologic phenomena that can be used to guide sound, hypothesis-driven examinations of new problems and analyze engineered implant performance in vitro and after implantation.[6] The broad field of engineering will also provide the monitoring strategies required to define success in the development of tissue-engineered constructs. One example is the use of nondestructive, high-resolution, nonlinear optical microscopic imaging to observe the development of collagen in tissue-engineered constructs over time.[40] Another example of advanced monitoring is the use of a computer-controlled closed-loop feedback bioreactor to study the effects of highly controlled pulsatile pressure and flow waveforms on biologically active heart valves.[37] As the field of tissue engineering evolves, the need for thoughtfully designed, well-monitored biomimetic culture systems that emulate physiologic conditions will be required to understand the complex culture protocols necessary to yield functional tissue grafts.[14,41]

## Cartilage and Bone Tissue Engineering

Pediatric surgeons encounter many congenital and acquired problems that are characterized by structural bone and cartilage defects. These defects may range from cleft palates and craniofacial abnormalities to significant long bone defects after cancer surgery. The current standard of care for most of these lesions includes bone grafting, but donor site morbidity after bone graft harvest remains a recognized limitation to this technique.[42] Grafting in children is also complicated by the fact that the pediatric skeletal system is still developing and the thickness of the nascent bone is thinner compared with adult bone.[43] To supplement the grafting approach, tissue engineers have sought to generate greater quantities of bone and cartilage. One of the earliest successes in bone and cartilage tissue engineering stemmed from the observation that chondrocytes harvested from articular surfaces differentiated in culture to cartilage, whereas chondrocytes from periosteum initially resembled cartilage but progressed in culture to

form new bone.[44] In the ensuing 15 years, the tissue engineering of bone and cartilage has evolved into a complex interaction of osteoinductive factors, osteoprogenitor cells, advanced scaffold technology, and an adequate blood supply.[25]

Cartilage is a relatively simple tissue with limited spontaneous regenerative capacity and a low metabolic rate.[45,46] However, early studies with polymer constructs of polyglycolic acid and polylactic acid molded into predetermined shapes led to the formation of cartilage in the shape of a human ear, a temporomandibular joint disk, and articular cartilage for meniscus replacement (Fig. 3-3).[47–50] Since these early studies, an entire research and industrial complex has evolved to develop adequate cartilage replacements for clinical use; a summary of the entire body of work would be beyond the scope of this book. The two principal limitations to the use of most of the resulting constructs are (1) the low replication rate of primary chondrocytes and (2) the relatively low construct strength compared with native tissue.[51] Several groups have addressed the cell source issue through the evaluation of stem cells focusing primarily on bone marrow–derived and adipose-derived mesenchymal stem cells. Both cell types are easily isolated and can be induced to secrete myriad cartilaginous ECM components after differentiation in chondrogenic culture conditions.[52,53] However, increasing construct cell density through the use of a stem cell source is not enough to address the issue of low construct strength. Several groups have shown that cartilaginous ECM secretion and subsequent construct strength are increased when

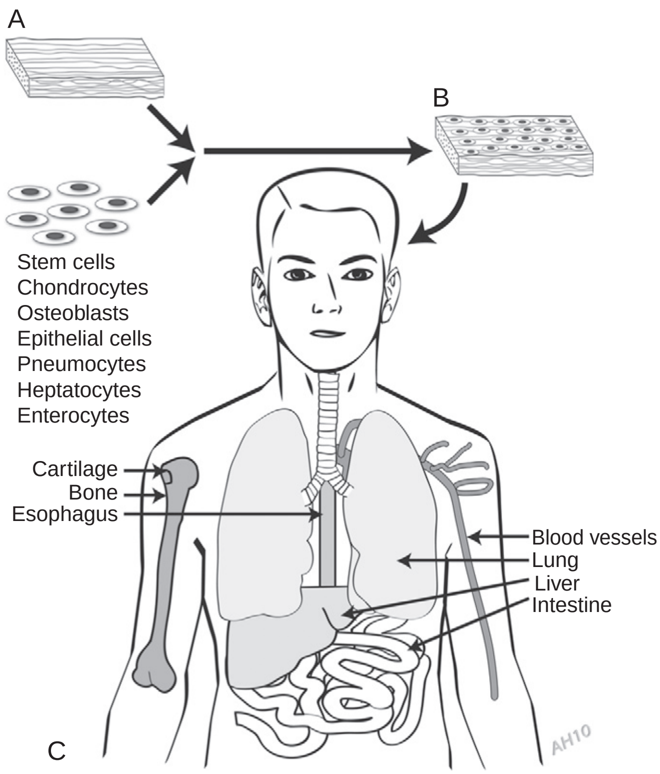


**FIGURE 3-3** The classic tissue-engineering paradigm. **A,** The classic tissue-engineering paradigm is based on the expansion of pluripotent or primary parenchymal cells in static culture and the creation of a biocompatible polymer scaffold. **B,** The expanded cellular population is seeded onto the scaffold and allowed to expand further in culture. **C** The tissue-engineered construct can then be implanted in a variety of positions to replace absent or lost tissue.

constructs are cultured under dynamic conditions. Such conditions include constant media perfusion, biaxial loading, and rolling media bottle bioreactors.[41,52,54] In each case, the histologic presence of cartilage ECM was markedly increased, and the compressive force sustained by each construct was significantly increased compared with controls. However the optimum culture conditions remain undefined and will likely be unique for each cartilage type applied in the clinical setting.

The tissue engineering of bone evolved from early studies in cartilage tissue engineering in which bovine periosteal cells were seeded onto polyglycolic acid scaffolds to repair cranial bone defects in nude rats.[55] Since these first steps, bone tissue engineering has been approached in many ways. Several methods have been tried, including the implantation of collagen scaffolds containing stem cells transfected with a virus for BMP-2 (a bone forming protein), which demonstrated accelerated osteogenesis.[25,56] Cellular implantation studies have demonstrated that biomimetic scaffolds with porosity greater than 90% and a pore size ranging from 300 to 500 μm improve bone tissue regeneration.[57,58] Ultrastructural evaluation has shown that when bone scaffolds contain nanometer surface features, bone regeneration can be further optimized.[59] As a tissue, bone is significantly more vascular than cartilage, and a principal limitation to bone construct size has been the diffusion distance from surface to center of the construct. One recent approach to this problem is the technique of co-culturing mesenchymal stem cells with endothelial cells in a fibronectin-collagen gel to induce spontaneous angiogenesis within the construct.[60] The use of vascular endothelial growth factor–releasing ADSCs and endothelial cells to more closely mimic the environment of developing bone and direct the growth of blood vessels into 3D PLAGA scaffolds has also been reported.[61] Applying typical engineering analytic tools, a mathematic framework for predicting the development of engineered collagenous matrix has been developed.[40] Some groups have taken advantage of the bone's natural regenerative capacity to use the periosteal space as a bioreactor to develop autologous bone grafts between the surface of a long bone and its periosteum.[13] Given the pace at which this field of tissue engineering is advancing, bone and cartilage tissue engineering will likely provide the most short-term clinically useful products, including constructs to address joint reconstruction and complex congenital anomalies with which pediatric orthopedic surgeons must contend.

## CARDIAC TISSUE ENGINEERING

Approximately 1% of all newborns are diagnosed with cardiac defects, including valvular disorders, making heart malformations the most common pathologic congenital condition in humans.[26] Limited options exist for the successful treatment of these patients and include mechanical valve replacement, biologic valve replacement, and ultimately, heart transplantation. Mechanical valves are an imperfect solution because they require lifelong anticoagulation and can spawn systemic thromboembolism.[62] Biologic valves do not require systemic anticoagulation but often calcify, and they must be replaced after several years.[59] Although heart transplantation is the ultimate therapeutic option, this modality is limited by the scarcity of suitable donor organs, requires lifelong immunosuppression, and is associated with serious complications,

such as kidney failure and malignancies.[26] The perfect solution to this clinical dilemma would be the development of a nonthrombotic, self-repairing tissue valve replacement that grows with the patient and remodels in response to in vivo stimuli.[59,63]

Over the past decade, an enormous amount of research has been focused on developing a tissue-engineered heart valve meeting these criteria. Although a thorough review would be outside the scope of this book, highlights from such research illustrating tissue engineering's interdisciplinary approach follow.

Initial studies evaluated single-cell populations grown on biocompatible scaffolds in static culture conditions and clearly demonstrated short-term hemodynamic functionality with minimal calcification when implanted in sheep.[64,65] Valves co-cultured with autologous medial and endothelial cells before implantation were shown to function in vivo for up to 5 months and resemble native valves in terms of matrix formation, histologic characteristics, and biomechanics.[66] It was hypothesized that further improvement in valve performance could be obtained by culturing valves under pulsatile flow to generate a biomimetic environment resembling in vivo conditions.[6] Valves cultured under these conditions have demonstrated increased mechanical strength and improved cellular function within the construct.

Although a great deal of progress has been made in the pursuit of a tissue-engineered heart valve, these valves still need to be tested and succeed in the aortic position, where they are needed most.[63] Furthermore, the critical ability of these tissue-engineered constructs to grow with the patient must be clearly demonstrated and will be the focus of the next decade of research.

## Vascular Tissue Engineering

In addition to valvular repair, children with complex *congenital heart defects* often require a new vascular conduit to reroute blood flow due to an anomaly. One such example is the Fontan procedure, in which *venous blood* is directed to the *pulmonary arteries* without passing through the *right ventricle*.[67] A host of synthetic and biologic conduits have been deployed in this location, but none of them has provided perfect results. Synthetic conduits incite a foreign body reaction and are a significant cause of thromboembolic complications.[68] Biologic grafts have significantly lower thromboembolic complication rates compared with synthetic grafts but become stenotic and calcify over time because of an immune-mediated process found to be more aggressive in younger patients.[69,70] Moreover, both graft types lack significant growth potential, and it is assumed that all such conduits will eventually need to be replaced.[69,71] Given the morbidity of repeated open-heart procedures on a child, investigators have looked to tissue engineering as an alternative to the use of synthetic and biologic conduits.[72]

As the most successful example of applied tissue engineering to date, Shin'oka and colleagues reported the first human use of a tissue-engineered blood vessel in a 4-year-old girl to replace an occluded pulmonary artery after a Fontan procedure (Fig. 3-4).[72] The conduit used was a 1:1 polycaprolactone, polylactic acid copolymer scaffold seeded with autologous peripheral venous endothelial cells. After 7 months of follow-up, no complications were noted. This successful experience has launched a clinical trial of 42 patients receiving similar scaffolds seeded with autologous bone marrow–derived cells.[73] At 16 months of follow-up, the group reported no significant complications, although one patient died from unrelated causes. The harvest of bone marrow–derived cells is associated with several morbidities, including pain and infection, so several alternative cells sources have been sought. Two such cell sources include adipose-derived endothelial progenitor cells and umbilical cord–derived cells.[23,74]

As the interdisciplinary approach of tissue engineering has been applied to the development of the tissue-engineered vascular graft (TEVG), several areas for improvement have been identified. Using a bioreactor that provided physiologic stimulation similar to the pulmonary artery, physiologically

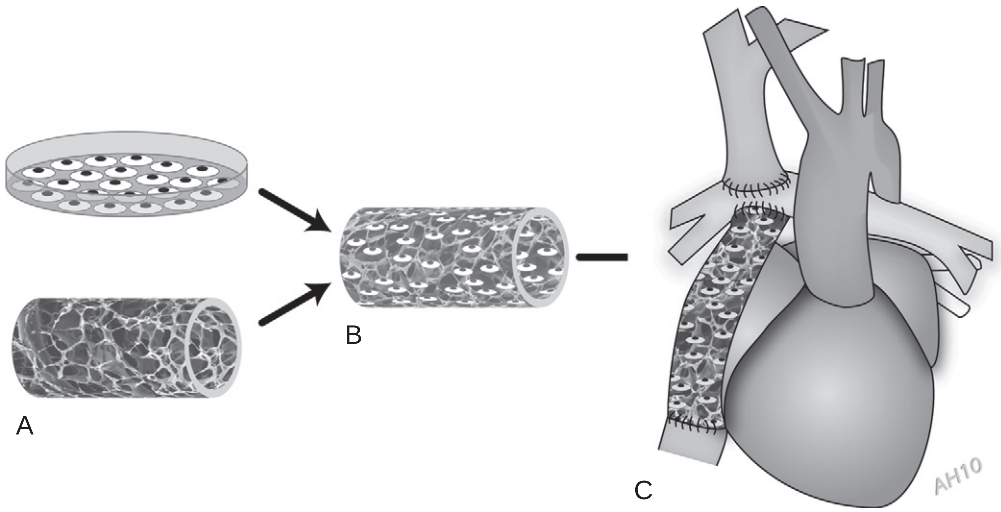


**FIGURE 3-4** Tissue-engineered vascular graft. **A,** Tissue-engineered vascular grafts are constructed from a host of cells expanded in culture (autologous peripheral venous endothelial cells, bone marrow–derived cells, adipose-derived endothelial progenitor cells, and umbilical cord–derived cells) and a conduit composed of 1:1 polycaprolactone and polylactic acid copolymer scaffold. **B,** The expanded cellular population is seeded onto the construct and allowed to attach in culture before implantation. **C,** The tissue-engineered vascular graft has been used as an extracardiac conduit in the Fontan procedure.

dynamic conditions up-regulated collagen production by fourfold over the static controls in an in vitro TEVG.[37] Sophisticated monitoring techniques have been developed to evaluate TEVG for the development of normal vascular architecture. Qualitative immunohistochemical and quantitative biochemical analyses demonstrate that the ECM of the TEVG resembled the ECM of the native inferior vena cava after explantation in animal studies.[75]

This type of successful translation of cardiovascular tissue-engineering principles from the bench to the clinic could lead to improved vascular grafts for other cardiovascular surgical applications.[68] Two obvious applications of this developing field are small-diameter vascular grafts and new vascular stent materials.[59] The development of a small-diameter tissue-engineered graft could fill a significant void in the field of vascular surgery, because grafts smaller than 6 mm cannot be satisfactorily constructed from textile or polytetrafluoroethylene (PTFE) and must be bypassed with autologous arteries and veins, with a limited supply for multiple operations.[76] Further, the development of an inexhaustible supply of vascular constructs for in vitro use could lead to the rapid advancement of stenting technologies by eliminating the expense and time expended in animal trials. The pursuit of these near-term goals would result in a dramatic expansion of the field of tissue engineering over the next 10 years.

## Gastrointestinal Tissue Engineering

Gastrointestinal tissue engineering has the potential to improve outcomes in two clinical settings for pediatric surgeons: esophageal atresia and short-bowel syndrome. Long-gap esophageal atresia is a daunting clinical problem requiring delayed repair and transposition of a remote portion of bowel.[77–79] Complications from these procedures abound, including stricture, leakage, and malnutrition secondary to shortening of the gastrointestinal tract.[80,81] Moreover, synthetic conduits are unavailable and would lack the critical ability to grow with the patient throughout childhood. As a result, many groups have sought to develop a tissue-engineered esophageal construct that could be used to treat long-gap atresia. Initially, it was demonstrated that organoid units transplanted from adult autologous esophagus onto a biodegradable scaffold form complex tissue indistinguishable from native esophagus.[82] Tissue-engineered esophagus has been used both as a patch and as an interposition graft in rats in preliminary studies.[82] However, these organoid units required resection of significant esophageal length. Recent studies have revealed that isolated esophageal cells could be seeded under low density on collagen polymers and could be expanded in vitro, leading to a potential autologous tissue–engineered esophageal construct.[83]

Of the morbid conditions associated with bowel resection, short-bowel syndrome is the most devastating. It is characterized by progressive weight loss, malnutrition, vitamin deficiency, and infections associated with the vascular access commonly used to support patients with this syndrome.[84,85] This clinical condition develops when less than one third of normal jejunal-ileal length remains, a distance of 25 to 100 cm in neonates.[86] Pediatric surgeons influence the morbidity and mortality of patients with pediatric gastrointestinal disorders such as inflammatory bowel disease and necrotizing enterocolitis because these disorders can require resection of large portions of small bowel.[20,87] Despite efforts to maximize bowel preservation at the time of surgery and the use of gut lengthening procedures to extend the remaining small bowel's functional surface area, many patients become dependent on total parenteral nutrition.[88] These patients are at risk for liver dysfunction as a result of impaired enterohepatic bile salt circulation and abnormal bile acid metabolism, resulting in overt liver failure. This liver dysfunction is recognized as an indication for small intestine transplantation, a procedure fraught with poor survival and lifelong morbidities.[89]

The generation of a composite tissue resembling small intestine from intestinal cells heterotopically transplanted as organoid units was first reported in 1998.[86] Organoid units were derived from full-thickness harvests of intestine and loaded on 2-mm cylindric bioresorbable polymers before implantation in the omentum. The resulting engineered bowel demonstrated polarization of the epithelial cells, which faced the lumen of the cyst. The other layers of the intestinal wall were histologically present with substantial vascularization.[86] Subsequent studies have evaluated a variety of scaffold and cellular combinations that further improve the clinical potential of this therapy.

These evaluations revealed that the ability of intestinal organoid units to recapitulate full-thickness bowel was based on the presence of a mesenchymal core surrounded by a polarized intestinal epithelium, representing all the cells within a full-thickness section of bowel.[90,91] The neomucosa generated by this method in rats demonstrated epithelial barrier function and active transepithelial electrolyte movement equal to that of native adult tissue.[86] Additional studies have supported the finding that the neointestine is not merely anatomically intact but is able to absorb energy-dense nutrients, suggesting a future human application for tissue-engineered intestine.[20] Unfortunately, the use of organoid units requires invasive procedures for harvest, and a more ideal cell source is needed. Such a source would possess the ability to differentiate into all aspects of the intestine, including absorptive and secretory cells as well as vasculature and physical support structures.[20]

The ideal scaffold material has similarly not yet been identified. Initial work on the topic evaluated several options, including AlloDerm and small intestinal submucosa (SIS).[92,93] The latter has been used to support mucosal regeneration across a gap in resected bowel in experimental models.[94] It has also been shown to degrade within 3 months after operative implantation replaced by host-derived tissue.[95] In one large animal study, a commonly used human biomaterial, polyglycolic acid, was used as the scaffold for the first engineered intestine implanted during a single anesthetic administration. It was seeded with autologous tissue arising from organ-specific stem cells.[96] Although all these results point to a future tissue-engineered construct that increases absorptive surface area, a future challenge will focus on the recovery of peristaltic activity of the regenerated bowel. This will require advances in both smooth muscle incorporation and reinnervation of the regenerated bowel.[95] Tissue-engineered gastrointestinal replacement with peristalsis would provide a critical advancement in the treatment of many pediatric surgical diseases and may significantly affect patient care, with improved surface area, transporter function, immune characteristics, and architecture.

## Liver Replacement and Tissue Engineering

The liver is a complex vital organ that supports homeostasis through metabolism, excretion, detoxification, storage, and phagocytosis of nutrients and toxins. Acute or chronic liver dysfunction accounts for the death of 29,000 Americans each year, with acute failure mortality rates exceeding 80%.[97,98] In children, liver dysfunction can be caused by biliary atresia–related liver cirrhosis and metabolic diseases such as alpha-1 antitrypsin deficiency, Wilson disease, tyrosinemia, and others.[99] Despite investigation into a wide array of liver support protocols, orthotopic liver transplantation remains the only definitive treatment for severe hepatic failure. Three thousand of these procedures are performed annually, leaving thousands of patients on waiting lists in need of an alternative option. The field of hepatic tissue engineering developed as an attempt to solve this problem.

Initial studies in the field of hepatic tissue engineering were based on the injection of isolated hepatocytes into the portal vein, peritoneal cavity, spleen, and pancreas.[100–102] These cells engrafted and corrected both isolated and global metabolic deficiencies, but these successes were time-limited because the mass of the injected cells was small, and the functional capacity of the cells decreased over time. Methods to increase the tissue-engineered liver mass included concurrent hepatotropic stimulation through partial hepatectomy, portacaval shunting, and injection of liver toxins.[103–106] Even with maximal hepatotropic stimulation, these methods failed to yield adequate hepatocellular function to detoxify a patient in fulminant hepatic failure. A more advanced tissue-engineered liver construct was sought to provide temporary liver function replacement based on the concept of kidney dialysis therapy and was referred to as an extracorporeal bioartificial liver device (BAL).[107] The goal of such a device is to support patients in acute liver failure while liver regeneration occurs and, if that fails, to serve as a bridge to transplantation.[108] Unfortunately, despite a wide array of devices tested, none has delivered the desired results.[107] Most BALs tested to date contain a singular hepatocyte cell population without associated nonparenchymal cells. Such a device's lifetime is limited because hepatocytes degenerate within hours to days in such an environment.

The cellular physiology of the liver is complex. Hepatocytes are anchorage-dependent cells and require an insoluble ECM for survival and proliferation.[85] The adult liver also requires a complex cell-cell interplay between hepatocytes and the nonparenchymal cell populations, including biliary epithelium, Kupffer cells, stellate cells, and sinusoidal endothelial cells. These interactions are essential for proper organ function, and hepatocytes dedifferentiate within 2 weeks when these communications are severed.[109] To preserve and encourage these necessary interactions in future BALs, several groups have proposed to organize the underlying scaffold to serve as a template to guide cell organization and growth.[85] Given the high metabolic requirements of liver tissue, this organized structure would allow more efficient diffusion of oxygen and nutrients and removal of waste. A further advance of this concept, being refined at the Massachusetts General Hospital Tissue Engineering and Organ Fabrication Laboratory, is the development of a polymer device with an integrated vascular network to provide immediate access to the blood supply after implantation (see the discussion on future directions in the next section).[18] This de novo vascular system could be used as a template for any complex tissue such as liver or lung. Future designs are based on a modular concept that allows for the fabrication of implantable devices containing a large mass of cells within a structured environment, complete with de novo blood supply.

One significant challenge that remains entirely unaddressed in the field of hepatic tissue engineering is the development of an artificial biliary system. One solution may lie in the use of multipotent cells that can differentiate down both the hepatocytic and biliary lineages during postimplantation remodeling.[99]

## Future Directions: Vascular Networks

The advances of tissue engineering have occurred primarily through interdisciplinary efforts of electrical, chemical, and mechanical engineers; scientists, in fields such as developmental biology, biomaterials science, and stem cell biology; and clinicians from surgical and medical fields.[110] This approach has been successful in the initial development of avascular or thin tissues with low metabolic activity and functions limited to mechanical activity, such as skin, bone, cartilage, and heart valves (Table 3-1).[12,18,59] Engineering more complex tissues with a significant homeostatic contribution and high metabolic activity necessitates the development of a vasculature within the construct that promotes cell survival, tissue organization, and rapid nutrient supply immediately after implantation.[12,18]

Native tissues are supplied by capillaries that are spaced a maximum of 200 μm from one another, permitting a natural diffusion limit for nutrients and gases.[111,112] Two approaches have been investigated to address this goal of providing nutrients to every cell in a tissue construct within the tissue's natural diffusion limit (Fig. 3-5).[12,113] One strategy relies on the tissue construct's natural ability to sprout new or bridging vessels or to invite ingrowth of existing vessels.[12] Despite numerous attempts, it has been difficult to develop a de novo angiogenesis-based vasculature within a tissue construct because of the challenges involved in the differentiation and sustenance of multiple (i.e., vascular progenitor and parenchymal) cell types in a concomitant fashion.[13] To date, only one group has had success in a tissue-engineered bone construct.[60] Several previous attempts to invite ingrowth after implantation have revealed that blood vessel invasion from the host tissue is limited to a depth of several hundred micrometers from the surface of the implant.[61] This results in a central zone of necrosis because only the periphery of the graft is efficiently vascularized.[60,114] The difficulties with in vitro vascularization have led to the development of an alternative solution: preformed vascular networks.[26]

The design of preformed vascular networks is only beginning to be defined as a natural extension of previously identified axioms of vascular biology. Such networks will have to be designed individually for the intended tissue based on the tissue's inherent resistance to flow, nutrient transfer requirements, and waste removal needs.[113] Such control of the microenvironmental niche within each tissue will be

**TABLE 3-1**
**Existing Tissue Engineered Products**

| *Brand Name* | *Application* | *Manufacturer* | *Cells* | *Matrix* |
|---|---|---|---|---|
| Bioseed Oral Bone | Bone | BioTissue Technologies | Autologous osteocytes | Fibrin gel |
| Osteotransplant | Bone | Co.Don AG | Autologous osteocytes | Fibrin gel |
| Carticel | Cartilage | Genzyme Biosurgery | Autologous chondrocytes | |
| Hyalograft C | Cartilage | Fidia Advanced Biopolymers | Autologous chondrocytes | Hyaluronic acid |
| MACI | Cartilage | Verigen AG | Autologous chondrocytes | Collagen |
| Chondrotransplant | Cartilage | Co.Don AG | Autologous chondrocytes | |
| Bioseed-C | Cartilage | BioTissue Technologies | Autologous chondrocytes | 3D fibrin matrix |
| NOVOCART | Cartilage | TETEC AG | Autologous chondrocytes | |
| Chondrotec | Cartilage | CellTec GmbH | Autologous chondrocytes | Fibrin gel |
| Cartilink-1<br>Cartilink-2 | Cartilage | Interface Biotech A/S | Autologous chondrocytes<br>Autologous chondrocytes | Periosteum<br>Bovine collagen |
| Bioseed-M | Oral mucosa | BioTissue Technologies | Oral mucosal cells | Fibrin gel |
| Integra | Skin | Integra LifeSciences | Dermal fibroblasts | Bovine collagen |
| Dermagraft | Skin | Advanced Tissue Sciences, Inc. | Neonatal fibroblast | Polyglactin mesh |
| Apligraf | Skin | Organogenesis Inc. | Allogenic fibroblasts and epidermal cells | Bovine collagen |
| Epicel | Skin | Genzyme Biosurgery | Autologous keratinocytes | |
| Transcyte | Skin | Smith & Nephew | Human fibroblast | Polymer membrane |
| Hyalograft 3D<br>Laserskin | Skin | Fidia Advanced Biomaterials | Autologous fibroblasts<br>Autologous keratinocytes | Hyaluronic acid<br>Hyaluronic acid |
| Bioseed-S<br>Melanoseed | Skin | BioTissue Technologies | Keratinocytes<br>Melanocytes | Gel-like fibrin<br>Gel-like fibrin |
| Autoderm Cryoceal | Skin | XCELLentis | Human Keratinocytes | None |
| Epibase | Skin | Laboratoire Genevrier | Autologous keratinocytes | Collagen |
| Orcell | Skin | Ortec Inc. | Allogeneic fibroblasts<br>Allogenic keratinocytes | Collagen |
| Vivoderm | Skin | ER Squibb & Sons Inc | Autologous keratinocytes | Hyaluronic acid |
| Acudress | Skin | Iso Tis SA | Keratinocyte precursors | Fibrin |
| Vascugel | Vascular | Pervasis | Allogenic endothelial cells | Gelatin sponge |

Data from references 115–119.

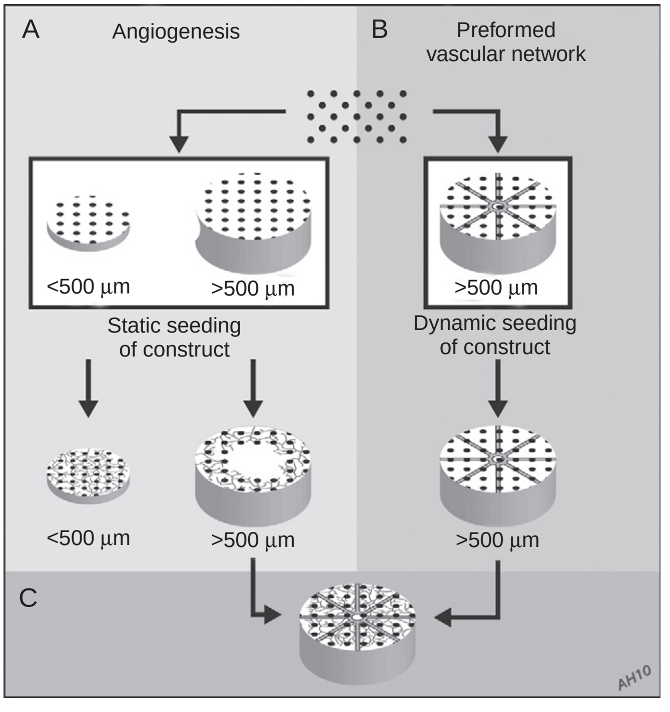


**FIGURE 3-5** Angiogenesis versus preformed vascular networks. **A,** The angiogenesis approach to vascularized tissue constructs relies on the natural ability of a construct to form new vessels or invite ingrowth of existing vessels. For constructs less than 500 µm in every dimension, cells can survive on diffusion alone as new vessel ingrowth reaches the entire cellular population. For constructs larger than 500 µm, a necrotic core develops because cells greater than 500 µm from nutrients cannot survive on diffusion long enough to allow vessel ingrowth. **B,** Using tissue-specific design criteria, preformed vascular networks can provide nutrients to within 150 µm of each cell in a construct with dimensions greater than 500 µm, thereby preventing a necrotic core. **C,** Using a resorbable scaffold to manufacture the preformed vascular network will allow the network to serve as a starting point for angiogenesis in the construct while providing the required nutrients during the ingrowth process.

key to successful tissue regeneration and has only been possible because of recent manufacturing advancements in the field of mechanical engineering, such as electrical discharge machining and micromilling.[113] Such networks can serve as the "vascular scaffold" for subsequent post-implantation remodeling.[12] As solutions to these near-term limitations evolve, more problems will be identified that will require an interdisciplinary approach to tissue engineering.

The future of tissue engineering is dependent on a robust blend of fundamental iterative engineering design, developmental and cellular biology, and surgical expertise to optimize the clinical use of new engineered constructs. The initial efforts to develop clinically useful tissues have succeeded in thin tissues supplied by diffusion. Future successful efforts in the design of vascularized structures and the evolution of autologous cell sources for tissues will eventually result in the development of clinically useful tissue-engineered organs.

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 4

# Advanced and Emerging Surgical Technologies and the Process of Innovation

Sanjeev Dutta, Russell K. Woo, and Thomas M. Krummel

*"Change is inevitable. Change is constant."*

**—Benjamin Disraeli**

From the eons of evolutionary change that gifted *Homo sapiens* with an opposable thumb, to the minute-to-minute changes of the neonatal surgical patient, change and the adaptive response to change defines either success or failure.

The development and use of tools and technologies remains a distinguishing characteristic of mankind. The first hunter-gatherers created, built, and modified tools to the demands of a specific task. In much the same fashion, the relentless development and use of surgical tools and technologies has defined both our craft and our care since the first bone needles were used in prehistoric times.

This chapter attempts to highlight those advanced and emerging surgical technologies that shape the present and direct future changes. A framework to facilitate both thought and action about those innovations to come is presented. Finally, the surgeon's role in the ethical process of innovation is discussed. The authors remain acutely attuned to Yogi Berra's admonition, "Predictions are difficult, especially about the future."

As advances in surgical technologies have occurred, our field has moved forward, often in quantum leaps. A thoughtful look around our operating rooms, interventional suites, critical care units, and even teaching facilities is cause to reflect on our use of and even dependence on tools and technologies. Clamps, catheters, retractors, energy sources, and monitors fill these spaces; they facilitate and enhance surgeons' capabilities in the process of diagnosis, imaging, physiologic care, molecular triage, and in the performance of surgical procedures. Surgeons constantly function as users of technology; thus a fundamental understanding underpins their thoughtful use. The use of a drug without understanding the mechanism and side effects would be regarded as malpractice. A similar case must be made for surgical tools and technologies.

New technologies result from an endless cycle through which innovation occurs. Such a cycle may begin with a fundamental research discovery or begin at the bedside with an unsolved patient problem. Frequently, innovation requires a complex interplay of both. Surgeons are uniquely positioned and privileged to contribute to and even define this cycle. The face of a patient with the unsolvable problem is a constant reminder of our responsibility to advance our field. Theodore Kocher's success in thyroid surgery was enabled by his toothed modification of existing clamps to facilitate thyroid operations. Tom Fogarty's development of the balloon catheter began as a surgical assistant witnessing both the failures and disastrous consequences of extensive arteriotomies for extraction of emboli. His simple, brilliant concept has arguably created the entire field of catheter-based manipulation. John Gibbon's successful construction of a heart-lung machine was initially motivated by the patient with the unsolved problem of pulmonary emboli and the need for surgical extraction. Although his original intention has been eclipsed by Lazar Greenfield's suction embolectomy catheter and vena-caval filter, and dwarfed by the utility of the heart-lung machine in cardiac surgery, the story remains the same. Unresolved problems and a surgeon determined to find a solution have led to countless innovations that have changed our field forever. The surgeon's role must extend outside the operating room. Surgeons must remain aware and connected to the tools and techniques of diagnosis, monitoring, and education. Mark M. Ravitch, an extraordinary pediatric surgeon, innovator, and one of the most literate surgeons of the twentieth century, described surgery as an intellectual discipline characterized not only by operative procedures but also by the attitude or responsibility toward care of the sick. Dr. Ravitch's contribution to the development of stapling devices deserves enormous credit.[1]

A surgical operation can be defined as "an act performed with instruments or by the hands of a surgeon." This implies an image and a manipulation; the manipulation implies an energy source. Historically, we have regarded the "image" to be that of a direct visual image and "manipulation" performed with the direct contact of two hands or surgical tools.

**TABLE 4-1**
**Surgical Operation: Image and Manipulation**

| *Image* | *Manipulation* |
|---|---|
| Direct visual | Two hands direct |
| Video image | Two hands, long tools robots |
| Ultrasonography (US) | Cold, thermal |
| Computed tomography | Radiofrequency |
| Magnetic resonance imaging | Photodynamic energy |
| | Focused US energy |

The laparoscopic revolution has taught us that the image can be a video image and the manipulation performed by two hands using long tools. Now those long tools are occasionally attached to surgical robots. Our notion about the image has come to include ultrasonography/ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI), and the manipulation can include such energy sources as cold, heat, radiofrequency, photodynamic, or chemical energy. Extracorporeal shock wave lithotripsy is an important example of this principle, when applied to renal calculi. How will the "image" and "manipulation" exist in the future (Table 4-1)?

## Current and Future Diagnostic Technologies

Accurate evaluation of surgical disease has always been a vital aspect of surgical practice, always preceding operation. Whether in the clinic, the emergency room, or a hospital bed, precise assessment to correctly guide operative or nonoperative therapy defines surgical judgment and care. A thorough history and detailed physical examination will forever remain the foundation of assessment; however, the thoughtful addition of adjunctive imaging studies has added considerably to the evaluation of surgical patients. Driven by advancements in medicine, engineering, and biology, these studies use increasingly sophisticated technologies. These technologies promise to arm surgeons with more detailed anatomic, functional, and even molecular information in the coming years.

During the last 3 decades, the introduction and improvement of US, CT, and MRI techniques have revolutionized the clinical evaluation of surgical disease. The fine anatomic data that these imaging modalities provide has facilitated the accurate diagnosis of a wide variety of conditions. Functional imaging techniques, such as positron emission tomography (PET) and functional MRI, have been developed to provide accurate and often real-time biologic or physiologic information. In the field of pediatric surgery, these imaging modalities may be used in the diagnosis and characterization of disease, for preoperative surgical planning, and for postoperative follow-up and evaluation. This section will provide an overview of the imaging modalities used in pediatric surgery, focusing on emerging techniques and systems.

### ULTRASONOGRAPHY

Ultrasound imaging has become a truly invaluable tool in the evaluation of the pediatric surgical patient. Providing anatomic as well as real-time functional information, US imaging has several unique advantages that have made it particularly useful in the care of children. These include their relatively low cost, their portability and flexibility (seamless movement from the operating room, intensive care unit, or emergency room), and their safety in children and fetuses because they do not rely on ionizing radiation. For these reasons, this section will pay particular attention to US imaging, highlighting emerging advances in its technology and practice including three-dimensional (3D) US imaging, US contrast imaging, and US harmonic imaging.

Ultrasonography uses the emission and reflection of sound waves to construct images of body structures. In essence, medical US operates on the same principle as active sound navigation and ranging (SONAR): a sound beam is projected by the US probe into the body, and based on the time to "hear" the echo, the distance to a target structure can be calculated.[2] In the body, the sound waves are primarily reflected at tissue interfaces, with the strength of the returning echoes mainly correlating with the properties of the tissues being examined. The advantages of US imaging include lack of ionizing radiation, real-time imaging with motion, and relatively fast procedure times.[3]

In modern US imagers, numerous transducer elements are placed side by side in the transducer probe. The majority of US imaging devices currently use linear or sector scan transducers. These consist of 64 to 256 piezoelectric elements arranged in a single row. With this arrangement, the transducer can interrogate a single slice of tissue whose thickness is correlated to the thickness of the transducer elements.[2] This information is then used to construct real-time, dynamic, two-dimensional images. Color, power, and pulsed wave Doppler imaging are variations of this technology that allow color or graphical visualization of motion.[3] Specifically, conventional Doppler imaging provides information of flow velocity and direction of flow by tracking scattering objects in a region of interest.[4] In contrast, power Doppler displays the power of the Doppler signal and has proven to be a more sensitive method in terms of signal-to-noise ratio and low flow detectability.[5]

In pediatric surgery, US imaging is widely used in the evaluation of multiple pathologies, including appendicitis, testicular torsion, intussusception, and hypertrophic pyloric stenosis.[6,7] In addition, US is a powerful and relatively safe tool for the prenatal diagnosis of congenital diseases. Prenatal US evaluation is useful in facilitating the prenatal diagnosis of abdominal wall defects, congenital diaphragmatic hernias, sacrococcygeal teratomas, cystic adenomatoid malformation, pulmonary sequestration, neural tube defects, obstructive uropathy, facial clefting, and twin-twin syndromes.[8] Furthermore, sonographic guidance is vital to accomplishing more invasive prenatal diagnostic techniques such as amniocentesis and fetal blood sampling.[8]

#### Three-Dimensional Ultrasonography

Although two-dimensional (2D) US systems have improved dramatically over the last 30 years, the two-dimensional images produced by these systems continue to require a relatively large amount of experience to effectively interpret. This stems from the fact that the images represent one cross section, or slice, of the target anatomy, requiring users to reconstruct the three-dimensional picture in their mind. Given these limitations, 3D US systems, which provide volumetric

instead of cross-sectional images, have recently been developed and have seen increased use for many applications.

The first reported clinical use of a 3D US system occurred in 1986 when Kazunori Baba at the Institute of Medical Electronics, University of Tokyo, Japan, succeeded in obtaining 3D fetal images by processing 2D images on a mini-computer.[9] Since then, multiple 3D US systems have been developed with the purpose of providing more detailed and user-friendly anatomic information. These multislice, or volumetric, images are generally acquired by one of the following techniques:

1. Use of a two-dimensional array where a transducer with multiple element rows is used to capture multiple slices at once and render a volume from real 3D data.
2. Use of a one-dimensional phased array to acquire several 2D slices over time. The resultant images are then fused by the US computer's reconstruction algorithm.

The three-dimensional information acquired by these techniques is then used to reconstruct and display a 3D image by either maximum signal intensity processing, volume rendering, or surface rendering. Currently, 3D US systems are available from several manufacturers, including General Electric, Phillips, and Siemens. When these three-dimensional images are displayed in a real-time fashion; they have the ability to provide functional information on the physiology of a patient. An example of this is the evaluation of cardiac function using real-time US. Real-time, 3D US is sometimes referred to as 4D US, though it is still essentially providing a three-dimensional image. Figure 4-1 represents a 3D US view of a fetus in utero.

In the field of pediatric surgery, 3D US systems have not yet seen routine clinical application. However, their utility in perinatal medicine has been increasingly investigated. Specifically, 3D US systems have been used for detailed prenatal evaluation of congenital anomalies. In a study published in 2000, Dyson and colleagues[10] prospectively scanned 63 patients with 103 anomalies with both 2D and 3D US techniques. Each anomaly was reviewed to determine whether 3D US data were either advantageous, equivalent, or disadvantageous compared with 2D US images. They found that the 3D US images provided additional information in 51% of the anomalies, provided equivalent information in 45% of the anomalies, and were disadvantageous in 4% of the anomalies. Specifically, they found that 3D US techniques were most helpful in evaluating fetuses with facial anomalies, hand and foot abnormalities, and axial spine and neural tube defects. 3D ultrasonography offered diagnostic advantages in about one half of the selected cases studied and affected patient management in 5% of cases. They concluded that 3D US was therefore a powerful adjunctive tool to 2D US in the prenatal evaluation of congenital anomalies.[10]

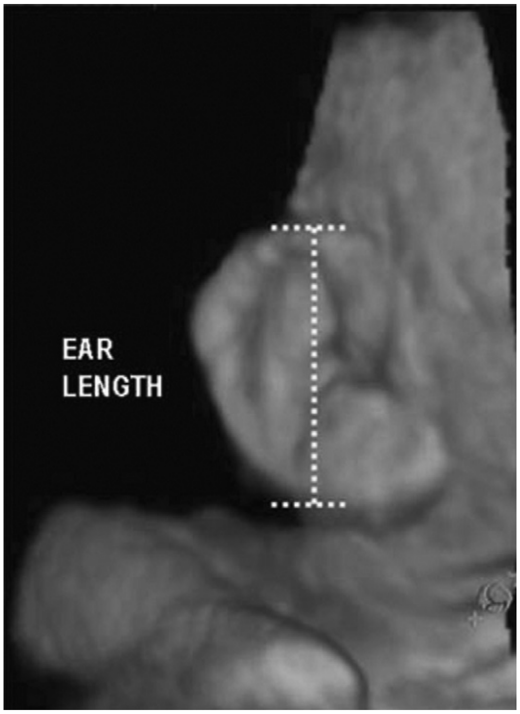



**FIGURE 4-1** Three-dimensional ultrasound image of a fetal ear. (From Kurjak A, Miskovic B, Andonotopo W, et al: How useful is 3D and 4D US in perinatal medicine? J Perinat Med, 2007;35:10-27.)

Similarly, Chang and colleagues reported several series where 3D US techniques were used to effectively evaluate fetal organ volumes, estimating fetal lung volume for the evaluation of pulmonary hypoplasia,[11] cerebellar volume,[13,14] heart volume,[15] adrenal gland volume,[16] and liver volume.[17] In all of these studies, 3D US images provided more accurate data than 2D images.[11]

In 2007, Kurjak and colleagues reviewed, in *Perinatology*, the published experience with 3D and 4D US.[18] Their analysis highlighted reports detailing the use of 3D US to more accurately evaluate fetal craniofacial anomalies. In one study, 4D US was used to measure external ear length, a parameter that is classically difficult to accurately determine using 2D US. Short external ear length is one of the most consistent anthropomorphic characteristics found in neonates with Down syndrome (see Fig. 4-1). In another report, 3D US evaluation of the fetal central nervous system was found to improve the diagnosis of malformations with a sensitivity of up to 80%. More relevant to pediatric surgery, 3D US systems combined with the use of high-frequency transvaginal US probes enhanced the detection rate of cystic hygromas, with earlier and more frequent detection of these lesions. The use of 3D US to evaluate the fetal heart has also shown promise. A recently introduced US technique, tomographic US imaging (TUI), allows the examiner to review multiple parallel images of the beating heart. Using the known advantages of multislice imaging commonly used in computed tomography and magnetic resonance imaging, TUI can provide a more precise determination of the relationships between adjacent cardiac structures.

In addition to prenatal evaluation, 3D US systems have been used to image the ventricular system in neonates and infants to aid in the preoperative planning of neuroendoscopic interventions.[19,20] Similarly, these systems have seen relatively extensive use in the area of transthoracic echocardiographic imaging for the evaluation of congenital cardiac anomalies.[21,22] From an experimental standpoint, Cannon and colleagues studied the ability of 3D US to guide basic surgical tasks in a simulated endoscopic environment.[23] They found that 3D US imaging guided these tasks more efficiently and more accurately than 2D US imaging.[23] Overall, 3D US systems appear to allow the visualization of complex structures in a more intuitive manner compared with 2D systems. In addition, they appear to enable more precise measurements of volume and the relative orientation of structures.[24] As technology improves, the use of such systems in the field of pediatric surgery is likely to increase.

### Ultrasound Contrast Imaging and Ultrasound Harmonic Imaging

In addition to 3D US, significant advances have recently been made with respect to US contrast imaging and harmonic imaging, which may serve to improve the quality of information obtained by US techniques and may expand the clinical use of US as an imaging modality.

Ultrasound contrast imaging techniques are currently used for the visualization of intracardiac blood flow to evaluate structural anomalies of the heart.[25] In general, US contrast agents are classified as free gas bubbles or encapsulated gas bubbles. Simply stated, these gas bubbles exhibit a unique resonance phenomenon when isonified by an US wave, resulting in a frequency-dependent volume pulsation that makes the resonating bubble behave as a source of sound, not just a reflector of it.[4] Currently, new methods are being developed to enhance the contrast effect, including harmonic imaging, harmonic power Doppler imaging, pulse inversion imaging, release-burst imaging, and subharmonic imaging.[4] As these methods improve, US contrast imaging may serve to provide clinicians with more detailed perfusion imaging of the heart as well as tumors and other anatomic structures. Figure 4-2 depicts an US image of the left ventricle using microbubble contrast.

Interest in US harmonic imaging occurred in 1996 after Burns observed harmonics generated by US contrast agents.[26] Since then, significant developments have occurred in the use of the harmonic properties of sound waves to improve the quality of US images. In brief, sound waves are the sum of different component frequencies, the fundamental frequency (first harmonic) and harmonics, which are integral multiples of the fundamental frequency. The combination of the fundamental frequency and its specific harmonics gives a signal its unique characteristics. When US contrast agents are used, harmonics are generated by reflections from the injected agent and not by reflections from tissue. When no contrast is used, harmonics are generated by the tissue itself.[27]

Although the fundamental frequency consists of echoes produced by tissue interfaces and differences in tissue properties, the harmonics are generated by the tissue itself. In this manner, harmonic intensity increases with depth until natural tissue attenuation overcomes this effect. In contrast, the intensity of the fundamental frequency is attenuated linearly with depth.[27] Tissue harmonic imaging takes advantage of these properties by using the harmonic signals that are generated by tissue and by filtering out the fundamental echo signals that are generated by the transmitted acoustic energy.[28] This theoretically leads to an improved signal-to-noise ratio and contrast-to-noise ratio. Additional benefits of US harmonic imaging include improved spatial resolution, better visualization of deep structures, and a reduction in artifacts produced by US contrast agents.[27] Figure 4-3 compares an image obtained by US harmonic imaging and one obtained by standard 2D US.

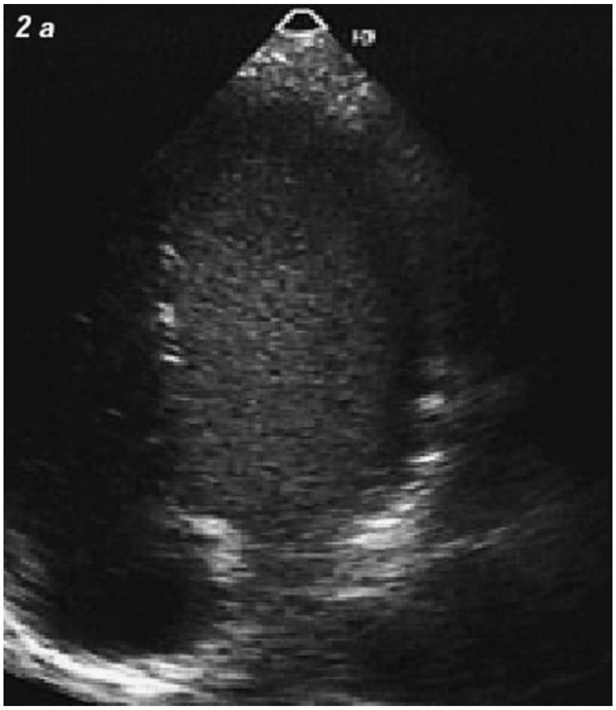



FIGURE 4-2 Ultrasound contrast image of the left ventricle. (From Frinking PJ, Bouakaz A, Kirkhorn J, et al: US contrast imaging: Current and new potential methods. US Med Biol 2000;26:965-975.)

### Ultrasonography and Fetal Surgery

With the advent of fetal surgery in 1980, US evaluation became an increasingly important noninvasive modality for diagnosing and characterizing diseases that are amenable to fetal surgical intervention.[29] Today, fetal surgical techniques are used in selected centers to perform a variety of procedures, including surgical repair of myelomeningocele, resection of sacrococcygeal teratoma in fetuses with nonimmune hydrops, resection of an enlarging congenital cystic adenomatoid malformation that is not amenable to thoracoamniotic shunting, and tracheal balloon occlusion for severe left congenital diaphragmatic hernia.[30,31] In all of these procedures, sonography currently remains the modality of choice for fetal diagnosis and treatment because of its safety and real-time capabilities. Specifically, fetal US can be used to characterize the severity of the congenital anomaly and to determine its appropriateness for intervention. During open hysterotomy, US is used to determine an appropriate location for the uterine incision away from the placenta and to monitor fetal heart rate and contractility. During procedures that do not use open hysterotomy, such as radiofrequency ablation for twin-reversed arterial perfusion sequence, laser ablation for twin-twin transfusion syndrome, and shunt placements for large pleural effusions, and bladder outlet obstruction, fetal US is used to directly guide the intervention. In addition, US imaging is vital to the postoperative care and follow-up of fetal surgical patients, because they remain in utero after their surgical procedure.

## COMPUTED TOMOGRAPHY

Computed tomography was invented in 1972 by British engineer Godfrey Hounsfield of EMI Laboratories, England, and independently by South African–born physicist Allan Cormack of Tufts University, Massachusetts. Since then, the use of CT imaging has become widespread in multiple fields of medicine and surgery. Currently, advances in technology have improved the speed, comfort, and image quality of modern CT scanners. In addition, recent advances, such as multidetector CT computed tomography (MDCT) and volumetric reconstruction, or 3D CT, may be particularly valuable in

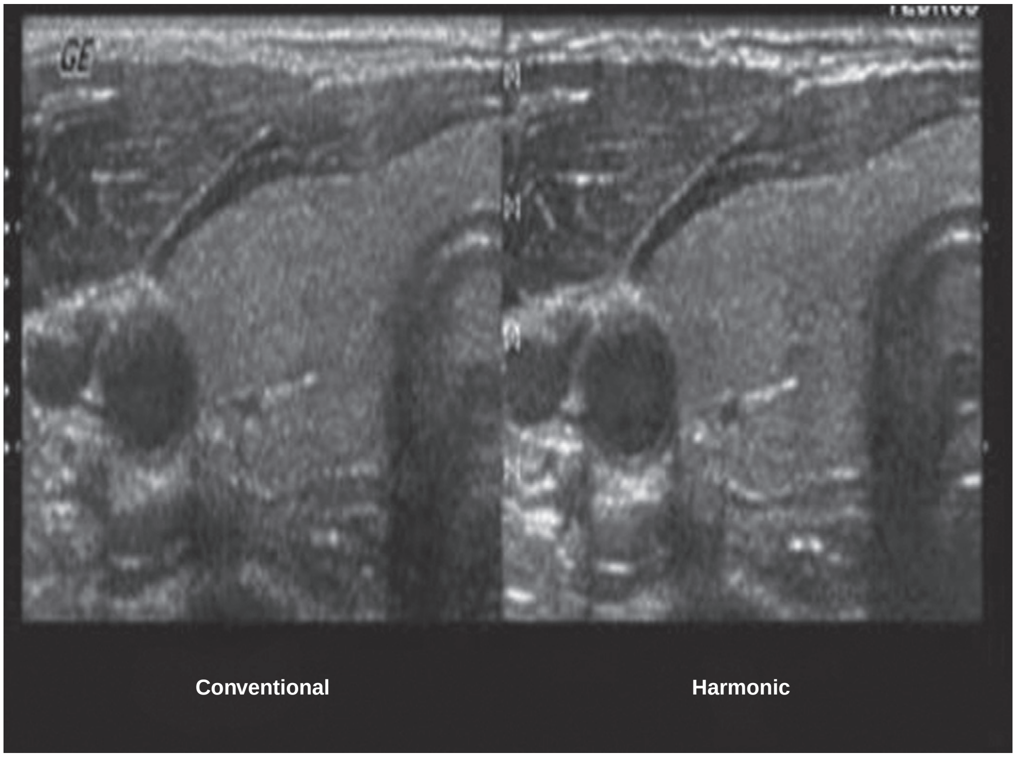



**FIGURE 4-3** Conventional versus ultrasound harmonic imaging. (From Tranquart F, Grener N, Eder V, Pourcelot L, et al: Clinical use of US tissue harmonic imaging. US Med Biol 1999;25:889-894.)

the care of pediatric surgical patients. This section will provide a brief overview of CT imaging, focusing on MDCT and volumetric imaging and their implications in pediatric surgery.

### Multidetector Computed Tomography

Computed tomography uses a tightly arranged strip of radiation emitters and detectors that circles around a patient to obtain a two-dimensional map of x-ray attenuation values. Numerical regression techniques are then used to turn this list of attenuation values into a two-dimensional slice image. CT has undergone several major developments since its introduction.

Introduced in the early 1990s, single-detector helical or spiral CT scanning revolutionized diagnostic CT imaging by using slip rings to allow for continuous image acquisition.[32] Before this development, the table and patient were moved in a stepwise fashion after the acquisition of each image slice, resulting in relatively long scanning times. Helical CT scanners use slip ring technology that allows the tube and detector to continually rotate around the patient. Combined with continuous table motion through the rotating gantry, this significantly improves the speed of CT studies. The improved speed of helical CT scanners enables the acquisition of large volumes of data in a single breath hold.

Helical CT has improved during the past 15 years, with faster gantry rotation, more powerful x-ray tubes, and improved interpolation algorithms.[33] However, the greatest advance has been the recent introduction of multidetector-row CT (MDCT) scanners.[32] In contrast to single-detector–row CT, MDCT uses multiple parallel rows of detectors that spiral around the patient simultaneously. Currently capable of acquiring four channels of helical data at the same time, MDCT scanners are significantly faster than single-detector helical CT scanners. This has profound implications for the clinical application of CT imaging, especially in the pediatric patient where the issues of radiation exposure and patient cooperation are magnified. Fundamental advantages of MDCT compared with earlier modalities include substantially shorter acquisition times, retrospective creation of thinner or thicker sections from the same raw data, and improved 3D rendering with diminished helical artifacts.[33]

In the pediatric population, MDCT provides a number of advantages compared with standard helical CT. Because of the increased speed of MDCT, there may be a decreased need for sedation in some pediatric studies. There is also a reduction in patient movement artifact as well as a potential for more optimal contrast enhancement over a greater portion of the anatomy of interest. The volumetric data acquired also provides for the ability of multiplanar reconstruction, which can be an important problem-solving tool. MDCT has been increasingly used for pediatric trauma, pediatric tumors, evaluation of solid abdominal parenchymal organ masses, suspected abscess, or inflammatory disorders.[34] Specifically, MDCT is increasingly used in the evaluation of children with abdominal pain, particularly in patients with suspected appendicitis.[35] Callahan and colleagues used MDCT in the evaluation of children with appendicitis and reduced the total number of hospital days, negative laparotomy rate, and cost per patient.[36] In addition, MDCT may be useful in identifying alternative diagnoses, including other bowel pathologies, ovarian pathologies, and urinary tract pathologies (Fig. 4-4).[35]

Similarly, MDCT may be valuable in the evaluation of urolithiasis and inflammatory bowel disease (IBD). MDCT has gained acceptance as a primary modality for the evaluation of children with abdominal pain and hematuria in which urolithiasis is suspected.[35] CT findings of urolithiasis include visualization of the radiopaque stone, dilatation of the ureter

**FIGURE 4-4** Multidetector computed tomography of an 8-year-old boy with appendicitis. The *arrows* point to an inflammatory mass in the right lower quadrant with a possible appendicolith *(arrowhead)*. (From Donnelly LF, Frush DP: Pediatric multidetector body CT. Radiol Clin North Am 2003;41:637–655.)

or collecting system, asymmetric enlargement of the kidney, and perinephric stranding.[35] Of note, MDCT evaluation of these patients usually requires a noncontrast study. Another area in which CT is showing increased use is for the evaluation of children with IBD.[35] In these patients, CT may be superior to fluoroscopy for demonstrating inflammatory changes within the bowel as well as extraluminal manifestations of IBD, such as peribowel inflammatory change or abscess.[35]

In the chest, MDCT is used for the evaluation of infection and complication of infections, as well as cancer detection and surveillance. Evaluation of congenital abnormalities of the lung, mediastinum, and heart are also indications. In particular, MDCT may be useful in the assessment of bronchopulmonary foregut malformations in which sequestration is a consideration.[34] Similarly, the use of MDCT in the evaluation of the pediatric cardiovascular system has been particularly valuable.[37] Assessment of cardiovascular conditions, such as aortic aneurysms, dissections, and vascular rings, may be significantly better than with echocardiography. Finally, MDCT is advantageous in the evaluation of patients with pectus malformations, because it allows for lower doses of radiation.[35]

### Three-Dimensional Computed Tomography

The advent of helical CT and MDCT has enabled the postacquisition processing of individual studies for the creation of three-dimensional CT image reconstructions. These 3D reconstructions are valuable in the preoperative planning of complex surgical procedures. Although 3D CT imaging has been possible for almost 25 years, the quality, speed, and affordability of these techniques have only recently improved enough to result in their incorporation into routine clinical practice.[38] Currently, four main visualization techniques are used in CT reconstruction labs to create 3D CT images. These include multiplanar reformation, maximum intensity projections, shaded surface displays, and volume rendering. Multiplanar reformation and maximum intensity projections are limited to external visualization, while shaded surface displays and volume rendering allow immersive or internal visualization, such as virtual endoscopy.[33]

**FIGURE 4-5** 3D computed tomography reconstruction of an infant skull showing premature closure of the right coronal suture. (From Rubin GD: 3-D imaging with MDCT. Eur J Radiol 2003;45(Suppl 1):S37–S41.)

Three-dimensional CT has been beneficial in the preoperative planning of pediatric craniofacial, vascular, and spinal operations. Specifically, 3D CT has been used to evaluate maxillofacial fractures[39] and craniofacial abnormalities, as well as vascular malformations. Figure 4-5 illustrates a 3D CT reconstruction of an infant with craniosynostosis. Similarly, 3D CT has been reported useful in the planning of hemivertebra excision procedures for thoracic and thoracolumbar congenital deformities.[40] A particularly interesting application of 3D CT is the creation of "virtual endoscopy" images for the interior surface of luminal structures, such as the bowel, airways, blood vessels, and urinary tract.[33] In particular, virtual endoscopy using 3D CT may be useful in the diagnosis of small bowel tumors, lesions that are often difficult to detect using standard modalities (Fig. 4-6).[38]

### Electron Beam Computed Tomography

Introduced clinically in the 1980s, electron beam computed tomography (EBCT) scanners are primarily used in adult cardiology to image the beating heart. As opposed to traditional CT scanners, EBCT systems do not use a rotating assembly consisting of an x-ray source directly opposite an x-ray detector. Instead, EBCT scanners use a large, stationary x-ray tube that partially surrounds the imaging field. The x-ray source is moved by electromagnetically sweeping the electron beam focal point along an array of tungsten anodes positioned around the patient. The anodes that are hit emit x-rays that are collimated in a similar fashion to standard CT scanners. Because this is not mechanically driven, the movement can be very fast. In fact, EBCT scanners can acquire images up to 10 times faster than helical CT scanners. Current EBCT systems are capable of performing an image sweep in 0.025 seconds compared with the 0.33

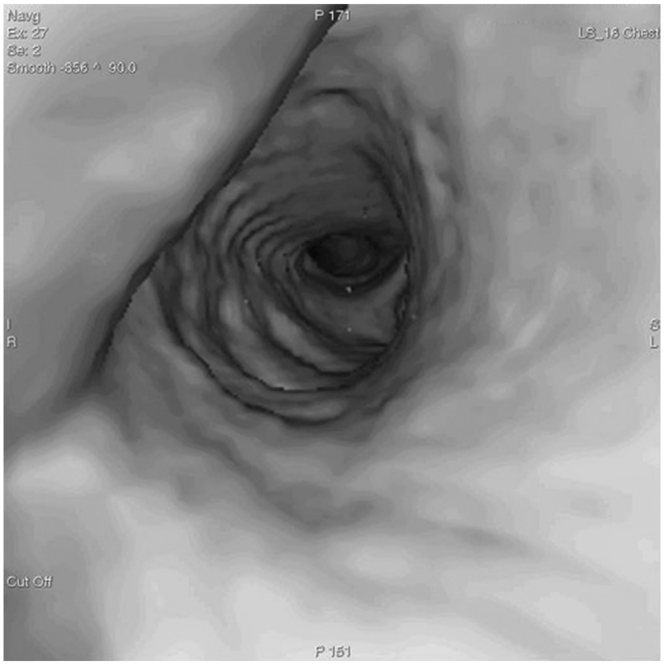



**FIGURE 4-6** Virtual colonoscopy.

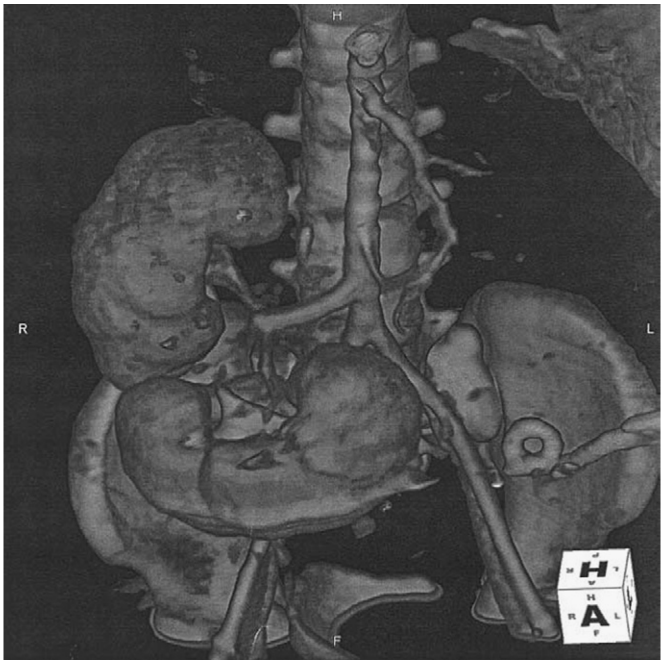



**FIGURE 4-7** Electron beam computed tomography of transplanted kidney. (From Talisetti A, Jelnin V, Ruiz C, et al: Electron beam CT scan is a valuable and safe imaging tool for the pediatric surgical patient. J Pediatr Surg 2004;39:1859–1862.)

seconds for the fastest mechanically swept CT systems. This rapid acquisition speed minimizes motion artifacts, enabling the use of EBCT scanners for imaging the beating heart. In addition to faster image acquisition times resulting in decreased motion artifacts, EBCT scanners generally result in a 6- to 10-fold decrease in radiation exposure compared with traditional CT scanners.

To date, EBCT scanners have not yet seen widespread adoption. The systems are necessarily larger and more expensive than helical CT scanners. Advances in multidetector helical CT scan designs have enabled cardiac imaging using standard, mechanically driven systems.

The use of EBCT in the pediatric population has primarily been reported for the imaging of cardiac anomalies.[41,42] However, as we increasingly understand the risks associated with ionizing radiation exposure in children, the decreased exposure associated with EBCT systems appears attractive. In addition, the faster acquisition times and minimization of motion artifact could theoretically result in decreased sedation requirements in young patients. Talisetti and colleagues reported the use of EBCT to evaluate several pediatric surgical patients—one patient with thoracic dystrophy and an abdominal wall hernia, one patient with ascites status postrenal transplant (Fig. 4-7), and several patients with renal and pelvic tumors.[43] In their report, they highlighted the potential advantages of decreased radiation exposure and sedation requirements associated with EBCT systems.

## MAGNETIC RESONANCE IMAGING

The first MRI examination on a human was performed in 1977 by Dr. Raymond Damadian, with colleagues Dr. Larry Minkoff and Dr. Michael Goldsmith. This initial exam took 5 hours to produce one, relatively poor quality image. Since then, technological improvements have increased the resolution and speed of MRI. Today, MRI is able to provide unparalleled noninvasive images of the human body. In addition, newer MRI systems now allow images to be obtained at subsecond intervals, facilitating fast, near real-time MRI. Similarly, new MRI techniques are now being developed to provide functional information on the physiologic state of the body. This section will provide a brief overview of MRI, focusing on recent technologic advances, such as *ultrafast MRI, higher field strength MRI systems, motion artifact reduction techniques,* and *functional MRI.*

MRI creates images by using a strong, uniform magnetic field to align the spinning hydrogen protons of the human body. A radiofrequency (RF) pulse is then applied, causing some of the protons to absorb the energy and spin in a different direction. When the RF pulse is turned off, these protons realign and release their stored energy. This release of energy gives off a signal that is detected, quantified, and sent to a computer. Because different tissues respond to the magnetic field and RF pulse in a different manner, they give off variable energy signals. These signals are then used to create an image using mathematical algorithms.

### Higher Field Strength MRI Systems

Over the last decade, MRI has advanced significantly with the transition from 1.5 Tesla (T) to 3.0 T field strength systems (Fig. 4-8). Using higher magnetic field strength, 3.0 T systems demonstrate improved image resolution, faster image acquisition speeds, and improved fat suppression.[44] In addition, 3.0 T systems theoretically enable a twofold increase in signal-to-noise ratio (SNR) compared with 1.5 T systems as SNR increases linearly with field strength. This is particularly important for imaging smaller patients with anatomical structures. Although 3.0 T systems are rapidly becoming the standard in pediatric MRI imaging, ultrahigh field strength 7.0 T systems are currently being evaluated. These systems

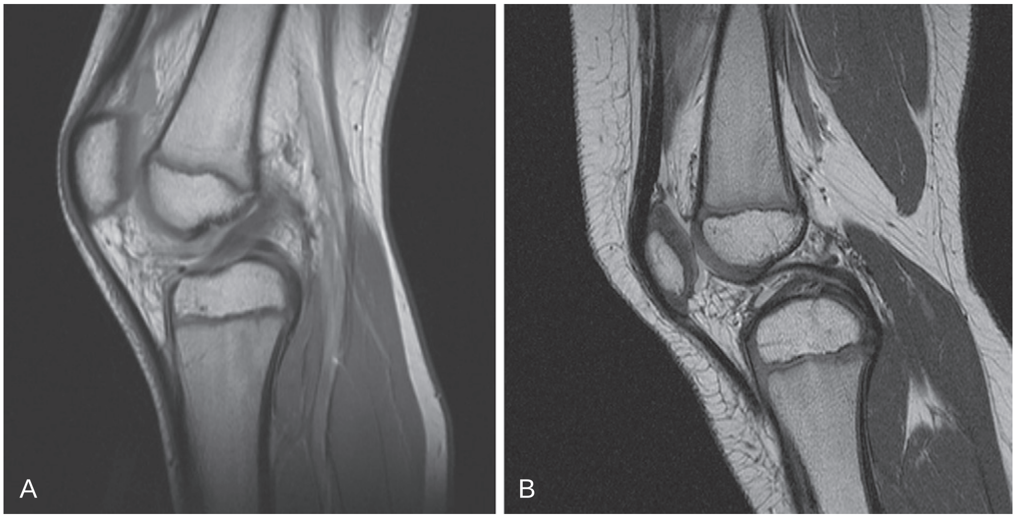



**FIGURE 4-8** Comparison of image quality between 1.5 T (**A**) and 3.0 T (**B**). (From MacKenzie JD, Vasanawala SS: Advances in pediatric MR imaging. Magn Reson Imaging Clin N Am 2008;16:385–402.)

potentially provide the same advantages listed above but to a higher degree. Disadvantages include higher deposition of radiofrequency energy, magnification of artifacts, and more challenging hardware and software design. Although still under investigation, ultrahigh field strength MRI may enable unique studies such as sodium imaging, which can be used to monitor renal physiology and function, myocardial viability, and phosphorous imaging, which has been suggested as a method of evaluating organ pH and cancer metabolism.[44]

## Ultrafast MRI

The first major development in high speed MRI occurred in 1986 with the introduction of the gradient-echo pulse sequence technique (GRE). This technique decreased practical scan times to as little as 10 seconds. In addition to increasing the patient throughput of MRI scanners, the faster scan times significantly increased the application of MR imaging in body regions (e.g., the abdomen) where suspended respiration could eliminate most motion-related image distortions.[45,46] Since then, GRE techniques have undergone iterations and further developments, such as balanced steady-state imaging, achieving subsecond level scan times.

More recently, parallel imaging (or parallel MRI) has emerged as a method of increasing MRI imaging speed. Parallel imaging techniques are able to construct images using reduced data sets by combining the signals of several coil elements in a phased array. In this manner, higher imaging speeds are achievable, generally allowing speed increases of two- to threefold.[44] In addition, MRI parallel imaging results in improved signal-to-noise ratio, thereby decreasing artifact and improving image quality.

The high speed of ultrafast MRI represents a significant advantage in the care of children. Most traditional MR protocols require 30 to 40 minutes of table occupancy. During this time the patient must remain still to avoid motion artifact.[47] For many children, this often requires sedation, general anesthesia, and even muscular blockade to enable them to remain motionless long enough for a quality study to be completed. This is obviously a significant impediment toward the widespread use of MRI in children. Ultrafast MRI significantly reduces this requirement, not only minimizing the potential side effects of sedation during routine MRI studies but also allowing the use of MRI to study high-risk infants who cannot be adequately sedated or paralyzed.[48]

Ultrafast MRI also significantly reduces the motion artifacts that occur in the abdomen and thorax resulting from normal respiratory and peristaltic movements. In particular, the smearing artifact associated with the use of oral contrast agents during MR imaging of the intestinal tract had previously decreased image quality.[49] Using GRE and parallel imaging techniques, modern MRI can achieve scan times that are fast enough to be completed during a breath hold and are fast relative to normal abdominal motion.[44] In addition, by decreasing motion artifact and enabling fast image acquisition, ultrafast MRI protocols enable the practical application of cardiac MRI and fetal MRI.[50] Similarly, volumetric or 3D MRI has become practically feasible in children with ultrafast MRI techniques that decrease the acquisition time required for these data intensive studies.[44]

### Motion Artifact Reduction Techniques

Motion artifacts may be secondary to physiologic movement (cardiac, respiratory, and peristaltic) as well as voluntary movement. This is particularly significant in pediatric patients. Recently, several techniques have been used to minimize motion artifacts. One broad method employs high-speed image acquisition as detailed above. Another method is navigation imaging where extra navigator echoes are used to detect image displacements. These displacements are used to reject or correct data reducing artifacts.[44] Currently, navigation imaging has been applied to cardiac imaging and hepatobiliary imaging to reduce motion artifacts caused by respiratory movement. Similarly, PROPELLER (periodically rotated overlapping parallel lines with enhanced reconstruction) imaging is a method for reducing motion artifacts by signal averaging successive rotating samples of data.

### Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a rapidly evolving imaging technique that uses blood flow differences in the brain to provide in vivo images of neuronal activity. First described just more than 15 years ago, fMRI has seen widespread clinical and research application in the adult

population. Functional MRI is founded on two basic physiologic assumptions regarding neuronal activity and metabolism. Specifically, fMRI assumes that neuronal activation induces an increase in local glucose metabolism, and that this increased metabolic demand is answered by an increase in local cerebral blood flow.[51] By detecting small changes in local blood flow, fMRI techniques are able to provide a "functional" image of brain activity. Currently, the most commonly used technique is known as "blood oxygen level–dependent" (BOLD) contrast, which uses blood as an internal contrast medium.[52] BOLD imaging takes advantage of small differences in the magnetic properties of oxygenated and deoxygenated hemoglobin. Since neuronal activation is followed by increased and relatively excessive local cerebral blood flow, more oxygenated hemoglobin appears in the venous capillaries of activated regions of the brain. These differences are detected as minute distortions in the magnetic field by fMRI and can be used to create a functional image of brain activity.[51]

Functional magnetic resonance imaging requires significant subject preparation in order to prepare the child to lie still in the scanner for the duration of the study. Various preparation techniques have been described that decrease the anxiety and uncertainty that a child might experience regarding the study. These include presession educational videos, presession tours with members of the radiology staff, and presession practice runs. Optimally, fMRI studies require a nonsedated, cooperative patient to assess functional neuronal activity. However, it has been recently shown that passive range of motion may activate the sensorimotor complex in sedated patients. This may enable functional motor mapping in patients who are unable to cooperate with active tasks.[53]

At this time, the use of fMRI in the pediatric population is still at the earliest stages. However, fMRI holds tremendous promise in the evaluation of central nervous system (CNS) organization and development, characterization of brain plasticity, and the evaluation and understanding of neurobehavioral disorders.[51] In addition, current clinical applications of fMRI include the delineation of eloquent cortex near a space-occupying lesion and the determination of the dominant hemisphere for language. fMRI is also used to map the motor cortex. These clinical applications are designed to provide preoperative functional information for patients undergoing epilepsy or tumor surgery.[53] This information can be used to guide resection and to predict postoperative deficits.[53]

### Fetal Magnetic Resonance Imaging

Magnetic resonance imaging has become an increasingly used imaging modality for the evaluation of fetal abnormalities. Rapid image acquisition times and motion artifact reduction techniques allow for effective imaging studies despite fetal movement. Although US remains the primary modality for imaging the unborn fetus, fetal MRI has demonstrated several distinct advantages. In addition to providing fine anatomic detail, fetal MRI is not limited by maternal obesity, fetal position, or oligohydramnios—all factors that can limit the effectiveness of US evaluation.[54] The use of fetal MRI to characterize fetal CNS, thoracic, abdominal, genitourinary, and extremity anomalies has been well described. Particularly relevant to the field of pediatric surgery, fetal MRI has been used to assist in the prenatal differentiation between enteric cysts and meconium pseudocysts. Similarly, fetal MRI is used to characterize the nature and origin of abdominal masses and to evaluate fetal tumors.[54] Such information may be valuable for prenatal counseling and decision making as well as for preoperative planning. As the field of fetal surgery matures, fetal MRI may become increasingly useful in the evaluation of abnormalities amenable to fetal intervention.

## POSITRON EMISSION TOMOGRAPHY IMAGING

Positron emission tomography, or PET, is an increasingly used imaging technology that provides information on the functional status of the human body. First developed in 1973 by Edward Hoffman, Michael Ter-Pogossian, and Michael Phelps at Washington University, PET imaging is now one of the most commonly performed nuclear medicine studies in the United States.[55] Although CT, MRI, and US imaging techniques provide detailed information regarding the anatomic state of a patient, PET imaging provides information on the current metabolic state of the patient's tissues. In this manner, PET imaging is often able to detect metabolic changes indicative of a pathologic state before anatomic changes can be visualized.

PET imaging is based on the detection of photons released when positron emitting radionuclides undergo annihilation with electrons.[56] These radionuclides are created by bombarding target material with protons that have been accelerated in a cyclotron.[56] These positron-emitting radionuclides are then used to synthesize radiopharmaceuticals that are part of biochemical pathways in the human body.[56] The most commonly used example of this is the use of the fluorinated analog of glucose, 2-deoxy-2-(18)F-fluoro-D-deoxyglucose (FDG).[57] Like glucose, FDG is phosphorylated by the intracellular enzyme hexokinase. In its phosphorylated form, FDG does not cross cell membranes and therefore accumulates within metabolically active cells. In this manner, PET imaging using FDG provides information about the glucose use in different body tissues.[57]

In order to be detected, FDG is synthesized using $^{18}F$, a radioisotope with a half-life of 110 minutes.[57] The synthesis process begins by accelerating negatively charged hydrogen ions in a cyclotron until they gain approximately 8 MeV of energy. The orbital electrons from these hydrogen ions are then removed by passing through a carbon foil. The resultant high-energy protons are then directed toward a target chamber that contains stable $^{18}O$ enriched water.[56] The protons undergo a nuclear reaction with the $^{18}O$ enriched water to form hydrogen $^{18}F$ fluoride. The reaction is detailed in the equation that follows.[56]

$$H_2(^{18}O) + {}^1H + \text{ energy} \rightarrow H_2(^{18}F)$$

$^{18}F$ is an unstable radioisotope that decays by beta-plus emission or electron capture and emits a neutrino ($\nu$) and a positron ($\beta^+$).[56] The emitted positrons are then annihilated with electrons to release energy in the form of photons, which are detected by modern PET scanners and are the basis of PET imaging. The detectors in PET scanners are scintillation crystals coupled to photomultiplier tubes. Currently, most PET scanners use crystals composed of bismuth germinate, cerium-doped lutetium oxyorthosilicate, or cerium-doped gadolinium silicate.[56] Because PET scanning uses unstable radioisotopes, PET probes must be synthesized immediately prior to a PET study. This limits the immediate and widespread

availability of PET imaging, because the studies must therefore be scheduled in advance. FDG is a convenient probe because its half-life of 110 minutes allows it to be transported from a remote cyclotron to a PET scanner in enough time to perform a typical whole-body PET imaging study ($\geq$30 minutes).[57]

In a typical PET study, the radiopharmaceutical agent is systemically administered to the patient by intravenous injection. The patient is then imaged by the PET scanner, which measures the radioactivity (photon emission as above) throughout the body and creates 3D pictures or images of tissue function. Currently, PET imaging is used extensively for the accurate evaluation and monitoring of tumors of the lung, colon, breast, lymph nodes, and skin.[58] PET imaging is used to facilitate tumor diagnosis, localization, and staging; monitoring of antitumor therapy; tumor tissue characterization; radionuclide therapy; and screening for tumor recurrence.[59] Though nonspecific, FDG is often used because malignant cells generally display increased glucose use with up-regulation of hexokinase activity.[56]

PET imaging has also been used to assess the activity of noncancerous tissues to provide information on their viability or metabolic activity. In adults, PET scans are used to determine the viability of cardiac tissue in order to decide whether a patient would benefit from coronary bypass grafting.[60,61] Recently, this application was extended to the pediatric population in order to assess cardiac function after arterial switch operations with suspected myocardial infarction.[62] Similarly, PET scans can be used to visualize viability of brain tissue in order to make prognostic determinations after stroke.[63] Finally, PET imaging is used to identify regions of abnormal activity in brain tissue, helping to localize seizure foci or diagnose functional disorders, such as Parkinson disease and Alzheimer disease.[64,65]

Though PET imaging provides important functional information regarding the metabolic activity of human tissues, it often provides relatively imprecise images compared with traditional anatomic imaging modalities. This is in large part because of the physics of PET as an imaging modality. Specifically, the positrons emitted by radionuclides, such as FDG, generally have enough kinetic energy to travel a small distance before annihilating with an electron.[56] This distance is called the *mean positron range* and varies depending on tissue density. The difference in position between the initial location of the positron and its site of annihilation results in positron range blurring. This limits the spatial resolution of PET imaging, which is typically considered to be approximately 5 mm using current scanners.[56] *Noncollinearity* or variation in the path of emitted photons other than the expected 180 degrees, also contributes to decreased spatial resolution in PET imaging. Because of these limitations, PET imaging is often useful for highlighting areas suspicious for malignancy but may be difficult to use during preoperative planning, because it does not accurately correlate the area of suspicion with detailed anatomic information.[58]

Recently, combined PET/CT scanners have been developed that simultaneously perform PET scans and high resolution CT scans. Introduced 10 years ago, these scanners provide functional information obtained from the PET scan and accurately map it to the fine anatomic detail of the CT scan (Fig. 4-9).[57] Prior to the availability of PET/CT scanners, CT and PET scans of the same patient acquired on different scanners at different times were often aligned using complex, labor-intensive algorithms.[57] However, other than for brain imaging, these algorithms often failed to adequately fuse the studies. In contrast, combined PET/CT scanners rely on hardware fusion and not solely software manipulation and do not suffer these limitations.

In the field of pediatric surgery, PET/CT scanning represents a new imaging modality with tremendous potential in regard to preoperative planning and postoperative follow-up. However, several issues specific to the pediatric population make the implementation of PET imaging challenging, including the need for fasting, intravenous access, bladder catheterization, sedation, and clearance from the urinary tract.[66,67] Currently, the clinical application of combined PET/CT imaging in the pediatric population has not been extensively studied. However, the combination of functional information with fine anatomic data provides obvious advantages with regard to surgical planning and will therefore likely play a large role in surgical practice.

## MOLECULAR IMAGING

Ultrasonography, CT, MRI, and PET imaging represent established technologies that are commonly used in the care of pediatric patients around the world. Although these technologies provide detailed anatomic and even functional information, their clinical application has yet to provide information at the cellular/molecular level. In contrast to these classical imaging modalities, a new field termed "molecular imaging" sets forth to probe the molecular abnormalities that are the basis of disease rather than to image the end effects of these alterations.[68] Molecular imaging is a rapidly growing research discipline that combines the modern tools of molecular and cell biology with noninvasive imaging technologies. The goal of this new field is to develop techniques and assays for imaging physiologic events and pathways in living organisms at the cellular/molecular level, particularly those pathways that are key targets in specific disease processes. The development and application of molecular imaging will someday directly affect patient care by elucidating the molecular processes underlying disease and lead to the early detection of molecular changes that represent "predisease" states.[69]

Molecular imaging can be defined as "the in vivo characterization and measurement of biologic processes at the cellular and molecular level."[68] From a simplistic standpoint, molecular imaging consists of two basic elements:

1. Molecular probes whose concentration, activity and/or luminescent properties are changed by the specific biologic process under investigation[69]
2. A means by which to monitor these probes[69]

Currently, most molecular probes are either radioisotopes that emit detectable radioactive signals or light- or near-infrared (NIR)–emitting molecules.[69] These probes are considered either direct binding probes or indirect binding probes.[70] Radiolabeled antibodies designed to facilitate the imaging of cell-specific surface antigens or epitopes are commonly used examples of direct binding probes.[70] Similarly, radiolabeled oligonucleotide antisense probes developed to specifically hybridize with target messenger RNA (mRNA) or proteins for the purpose of direct, in vivo imaging are more recent examples.[70] Radiolabeled oligonucleotides represent complimentary sequences to a small segment of target mRNA or DNA, allowing for the direct imaging of endogenous gene

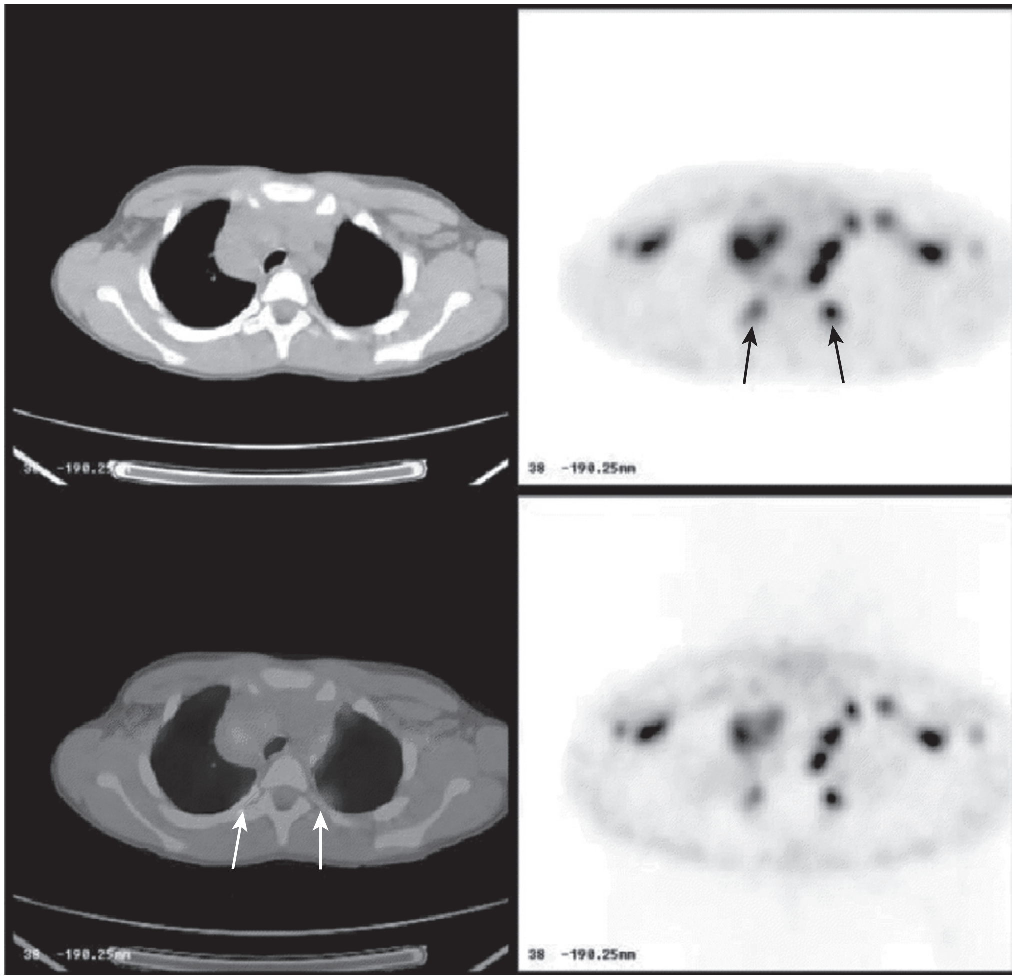



**FIGURE 4-9** Combined positron emission tomography (PET)-CT images (axial) through the upper chest of a 7-year-old girl with a mediastinal mass found to be a necrotizing granuloma. Multiple sites of 2-deoxy-2-(18)F-fluoro-D-deoxyglucose (FDG)–avid axillary lymph nodes and multiple foci within the mediastinal mass are visualized. Arrows highlight the symmetric avidity of the costovertebral junctions for FDG that can be seen in children. (From Kaste SC: Issues specific to implementing PET-CT for pediatric oncology: What we have learned along the way? Pediatr Radiol 2004;34:205-213.)

expression at the transcriptional level.[70] Finally, positron-emitting analogs of dopamine, used to image the dopamine receptors of the brain, are other examples of direct binding probes.[69]

Although direct binding probes assist in the imaging of the amount or concentration of their targets, indirect probes reflect the activities of their macromolecular targets. Perhaps the most widely used example of an indirect binding probe is the hexokinase substrate FDG. The most common probe used in clinical PET imaging, FDG is used for neurologic, cardiovascular, and oncology investigations.[69] Systemically administered FDG is accessible to essentially all tissues.[69]

The use of reporter transgene technology is another powerful example of molecular imaging with indirect binding probes. Reporter genes are nucleic acid sequences encoding easily assayed proteins. Such reporter genes have been long used in molecular biology and genetics studies to investigate intracellular properties and events, such as promoter function/strength, protein trafficking, and gene delivery. Using molecular imaging techniques, reporter genes have now been used to analyze gene delivery, immune cell therapies, and the in vivo efficacy of inhibitory mRNAs in animal models.[71] In vivo bioluminescent imaging using the firefly or *Rinella* luciferase or fluorescent optical imaging using green fluorescent protein (GFP) or DsRed are optical imaging examples of this technique (Fig. 4-10).[72,73] Recently, semiconductor quantum dots have been used in fluorescent optical imaging studies. Although fluorescent proteins are limited in their number of available colors, quantum dots can fluoresce at different colors over a broad region of the spectrum by altering their size and surface coating. To date, the quantum dots that have been tested with in vivo experimental models include amphiphilicpoly (acrylic acid), short-chain (750 D) methoxy-PEG and long-chain (3400 D) carboxy-PEG quantum dots, and long-chain (5000 D) methoxy-PEG quantum dots.[74]

In the field of immunology and immunotherapy research, Costa and colleagues transduced the autoantigen-reactive CD4+ T-cell population specific for myelin basic protein (MBP) with a retrovirus that encoded a dual reporter protein composed of GFP and luciferase, along with a 40 kD monomer of interleukin-12 as a therapeutic protein.[75] Bioluminescent imaging (BLI) techniques were then used to monitor the migratory patterns of the cells in an animal model of multiple sclerosis. BLI demonstrated that the immune cells that would typically cause destruction of myelin trafficked to the central nervous system in symptomatic animals. Furthermore, they

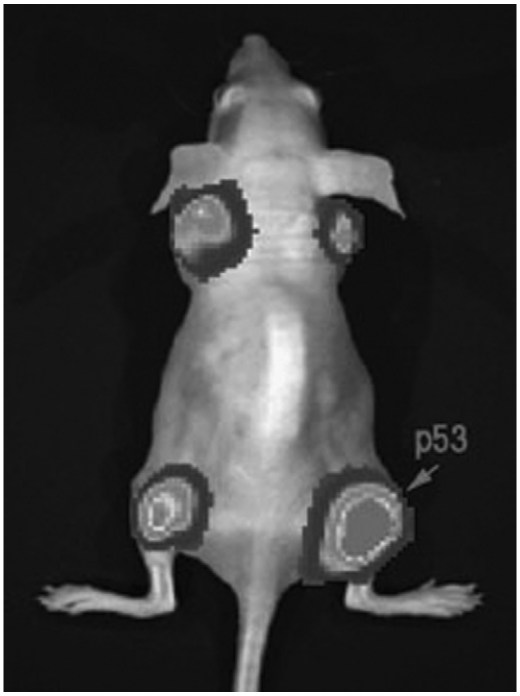



FIGURE 4-10 Nude mouse carrying a wild-type *TP53*-expressing human colon xenograft with a stably integrated *TP53*-responsive luciferase reporter gene. Injection of exogenous *TP53* expressed by an adenovirus vector led to detectable increase in luciferase activity within an established tumor *(arrow)*. (From Wang W, El-Deiry WS. Bioluminescent molecular imaging of endogenous and exogenous p53-mediated transcription in vitro and in vivo using an HCT116 human colon carcinoma xenograft model. Cancer Biol Ther. 2003 Mar-Apr;2(2):196-202.) *(See Expert Consult site for color version.)*

found that CD4 T-cell expression of the IL-12 immune modulator resulted in a clinical reduction in disease severity.[75]

Similarly, Vooijs and colleagues generated transgenic mice in which activation of luciferase expression was coupled to deletion of the retinoblastoma (*Rb*) tumor suppressor gene.[76] Loss of *Rb* triggered the development of pituitary tumors in their animal model, allowing them to monitor tumor onset, progression, and response to therapy in individual animals by repeated CCD (charged coupled device) imaging of luciferase activity.[76] Although optical imaging techniques are commonly used, reporter genes can also encode for extracellular or intracellular receptors or transporters that bind or transport a radiolabeled or paramagnetic probe, allowing for PET-, SPECT- (single-photon emission tomography), or MRI-based molecular imaging.[70]

The second major element of molecular imaging is the imaging modality/technology itself. Direct and indirect binding probes can be radiolabeled to allow nuclear-based in vivo imaging of a desired cellular/molecular event or process using PET or SPECT imaging. In fact, micro-PET and micro-SPECT systems have been developed specifically for molecular imaging studies in animal models.[68] Similarly, optical imaging techniques, such as bioluminescent imaging, near-infrared spectroscopy, and visible light imaging using sensitive CCDs can be used with optically active probes to visualize desired cellular events. Finally, anatomic imaging modalities, such as MRI, CT, and US, have all been adopted for use in animal-based molecular imaging studies.[68]

At this time, the field of molecular imaging is largely an experimental one, with significant activity in the laboratory and little current clinical application. Molecular imaging research is largely focused on investigating the molecular basis of clinical disease states and their potential treatments, including mechanisms surrounding apoptosis, angiogenesis, tumor growth and development, and gene therapy.[68]

### DNA MICROARRAYS

The descriptive term *genomics* acknowledges the shift from a desire to understand the actions of single genes and their individual functions to a more integrated understanding of the simultaneous actions of multiple genes and the subsequent effect exerted on cellular behavior. DNA microarrays, or gene chips, are a recent advancement that allows the simultaneous assay of thousands of genes.[77] Microarray technology has been applied to redefine biologic behavior of tumors, cross-species genomic comparisons, and large scale analyses of gene expression in a variety of conditions. In essence, it represents a new form of patient and disease triage, *molecular triage*.

## Innovative Therapeutics: Technologies and Techniques

A surgical operation requires two key elements: an "image," or more broadly, information regarding the anatomy of interest, and a "manipulation" of the patient's tissue with the goal of a therapeutic effect. Classically, the "image" is obtained through the eyes of the surgeon and the "manipulation" is performed using the surgeon's hands and simple, traditional surgical instruments. During the last several decades, this paradigm has been broadened by technologies that enhance these two fundamental elements.

As opposed to standard, line-of-sight vision, an "image" may now be obtained through an operating microscope or through a flexible endoscope or laparoscope. This endoscope may be monocular or binocular, providing 2D or 3D visualization. These technologies provide the surgeon with high-quality, magnified images of anatomical areas that may be inaccessible to the naked eye. Similarly, a surgical "manipulation" of tissue and organs may be accomplished using a catheter, flexible endoscope, or longer laparoscopic instruments. Furthermore, devices such as staplers, electrocautery, ultrasonic energy tools, and radiofrequency emitters are all used to manipulate and affect tissue with a therapeutic goal. These technologies have changed the way surgical procedures are performed, enabling and even creating fields such as laparoscopic surgery, interventional endoscopy, and catheter-based intervention. In addition to these advances, several emerging technology platforms promise to further broaden this definition of surgery. These include stereotactic radiosurgery and surgical robotics. This section presents a review of several of these technologies with a focus on the current status of hemostatic and tissue ablative instruments, stereotactic radiosurgery, and surgical robotics.

### HEMOSTATIC AND TISSUE ABLATIVE INSTRUMENTS

Handheld energy devices designed to provide hemostasis and ablate tissue are some of the most widely used surgical technologies throughout the world. Since the first reports of

electrosurgery in the 1920s,[78] multiple devices and forms of energy have been developed to minimize blood loss during tissue dissection. These instruments, including monopolar and bipolar electrocautery, ultrasonic dissectors, argon beam coagulators, cryotherapy, and infrared coagulators, are used in operating rooms on a daily basis. In addition, improvements to these tools and their techniques or use are continually being developed.

### Electrocautery

The application of high-frequency alternating current is now known variously as electrocautery, electrosurgery, or simply "the Bovie." Although the concept of applying an electrical current to living tissue was reported as far back as the late sixteenth century, the practical application of electrocautery in surgery did not begin to develop until the early 1900s. In 1908, Lee de Forest developed a high-frequency generator that was capable of delivering a controlled cutting current. However, this device used expensive vacuum tubes and therefore saw very limited clinical application. In the 1920s, W.T. Bovie developed a low-cost spark-gap generator. The potential for using this device in surgery was recognized by Harvey Cushing during a demonstration in 1926, and the first practical electrosurgery units were in use soon thereafter.[78]

Monopolar electrocautery devices deliver the current through an application electrode through the patient's body returning to a grounding pad. Without a grounding pad, the patient would suffer a thermal burn injury wherever the current sought reentry. The area of contact is critical, because heat is inversely related to the size of the application device. Accordingly, the tip of the device is typically small, in order to generate heat efficiently, and the returning electrode is large, to broadly disperse energy. There are three other settings that are pertinent: the frequency of the current (power setting), the activation time, and the characteristics of the waveform produced by the generator (intermittent or continuous).

In the "cut" mode, heat is generated quickly with minimal lateral spread. As a result, the device separates tissue without significant coagulation of underlying vessels. In the "coag" mode, the device generates less heat at a slower frequency with larger lateral thermal spread. Consequently, tissue is desiccated and vessels become thrombosed.

Bipolar cautery creates a short circuit between the grasping tips of the instruments; thus the circuit is completed through the grasped tissue between the tips. Because heat develops only within the short-circuited tissue, there is less lateral thermal spread and the mechanical advantage of tissue compression, as well as thermal coagulation.

Recently, advanced bipolar devices use a combination of pressure and bipolar electrocautery to seal tissues. These devices then use a feedback-controlled system that automatically stops the energy delivery when the seal cycle is complete. The tissues are then divided sharply within the sealed zone. Advanced bipolar devices are capable of sealing blood vessels up to 7 mm in diameter, with the seal reportedly capable of withstanding 3 times normal systolic blood pressure. Examples of this class of device include the LigaSure distributed by Covidien (Mansfield, Mass.) and the ENSEAL device distributed by Ethicon Endosurgery (Cincinnati, Ohio).

### Argon Beam Coagulator

The argon beam coagulator creates an electric circuit between the tip of the probe and the target tissue through a flowing stream of ionized argon gas. The electrical current is conducted to the tissue through the argon gas and produces thermal coagulation. The flow of the argon gas improves visibility and disperses any surface blood, enhancing coagulation. Its applications in hepatic surgery are unparalleled.

### Surgical Lasers

Lasers (*L*ight *A*mplification by *S*timulated *E*mission of *R*adiation) are devices that produce an extremely intense and nearly nondivergent beam of monochromic radiation, usually in the visible region. When focused at close range, laser light is capable of producing intense heat with resultant coagulation. Lateral spread tends to be minimal, and critically, the laser can be delivered through a fiber optic system.

Based on power setting and the photon chosen, depth can be controlled. Penetration depth within the tissue is most shallow with the argon laser, intermediate with the carbon dioxide laser, and of greatest depth with the neodymium-yttrium aluminum garnet (Nd-YAG) laser. Photosensitizing agents provide an additional targeting advantage. The degree of absorption, and thus destruction, depends upon the wavelength selected and the absorptive properties of the tissue based on density, fibrosis, and vascularity.

### Photodynamic Therapy

A novel use of light energy is used in photodynamic therapy. A photosensitizer that is target cell–specific is administered and subsequently concentrated in the tissue to be eradicated. The photosensitizing agent may then be activated with a light energy source, leading to tissue destruction. Applications have been widespread.[79] Metaplastic cells, in particular in Barrett esophagus, may also be susceptible.[80]

### Ultrasonography

In addition to the diagnostic use of US at low frequency, the delivery of high-frequency US can be used to separate and coagulate tissue. Focused acoustic waves are now used extensively in the treatment of renal calculi as extracorporeal shock wave lithotripsy (ESWL). The focused energy produces a shock wave resulting in fragmentation of the stones to a size that can be spontaneously passed.

When high-intensity focused US (HIFU) energy from multiple beams is focused at a point on a target tissue, heating and thermal necrosis results. None of the individual ultrasonic beams is of sufficient magnitude to cause injury, only at the focus point does thermal injury result. Thus subcutaneous nodules may be targeted without injury to the skin, or nodules within the parenchyma of a solid organ may be destroyed without penetrating the surface. Thus far, however, the focal point is extremely small, thus limiting utility.

### Harmonic Scalpel

When US energy at very-high frequency (55,000 Hz) is used, tissue can be separated with minimal peripheral damage. Such high-frequency energy creates vibration, friction, heat, and ultimately, tissue destruction.

### Cavitation Devices

The CUSA, a cavitation ultrasonic aspirator, uses lower-frequency US energy with concomitant aspiration. Fragmentation of high-water–content tissue allows for parenchymal destruction, while highlighting vascular structures and permitting their precise coagulation.

### Radiofrequency Energy

High-frequency alternating current (350 to 500 kHz) may be used for tissue division, vessel sealing, or tissue ablation. The application of this energy source heats the target tissue, causing protein denaturization and necrosis. A feedback loop sensor discontinues the current at a selected point, minimizing collateral damage. Its targeted use in modulating the lower esophageal sphincter for the treatment of reflux has been reported.[81]

### Microwave Energy

Microwave energy (2,450 MHz) can be delivered by a probe to a target tissue. This rapidly alternating electrical signal produces heat and thus coagulation necrosis.

### Cryotherapy

At the other end of the temperature spectrum, cold temperatures destroy tissue with a cycle of freezing and thawing with ice crystal formation in the freezing phase and disruption during the thawing phase. Thus far this modality has less utility because high vascular flow, especially in tumors, tends to siphon off the cold.

## IMAGE-GUIDED THERAPY

In recent years, ultrasonography, computerized tomography, and magnetic resonance imaging have expanded beyond their role as mere diagnostic modalities, and are now the foundation of sophisticated interactive computer applications that directly guide surgical procedures.[3,82,83] Recent developments in computation technology have fundamentally enhanced the role of medical imaging, from diagnostics described previously to computer-assisted surgery (CAS). During the last decade, medical imaging methods have grown from their initial use as physically based models of human anatomy to applied computer vision and graphical techniques for planning and analyzing surgical procedures. With rapid advances in high-speed computation, the task of assembling and visualizing clinical data has been greatly facilitated, creating new opportunities for real-time, interactive computer applications during surgical procedures.[77–80] This area of development, termed image-guided surgery, has slowly evolved into a field best called *information-guided therapy* (IGT), reflecting the use of a variety of data sources to implement the best therapeutic intervention. Such therapeutic interventions could conceivably range from biopsy to simulation of tissue to direct implantation of medication to radiotherapy. Common to all these highly technical interventions is the need to precisely intervene with the therapeutic modality at a specific point.

However, the effective use of biomedical engineering, computation, and imaging concepts for IGT has not reached its full potential. Significant challenges remain in the development of basic scientific and mathematical frameworks that form the foundation for improving therapeutic interventions through application of relevant information sources.

### Significance

As stated in the National Institutes of Health 1995 *Support for Bioengineering Research Report* (http://grants.nih.gov/grants/becon/externalreport.html), an appropriate use of technology would be to replace traditional invasive procedures with non-invasive techniques. The current interest in research in CAS, or IGT, can be attributed in part to the considerable clinical interest in the well-recognized benefits of minimal access surgery (MAS), remaining cognizant of its limitations.

Image-based surgical guidance, on the other hand, addresses these limitations. Image-guided surgical navigational systems have now become the standard of care for cranial neurosurgical procedures in which precise localization within and movement through the brain is of utmost importance.

Patient-specific image data sets such as CT or MRI, when correlated with fixed anatomic reference points (fiducials), can provide surgeons with detailed spatial information about the region of interest. Surgeons can then use these images to precisely target and localize pathologies. Intraoperative computer-assisted imaging improves the surgeon's ability to follow preoperative plans by showing location and optimal directionality. Thus the addition of CAS provides the advantages of MAS with the added benefits of greater precision and the increased likelihood of complete and accurate resections. The junction between CAS and MAS presents research opportunities and challenges for both imaging scientists and surgeons.

### General Requirements

***Patient-Specific Models*** Unlike simulation, IGT requires that modeling data be matched specifically to the patient being treated, since standard fabricated models based upon typical anatomy are inadequate during actual surgical procedures upon a specific patient. Patient-specific images can be generated preoperatively (e.g., by CT or MRI) or intraoperatively (e.g., by US or x-ray).

***High Image Quality*** IGT depends on spatially accurate models. Images require exceptional resolution in order to portray realistic and consistent information.

***Real-Time Feedback*** Current systems make the surgeon wait while new images are being segmented and updated. Thus fast dynamic feedback is needed, and the latencies associated with visualization segmentation and registration should be minimized.

***High Accuracy and Precision*** An American Association of Neurosurgeons survey of 250 neurosurgeons[57] disclosed that surgeons had little tolerance for error (102-mm accuracy in general, and 2 to 3 mm for spinal and orthopedic applications). All elements of visualization, registration, and tracking must be accurate and precise, with special attention given to errors associated with intraoperative tissue deformation.

***Repeatability and Robustness*** Image-guided therapy systems must be able to automatically incorporate a variety of data so that algorithms work consistently and reliably in any situation.

***Correlation of Intraoperative Information with Preoperative Images*** This requirement is a critical area of interest to biomedical engineers and is especially critical for compensation of tissue deformation. Whether produced by microscopes, endoscopes, fluoroscopes, electrical recordings, physiological simulation, or other imaging techniques, preoperative and intraoperative images and information need to be incorporated into and correlated by the surgical guidance system.

***Intuitive Machine and User Interfaces*** The most important part of any IGT system is its usability. The surgeon's attention must be focused on the patient and not the details of the computational model.

### Ultrasound Image-Guided Therapy

Compared with adults, children have excellent US image resolution because of minimal subcutaneous tissue. Furthermore, the lack of ionizing radiation, fast procedure times, relatively low cost, as well as its real-time and multiplanar imaging capabilities, make US especially attractive in the pediatric population. US is the most accessible advanced imaging tool that surgeons can currently use independently. Intraoperative applications include using it as an aid to vascular access, intraoperative tumor localization and resection, and drainage procedures.[84–87]

### Computed Tomography and Magnetic Resonance Image-Guided Therapy

Computed tomography and magnetic resonance imaging are not widely used by surgeons without the involvement of radiologists. Although CT-based IGT offers excellent visualization that is not limited by the presence of air or bone, its use in the pediatric population has been limited by concern for the downstream effects of ionizing radiation.[88,89] In addition, there are limited imaging planes, poor differentiation of some lesions related to less fat in babies and children, as well as longer procedure times and greater costs than for US intervention. Nonetheless, CT-guided therapeutic interventions, such as lung and bone biopsies or drainage of deep fluid collections, are routinely done, particularly now that radiation exposure can be reduced with pulsed or intermittent fluoroscopic techniques and dedicated pediatric CT parameters.[82]

The advantages of MRI as a guiding tool include exquisite soft tissue detail, multiplanar real-time imaging, and the ability to assess physiologic and functional parameters (temperature, flow, perfusion).[82,90] Traditional interventional MRI units include an opening that allows easy access to the patient. These units have relatively low field strength, however, which results in poorer image resolution. Higher field strength magnets are now preferred, albeit at the cost of decreased patient accessibility and the requirement of nonferromagnetic instruments. To date, the majority of pediatric applications of MRI-guided therapy have been in the field of neurosurgery. Common applications include tumor ablation/resection or biopsy.[90,91] Currently, there are no data on MRI-guided abdominal interventions in the pediatric population. In 2005, Schulz and colleagues[90] reviewed indications for MR-guided interventions in children. They determined that MR-guided imaging is not a reliable method for chest interventions. They also suggested that the primary use of intraoperative MRI will be for lesions in particularly difficult-to-access areas with nonpalpable findings, such as intracranial and skull base tumors. Future potential applications of MRI include endovascular procedures[91] and thermal ablation of tumors.

Navigational systems establish the relationship between the surgeon's movements and image-based information. They enable the use of preoperative imaging for precise intraoperative localization and resection of lesions using an exact navigation pathway. Neuronavigation systems provide this precise surgical guidance by referencing a coordinate system of the brain with a parallel coordinate system of the three-dimensional image data of the patient.[92,93] These data are displayed on the console of the computer workstation so that the medical images become point-to-point maps of the corresponding actual locations within the brain. The spatial accuracy of these systems is further enhanced by the use of intraoperative MRI that provides real-time images to document the residual lesion and to assess for brain shift during surgery.[94] The precision (error rates of 0.1 to 0.6 mm) provided by neuronavigation systems enables minimal access neurosurgical procedures, significantly reducing morbidity for both adult and pediatric patients.[95] Neuronavigation has not yet been successfully deployed for abdominal surgery. The inability to simply transfer the methodology from neurosurgery is mainly a result of intraoperative organ shifting and corresponding technical difficulties in the online applicability of presurgical cross-sectional imaging data. Furthermore, it remains unclear whether 3D planning and interactive planning tools will increase precision and safety of abdominal surgery.

### Radiotherapy and Fractionation

The field of radiation oncology represents perhaps the most mature example of IGT. Radiation therapy, or *radiotherapy*, refers to the use of ionizing radiation for the treatment of pathologic disorders. The use of radiation to cure cancer was first reported in 1899, very soon after Roentgen's discovery of x-rays in 1895.[96] In the 1930s, Coutard described the practice of "fractionation," [96] which refers to the division of a total dose of radiation into multiple smaller doses, typically given on a daily basis. Fractionation is a bedrock principle that underlies the entire field of radiotherapy.[97,98] By administering radiation in multiple daily fractions over the course of several weeks, it is possible to irradiate a tumor with a higher total dose while relatively sparing the surrounding normal tissue from the most injurious effects of treatment. By fractionating the therapy, normal tissue should be allowed to recover while pathologic tissue is destroyed. Though fractionation regimens differ depending on specific pathology, current regimens often involve up to 30 treatments.[96]

### Stereotactic Radiosurgery

*Stereotactic radiosurgery* refers to the method and corresponding technology for delivering a single high dose of ablative radiation to target tissue using precision targeting and large numbers of cross-fired highly collimated beams of high-energy ionizing radiation. Conceptualized in the 1950s by Swedish neurosurgeon Lars Leksell, this technology has been used to treat/ablate a variety of benign and malignant intracranial lesions without any incision.[99] Leksell showed that there was an exponential relation between dose and the time during which necrosis developed.[96]

Most recently, radiosurgical techniques are being applied toward the treatment of extracranial diseases, including spinal tumors and lesions of the thoracic and abdominal cavities.[100,101] Many of the newest applications of stereotactic radiosurgery fall under the traditional realm of general surgery, including lung, liver, and pancreatic cancers. The lesioning of normal brain tissue, such as the trigeminal nerve (trigeminal neuralgia), thalamus (tremor), and epileptic foci (intractable seizures) is also an important clinical application of this technology.[102] Numerous studies have demonstrated radiosurgery to be an important treatment option for many otolaryngologic conditions, such as skull base and neck tumors.[103–106] As the scientific understanding and clinical practice of radiosurgery develops, such technology may become an increasingly valuable, minimally invasive option for treating a range of pediatric general surgical diseases.

Stereotactic radiosurgery has the potential advantage of delivering a much larger radiation dose to a pathologic lesion without exceeding the radiation tolerance of the surrounding normal tissue. This single, or limited, dose treatment of a small volume of tissue is achieved by targeting the tissue with large numbers of intersecting beams of radiation. "Stereotactic" refers to the fact that radiosurgery uses computer algorithms to coordinate the patient's real-time anatomy in the treatment suite with a preoperative image to allow precise targeting of a desired tissue area. To achieve this, the patient's anatomy must usually be fixed using a stereotactic frame.[96] The preoperative images are then taken with the frame in place, and the patient's anatomy is mapped in relation to the frame. This stereotactic frame is rigidly fixed to the patient's skull, thereby limiting movement of the target anatomy. In addition, the frame serves as an external fiducial system that correlates the coordinates of the target tissues, determined during preoperative imaging and planning, to the treatment room. Radiosurgical treatment is then delivered to the appropriate tissue using this coordinate system.

### Stereotactic Radiosurgical Platforms

Currently, there are several classes of stereotactic radiosurgery systems in use. These include heavy-particle radiosurgery systems, Gamma Knife radiosurgery, and linear accelerator radiosurgery. Currently, heavy particle radiosurgery systems and Gamma Knife radiosurgery systems are only used to treat intracranial lesions. In contrast, linear accelerator systems have been adapted to treat both cranial and extracranial lesions.

### Linear Accelerator Radiosurgery

Linear accelerators, or linacs, have long been a mainstay of standard fractionated radiotherapy and were modified for radiosurgery in 1982.[96] Linac radiosurgery has become a cost effective and widely used alternative to Gamma Knife radiosurgery. When used for radiosurgery, linacs crossfire a photon beam by moving in multiple arc-shaped paths around the patient's head. The area of crossfire where the multiple fired beams intersect receives a high amount of radiation, with minimal exposure to the surrounding normal tissue.[96] Patients treated with linac radiosurgery must also wear a stereotactic frame fixed to the skull for preoperative imaging and therapy. Currently, linac radiosurgery is the predominant modality in the United States, with approximately 6 times more active centers than Gamma Knife facilities.[96]

### Frameless Image-Guided Radiosurgery

Recently, novel systems have been developed that use linear accelerators with innovative hardware and software systems capable of performing frameless image-guided radiosurgery. One such system, the CyberKnife (Accuray, Sunnyvale, Calif.), uses a lightweight linac unit, designed for radiosurgery, mounted on a highly maneuverable robotic arm.[107] The robotic arm can position and point the linear accelerator with 6 degrees of freedom and 0.3-mm precision. In addition, the CyberKnife system features image guidance, which eliminates the need to use skeletal fixation.[102,108] The CyberKnife acquires a series of stereoscopic radiographs that identify a preoperatively placed gold fiducial. This fiducial is placed under local anesthetic during the preoperative imaging and planning sessions to allow the system to correlate the patient's target anatomy with the preoperative image for treatment. By actively acquiring radiographs during the treatment session, the system is able to track and follow the patient's target anatomy in near real-time during treatment.[102,108] With this image guidance system, the CyberKnife is able to function without a fixed stereotactic frame, enabling fractionation (often termed hypofractionated radiosurgery or radiotherapy) of treatments as well as extracorporeal stereotactic radiosurgery. In pediatric surgery, this may represent a significant technical advantage, because it may enable the use of radiosurgery for the treatment of intrathoracic and intraabdominal pathologies (Fig. 4-11). Similarly, the Novalis Tx (Varian Medical Systems, Palo Alto, Calif.) uses an integrated cone beam CT scan system to provide volumetric imaging as well as fluoroscopic imaging to compensate for respiratory motion to enable frameless, image-guided radiosurgery. In contrast, the Trilogy system (Varian Medical Systems, Palo Alto, Calif.) uses real-time optical guidance to direct radiation delivery to the target lesion (Fig. 4-12). Both of these systems use a multileaf collimator that adapts radiation treatment to complex shapes. In addition, they use intensity modulation to help limit toxicity to surrounding tissue. Both systems deliver treatments in sessions of less than 30 minutes, which may decrease the need for sedation in pediatric patients.[109] Furthermore, the Trilogy system minimizes radiation exposure further by using an optically based guidance system.[109]

FIGURE 4-11 Cyberknife System (Courtesy Accuray, Sunnyvale, Calif.)

**FIGURE 4-12** Trilogy Radiosurgery System (Courtesy Varian Medical Systems, Palo Alto, Calif.)

## CLINICAL APPLICATION OF STEREOTACTIC RADIOSURGERY IN CHILDREN

To date, pediatric radiosurgery has primarily been used to treat intracranial pathologies. Hadjipanavis and colleagues reported a series of 37 patients (mean age 14) with unresectable pylocytic astrocytomas treated with stereotactic radiosurgery.[110] They found radiosurgery to be a valuable adjunctive strategy in patients whose disease was not amenable to surgical therapy.[110] Somaza and colleagues reported their experience with the use of stereotactic radiosurgery for the treatment of growing and unresectable deep-seated pilocytic astrocytomas in 9 pediatric patients.[111] Two of the patients had already failed fractionated radiotherapy, and 7 patients were considered to be at high risk for adverse radiation effects given their young age. After 19 months follow-up, there was a marked decrease in tumor size in 5 patients, while the remaining 4 patients displayed no further tumor growth. Overall, the authors felt that stereotactic radiosurgery offered a safe and effective therapy in the management of children with deep, small-volume pilocytic astrocytomas.[111]

The use of stereotactic radiosurgery for the treatment of nonmalignant intracranial lesions in children has also been described. Specifically, the use of radiosurgery for the treatment of cerebral arteriovenous malformations (AVMs) has been reported. Although microsurgical resection remains the treatment of choice for most accessible AVMs, lesions located in critical cortical areas or in deep portions of the brain are increasingly treated with radiosurgery because of the risk of surgical resection.[112] Foy and colleagues reported a series of 60 pediatric patients with AVMs treated with radiosurgery. Nidus obliteration was reported at 52% after a single radiosurgery session, increasing to 63% with repeated sessions.[112] Similarly Nicolato and colleagues reported a cohort of 62 children with AVMs treated with radiosurgery. They reported an obliteration rate of 85.5%.[113] Overall, these authors conclude that stereotactic radiosurgery is a safe and effective option for properly selected children with AVMs. In particular, it may benefit children with AVMs located in critical portions of the brain where surgical resection may pose a large risk.[112]

Compared with the adult population, the experience with stereotactic radiosurgery in children is still limited. The early reports described above all highlight the safety and efficacy of radiosurgery as a treatment modality, but clinical follow-up is still early, with many of the reports limiting the use of radiosurgery to the treatment of surgically unresectable disease. Despite relatively limited experience, the use of stereotactic radiosurgery in children may offer several theoretical advantages specific to the pediatric population. Compared with standard, fractionated radiotherapy, stereotactic radiosurgical techniques deliver conformal radiation treatment with millimeter versus centimeter accuracy. All radiation treatments are a balance between providing enough radiation to effectively treat pathologic tissues while minimizing harmful exposure to adjacent normal tissues. In pediatric patients, the distances between normal and pathologic tissues may be very small. In addition, the developing brains of children may be more sensitive to the effects of ionizing radiation than adult brains. In particular, potential cognitive and endocrine disabilities have been described in children after radiotherapy to the brain.[111,114,115] These concerns have largely limited the use of radiation for the treatment of intracranial tumors in infants. Therefore the improved accuracy provided by stereotactic radiosurgery may be particularly important in the pediatric population.

In addition to accuracy, stereotactic radiosurgical techniques differ from radiotherapy in that they use only one or few treatment sessions. As detailed above, standard, fractionated radiotherapy often uses tens of treatment sessions to maximize the beneficial effects of the treatment while minimizing the harmful effects to normal tissues. In children, these multiple treatment sessions may represent a significant challenge. In smaller children, sedation, or even anesthesia, may be necessary to avoid movement. Such interventions are not without risk, and limiting the number of treatment sessions may serve to minimize the overall risk to the child.

Although the advantages of stereotactic radiosurgery in the pediatric population appear promising, it should be noted that there also exist specific disadvantages and limitations that must be overcome. Radiosurgical techniques generally use a stereotactic frame to coordinate preoperative imaging with actual radiation delivery. However, these frames must be secured to the skull using pins and screws. In adults, this can often be performed using only local anesthetic agents. In children, this likely requires significant sedation and possibly general anesthesia. Furthermore, the skulls of infants are soft and less rigid, because their cranial sutures have not yet fused. Because of this, standard stereotactic frames often cannot be applied. Similarly, radiosurgery treatment sessions require the patient to remain still in order for the systems to accurately deliver the radiation treatment. Adults are able to cooperate with the therapy and do not require sedation, whereas younger children and infants may require conscious sedation or general anesthesia. Although this drawback is limited by the relatively few sessions necessary with radiosurgery, it still diminishes the minimally invasive nature of the therapy compared with its application in the adults.

Recently, frameless, image-guided stereotactic radiosurgery has been reported in children. Giller and colleagues described the use of the CyberKnife system in 21 patients, ages ranging from 8 months to 16 years, with tumors considered unresectable. Diagnoses included pilocytic astrocytomas, anaplastic astrocytomas, ependymomas, medulloblastomas, atypical teratoid/rhabdoid tumors, and craniopharyngiomas. Local control was achieved in the patients with pilocytic and anaplastic astrocytoma, three of the patients with medulloblastoma, and the three with craniopharyngioma, but not for those with ependymoma. There were no procedure-related mortalities or complications, and local control was achieved in more than half of the patients. Seventy-one percent of patients received only one treatment session, and 38% of patients did not require general anesthesia. No patients required rigid skull fixation.[115] In an additional report, the same group highlighted the use of the CyberKnife system to perform radiosurgery in five infants.[114] Although standard stereotactic frames were not required, patient immobilization was aided by general anesthesia, form-fitting head supports, face masks, and body molds. No treatment-related toxicity was encountered, and the authors concluded that "radiosurgery with minimal toxicity can be delivered to infants by use of a robotically controlled system that does not require rigid fixation."[114]

Whereas the use of stereotactic radiosurgery for intracranial lesions is well established, its use for treatment of extracranial lesions, specifically intrathoracic and intraabdominal pathologies is still developing. Intracranial contents can be easily immobilized using stereotactic frames, while abdominal and thoracic organs show significant movement resulting from respiration, peristalsis, and so on. As a result, only a small body of literature exists regarding the application of stereotactic radiosurgery for extracranial lesions. Recently, several reports have described the efficacy of stereotactic radiosurgery in adults for the treatment of lesions in the liver,[117,118] pancreas,[119,120] lung,[118,121] and kidney[122,123]—anatomical areas that have traditionally been under the watch of general surgeons. Novel image guidance technologies as well as soft tissue immobilization devices are used to make these therapies possible.

At this time, the majority of the literature represents case reports and series detailing the safety and feasibility of extracranial radiosurgery. In addition, many of the reports focus on the technical and engineering aspects of applying radiosurgical techniques to extracranial targets, with little data on patient outcomes. All of these reports have focused on the adult patient population with no significant reports in children. Despite this inexperience, the technology surrounding stereotactic radiosurgery is rapidly developing and shows significant promise toward the minimally invasive treatment of potentially poorly accessible lesions. Newer, frameless, image-guided systems may some day enable the minimally invasive treatment of a variety of pediatric malignancies.

### Radioimmunoguided Surgery

Antibodies labeled with radionuclides, when injected systemically, may bind specifically to tumors, thus allowing gamma probe detection.[124–126] For the most part, nonspecific binding and systemic persistence has minimized the signal-to-noise ratio, thus limiting this approach. The Food and Drug Administration (FDA) approved several new radiolabeled antibodies for the identification of occult metastases in patients. Beyond imaging, the theoretical opportunity to use a gamma probe to identify "hot spots" adds a new source of information to the surgeon. Full exploitation of this methodology beyond specific functioning endocrine tumors and draining nodal basins in breast cancer and melanoma shows real promise.

## NEXT-GENERATION MINIMAL ACCESS SURGERY

Minimal access surgery (MAS) forms the cornerstone of clinical innovation in present day pediatric surgery. Most pediatric general surgical procedures are now performed using some minimal access approach, and in many cases, these approaches are now considered standard of care. The next evolution in pediatric MAS involves further implementation of laparoscopic, endoscopic, and imaging techniques, with the ultimate goal of achieving scarless and painless surgery. Termed *stealth surgery,* this is an emerging surgical paradigm that encompasses a variety of techniques, each with the goal of performing complex operations without leaving visible evidence that they occurred.[127] This is achieved by placing incisions in inconspicuous or camouflaged locations and using MAS technologies to perform the operation. Examples of stealth surgery include subcutaneous endoscopy, single-incision laparoscopy, and natural orifice translumenal surgery (NOTES).

Traditionally, surgical culture has discounted the importance of scarring caused by surgical procedures. Scarring has been seen as either an unfortunate necessity or a minor outcome issue. This is interesting considering that the surgical scar is often the only collateral outcome of an operation that lasts a lifetime. At best, incisions have been placed in skin creases in an effort to camouflage the scar. Despite this, scarring is unpredictable, particularly if the scar is hypertrophic, keloid, or stretched, or if it becomes infected. There is evidence to suggest that visible scarring in children can result in reduced self-esteem, impaired socialization skills, and lower self-ratings of problem-solving ability.[128,129] Furthermore, other children judge children with facial deformities more negatively than those without facial deformities. Scarring of the chest and abdominal wall has not been as extensively studied, but it is likely that, at least in some circumstances, it can also have psychological implications. Stealth surgery aims to address surgical scarring, and collectively reflects a greater responsibility of surgeons toward the collateral damage of surgical procedures.

### Subcutaneous Endoscopy

Subcutaneous endoscopy involves tunneling under the skin from inconspicuous locations to target removal of lesions at more conspicuous locations. Many surgical subspecialties, including plastic surgery,[130] otolaryngology,[131] and maxillofacial surgery,[132] have used subcutaneous endoscopic techniques, typically through hidden incisions on the scalp, for management of a variety of benign forehead lesions. Endoscopic removal of such lesions through scalp incisions using browlift equipment is also described in the pediatric general surgery literature,[133] as is removal of neck lesions through two or three small incisions placed in the axilla. This latter approach, called transaxillary subcutaneous endoscopy, has been used to address torticollis,[134] and also to remove lesions, such as

thyroglossal cysts, cervical lymph nodes, parathyroid adenomas,[135] and thyroid nodules.[136] Transaxillary access has also been used for subcutaneous lesions of the chest wall, such as dermoid cysts and lipomas.[137]

Subcutaneous endoscopy for forehead lesions is performed through a 1.5- to 2.0-cm scalp incision using standard browlift equipment (Fig. 4-13). Dissecting instruments of 2- to 3-mm diameter are passed inline through the same incision as the endoscope. The subperiosteal plane is most commonly used to approach the lesion, but the subgaleal plane can also be used. The approach is ideal for lateral brow dermoid cysts or those found between the eyebrows (nasoglabellar cyst). The approach is not used for lesions that have intracranial extension.

Transaxillary subcutaneous endoscopic excision of neck lesions is performed by placing two or three endoscopic ports in the ipsilateral axilla, posterior to the lateral border of the pectoralis major muscle (Fig. 4-14). A subcutaneous workspace is then created, extending to the neck. The platysma muscle is traversed superior to the clavicle, and the target lesion is then dissected free. Recognition of landmarks and accurate anatomical orientation is subject to a learning curve, but visualization of all structures, including recurrent laryngeal nerves, is excellent. It is important to avoid extensive use of thermal energy sources in the neck, especially monopolar cautery, because of the thermal spread of such instruments. It is preferable to use bipolar cautery when possible, or else a thermal sealing/cutting device such as the Ligasure (Valleylab, Boulder, Colo.). The cosmetic benefits of this approach are apparent, because the patient is left with no scar on the face or neck. Pain is controlled with non-narcotic analgesics, and patients can typically be discharged the same day.

### Single Incision Laparoscopy

Single incision laparoscopy is an evolution of minimal access surgery that promises virtually scarless abdominal operations. Various acronyms, including SILS (single-incision laparoscopic surgery; Covidien), LESS (laparoendoscopic single-site surgery), SPA (single-port access surgery),[138] OPUS (one-port umbilical surgery), and SAS (single-access site surgery) have been applied to this technique. The essential element is the use of a single small incision, usually placed at the umbilicus through which multiple laparoscopic instruments are passed either through a single-port device with multiple conduits or through multiple closely spaced ports (Fig. 4-15). Single incision approaches have been described in the adult literature for appendectomy, nephrectomy,[139] adrenalectomy,[140] cholecystectomy,[141] and colectomy,[142] and in the pediatric general surgical literature for appendectomy,[143] varicocelectomy,[144] cholecystectomy, and splenectomy.[145]

Cosmesis is the most apparent benefit of single-incision laparoscopy, because the single scar produced can be effectively hidden in the existing umbilical scar. The cosmetic benefit, including psychosocial factors, has not been objectively demonstrated, but the complete absence of a visible scar is achievable with this method. The procedures are feasible in equivalent operative times to standard laparoscopy,

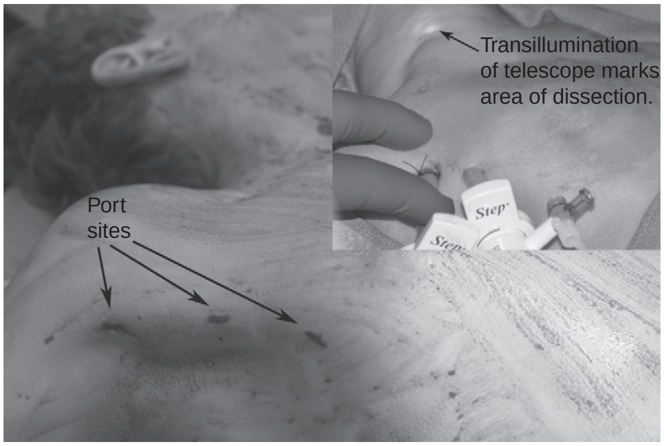



**FIGURE 4-14** Transaxillary subcutaneous access can be used to access lesions in the neck and chest wall. A cavernous subcutaneous workspace is created to facilitate dissection. In this image, the light at the tip of the telescope can be seen transilluminating the skin.

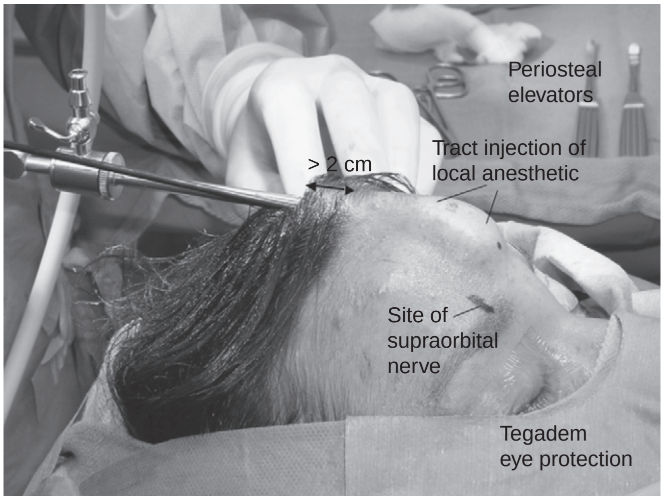



**FIGURE 4-13** For endoscopic excision of forehead lesions, hydrodissection with local anesthetic is used to create a path toward the lesion in the subperiosteal or subgaleal plane, starting about 2 centimeters posterior to the hairline. The telescope and dissecting instruments are placed through a 1 to 2 cm V-shaped incision on the scalp.

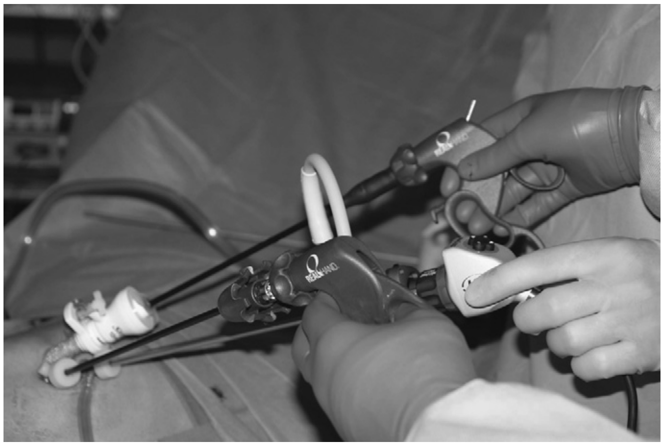


**FIGURE 4-15** Single-incision laparoscopic surgery involves placing multiple ports, or a commercially available single-port device, at the umbilicus. Instruments with dexterous end effectors can be exploited to achieve triangulation around the target tissue, which is otherwise difficult to achieve with standard rigid laparoscopic instruments in this setting.

without additional safety concerns. Although clinical trials are underway, outcomes in terms of pain, recovery, and hospital stay have not been assessed—anecdotally these outcomes mirror those of standard laparoscopy.

A number of critical challenges in performing single-incision laparoscopy have led to some innovative solutions. (1) Close co-location of the instruments can result in bothersome instrument backend, hand, and camera collisions that impair mobility. This is addressed with the use of ports and instruments of varying lengths to offset backends, angled light-cord adapters for rigid telescopes, or flexible tip telescopes with low-profile backends. (2) When using standard rigid laparoscopic instruments, it is difficult or impossible to achieve an equal degree of triangulation around the target tissues (ideally 60 degrees) as can be achieved in standard laparoscopy and that is necessary for safe, precise, and efficient dissection. Instruments with an additional joint near their tip that gives two additional degrees of freedom (Realhand, Novare Surgical, Cupertino, Calif.; Autonomy Laparo-Angle, Cambridge Endo, Framingham, Mass.; Roticulator, Covidien, Norwalk, Conn.) have been applied to single-incision laparoscopy for this reason. With these "dexterous" instruments, triangulation can be achieved by first crossing the instrument shafts at or just below the level of the fascia, then deflecting the tips inward to create triangulation. (3) The maneuvers necessary to work with instruments in this configuration can be confusing and counterintuitive, because the instrument tips are frequently opposite the hand configuration, or the surgeon's hands are sometimes crossed. Developers of surgical telemanipulation platforms have taken advantage of computer algorithms used in their existing telemanipulation platforms (e.g., da Vinci Si, Intuitive Surgical, Sunnyvale, Calif.) to provide a single-incision laparoscopy platform that can correct for paradoxical movements and give the surgeon the perception that their hand movements are being mirrored by the robotic instruments.[146]

Single-incision laparoscopy will likely play a role in pediatric surgical procedures for larger children and adolescents, primarily because of the avoidance of visible scarring. Its role in neonatal surgery is less clear. Existing instrumentation is too large for neonatal anatomy. Furthermore, proponents of umbilical laparotomy show that most abdominal procedures can be performed in neonates through umbilical incisions that can be camouflaged with an umbilicoplasty.[147] When possible, this approach offers a cheaper alternative to single-incision laparoscopy. Cost continues to be a consideration when adopting these novel minimal access procedures, because they generate the need for more complex technologies, but a cost assessment is difficult to perform in the early stages of adoption because of the dynamic nature of the technologies used and the costs they incur.

## NATURAL ORIFICE TRANSLUMENAL ENDOSURGERY

Perhaps a more extreme evolution of scarless surgery is natural orifice translumenal endosurgery (NOTES), which aims to perform abdominal or thoracic procedures by way of transoral, transgastric/transesophageal, transrectal or transvaginal access. Some surgeons consider single-incision laparoscopy a bridge to NOTES, while others see at as a more palatable alternative to NOTES. In adults, the potential advantages of NOTES include decreased or no postoperative pain, no requirement of general anesthetic, the performance of procedures in an outpatient setting, and possibility of reducing costs. In children, NOTES remains uncharted, and its application in this population seems not only conceptually unappealing (transvaginal access is unlikely to be considered in a young girl), but also currently fraught with undue risk (leakage and infection risk with transgastric or transrectal access). Adult subjects asked to rate their preference of technique in the absence of safety profile data preferred single-incision laparoscopy and standard laparoscopy versus NOTES and open surgery.[148] However, there are unique pediatric surgical conditions described below that are intriguing targets for this approach, and research in this area allows an opportunity to discover novel techniques and technologies that may be more generally applicable to pediatric minimal access surgery.

The development of NOTES is an interesting case study in surgical innovation because of the way it has progressed, in contrast to conventional laparoscopy. The rapid adoption of laparoscopy into mainstream surgical practice without oversight or appropriate training heralded increased complication rates, such as that of bile duct injury during laparoscopic cholecystectomy[149] and complications not previously seen, such as intestinal and vascular injury from port placement. To avoid a similar scenario with NOTES, delegates from the American Society of Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) established the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR),[150] with the purpose of defining guidelines for the safe, ethical, and evidence-based development of NOTES. The technical challenges, and hence areas of research focus, they identified included (1) creation and secure closure of the defect created in the hollow viscus for peritoneal access, (2) prevention of peritoneal contamination and maintenance of sterility, (3) adequate visualization and orientation in the peritoneal cavity, and (4) effective instrument triangulation around target tissues and adequate retraction of adjacent tissues.

A second unique feature of NOTES is the early involvement of industry in device development, in close collaboration with both surgeons and gastroenterologists with an interest in therapeutic endoscopy. Both specialties have recognized the need to collaborate on NOTES development because of its hybrid use of endoscopic and laparoscopic techniques. The medical device industry, in turn, has engaged early in this effort to remain competitive and obtain market share in this potentially large market. Although widespread use of NOTES has not materialized, research and development in this area has resulted in the development of a host of novel technologies ranging from dexterous flexible endoscopic surgical tools to intraluminal suturing devices.

In pediatric surgery, the adoption of NOTES for common pediatric conditions in the near future seems improbable because of small markets, the persistent need for general anesthetic, and a lack of any clear significant benefit versus single-incision laparoscopy. There are, however, some interesting possibilities for the use of NOTES in neonatal surgery, such as for duodenal atresia, urologic anomalies, and esophageal atresia. The latter is perhaps the most compelling. Although a thoracoscopic approach to esophageal atresia is well described, there has been slow adoption of this approach because of its technical difficulty, particularly with respect to

thoracoscopic suturing of the anastomosis, which requires very precise movements in a limited workspace with highly fragile tissues that are under tension. The possibility of performing some or all of the operation transorally using flexible tools with purpose-specific attachments that allow fistula closure and/or esophageal anastomosis may allow a wider adoption of a minimal access approach to this condition by trivializing the technical difficulty of creating the anastomosis. Unfortunately, market sizes for diseases such as esophageal atresia do not support investment in purpose-specific technology, but development of dual-purpose tools that can also be applied to larger (adult) markets may provide the basis for their development.

### Endolumenal Therapies

Innovations in intraluminal endoscopic therapies have centered mainly on totally endoscopic antireflux procedures, some of which have been applied to children. Some of these procedures (Enteryx, Gatekeeper) have fallen out of favor because of safety concerns or lack of efficacy. Use of Enteryx came to a halt in 2005 when the FDA requested a recall by Boston Scientific of all Enteryx systems following reports of adverse effects (and cases of fatality) resulting from inadvertent Enteryx injection into the mediastinum, pleural space, and aorta (with consequent arterial embolism). The Enteryx system is mentioned here only to exemplify the potential for serious complications with novel technologies, and reinforce the need for proper efficacy and safety trials before their widespread application, particularly in the pediatric population.

Use of other devices, such as Endocinch (Bard, Warwick, RI), Stretta (Curon Medical, Sunnyvale, Calif.), NDO Plicator (NDO Surgical, Mansfield, Mass.), have shown short-term improvements in gastroesophageal reflux disease (GERD) symptoms but without objective evidence of reduced lower esophageal acid exposure or long-term durability.[151] The Stretta procedure was the first interventional endoscopic GERD therapy to gain FDA approval in 2000. Consisting of a catheter, soft guidewire tip, balloon basket assembly, and four electrode delivery sheaths positioned radially, the Stretta device uses radiofrequency (RF) energy to increase the tone of the lower esophageal sphincter (LES). Its mechanism of action is unclear, but it is believed that the RF energy results in shrinkage of collagen fibers, resulting in elevation of postprandial LES pressure[152] and reduction of transient lower esophageal sphincter relaxations. Islam and colleagues studied the effects of the Stretta procedure on a small series of six pediatric patients (mean age 12 +/− 4 years), concluding that the procedure was safe and effective.[153] Five of the six patients were asymptomatic at 3 months, and three were able to discontinue antisecretory medication. Mean reflux score improved significantly after 6 months; however, pH studies were not done. Without significant improvements in acid exposure, the benefit of this procedure in children is questionable, because common indications for surgical management of pediatric GERD consist mainly of complications of esophageal acid exposure, such as esophagitis, pharyngitis, or aspiration, as opposed to minor GERD symptoms.

Also approved for use by the FDA in 2000, the EndoCinch system aims to reduce gastric reflux by pleating the gastroesophageal junction (GEJ). The 30- to 60-minute procedure begins with insertion of the Endocinch device through an overtube. Suction applied 1 to 2 cm below the squamocolumnar junction facilitates full-thickness placement of two adjacent sutures. The sutures are then "cinched" together or brought into approximation, to create a pleat. Usually several pleats are created, significantly narrowing the lumen at the GEJ. The resulting rosette of tissue (gastroplication) is intended to prevent reflux of gastric contents into the esophagus. Only one pediatric study describes the effects of the Endocinch system for treating GERD.[154] Seventeen patients with median age 12.4 years (range, 6.1 to 15.9 years) underwent gastroplication. All patients showed significant improvement in early postoperative assessments of symptom severity, symptom frequency, and quality of life. These effects persisted at 1-year follow-up in the majority of patients and were reflected in reduced pH indices. In adult patients, lack of long-term durability has been attributed to suture degradation and loss, both demonstrated on follow-up endoscopy.[155,156] The reason for the longer durability of this procedure in children compared with adults is unclear but may be a consequence of a greater ability to achieve full-thickness esophageal bites in the smaller patients.

The latest transoral endoscopic device on the market is the EsophyX (Endogastric Solutions, Redmond, Wash.), which is designed to achieve transoral incisionless fundoplication (TIF). The goal of this antireflux procedure is to endoluminally create an anteriorly placed 3- to 5-cm, 200- to 270-degree valve at the distal esophagus secured by special fasteners. The end result is creation of an antireflux barrier and reestablishment of the angle of His. The device does not have to be inserted and removed for each stitch, and its function allows reduction of a small hiatal hernia, although the crura remains unapproximated. Although adult studies have shown long-term reductions in proton pump inhibitor use, improved quality of life, and reduced esophageal acid exposure, data for the pediatric population is forthcoming.[157] Use of the device is limited only to larger children whose esophagi can accommodate a device that is 18 mm in diameter.

## SURGICAL ROBOTICS

Innovations in endoscopic technique and equipment continue to broaden the range of applications in minimal access surgery. However, many minimal access procedures have yet to replace the traditional open approach. Difficulties remain in achieving dexterity and precision of instrument control within the confines of a limited operating space. These difficulties are further compounded by the need to operate from a 2D video image. Robotic surgical systems have evolved to address these limitations.

Since their introduction in the late 1990s, the use of computer-enhanced robotic surgical systems has grown rapidly. Originally conceived to facilitate battlefield surgery, these systems are now used to enable complex minimal access surgical (MAS) procedures. In children, early reports described the feasibility of using surgical robots to complete common and relatively simple pediatric general surgical procedures.[158–160] More recently, the use of robotic surgical systems in human patients has been described in multiple surgical disciplines, including pediatric general surgery, pediatric urology, and pediatric cardiothoracic surgery.[161–163] In addition, the feasibility of complex, technically challenging procedures, such as robotic-assisted fetal surgery, has been reported in animal models.[164,165]

## Robotic Technology in Surgery

For several decades, robots have served in a variety of applications, such as manufacturing, deep-sea exploration, munitions detonation, military surveillance, and entertainment. In contrast, the use of robotic technology in surgery is still a relatively young field. Improvements in mechanical design, kinematics, and control algorithms originally created for industrial robots are directly applicable to surgical robotics.

The first recorded application of surgical robotics was for CT-guided stereotactic brain biopsy in 1987.[166] Since then, technologic advancements have led to the development of several different robotic systems. These systems vary significantly in complexity and function.

## Classification of Robotic Surgical Systems

One method of classifying robots is by their level of autonomy. Under this classification, there are currently three types of robots used in surgery: autonomous robots, surgical-assist devices, and teleoperators (Table 4-2).

An autonomously operating robot carries out a preoperative plan without any immediate control from the surgeon. The tasks performed are typically focused or repetitive but require a degree of precision not attainable by human hands. An example is the ROBODOC system (Curexo Technology, Fremont, Calif.) that is used in orthopedic surgery to accurately mill out the femoral canal for hip implants.[167] Another example is the CyberKnife system, previously referenced, which consists of a linac mounted on a robotic arm to precisely deliver radiotherapy to intracranial and spinal tumors.[168,169]

The second class of robot is the surgical-assist devices, where the surgeon and robot share control. The most well-known example of this group is the AESOP (*A*utomatic *E*ndoscopic *S*ystem for *O*ptimal *P*ositioning; formerly produced by Computer Motion, Goleta, Calif.). This system allows a surgeon to attach an endoscope to a robotic arm that provides a steady image by eliminating the natural movements inherent in a live camera holder. The surgeon is then able to reposition the camera by voice commands.

The final class consists of robots whose every function is explicitly controlled by the surgeon. The hand motions of the surgeon at a control console are tracked by the electronic controller and then relayed to the slave robot in such a manner that the instrument tips perfectly mirror every movement of the surgeon. Because the control console is physically separated from the slave robot, these systems are referred to as teleoperators. All the recent advances in robotic-assisted surgery have involved this class of machines.

**TABLE 4-2**
**Classification of Robotic Surgical Systems**

| *Type of System* | *Definition* | *Example* |
|---|---|---|
| Autonomous | System carries out treatment without immediate input from the surgeon | CyberKnife ROBODOC |
| Surgical-Assist | Surgeon and robot share control | Aesop |
| Teleoperators | Input from the surgeon directs movement of instruments | da Vinci System |

## Current Status of Robotic Technology Used in Pediatric Surgery

Currently, there is only one commercially available robotic surgical system—the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, Calif.). Though the da Vinci is popularly referred to as a surgical robot, this is a misnomer, because "robot" implies autonomous movement. The da Vinci does not operate without the immediate control of a surgeon. A better term may be "computer-enhanced telemanipulators." However, for the sake of consistency with published literature, this chapter will continue to refer to such systems as robots.

***The da Vinci Surgical System*** The da Vinci system is made up of two major components (Figs. 4-16 and 4-17).[162] The first component is the surgeon's console, which houses the visual display system, the surgeon's control handles, and the user interface panels. The second component is the patient side cart, which consists of two to three arms that control the operative instruments and another arm that controls the video endoscope.

The operative surgeon is seated at the surgeon's console, which can be located up to 10 meters away from the operating table. Within the console are located the surgeon's control handles, or masters, which act as high-resolution input devices that read the position, orientation, and grip commands from the surgeon's finger tips. This control system also allows for computer enhancement of functions, such as motion scaling and tremor reduction. The image of the operative site is projected to the surgeon through a high-resolution stereo display that uses two medical-grade cathode ray tube (CRT) monitors to display a separate image to each of the surgeon's eyes.

The standard da Vinci instrument platform consists of an array of 8.5-mm diameter instruments. These instruments provide 7 degrees of freedom through a cable-driven system.

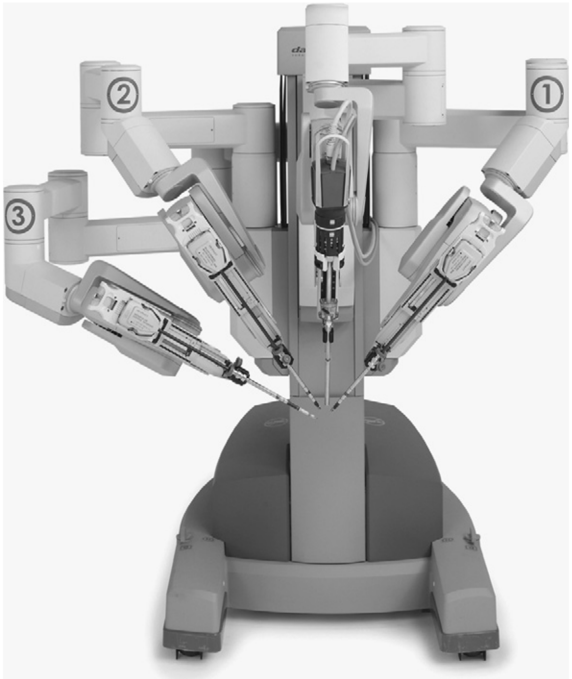



**FIGURE 4-16** The Intuitive Surgical da Vinci Si robotic surgical system (Courtesy Intuitive Surgical, Sunnyvale, Calif.)

FIGURE 4-17 The Intuitive Surgical da Vinci Si robotic surgical system. (Courtesy Intuitive Surgical, Sunnyvale, Calif.)

A set of 5-mm instruments are also available. These instruments use a "snake wrist" design and also provide 7 degrees of freedom (Fig. 4-18).

Since its inception in 1995, the da Vinci system has undergone several iterations. The current system, called the da Vinci Si, features high-definition optics and display as well as smaller and more maneuverable robotic arms. Other features include dual console capability for training purposes.

### Current Advantages and Limitations of Robotic Pediatric Surgery

The utility of the different robotic surgical systems is highly influenced by the smaller size of pediatric patients and the reconstructive nature of many pediatric surgical procedures. Overall, the advantages of the robotic systems stem from technical features and capabilities that directly address many of the limitations of standard endoscopic techniques and equipment. Unlike conventional laparoscopic instrumentation, which requires manipulation in reverse, the movement of the robotic device allows the instruments to directly track the movement of the surgeon's hands. Intuitive nonreversed instrument control is therefore restored, while preserving the minimal access nature of the approach. The intuitive control of the instruments is particularly advantageous for the novice laparoscopist.

In infants and neonates, the use of a magnified image via operating loupes or endoscopes is often necessary to provide more accurate visualization of tiny structures.[170,171] This enhanced visualization is taken a step further with robotic systems, because they are capable of providing a highly magnified, 3D image. The 3D vision system adds an additional measure of accuracy by enhancing depth perception and magnifying images by a factor of ten. The alignment of the visual axis with the surgeon's hands in the console further enhances hand–eye coordination to a degree uncommon in traditional laparoscopic surgery.

FIGURE 4-18 Articulated robotic instrument. (Courtesy Intuitive Surgical, Sunnyvale, Calif.)

Similarly, the presence of a computer control system enables electronic tremor filtration, which makes the motion of the endoscope and the instrument tips steadier than with the unassisted hand. The system also allows for variable motion scaling from the surgeon's hand to the instrument tips. For instance, a 3:1 scale factor maps 3 cm of movement of the surgeon's hand into 1 cm of motion at the instrument tip. In combination with image magnification from the video endoscope, motion scaling makes delicate motions in smaller anatomic areas easier and more precise.[160]

The da Vinci system uses instruments that are engineered with articulations at the distal end that increase their dexterity compared with traditional MAS tools. This technology permits a larger range of motion and rotation, similar to the natural range of articulation of the human wrist, and may be particularly helpful when working space is limited. The da Vinci instruments feature 7 degrees of freedom (including grip), while standard laparoscopic instruments are only capable of 5 degrees of freedom, including grip. This increased dexterity may be particularly advantageous during complex, reconstructive operations that require fine dissection and intracorporeal suturing.

Finally, by separating the surgeon from the patient, teleoperator systems feature ergonomically designed consoles that may decrease the fatigue often associated with long MAS procedures. This may become a more significant issue as the field of pediatric bariatric surgery develops because of the larger size and thicker body walls of bariatric patients.

Although robotic surgical systems provide several key advantages versus standard minimal access surgery, there are a number of technological limitations specific to pediatric surgery. First and foremost is the size of the robotic system. Compared with many pediatric surgical patients, the size of the da Vinci surgical cart may be overwhelming. This size discrepancy may restrict a bedside surgical assistant's access to the patient while the arms are in use, and may require the anesthesiology team to make special preparations to ensure prompt access to the patient's airway.[170]

The size and variety of available robotic instruments is limited compared with those offered for standard laparoscopy. Currently, the da Vinci system is the only platform undergoing further development at the industry level. A suite of 5-mm instruments with 7 degrees of freedom has been introduced for

use with this system. Although these instruments represent a significant improvement compared with the original 8.5-mm instruments regarding diameter, the number of instruments offered is still somewhat limited. Furthermore, these instruments use a new "snakewrist" architecture that requires a slightly larger amount of intracorporeal working room to take full advantage of their enhanced dexterity. Specifically, the instruments are limited by a greater than 10-mm distance from the distal articulating joint or wrist and the instrument tip.

There are a number of general limitations inherent to the available robotic surgical system that must be overcome before they are universally accepted in pediatric as well as adult surgery. These include the high initial cost of the robotic systems as well as the relatively high recurring costs of the instruments and maintenance.[162] In addition, this system does not offer true haptic feedback.[170] Even though such feedback is reduced in standard minimal access surgery compared with open surgery, it is further reduced or absent with a robotic interface. This disadvantage is partially compensated for by the improved visualization offered by the robotic systems, but it remains a potential drawback when precise surgical dissection is required.

The robotic systems require additional, specialized training for the entire operating room team. This translates into robotic procedure times that are predictably longer when compared with the conventional laparoscopic approach, at least until the surgical team becomes facile with the use of the new technology. Even with an experienced team, setup times have been reported to require an additional 10 to 35 minutes at the beginning of each robotic-assisted case.[170]

### Applications of Robotic Technology to Pediatric Surgery

To date, only a small body of literature regarding the application of robotic technology for pediatric surgical procedures has shown the feasibility of robotic-assisted surgery. A wide variety of abdominal and thoracic procedures have been reported in the fields of pediatric general, cardiothoracic, and urologic surgery. The bulk of the literature represents class IV evidence, consisting of case reports and case series with no class I evidence. In 2009, van Haasteren and colleagues[172] reviewed the literature and found a total of eight peer-reviewed case series and five studies comparing robotic surgery with open or conventional laparoscopic surgery. Several of the studies had a retrospective design, and there were no randomized studies. From their review, they concluded that the published literature demonstrates that robotic surgical systems can be safely used to perform a variety of abdominal and thoracic operations. They were not able to identify evidence that robotic-assisted surgery provided any improvement in clinical outcomes compared with conventional open or laparoscopic surgery.[172]

The first reports describing the use of robotic surgical systems for abdominal procedures in children were published in 2002,[158,160] and robotic-assisted surgery has only seen modest adoption in the field of pediatric general surgery. The cause of this is likely multifactorial and in many ways mirrors the adoption curve seen in adult general surgery. To date, robotic-assisted surgery has found the most widespread adoption in the field of adult urology, specifically for prostatectomies. This operation takes advantage of the strengths of the current robot, namely articulated instruments and 3D visualization that assist in the complex dissection and reconstruction required in a narrow space. It is also a single quadrant operation that does not require significant repositioning of either the patient or the robotic system once the procedure begins. Lastly, prostatectomies are a relatively high-volume operation that is reproducible. This leads to improved efficiency, because the operating room team has only one setup to master. In contrast, the field of pediatric general surgery is characterized by a wide variety of complex but low-volume operations performed in small children. There is no high-volume operation in pediatric general surgery that takes advantage of robotic assistance. In addition, the instrument size and haptic limitations of the current robotic system are not ideal for use in many of our smaller patients.[173] These issues will likely be addressed by further advancement of the technology, with evolved incarnations of robotic surgery possibly playing a larger role in pediatric general surgery in the future.

## Microtechnologies and Nanotechnologies—Size Matters

An arsenal of technology will emerge from material science and its application principles to microelectromechanical systems (MEMS)[174,175] and nanoelectromechanical systems (NEMS). Just as the electronics industry was transformed by the ability to manipulate electronic properties of silicon, the manipulation of biomaterials at a similar scale is now possible. For the last 40 years the common materials of stainless steel, polypropylene, polyester, and polytetrafluroethylene have been unchanged. A recent example of this potential is the use of nitinol (equiatomic nickel-titanium), a metal alloy with the property of shape memory.

An important concept and distinction in device manufacturing is that of the "top down" versus "bottom up" assembly. Top down refers to the concept of starting with a raw material and shaping it into a device. In a typical MEMS device, silicon is etched, heated, and manipulated to its final form. In the nascent field of nanotechnology, the underlying conceptual principle is that of self-assembly. Here component ingredients are placed together under optimal conditions and self assemble into materials. This process is much more one of biologic assembly.

### Microelectromechanical Systems

The evolution of surgical technology has followed the trends of most industries—the use of technology that is smaller, more efficient, and more powerful. This trend, which has application in the medical and surgical world, is embodied in MEMS devices.

Most MEMS devices are less than the size of a human hair, and although they are scaled on the micron level, they may be used singly or in groups. MEMS devices have been used for years in automobile airbag systems and in inkjet printers.

Because the medical community relies increasingly on computers to enhance treatment plans, it requires instruments that are functional and diagnostic. Such a level of efficiency lies at the heart of MEMS design technology, which is based

on creating devices that can actuate, sense, and modify the outside world on the micron scale. The basic design and fabrication of most MEMS devices resemble the fabrication of the standard integrated circuit, which includes crystal growth, patterning, and etching.[176]

MEMS devices have a particular usefulness in biologic applications because of their small volumes, low energy, and nominal forces.[177] Increased efficacy of instruments and new areas of application are also emerging from specific and successful biomedical applications of MEMS.[178] There are two basic types of MEMS devices: sensors and actuators. Sensors transduce one type of energy (such as mechanical, optical, thermal, or otherwise) into electrical energy or signals. Actuators take energy and transform it into an action.

### Sensors

Sensors transduce or transform energy into an electrical signal. The incoming energy may be mechanical, thermal, optical, or magnetic. Sensors may be active or passive systems. Active sensors can derive their own energy from an input signal, whereas passive sensors require an outside energy source to function. Almost all of these devices are in their developmental stage but give form to the concept.

***Data Knife and H-Probe Surgical Instruments*** MEMS devices are particularly suited to surgical applications, because their small dimensions naturally integrate onto the tips of surgical tools. One example is the “Data Knife” (Verimetra, Pittsburgh, Penn.), which uses microfabricated pressure sensors that are attached to the blade of a scalpel (Fig. 4-19). While cutting, the Data Knife pressure sensors cross reference with previously gathered ex vivo data to inform the surgeon about the type of tissue that is being divided. This information becomes particularly useful during endoscopic cases in which a sense of tactile feedback is reduced or lost entirely.

Verimetra’s H-probe uses similar sensors to “palpate” calcified plaques transmurally during coronary bypass surgery. The intention is to eliminate poor positioning of the bypass graft conduit by more precisely targeting an ideal anastomotic site before arteriotomy.

***Arterial Blood Gas Analyzer*** MEMS technology can be applied to the analysis of arterial blood gases. This MEMS-based analyzer was founded on established methods in infrared spectroscopy. It consists of an infrared light source, an infrared sensor, and an optical filter. The infrared light is passed through the filter, which is designed to monitor the infrared spectrums of oxygen, carbon dioxide, and other associated blood gases. Because most gases have a known infrared absorption, the sensor can be designed with specific values for infrared signatures.

Once again, because of microscaling techniques and because of the relatively small sample size, the test can be performed in less time than conventional arterial blood gas analysis. One specific example is an arterial blood gas catheter for monitoring blood in preterm infants, in which real-time data can be gathered by way of oxygen and carbon dioxide–specific sensors.

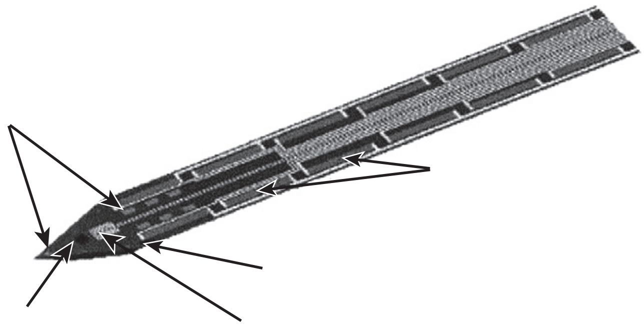


**FIGURE 4-19** Data Knife MEMS-based scalpel. (Courtesy of Verimetra, Pittsburgh, Penn.)

***Blood Pressure Sensor*** The biggest success story in medical MEMS technology is the disposable blood pressure sensor. Disposable blood pressure sensors replace reusable silicon-beam or quartz-capacitive pressure transducers that can cost as much as $600 and have to be sterilized and recalibrated for reuse. These expensive devices measure blood pressure with a saline solution–filled tube-and-diaphragm arrangement that must be connected directly to the arterial lumen. In the silicon MEMS blood pressure transducer, pressure corresponds to deflection of a micromachined diaphragm. A resistive element, a strain gauge, is ion implanted on the thin silicon diaphragm. The piezo-resistor changes output voltage with variations in pressure. Temperature compensation and calibration can be integrated in one sensor.

***Other MEMS Sensors in Medicine*** The Wheatstone bridge piezo-resistive silicon pressure sensor is a prime example of a MEMS device that is used commonly in medical applications. Able to measure pressures that range from less than 0.1 to more than 10,000 psi, this sensor combines resistors and an etched diaphragm structure to provide an electrical signal that changes with pressure. These types of sensors are used primarily in blood pressure monitoring equipment, but their use in the medical field extends to respiratory monitors, dialysis machines, infusion pumps, and medical drilling equipment. They are also used in inflatable hospital bed mattresses to signal an alarm upon detection of a lack of motion over a significant period of time.

### Actuators

An actuator is a fluid-powered or electrically powered device that supplies force and motion. There are several kinds of actuators used in MEMS devices. These include electrostatic, piezoelectric, thermal, magnetic, and phase recovery. Actuators in medicine are used in valves, accelerometers, and drug delivery systems. Future use to produce muscle activation or “artificial muscles” is predicted.

### Drug Delivery Systems

MEMS devices are used in drug delivery systems in the form of micropumps. A typical drug pump consists of a pump chamber, an inlet valve, an outlet valve, a deformable diaphragm, and an electrode. When a charge is applied to the electrode, the diaphragm deforms, which increases the volume in the pump chamber. The change in volume induces a decrease in pressure in the pump chamber. This opens the inlet valve. When the charge is terminated, the pressure returns to normal, by closing the inlet valve, opening the outlet valve, and allowing the fluid to exit. Other micropumps incorporate pistons or pressurized gas to open the outlet valves.

One of the more attractive applications for implantable pumps is insulin delivery. There are disadvantages of current insulin micropumps, most notably their expense. The drug supply must be refilled once every 3 months, and each pump costs between $10,000 and $12,000. Furthermore, insulin is unstable at core body temperature. Therefore an insulin analogue must be synthesized that would be stable at physiologic temperatures. Thinking forward, a biomechanical pancreas, which senses glucose and insulin levels and titrates insulin delivery, would be an interesting MEMS combination of a sensor and an actuator.

### Next Steps for MEMS

MEMS devices are in the same state today as the semiconductor industry was in the 1960s. Like the first semiconductors, MEMS devices are now largely funded by government agencies, such as the Defense Advanced Research Projects Agency (DARPA). Relatively few commercial companies have taken on MEMS devices as a principal product. However, no one could have predicted in 1960 that, 40 years later, a conglomerate of semiconductors would be on virtually every desktop in the United States. It is then not unreasonable to predict potential value, including surgical applications, for MEMS devices.

Indwelling microsensors for hormone and peptide growth factors might replace episodic examinations, lab determinations, or CT scans to monitor tumor recurrence. As more devices are fabricated, the design process becomes easier, and the next technology can be based on what was learned from the last. At some point in the future, we will view MEMS devices as common surgical modalities, smart instruments, inline laboratories, surveillance devices, and perhaps for cellular or even DNA insertion.

## NANOELECTROMECHANICAL SYSTEMS

Applications of nanotechnology and nanoelectromechanical systems in medicine and surgery have been recently reviewed.[175] Size does matter. In medicine and biology, the major advantage of decreasing size scale is the ability to enable materials or particles to find places in body compartments to which they could otherwise not be delivered. Current and future applications of surgical interest include coating and surface manipulation, the self-assembly or biomimicry of existing biologic systems, and targeted therapy in oncology.

### Coating and Surface Manipulation

Although most medical devices are composed of a bulk material, biologic incorporation or interaction occurs only at the thinnest of surfaces. To optimize this surface interaction, sintered orthopedic biomaterials have been developed. A thin layer of beads are welded or "sintered" by heat treatment on top of the bulk material.[179] This bead layer optimizes bone ingrowth, while the bulk material is responsible for the mechanical stability of the device. Hydroxyapatite-coated implants represent a biologically advanced coating of the device with ceramic hydroxyapatite,[180] thereby inducing bony ingrowth by mimicking the crystalline nature of bone (biomimicry). Future attempts involve coating with the RGD peptide, the major cell attachment site in many structural proteins.

Cardiovascular stents, and now drug-eluting stents, provide a similar example. The current generation of drug eluting stents has a micron-thick coating made of a single polymer that releases a drug beginning at the time of implantation.[181] The drug coating of rapamycin or paclitaxel diffuses slowly into the tissue microenvironment to prevent a fibrotic reaction. The future ideal stent will likely be engineered to optimize the bulk material and the coating. Indeed, the perfectly biocompatible material may be one in which a bulk material is artificial and the surface is seeded with the patient's own cells, for example, an endothelialized Goretex vascular stent.[182]

### Self Assembly

NEMS materials are produced from a self-directed or self-assembly process in which mixtures of materials are allowed to condense into particles, materials, or composites.[183] Thus NEMS processing starts with a nonsolid phase, typically a solution, and by manipulating the environment, materials are created.

Recently, biologic molecules such as proteins and DNA have been used to stabilize nanoparticle crystals and create materials with unique properties, opening the door to unlimited diversity in the next generation of nanoparticles and materials.[184,185] Such processes mimic nature's ability to produce materials such as pearls, coral, and collagen.

### NEMS in Oncology

More than in any other field, microscale and nanoscale technologies will provide the field of oncology with critical therapeutic advances. In considering the perverse biologic process of malignant transformation and spread, our current therapies are gross and nontargeted. Figure 4-20 depicts a complex nanoparticle[186] composed of an iron oxide core surrounded by silicon oxide shells. Ligands may be attached to the silicon oxide coating that may then target the iron oxide to a specific site. Such technology can be used for diagnostic purposes based on tumor permeability and therapeutic options.

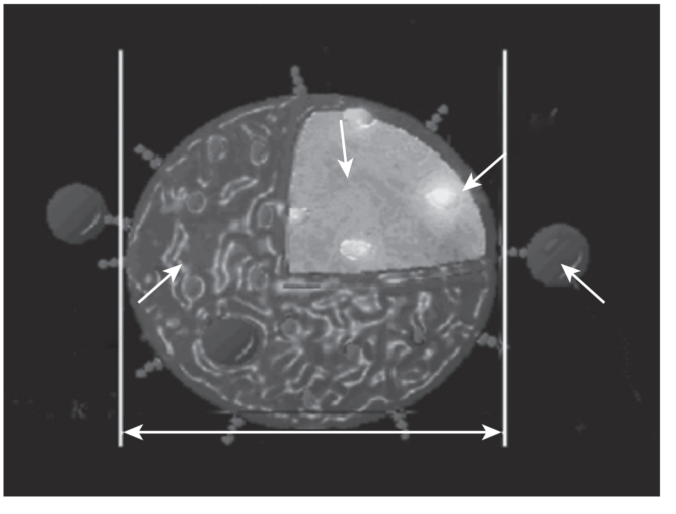


FIGURE 4-20 A schematic of a nanoparticle. An iron oxide core is surrounded by a silicon oxide shelf. Ligands attached to the silicon oxide can target the iron oxide to a specific site or potentially a tumor. The iron oxide can be heated in a magnetic field. Alternatively, the iron oxide may carry a toxin, a gene, or a pharmaceutical. Surface arrows highlight customized ligands while inner arrows point out therapeutic materials that can be placed in the iron oxide core.

Harisinghani and colleagues[186] used iron oxide nanoparticles to identify tumor metastases in lymph nodes of patients with prostate cancer. The authors demonstrated increased sensitivity and specificity in identifying nodes that ultimately contained tumor. Further work with magnetic nanoparticles functionalized with tumor-specific antibodies will enhance a specific uptake by tumors.

# Surgical Innovator

Most clinical innovations in surgery relate to a novel operation, a novel device, or both. Occasionally, the novel procedure or device is of the surgeon's own development. In all cases, the surgeon holds the responsibility of ensuring that the implementation of these innovations is done in an ethical fashion. There are guidelines that surgeons can follow to help them safely and ethically introduce innovative solutions to their practice.

## INNOVATIVE DEVICES

In the United States, pediatric research falls under the regulation of institutional review boards (IRBs), which serve the purpose of upholding the guidelines set forth by state and federal legislative bodies. The FDA regulates the use of all surgical devices.[187] Although the majority of pediatric surgeons will not design large clinical trials or novel devices, it is helpful to understand the regulatory processes when implementing new techniques or devices into one's practice.

The FDA categorizes new devices into three classes based on the potential risk incurred by using the device in humans. Class I devices pose minimal harm to the recipient and do not typically require premarket notification or approval (i.e., clinical data supporting safety and efficacy). Class II devices pose an intermediate level of potential harm but have demonstrated clinical efficacy comparable to similar existing devices. Class III devices pose significant potential harm to the recipient and require premarket approval with clinical data supporting safety and efficacy.

If a surgeon intends to study a novel device as part of a clinical trial in humans, the collection of preliminary data for non-FDA–approved devices is regulated by IRBs. If an IRB determines that the device provides insignificant risk to the study participants, the study may proceed. However, if an IRB concludes that the proposed study exposes the participants to significant risk, the FDA must approve an investigational device exemption prior to commencement of the study.[187]

If a device treats a condition that affects less than 4000 people per year in the United States, which applies to most pediatric conditions, it may qualify for humanitarian device exemptions (HDE). This allows approval of such devices when safety has been demonstrated and the probable benefits outweigh the risks of using the device.[187] HDE aids in disseminating high-impact technologies designed for rare conditions, technologies that would otherwise have delayed time to market because of the inability to properly power premarket clinical trials.

The pediatric surgeon using a novel non-FDA–approved device should obtain IRB approval. If there is sufficient patient risk associated with the use of the novel device, the investigator must obtain investigational device exemption from the FDA. Once clinical safety and efficacy are established, one can apply for FDA approval. If the device has significant potential benefit for an uncommon disease, the investigator has the option to apply for an HDE.

## INNOVATIVE PROCEDURES

An innovative procedure may be composed of a new way of surgically correcting a condition, with or without the use of a device not approved for that use. Minor modifications to existing procedures would not be included in this category. The off-label use of an adult device in children may or may not be seen as innovative, depending on the circumstances surrounding its use. In all cases, a reasoned approach, such as that outlined in Table 4-3, can help to ensure safe and effective implementation of the innovation.

The Department of Health and Human Services (DHHS) categorizes pediatric research into four successive categories based on the degree of risk and the potential benefit to the study participant.[188] The first three of these codes encompass studies with potential for benefit to the participant with relatively low levels of risk exposure. The fourth code includes research that exposes participants to the potential risk in the *absence* of direct or indirect benefit but that has the potential to benefit children in general. A study that falls under this category may not be approved solely by an IRB but must have the authorization of the Secretary of the DHHS.

All pediatric research proposals, regardless of which DHHS code they fall under, must demonstrate an appropriate process for obtaining both patient *assent* and parent/guardian *consent* as defined by The American Academy of Pediatrics Committee on Bioethics.[189] The currently accepted standard of care is to obtain patient assent prior to enrollment in a study when feasible (i.e., when the patient is developmentally capable of affirming participation after receiving a cognitive age-appropriate explanation of the study/procedure, risks, benefits, and alternative options). Parental permission/consent is required whenever possible (i.e., nonemergent settings) if the patient is a nonemancipated minor. Practically speaking, parental permission/consent involves all of the components of informed consent in an adult population.

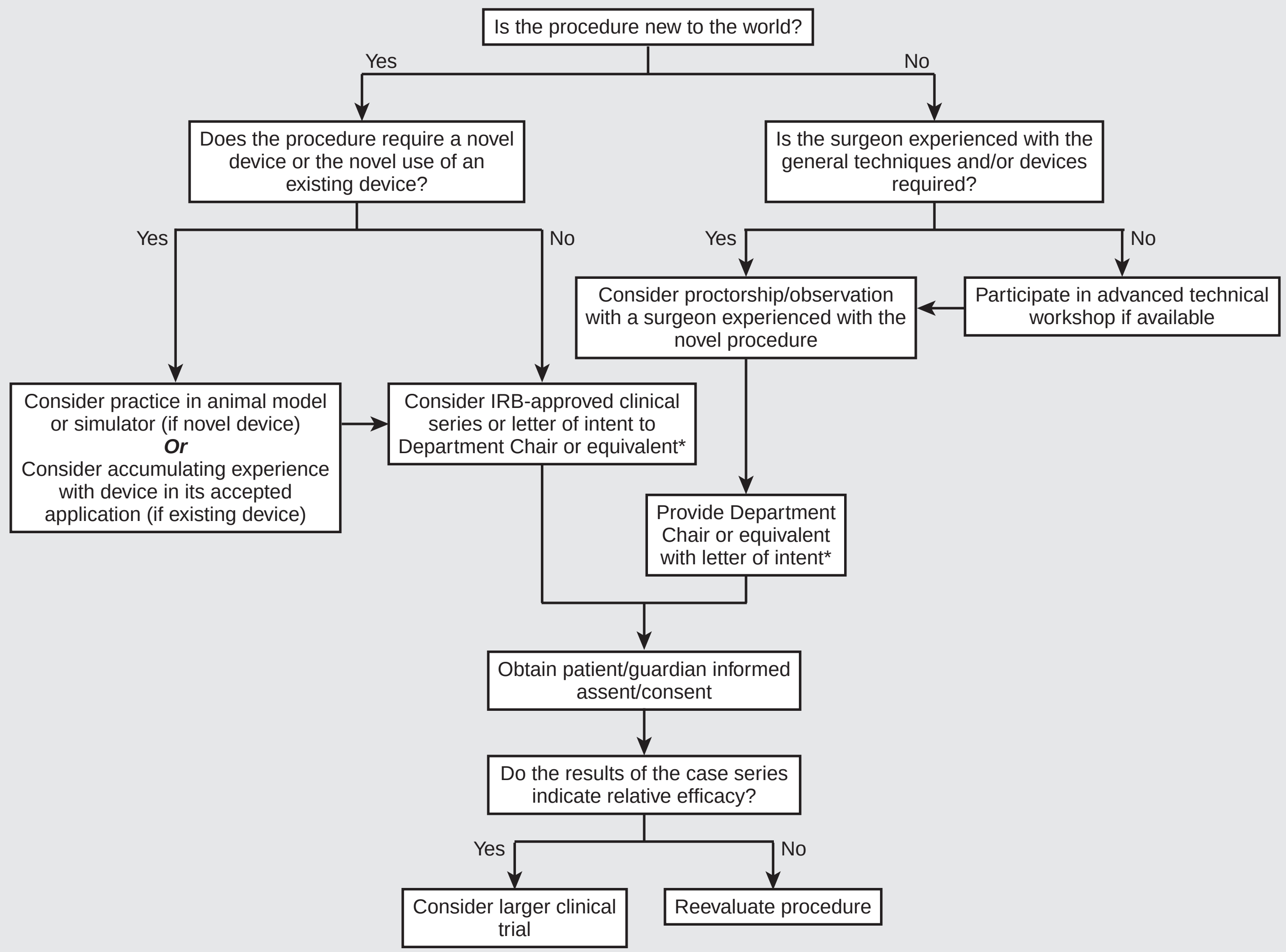
## PEDIATRIC DEVICE DEVELOPMENT

The medical device industry has shown little interest in pediatric device development because of small market sizes and regulatory hurdles.[190] Similarly, entrepreneurs trying to promote medical device concepts have had little success in getting their ideas funded through typical funding channels, such as venture capital, for these same reasons. The consequence is that pediatric surgeons and others performing pediatric procedures are left to use adult devices off-label in children, "jerry-rig" their own devices, or simply do without. All of these approaches potentially result in a substandard level of care for pediatric patients.

Recognizing the dire need for pediatric-specific devices and the lack of interest from medical device companies, medical practitioners have in recent years taken a more active role in pediatric device development. More focused efforts at pediatric specific medical device innovation have emerged, in response to the dearth of innovation for this population.

**TABLE 4-3**

**Approach to Introducing Innovative Procedures into Pediatric Surgical Practice**




*Letter should include description of existing foundational technique(s), a description of the novel technique, a summary of the published results comparing the novel technique to existing technique(s) if available, and a description of the preparation undertaken by the surgeon prior to attempting the novel procedure.

From Kastenberg Z, Dutta S: Guidelines for innovation in pediatric surgery. J Laparoendosc Adv Surg Tech A 2011;21:371–374.

In September 2007, President George W. Bush signed into law the *FDA Amendments Act of 2007*, which included *Title III: Pediatric Medical Device Safety and Improvement Act*. This Act, which was designed to improve the research, manufacture, and regulatory processes for pediatric medical devices, also aimed to establish nonprofit consortia to stimulate development of pediatric devices. As a consequence, the United States Congress charged the FDA with dispersing grant funds for the creation of pediatric device consortia (PDC), organizations devoted to creating a national platform for the development of pediatric-specific medical devices, and demonstrating the timely creation of such devices. The first of these consortia include the PDC at University of California, San Francisco (http://www.pediatricdeviceconsortium.org) led by Dr. Michael Harrison, the University of Michigan PDC (http://peddev.org) led by Dr. James Geiger, the Pediatric Cardiovascular Device Consortium at Boston Children's Hospital led by Dr. Pedro Del Nido, and the Multidisciplinary Initiative for Surgical Technology Research (MISTRAL; www.mistralpediatric.org), a collaborative effort between one of the authors (SD) representing Stanford University and SRI International, an engineering firm based in Menlo Park, Calif. Notably, three of these four consortia are led by pediatric general surgeons, attesting to the pioneering role our specialty can play in the advancement of pediatric medical technologies. These consortia have taken the lead in establishing formalized collaborative ventures that engage clinical and technical expertise in needs identification, foundational science research, and device design and prototyping. Going beyond the typical role of the academic institution, these collaborative groups are also identifying paths to market for the devices they develop through such strategies as spin-off companies or partnerships with commercialization entities.

Furthermore, the consortia provide pediatric surgeons-in-training an opportunity to immerse themselves in the innovation process, focusing specifically on the unique challenges of developing devices for children.

The market strategy for pediatric devices depends on the nature of the device. For example, many pediatric applications may require a device to be miniaturized for use in children. The technical solutions used to achieve this can then be applied in much larger adult markets. In areas such as minimal access surgery, smaller devices are also seen as beneficial for adult applications. This "trickle up" effect of the technology to adult applications can justify production of the device for pediatric markets because of the potential to also use it in much larger adult markets. Licensing to commercialization entities interested in applying the technology to adult markets may come with the caveat that they also address the pediatric need. In some circumstances where the device is quite specific to a rare pediatric condition, philanthropic support may be necessary to help it get to market, such as that by an individual or a foundation with particular interest in child health or the specific disease.

Device development can be seen as a form of translational science, where the basic research, design, prototyping, and testing of novel devices comprise unique intellectual contributions. Some institutions are beginning to recognize the scholarly potential for device innovation and crediting the researchers engaged in it, thus making it a potential basis for academic promotion. The measures of scholarly productivity may be different than traditional research tracks but nevertheless hold value for the academic institution. For example, device innovators may not be able to publish extensively because of concerns about protection of intellectual property (at least in the initial stages of device development), but the generation of grants, patents, and usable devices that positively impact healthcare can have great value for the institution.

# Innovative Surgical Training

The practice of surgery is a visual, cognitive, and manual art and science that requires the physician to process increasingly large amounts of information. Techniques are becoming more specific and complex, and decisions are often made with great speed and under urgent circumstances, even when rare problems are being addressed. Simulation and virtual reality (VR)[191,192] are two concepts that may reshape the way we think about surgical education, rehearsal, and practice.

## SURGICAL SIMULATION

Simulation is a device or exercise that enables the participant to reproduce or represent, under test conditions, phenomena that are likely to occur in actual performance. There must be sufficient realism to suspend the disbelief of the participant. Simulation is firmly established in the commercial airline business as the most cost-effective method of training pilots. Pilots must achieve a certain level of proficiency in the simulator before they are allowed to fly a particular aircraft and must pass regular proficiency testing in the simulator to keep their licenses. Military organizations use a similar method for training in basic flying skills and find simulation useful in teaching combat skills in complex tactical situations. Surgical simulation therefore has roots in the techniques and experiences that have been validated in other high-performance, high-risk organizations.

The expense and risk of learning to fly motivated Edward Link to construct a mechanical device he called "the pilot maker" (Link, http://www.link.com/history.html). The addition of instrument sophistication enables the training of individuals to fly in bad weather. At the onset of World War II, with an unprecedented demand for pilot trainees, tens of thousands were trained in Link simulators.[193]

The medical community is beginning to use simulation in several areas for training medical personnel, notably surgeons, anesthesiologists, phlebotomists, paramedics, and nurses. The ability of the simulator to drill rehearsed pattern recognition repetitively in clinical practice makes just as much sense for the surgical disciplines as it does for aviators. Surgical care entails a human risk factor, which is related to both the underlying disease and the therapeutic modality. Risk can be reduced through training. One of the ways to accomplish both of these goals is through simulation.

Simulation is loosely defined as the act of assuming the outward qualities or appearances of a given object or series of processes.[194] It is commonly assumed that the simulation will be coupled with a computer, but this is not requisite. Simulation is a technique, not a technology, used to replace or amplify real experiences with guided experiences that evolve substantial aspects of the real world in a fully interactive manner.[195] To perform a simulation, it is only necessary to involve the user in a task or environment that is sufficiently "immersive" so that the user is able to suspend reality to learn or visualize a surgical teaching point. The knowledge that is gained is then put to use in education or in the live performance of a similar task. Just as one can simulate a National Football League football game with a console gaming system, surgeons can learn to tie knots using computer-generated virtual reality, or simulate the actions of a laparoscopic appendectomy with the use of a cardboard box painted to resemble a draped abdomen.

### Visual Display Systems in Simulation

Simulator technology involves the design of training systems that are safe, efficient, and effective for orienting new trainees or providing advanced training to established clinicians. This involves teaching specific skills and generating scenarios for the simulation of critical or emergent situations. The entertainment industry is by far the main user and developer of visual displays. So much headway has been made in the advancement of visual technologies by the entertainment industry that many visual devices that are used in simulation are borrowed from these foundations. Considering that the graphic computing power of a $100,000 supercomputer in 1990 was essentially matched by the graphic capability of a $150.00 video game system in 1998, the available technology today is more than capable of representing a useful surgical simulation faithfully.[196]

Props are a key component of the visual act of simulation. Although laparoscopic surgical procedures can be represented on a desktop computer, a much more immersive experience can be carried out by involving monitors and the equipment used in an actual operating room. For example, mannequin simulators, although internally complex, can serve to complement the

simulation environment. Simulation of procedures, such as laparoscopic operations, should use displays similar to those used in the actual operating room.

Simulation of open procedures, on the other hand, requires systems that are presently in the developmental stages. The level of interaction between the surgeon and the simulated patient requires an immersive visualization system, such as a head-mounted display. The best approach for a developer of a simulator for open procedures would be to choose a system with good optical qualities and concentrate on developing a clear, stable image. Designs for this type of visualization include "see-through displays" in which a synthetic image is superimposed on an actual model.[176] These systems involve the use of a high-resolution monitor screen at the level of the operating table. The characteristics of the displayed image must be defined in great detail.

### Human/Simulator Interface and Tactile Feedback

Force feedback is the simulation of weight or resistance in a virtual world. Tactile feedback is the perception of a sensation applied to the skin, typically in response to contact. Both tactile and force feedback were necessary developments, because the user needs the sensation of touching the involved virtual objects. This so-called ***haptic loop***, or the human-device interface, was originally developed with remote surgical procedures in mind and has much to lend to the evolution of surgical simulation.

Technologies that can address haptic feedback are maturing, as noted by rapid development of haptic design industries in the United States, Europe, and Japan and in many university-based centers.[197] Haptic technologies are used in simulations of laparoscopic surgical procedures, but extending this technology to open procedures in which a surgeon can, at will, select various instruments will require a critical innovation.

### Image Generation

The generation of 3D, interactive, graphic images of a surgical field is the next level in surgical simulation. Seeing and manipulating an object in the real world is altogether different from manipulating the same object in virtual space. Most objects that are modeled for simulations are assumed to be solids. In human tissue, with the possible exception of bone, this is not the case. Many organs are deformable semisolids, with potential spaces. Virtual objects must mirror the characteristics of objects in the real world. Even with today's computing power, the task of creating a workable surgical surface (whether skin, organ, or vessel) is extremely difficult.

A major challenge in the creation of interactive surgical objects is the reality that surgeons change the structural aspects of the field through dissection. On a simulator, performing an incision or excising a problem produces such drastic changes that the computer program supporting the simulation is frequently incapable of handling such complexity. This also does not include the issue of blood flow, which would cause additional changes to the appearance of the simulated organ. Furthermore, the simulation would have to be represented in real time, which means that changes must appear instantaneously.

To be physically realistic, simulated surgical surfaces and internal organs must be compressible in response to pressure applied on the surface, either bluntly or by incision. Several methods of creating deformable, compressible objects exist in computer graphic design.

Frequently, simulator graphic design is based on voxel graphics. A voxel is an approximation of volume, much in the same way a pixel is an approximation of area. Imagine a voxel as a cube in space, with length, width, and depth. Just as pixels have a fixed length and width, voxels have a fixed length, width, and depth. The use of volume as the sole modality to define a "deformable object," however, does not incorporate the physics of pressure, stress, or strain. Therefore the graphic image will not reflect an accurate response to manipulation. The voxel method does not provide a realistic representation of real-time changes in the organ's architecture, which would occur after a simulated incision.

A more distinct approach to the solution for this problem is with the use of finite elements. Finite elements allow the programmer to use volume, pressure, stress, strain, and density as bulk variables. This creates a more detailed image, which can be manipulated through blunt pressure or incision. Real-time topologic changes are also supported.

For the moment, a good alternate solution to the problem is to avoid computational models. Some groups have used hollow mannequins with instruments linked to tracking devices that record position. Task trainers allow one to practice laparoscopic skills directly by the use of the equivalent of a cardboard box with ports to insert endoscopic tools. These tools are used to complete certain tasks, such as knot tying or object manipulation.

### Simulation in Education, Training, and Practice

Historically, surgical training has been likened to an apprenticeship. Residents learn by participating, taking more active roles in patient care or the operative procedure as their experience increases. Despite potential flaws, this model has successfully trained generations of surgeons throughout the world. Error and risk to patients are inherent in this traditional method of education, despite honest attempts at mitigation, and will always be a factor in the field of surgery, no matter how it is taught. New methods of surgical training exist, however, that can help to reduce error and risk to the patient.[198,199]

Training in simulated environments has many advantages. The first advantage is truly the crux of simulation: It provides an environment for consequence-free error, or freedom to fail. Simulator-based training incurs no real harm, injury, or death to the virtual patient. If a student transects the common duct during a simulated cholecystectomy, the student simply notes the technical error and learns from the mistake. Furthermore, simulations can be self directed and led by a virtual instructor or can be monitored and proctored by a real instructor. This means that the student can learn on his or her own time, outside of the operating room.[200]

Simulators are pliable tools. Depending on the assessment goals of a particular simulator, tasks can be modified to suit the educational target. For example, self-contained "box trainers," which are used to teach a particular dexterous skill, can be modified to be less or more difficult or to teach grasping skills versus tying skills. In more complex computer-based simulations, variables can be changed automatically by the computer or manually by the instructor, even during the simulation. These variables range from changes in the graphic overlay to the introduction of an unexpected medical emergency. Approaches to learning laparoscopic navigational skills within the human body have benefited considerably from

such techniques. A prime objective of surgical education is to learn how to function mentally and dexterously in a 3D environment. Surgical "fly-through" programs can be invaluable resources to learn this kind of special orientation inside the human body.[201]

Perhaps one of the greatest benefits of surgical simulation is the ability of early learners to become skilled in basic tasks that have not been previously presented in formal training. The orientation of medical students, now frequently excluded from patient care tasks, may aid in their engagement, education, and recruitment to surgical careers. Therefore the most consistent success has been the discovery that simulators are most beneficial to individuals with little or no previous experience in the simulated task.[202]

### Looking Forward

Simulation successes, particularly in the aviation industry, strongly suggest utility to medical and surgical applications. As with any form of new technology, advances depend on many factors. A product made solely for the sake of technology is doomed to fail; therefore the simulation market must be driven by clinical and educational need. In these early stages of surgical simulation, simpler, mannequin-based trainers have proven to be more useful. However, as graphic design and human interface technology evolve, simulations become more realistic, and equipment prices fall, more immersive computer-generated models will lead the way for this unique form of continuing medical education.

## VIRTUAL REALITY

Virtual reality (VR), although closely related to simulation, has many unique aspects. Simulation is the method for education and training; VR is the modality for making simulation look more real. VR, simply stated, is the creation of a 3D artificial environment with which a user in the real world may interact. VR, in contrast to simulation, almost always relies on computers and computer software to generate a virtual environment. Furthermore, an interface device is required to immerse the user.[203] This device could be as simple as a mouse or keyboard or as complex as VR-based goggles or headsets. The basic intention of VR is to divert the user's attention from the outside world to a manufactured, virtual world with detailed, interactive content based on visuals, sound, and touch. When optimized, such an experience would immerse the participants such that reality becomes this virtual environment.

Although the term *virtual reality* was introduced by Jaron Lanier in 1989, the concept as we currently know it emerged long before that time. In 1963, funding from the Advanced Research Projects Agency (ARPA) gave Ivan Sutherland the opportunity to create Sketchpad, one of the first graphics design tools. By this time, Sutherland was developing the head-mounted display (HMD), which heralded the theories and themes of modern immersive science (Fig. 4-21).

Sutherland used what he learned in his research with HMDs to create scene generators for Bell Helicopter Laboratories. With scene generation, computer graphics would replace the standard video camera–generated display used in the flight simulators manufactured by Bell Laboratories (Fig. 4-22). With his partner, David Evans, Sutherland founded Evans & Sutherland, Inc., which is currently based in Salt Lake City

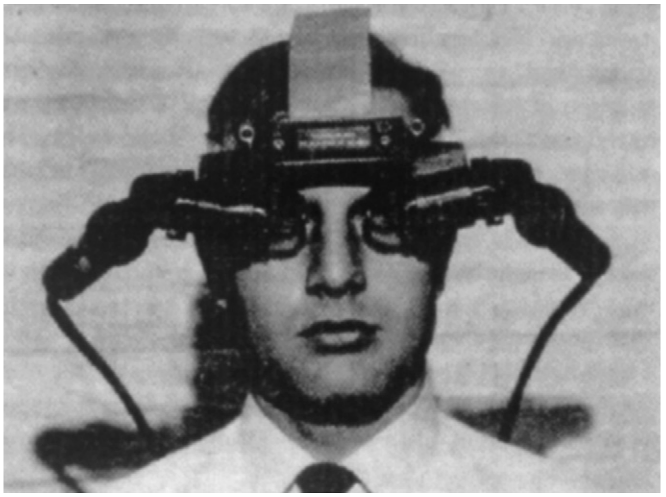


**FIGURE 4-21** Sutherland's head-mounted display. (From National Systems Contractors Association Multimedia Online Expo, "Science for the New Millenium.")

**FIGURE 4-22** Scene Generation Software, Evans & Sutherland. (From National Systems Contractors Association Multimedia Online Expo, "Science for the New Millenium.")

and designs several VR-based products. Sutherland's foray into medicine occurred in 1971, when he developed the first arterial anastomosis simulation. With the simultaneous development of computer interface tools, such as the mouse, VR immersion became possible, because the ordinary user could now interact easily with the computer in a manner that was more intuitive than a keyboard.

By the early 1970s, ARPA was forced to concentrate its research and development on weapons for the Vietnam conflict. This led to an exodus of talent from ARPA to Xerox, which had established the Palo Alto Research Center (PARC). During the 1970s, major advances in technology meant that computers were becoming more powerful, smaller, and cheaper. The personal computer, laser printer, and desktop architecture were all developed at Xerox PARC.[204]

After the Vietnam conflict, the technologies advanced in war were directed towards other industries. Science and, even more so, entertainment began to look at VR as a way to

enhance their respective businesses. VR has had obvious application in making blockbuster films with dazzling special effects (e.g., *Star Wars*, *The Terminator*, and *The Perfect Storm*). It was during the 1970s that many different industries began to see the applications and implications of VR. Three-dimensional mapping of genomes in DNA research led VR into medicine. For the first time, real-time modification of computer-aided design models became available. Thomas Zimmerman designed a "data glove," a type of human interface device, out of the desire to convert gestures into music by feeding these gestures directly into a computer, which could interpret the movements as sound. He patented the glove in 1982. The glove could interpret the wearer's hand movements and finger flexion, allowing them to interact with a 3D environment.

Jaron Lanier first combined the HMD and data glove in 1986, giving the world a more realistic version of immersive VR. This step meant that users could not only see the 3D environment but could also interact with it, feeling the objects and seeing themselves interacting in VR at the same time. Since these forefathers of VR presented their ideas and concepts to the world, there have been many groups, organizations, and individuals that have been interested in exploring and adding to the general knowledge of this field.

The evolution of VR for surgery began in the 1980s. It was quickly realized that simulation and VR for surgical procedures did not have to rely on an especially detailed graphic terrain, which was the case for complex professional flight simulators. In fact, even moderately detailed surgical VR systems could accomplish the purpose of "task training." This reinforced the fact that, for surgeons, one of the primary goals of training was to establish technical skills. Therefore simple graphic representations of two hollow tubes with an interface for needle holders and forceps would be enough to teach someone about the principles of bowel anastomosis. In the late 1980s, Scott Delp of Stanford University developed one of the first surgical VR-based simulators for lower extremity tendon transfers. In 1991, Richard Satava and Jaron Lanier designed the world's first intra-abdominal interactive simulation.

These seminal events in surgical VR were followed by more improved versions based on similar computer-assisted digitizing and rendering techniques. Although these early iterations lacked the computing power to combine maximum detail with surgical flexibility and dynamic change, they proved to be more than enough to establish the concept.

### Components of Virtual Reality

Construction of a virtual environment requires a computer system, a display monitor, an interface device, and compiler software. Surgical simulations and artificial environments are based on the same types of programming methods. Computational speed must be sufficient to power the graphics to deliver a minimum frame rate so that the user does not experience flicker or the perception of frames changing on the monitor. To accomplish this, the simulation should be delivered to the user's eye at no less than 30 Hz, or 30 frames per second. This is equivalent to most televisions. Five years ago, this kind of graphic generation required high-end graphics (Silicon Graphics, Mountain View, Calif.) or a workstation (SUN, Mountain View, Calif.). Now, dual-processor or single-processor personal computers can render graphics at this speed.

The software required to produce virtual worlds has specific requirements. First, the programmer must design the software to match the physical constraints of the real world. The heart, for example, cannot be allowed to float in thin air during a coronary bypass graft simulation. It must have some representation of gravity, compressibility, volume, and mass. These constraints, and more, must be considered for the virtual world to approach reality. Second, the software must be designed so that user interaction will be compiled and processed efficiently and accurately, so as not to become unstable to the user who is dynamically changing the simulation. Forceps pulling on tissue must appropriately deform the graphic representation of that tissue, for example. The software also must be able to communicate force feedback, through external devices, to the user in real time.

### Patient-Specific Virtual Reality

Surgical dissection, although second nature to a surgeon, is difficult to program into a computer system. The thousands of anatomic interactions can easily exceed the processor power; therefore digital rendering of patient data must be performed as efficiently as possible.

Patient-specific data for VR can come from several sources. MRI, magnetic resonance angiography, CT imaging, PET scanning, US scanning, and single photon emission CT imaging are among the common modalities. Traditionally, a physician mentally organizes these two-dimensional stacks of data, compiles it in his or her brain, and visualizes a 3D representation of the patient, not unlike the Visible Human data set (Fig. 4-23). With VR, these image stacks are meshed by the computer to realize the data in three dimensions automatically; this was previously a mental task, performed by the surgeon before an operation.[197]

Using different types of data sources, such as MRI or CT scanning, allows VR programmers to take advantage of the unique properties of each scanning method. CT scanning, for example, is particularly useful for scanning bones. MRI is more useful for soft tissue scanning. These properties can be combined to create a realistic VR image.

The manner in which these 3D images are represented within the system has a profound impact on the overall performance of the simulation. Patient data sets from CT scans, MRI, and other methods originate as voxels.[205,206] Voxel graphics are based on volume and result in an image that contains an infinite amount of data points. To compute changes in each point would put a tremendous strain on any computer. Other forms of VR rendering exist, however, to ease the strain on the system and to speed up the simulation.

### Surface Rendering

Rendering is the process of digitizing data into a computerized image by applying parameters to the data. To reduce the number of data points that require computation, surface rendering converts volume-based images into geometric primitives, which have far fewer data points.[207] This could be a patchwork of polygons that are based on the boundaries of different regions in the image. Boundary regions could be between fascia and fat or gray matter and white matter. Such separation requires knowledge of the properties of each region, because some blurring occurs in voxel images, such as CT scans. Shading algorithms can blend layers or regions so that the final product has a smooth appearance (Fig. 4-24). The number

**FIGURE 4-23** Visible Human Project. Reconstruction of a 3D model based on MRI and CT data. (Courtesy the National Library of Medicine Dataset.)

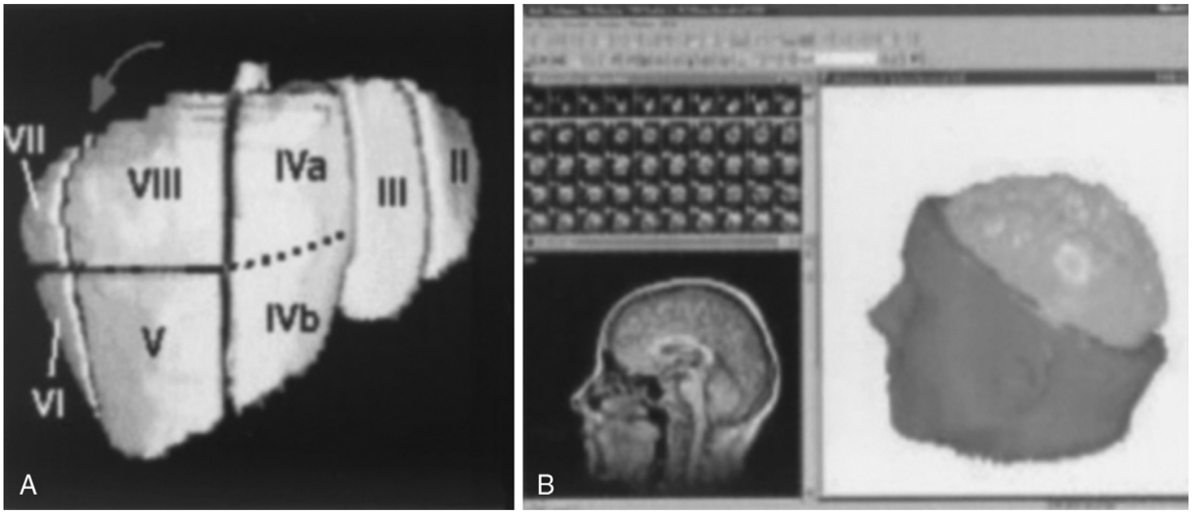



**FIGURE 4-24** Surface-rendered view of the liver (**A**) and brain (**B**). (Courtesy 3-D Doctor: 3-D Imaging, Rendering, and Measurement Software for Medical Images, Lexington, Mass.)

of geometric elements is extremely important in the surface method of VR. One must remember that each movement of the simulation by the user in virtual space requires a recalculation of each geometric object by the computer in real time. If there are too many polygons to reproduce quickly, then the simulation will "jerk," making it less real and perhaps unusable. When compared with voxel-based imagery, surface-rendered objects run unequivocally faster.

## Volume Rendering

Volume rendering requires special equipment to handle the immense amounts of data that must be compiled. This method works explicitly with volumetric data and renders them each time the data set is manipulated by the user. This is different from surface rendering in that surface rendering splits the volume into groups of polygonal surfaces. Surface-rendered objects are adequate when the surgeon wants to limit the inspection to the surface of an object, but as its name implies, surface rendering only displays the surface part of the data set. Currently, higher-end computer equipment, such as a graphics workstation, is necessary to render volume-based graphics.

## Finite Elements

Finite elements are based on geometric networks that are placed under the constraints of physics. Forces of pressure, elasticity, stress, and strain affect the shape and nature of

the object being manipulated. Such manipulation will affect not only the surface of the model but also the volume. When combined with a detailed graphic overlay, finite element models can provide the most accurate simulation to date.[206]

### Visual Displays

In a perfect world, VR can incorporate any, or all, of our five senses, but it usually relies most heavily on our most critical visual sense. The basics of our visual system can be categorized in three groups: depth perception, field of view, and critical fusion frequency.

Depth perception in humans is limited to approximately 30 meters, because the eyes are close together in relation to the distance being seen. VR systems must allow the user to reproduce these mechanisms, or proper depth cannot be achieved. The eye needs only a limited field of view to feel as though it is part of a virtual environment. Critical fusion frequency is the frequency at which static images, in rapid succession, appear to be a seamless stream of moving data. This is much like the old methods of animation in which shuffled flash cards gave the appearance of an animated cartoon. The approximate frequency for smooth video is approximately 30 to 40 Hz. Such displays must be capable of delivering a 3D image. The most dynamic form of VR visual display is the head mounted display. Although VR can be, and often is, represented on desktop monitors, the sense of immersion is not as complete when the participant is not in a closed system like an HMD. On a desktop monitor, a 3D environment is being projected on a 2D screen.

There are two basic methods of 3D visualization. The first method uses two separate displays, one to each eye, giving a stereoscopic effect. The second method uses a head-mounted tracking system that changes the perspective of the system to match the direction in which the user is looking. This tracking method must coordinate the movement of the user's head and hands.

Many different types of HMDs are available. The capabilities of a particular HMD depend on its final purpose. HMDs exist for personal video gaming, architecture, and missile guidance alike. There are also many modes of HMD instrumentation. Opaque displays, for example, completely occlude any visual contact with the outside world. Any visual input comes solely from the head-mounted video display.

Fakespace, Inc. (Menlo Park, Calif.) offers a binocular omni-orientation monitor (BOOM). This is a head-coupled display that is externally supported by a counterbalanced stand. Because this is not worn by the user and is supported by an external platform, the BOOM system can allow for additional hardware technology to be added to the system, thereby creating a very high-fidelity visual. Resolutions of 1280 × 1024, which are better than most computer monitors, are standard on the Fakespace system. The BOOM device is, of course, weightless to the user and relies on a motion-tracking system to keep face-forward perspective. The swivel stand allows for a superior degree of freedom (DOF) and field of view.

One of the more novel and immersive visual display systems is the Cave Automatic Virtual Environment (CAVE; Fakespace/Electronic Visualization Laboratories), which is a room-sized multiuser system. Graphics are projected stereoscopically onto the walls and the floor and are viewed with shutter glasses. Users wear position trackers that monitor the user's position within the CAVE by way of a supercomputer. Changes in perspective are constantly updated as the user moves around this "confined" space. Monocular head-mounted systems allow the wearer to have contact with the outside environment while data are delivered (Fig. 4-25). Surgical applications include the ability to perform an operation while simultaneously processing data about the patient's vital signs and imaging studies.

Virtual retinal displays scan light directly onto the viewer's retina. Because of this feature, the viewer perceives an especially wide field of view. Although still in development, retinal displays have so far been able to deliver resolutions close to human vision, while encased in a lightweight, portable system.[208] Virtual retinal displays have been developed at the University of Washington's Human Interface Technology laboratory.

### Input Devices

The best way to interact with the virtual world is with one's hands. It is both natural and intuitive. The DataGlove system (VPL Research, Redwood City, Calif.) (Fig. 4-26) is the archetypical system.

The DataGlove System frees up the user's hands from a keyboard. Commands are simplified, and tasks are carried out by rudimentary pointing or grasping in the virtual environment. Since the conception of the DataGlove, many manufacturers

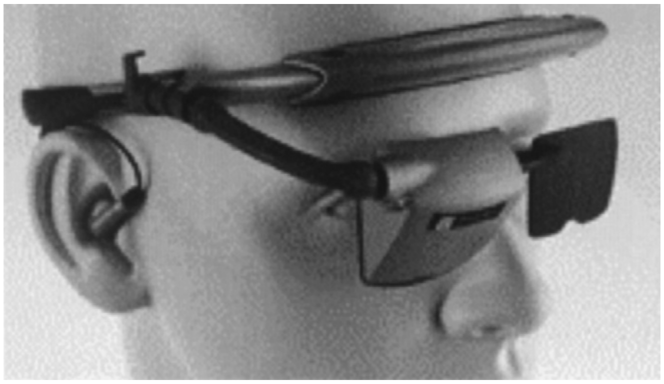


**FIGURE 4-25** eGlass II, with eye Blocker. (VirtualVision, Redmond, Wash.)

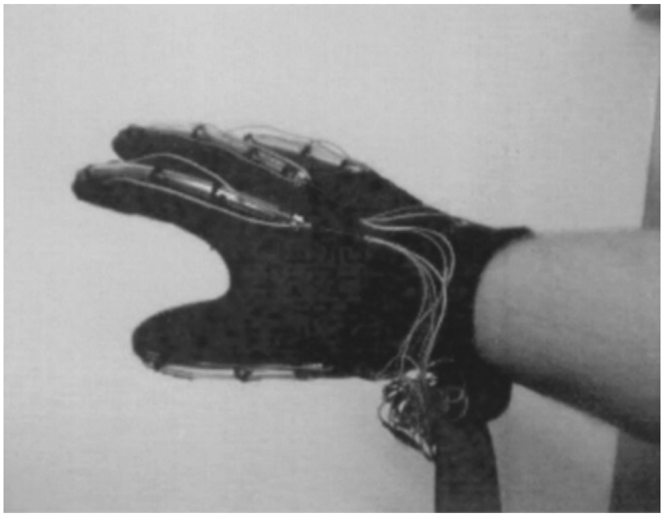


**FIGURE 4-26** Generic dataglove.

have developed similar interface products. Data gloves process information by many different methods. Some gloves use mechanical sensors or strain gauges over the joints of the hand to determine position. Other gloves use fiberoptic circuits to measure the change in light intensity and angle of the fiberoptic band as the hand flexes and extends. Trackers are also positioned on some gloves to monitor their position in free space. In any configuration, the data glove remains an intuitive solution to a complex problem.

### Force and Tactile Feedback

Force (resistance) and tactile (contact or touch) feedback could be the two most important goals of surgical VR, yet they are also among the most difficult to achieve. Surgeons rely on a keen sense of touch and resistance with the human environment, and without these senses, fidelity suffers. Laparoscopy is one example of how touch sense is displaced from the surgeon's hands.[209]

The tangible senses are very hard to generate artificially. Humans can easily judge the force with which to pick up a glass of water to bring it smoothly to the mouth. A computer, if incorrectly programmed, may mistake the picking up of a glass to the hoisting of a cinderblock, causing the virtual glass of water to be thrown completely across the room. Until recently, the one major component that was lacking in VR simulations was the sense of touch, or haptics.

Haptic feedback requires two basic features to render the sense of touch back to the user. First, the system needs a computer that is capable of calculating the interaction between the 3D graphics of the simulation and the user's hand, all in real time. Second, the loop requires some form of interface device (whether a joystick, a glove, or other device) for the user to be able to interact with the computer. The computer systems that support haptics are typically 3D graphics workstations with hardware video acceleration.[197,210] These systems are connected to an interface device, such as the popular PhanTOM joystick (SenseAble Technologies, Woburn, Mass.) (Fig. 4-27). Such joystick-based devices can function to provide up to six DOF. Again, the computer's visuals must refresh at a rate approximately 30 times per second to create a smooth simulation.

Like muscle linkages to bone, since all forces must be generated in relation to a point of fixation and an axis of motion, current force feedback systems require an exoskeleton of mechanical linkages. Force feedback systems currently use one of two approaches to this exoskeleton. The first system uses an exoskeleton that is mounted on the outside of the hand, similar to the ones used for electromechanical tracking. The linkages consist of several pulleys that are attached to small motors that use long cables. The motors are mounted away from the hand to reduce weight but can exert a force on various points of the fingers by pulling the appropriate cable. The second system consists of a set of small pneumatic pistons between the fingertips and a base plate on the palm of the hand. Forces can be applied to the fingertips only, by applying pressure to the pistons.

**FIGURE 4-27** PhanTOM interfaces. (SenseAble Technologies, Woburn, Mass.)

Because these systems reflect all their forces back to somewhere on the hand or wrist, they can allow you to grasp a virtual object and feel its shape but cannot stop you from passing your hand through that object. To prevent this, the exoskeleton must be extended to a base that is mounted on the floor through more linkages along the arm and body or an external system similar to a robot arm.

Multiple methods of generating force or tactile feedback have been developed. Piezoelectric vibration systems generate slight vibrations onto the user's fingertips when simulated contact is made. Electrotactile feedback works on the same principle of fingertip sensation, although there are no moving parts. A small current is passed over the skin surface in the case of virtual contact. Micropin arrays consist of a bed of fine pins that extend onto a fingertip to produce extremely fine details. Micropins can recreate the feeling of edges. Pneumatic feedback uses gloves with air pockets placed within the glove. These pockets inflate at the desired time to represent the sense of touching a surface. Temperature feedback uses heating coils on the hand to represent temperature change.

### Tracking in Virtual Reality

Virtual reality is based on spacial relationships. Even though the user is presented with a virtual representation of certain objects, the computer must know where the user is in relation to such objects. Otherwise, the user's hand, for example, would pass through a virtual glass rather than grasping it. Some VR systems solve this problem by following, or tracking, the critical interface points between the user and the computer. Tracking systems are placed on helmets and gloves so that the computer knows when to react. Several tracking methods exist.[202]

Mechanical tracking systems are physically in connection with the user's interface. The user's helmet is tethered at one end and interfaced with the computer at the other. This direct connection is fast, but the subject is always attached to the system, which limits movement.

Cameras in conjunction with small flashing beacons placed on the body can be used as a method for optical tracking. Multiple cameras taking pictures from different perspectives can analyze the configuration of the flashing light-emitting diodes on the body. These pieces of 2D data are compiled into a single 3D image. Such processing takes time, a critical drawback of optical tracking. Magnetic-field signals can be used; source elements placed on the hand can be tracked with a sensor. Disadvantages include interference from nearby magnetic sources and a maximum useable distance.

Acoustic trackers use high-frequency sound to triangulate to a source within the work area. These systems rely on line-of-sight between the source and the microphones and can suffer from acoustic reflections if they are surrounded by hard walls or other acoustically reflective surfaces. If multiple

acoustic trackers are used together, they must operate at nonconflicting frequencies, a strategy also used in magnetic tracking.

### Challenges of Virtual Reality

As with any emerging technology, there is an ebb and flow of hype and hope.[210] VR is no exception. In order to exceed the hype, areas that have the greatest room for improvement are graphics and haptic feedback. Because of the massive processing power that is required to create a full VR production, one must currently trade off graphic detail for performance. Currently, this means VR is defined by the phrase, "It can be good, fast, and cheap; pick two." This results in simulations that have a cartoon quality, so that they may have a reasonable run time. Even with a forced reduction in graphic detail, there is still a slight perception of delay, or lag, in the time between user interface and VR reaction. The visual representation of an incision is still very difficult to achieve accurately.

Haptic feedback requires equal computing power (if not more) and can cause instabilities or inaccuracies in the system. Many VR forced feedback systems can be forced to fail, by "pushing through" the force feedback and ruining the illusion.

### Virtual Reality Preoperative Planning

Beyond simple task training, one of the great advantages and goals of VR is the ability to plan and perform an operation on patient-specific data before actually performing the operation on the same human being. This goes far beyond early learning on a generic task or human. Surgeons, when planning an operation, traditionally compile data such as CT scans or MRIs, along with patient examinations and charts, into a solution envisioned in their head. It takes years of experience and training to master such visualization, especially when it comes to translating multiple 2D images into a 3D paradigm.

For many surgical specialties, VR techniques can assemble patient-specific data into graphic "before and after" images, which can be manipulated by the surgeon before the operation so that the outcome of the case may be predicted. These outcomes would be based on decisions that the surgeon would make during the operation. Furthermore, as more procedures are developed, VR preplanning can be used as a research model based on actual patient data that would be used to predict the outcome of a novel surgical application. VR enhancement also preemptively speeds up decision processes for complicated cases by providing the surgeon with a preplanned outline of the procedure, thereby making the hospital system more efficient. VR preoperative planning is available for general surgery, vascular surgery, plastic surgery, neurosurgery, and orthopedic surgery.

Craniofacial reconstructive surgery is a difficult task. The surgeon who is asked to handle a difficult or even routine operation of this kind reconstructs 3D data from 2D CT or MRI scans. No matter how experienced the surgeon, the predictions of outcomes in plastic reconstructions are limited, at best, with the use of this traditional method. As a result, the preoperative plan is often modified in the operating room during the operation. For these reasons, rehearsal and preparation with VR have been applied with increasing frequency in this area.[211,212]

There are many methods of computer-assisted planning for craniofacial surgery, but most produce a 3D interactive image that can predict the outcome of the case based on what the surgeon does on a workstation ahead of time. This process starts with a patient-specific CT or MRI scan that is cut in transverse sections, as is the case in facial reconstruction for trauma or malformation.[213] Once the images are scanned from the patient, they are segmented and specified into bone and soft tissue windows. This results in a mass of 2D cuts that must be rendered into a 3D environment. Patient-specific CT images are typically processed on a graphics workstation.

The University of Erlangen in Germany has demonstrated a method with "marching cubes" for 2D to 3D reconstruction from CT scans.[214] In this process, a CyberWare (Cyberware, Monterey, Calif.) scanner is used to scan the patient's skin surface features, which are compressed to reduce the volume of data. The skin and bone windows are compiled similarly into a 3D image. This image may be cut at any plane to focus on a particular area of interest. Keeve and colleagues[211] simulated a Dal-Pont osteotomy of the mandible using this technique. After the 3D image is rendered, any number of cutting, moving, and manipulating steps may be performed, which will predict the reconstructive outcome in the operating room (Fig. 4-28). "Before and after" pictures of actual patients with this type of computer-aided design models for facial reconstruction yield positive results.

The National Biocomputational Center at Stanford University uses a slightly different rendering paradigm that is based on CT images, called virtual environment for surgical planning and analysis (VESPA). Montgomery and colleagues[213] developed VESPA for use in craniofacial reconstruction, as well as breast

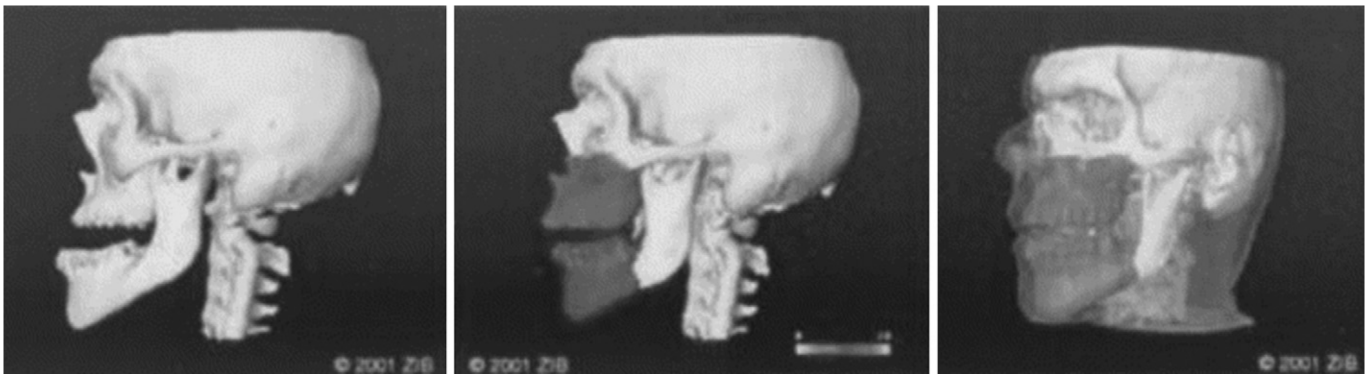


**FIGURE 4-28** 3D planning of a high Le Fort I-Osteotomy (Konrad-Zue-Zentrum for Informationstechnik, Berlin, Germany). (Courtesy SenseAble Technologies, Woburn, Mass.)

surgery, soft tissue reconstruction, and repair of congenital defects. Once CT images are acquired, voxel-based or volume-based images are focused down the area of interest, which results in very specific, segmented data. 3D images are broadcast onto a high-definition CRT monitor, and the user, who is wearing tracked CrystalEyes (StereoGraphics, San Rafael, Calif.) shutter glasses and a FasTrak (Polhemus, Colchester, Vt.) stylus for user input, can view and manipulate the virtual object.

The complexity of facial reconstructive surgery almost demands this kind of preoperative power, because conventionally there is only so much planning and prediction that can be performed by the surgeon who uses 2D conventions. Preplanning will allow the physician and the patient to view precise outcomes; this not only reassures both parties but also allows for reduced anesthesia times.

### Virtual Reality–Based Three-Dimensional Surgical Simulators

The actual practice of surgical procedures is a highly visual and, subsequently, manual task with constant visual and haptic feedback and modification.[215] This represents a formidable challenge. To create a VR surgical simulator for education or practice, the programmers must develop a system that adequately represents the surgical environment; it must react to the surgical changes (e.g., incision, dissection, resection) that the surgeon imparts to the operative field and must give the surgeon appropriate forced feedback. These prerequisites must be accomplished in a manner that is transparent to the surgeon (i.e., the virtual operation room should mimic a real operating room). Depending on the target audience and application, many surgical simulators have been developed. VR surgical simulators have been applied to open surgical procedures, laparoscopic surgery, and remote telepresent surgery.

The Karlsruhe "VEST" Endoscopic Surgery Trainer (IT VEST Systems AG, Bremen, Germany) is likely the most developed surgical endoscopic simulator (Fig. 4-29). This device mimics the surgically draped human abdomen and allows for the insertion of multiple laparoscopic instruments and an endoscopic camera. Force feedback is provided and applied to the laparoscopic instruments. Visual displays are generated with proprietary KISMET (Kinematic Simulation, Monitoring, and Off-Line Programming Environment for Telerobotics) 3D generation surgical environments.[216] This software affords the user high-fidelity immersion into a virtual laparoscopic scenario of a minimally invasive cholecystectomy, complete with real-time tissue dynamics and kinematic tissue response to user interaction. The laparoscopic instruments are tracked with sensors, to mimic the same DOF of actual endoscopic tools that are placed into a human abdominal cavity. This system is processed by a graphics workstation and has the ability to support total immersion goggles and telepresence training. As computing and graphic power become more developed, the graphic representations will become more detailed and hopefully approach that of the video monitors in an actual operating room.

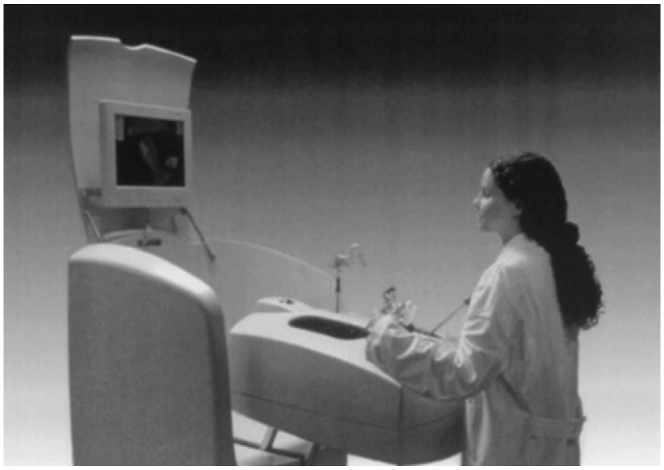


**FIGURE 4-29** VEST/LapSim One endoscopic surgical trainer. (IT VEST Systems AG, Bremen, Germany). (Courtesy of IT VEST Systems AG.)

Other surgical simulation systems are also available. Boston Dynamics (Cambridge, Mass.) has developed an anastomosis simulation with Pennsylvania State University based on force feedback surgical instruments and 3D vision with shutter goggles. This system allows the user to place sutures in a bowel or vessels to simulate the delicate nature of anastomosis. A "surgical report card" is a unique implementation in this system, which analyzes the surgeon's performance in real time. Comments on performance include time, accuracy, angle of needle insertion, and tissue damage.[217]

Virtual reality simulators for bronchoscopy, catheter insertion, and endoscopy are so real that residents and fellows use these to get exposure to procedures not already in their arsenal of experience. Stanford University has used the BronchSim and CathSim devices (Immersion Medical Technologies, Gaithersburg, Md.) and the VR Med Upper GI simulator (Fifth Dimension Technologies, Pretoria, South Africa) to evaluate surgical procedure training. A study that involved the BronchSim device that was conducted at Stanford University consisted of three sections: practice, navigation and visualization, and diagnosis and therapy. The subject was introduced to the bronchoscope and the simulation by a narrative from the training staff, which was supplemented by four videos on basic bronchoscopy, which were supplied with the Immersion Medical Technologies software. One of the tasks involved diagnosing an intraluminal bronchial wall tumor from CT scans and plain radiographs of the chest, then using the provided biopsy tool to safely take a sample of the tumor and control hemorrhage. The BronchSim device was able to distinguish between experts and novices, and subjective data from Likert questionnaires suggested an increase in procedural ability and familiarity in bronchoscopy. Similar educational studies were completed with the same internal structure for evaluation. These studies returned equally encouraging results.

With the advent of computer-assisted medicine, VR training tools have never been so accessible to medical educational programs as they are today. Our results, and the results of many others, suggest that surgical education that incorporates VR systems can be used in a training program, for both medical students and residents entering careers for which this procedure might be performed. Experience suggests that many VR simulator interfaces are realistic enough to serve not only as a teaching tool but also as a method for honing present skills.

## SIMULATION IN SURGICAL EDUCATION

Current training in surgery is focused on core knowledge, patient care, team training, and procedural skills. Surgical simulators can be used to enhance each of these components.

Simulation can be used for skills training, patient treatment, and crisis training in primary and continuing education for both residents and practicing surgeons.

Surgical simulation has been adopted by several surgical centers and residency programs through the formation of “simulation centers.” Mannequin simulators are being used to train surgical interns and residents in crisis treatment, and as a formal credentialing method for certain aspects of advanced cardiac life support (ACLS) and advanced trauma life support (ATLS).

As an example of mannequin-based core knowledge training, a simulation of initial burn surgical treatment has been developed. Treatment of acute burn injury is a core surgical skill, and proper treatment ranks in urgency with the care of a myocardial infarction. Despite the expertise needed to treat burns, only 20% of surgical residencies have a formal burn rotation.

The METI (Medical Education Technologies, Incorporated, Sarasota, Fla.) human patient simulator (HPS), a life-sized male mannequin model that is linked to a customizable computer system, was used. The HPS has been proven to simulate normal and pathologic states reliably and is certified for ATLS and ACLS credentialing. Simulated output is through standard bedside monitoring equipment, spontaneous respiration, eye opening, pulses, voice response, and robotic limb motion. The test scenario demonstrated a 40%, third-degree burn. Initially, expert intensive care and burn surgeons were asked to validate the scenario for accuracy and relevancy. Next, senior surgery residents were exposed to the 30-minute simulation. Lickert scale questionnaires and expert debriefings were provided to each of the subjects. Each resident’s performance was filmed for expert review by an attending physician. The computer-driven response of the HPS was based on the residents’ ability to perform ATLS, while simultaneously treating the burned patient with fluids, intubation, and escharotomy.

Attending physicians responded that the proposed scenario accurately reflected the key treatment points for ATLS protocols and burn treatment. These experts also perceived that residents who were exposed to the simulation could function as a physician responder in a similar situation. After being debriefed, each subject was more confident with burn treatment, fluid calculation, intubation and ventilator management, and thoracic and extremity escharotomies. Burn treatment simulation can teach residents to process situations that are not experienced in training and can function as a credentialing platform for new faculty. This first validation of simulated burn training with the HPS suggests a feasible solution to a serious educational dilemma.

Also popular are surgical “fly-through” VR-based tools that are designed to provide a medical student or resident with a first exposure to surgical anatomic relationships in three dimensions. Projects that involve the virtual human male have taken advantage of the data sets that were acquired from this model to create a virtual human anatomy resource in which the student may approach any anatomic structure from any angle or route. The Visible Human Project data sets can be rendered in three dimensions to create virtual detailed fly-through movies. These fly-throughs can be modified to demonstrate the before and after effects of many common surgical procedures and to provide an “endoscopic” view of the abdominal cavity. As more surgical procedures are developed that require more detailed and specific knowledge of surgical relationships, and as the time for surgical education continues to decrease, VR fly-throughs will provide an efficient solution to the education problem.

## TRAINING THE MINIMAL ACCESS THERAPIST

Because of the overlap between IGT, endoscopy, and surgery, interspecialty battles over the control of this field are to some extent inevitable. There is, however, a move toward the concept of a “minimal access therapist,” an individual with training in minimal access surgery, endoscopy, and imaging, and one who can independently deliver complex minimal access care.[82,218] How such a minimal access therapist will be trained and credentialed remains to be seen, but the development of this field will require the cooperation of surgeons, endoscopists, and radiologists. Simulation and the use of virtual reality will likely play a role. Pediatric surgery is already seeing a move in this direction as minimal access pediatric surgeons embrace the use of intraoperative US, fluoroscopy, and therapeutic endoscopy.

The vision for the integrated environment in which the minimal access therapist will work is radically different from the conventional operating room. Most notably, the surgeon’s view of the operative field will be complemented by augmented reality visualization in which the surgeon is aided by images showing what is beyond the visible surface. Instrumentation combining features of laparoscopic tools with endoscopic tools will be used, potentially with robotic guidance. The overall goal is to integrate preoperative and intraoperative imaging data with a robotic-assisted platform into a unified surgical delivery system.

## TRAINING THE SURGICAL INNOVATOR

Technology continues to advance rapidly, becoming more complex and interdisciplinary; at the same time, clinical surgery has become increasingly demanding, requiring intense focus. As a result, the gap between technical advances and creative surgeons is growing. This chapter is an attempt to narrow that gap.

If, indeed, change is constant, and that constant cycling has advanced our field, then it is incumbent upon us as a specialty to understand, thoughtfully incorporate, and even direct the useful change of surgical innovation. Surgeons are undeniably uniquely positioned and privileged to contribute to this cycle, but the growing gap creates a special field of knowledge perhaps requiring a specialized education program.

Formal education programs that teach the process of innovation to young surgeons are appearing across the country. One example is the Biodesign Program at Stanford University, a 2-year fellowship in surgical innovation offered to graduate level engineering students and residents. In the first year, fellows participate in didactic courses that teach the practical issues in needs assessment, technology solutions, intellectual property, ownership, the FDA approval process, and the underpinning economics of this process. A team-based project course is a large component of the first year. A second year is spent further developing an identified project. At the completion of the program the fellow has the requisite skills to become a significant contributor to the next cycle of surgical innovation in children and in adults. Depending on the prior background of the fellow, a Masters degree in bioengineering

is also achievable. Now in its 10th year, more than 80 graduates are now dispersed around the world, including one of the authors (RKW).

The Biodesign Program is part of a campus-wide interdisciplinary program entitled "Stanford's Bio-X Initiative" involving over 500 scientists from the life sciences, engineering, chemistry, and physics, with broad research themes in biocomputation, biophysics, genomics and proteomics, regenerative medicine, and chemical biology. Networks such as Bio-X focus explicitly on technology transfer to bring innovations bidirectionally to the bedside-to-bench cycle. This represents a unique academic program focused on the invention and implementation of new health-care technologies through interdisciplinary research and education at the emerging frontiers of engineering and the biomedical sciences.

## Conclusion

If pediatric surgery is to remain an active participant in the endless cycle of change, then an acknowledgement of the role of technology in advancing our care and a desire to actively embrace and drive the process forward in an ethical fashion is essential. To sit on the sideline is to invite a slow and agonizing death of us as individuals and, more critically, of our field and our responsibility to it. This two-volume text is a tribute to those who came before us and, in the space of less than 50 years, defined our specialty. We, as stewards of this generation, must be architects of the next 50 years.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 5

# Prenatal Diagnosis and Fetal Therapy

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As the field of fetal diagnosis and therapy expands, pediatric surgeons are increasingly involved in the management of surgical anomalies before birth. Advances in imaging and sampling of the fetus have increased the accuracy of the diagnosis of many anomalies and improved stratification of disease severity. These advances in prenatal diagnosis have led to improved perinatal care. Severe lesions detected early enough may lead to counseling and termination of pregnancy. Most correctable defects are best managed by optimizing location, mode and timing of delivery, and postnatal care of the infant (Table 5-1). Some prenatally diagnosed conditions have progressive and severe sequelae and may be treated with fetal intervention. Some attempts at fetal therapy have resulted in tremendous success, whereas many others have resulted in unclear or no improvement.

Finally, serial study of affected fetuses may help unravel the developmental pathophysiology of some surgically correctable lesions and thus lead to improved treatment before or after birth. It is important that surgeons familiar with the management of lesions after birth be involved in management decisions and family counseling.[1]

In this chapter we review the current techniques of fetal diagnosis and intervention and specific fetal anomalies that have particular interest to pediatric surgeons.

## Fetal Diagnosis

Over the past 4 decades, fetal diagnosis has improved tremendously. Obstetricians are now able to accurately detect many genetic anomalies prenatally and are able to detect many anatomic abnormalities by fetal ultrasonography (US), echocardiography, and magnetic resonance imaging (MRI). In this section we discuss invasive and noninvasive methods of diagnosis of fetal anomalies.

### BIOCHEMICAL SCREENING

An elevated alpha fetoprotein (AFP) level in maternal serum and amniotic fluid is a reliable indicator of a fetal abnormality. Although used to screen for neural tube defects, AFP is also elevated in defects such as omphalocele, gastroschisis, and sacrococcygeal teratoma, in which transudation of fetal serum is increased. AFP is the major glycoprotein of fetal serum and resembles albumin in molecular weight, amino acid sequence, and immunologic characteristics. The AFP level in fetal serum reaches a peak of 3 mg/mL at 13 to 15 weeks of gestation. AFP concentration in amniotic fluid follows a curve similar to that of fetal serum, but at a 150-fold dilution. Maternal serum levels continue to rise throughout pregnancy until the middle of the third trimester. Typically AFP is measured in the second trimester at 15 to 18 weeks. Measuring other markers—inhibin, estriol, and human chorionic gonadotropin—enhances aneuploidy screening. Testing of these four markers is referred to as a *quad screen.*

Increasingly screening for aneuploidy is being performed in the first trimester because of the results of the First and Second Trimester Evaluation of Risk (FASTER) trial. The FASTER trial compared the accuracy of second-trimester serum quad screening to first-trimester triple screening consisting of maternal serum testing for pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (beta-hCG) combined with an ultrasonographic examination to determine the fetal nuchal translucency. The sensitivity and specificity of detecting trisomy 21 in this study by noninvasive first-trimester screening were found to be comparable to noninvasive quad screening performed in the second trimester.[2]

### FETAL SAMPLING

Cells can be obtained for karyotyping and DNA-based diagnosis of many genetic defects and inherited metabolic abnormalities. Amniocentesis in the middle of the second trimester has been the most common method of fetal sampling. Chorionic villus sampling (transvaginal or transabdominal) as early as 10 weeks of gestation has become used increasingly because complication rates for the procedure are now comparable to those of amniocentesis.[3] Thus current first-trimester noninvasive screening or chorionic villus sampling, or both, give women earlier information with which to make decisions concerning their pregnancies.

Powerful new sorting techniques now allow isolation of fetal cells and free fetal DNA in the maternal circulation, allowing noninvasive genetic testing for fetal diseases by maternal blood sampling.[4,5] Increased access to fetal genetic

**TABLE 5-1**
**Prenatal Diagnosis and Management**

| |
|---|
| **Defects Usually Managed by Pregnancy Termination** |
| Anencephaly, hydranencephaly, alobar holoprosencephaly |
| Severe anomalies associated with chromosomal abnormalities (e.g., trisomy 13) |
| Bilateral renal agenesis, infantile polycystic kidney disease |
| Severe untreatable inherited metabolic disorders (e.g., Tay-Sachs disease) |
| Lethal bone dysplasias (e.g., thanatophoric dysplasia, recessive osteogenesis imperfecta) |
| **Defects Detectable In Utero but Best Corrected After Delivery Near Term** |
| Esophageal, duodenal, jejunoileal, and anorectal atresias |
| Meconium ileus (cystic fibrosis) |
| Enteric cysts and duplications |
| Small intact omphalocele and gastroschisis |
| Unilateral multicystic dysplastic kidney, hydronephrosis |
| Craniofacial, limb, and chest wall deformities |
| Simple cystic hygroma |
| Small sacrococcygeal teratoma, mesoblastic nephroma, neuroblastoma |
| Benign cysts (e.g., ovarian, mesenteric, choledochal) |
| **Defects That May Lead to Cesarean Delivery** |
| Conjoined twins |
| Giant or ruptured omphalocele, gastroschisis |
| Severe hydrocephalus; large or ruptured meningomyelocele |
| Large sacrococcygeal teratoma or cervical cystic hygroma |
| Malformations requiring preterm delivery in the presence of inadequate labor or fetal distress |
| **Defects That May Lead to Induced Preterm Delivery** |
| Progressively enlarging hydrocephalus, hydrothorax |
| Gastroschisis or ruptured omphalocele with damaged bowel |
| Intestinal ischemia and necrosis secondary to volvulus or meconium ileus |
| Progressive hydrops fetalis |
| Intrauterine growth retardation |
| Arrhythmias (e.g., supraventricular tachycardia with failure) |
| **Defects That May Require EXIT Procedure** |
| Congenital high airway obstruction syndrome (CHAOS) |
| Large cervical tumors (e.g., teratoma) |
| Masses obstructing trachea or mouth (e.g., cystic hygroma) |
| Conditions requiring immediate ECMO cannulation |
| Chest mass preventing lung expansion |

ECMO, extracorporeal membrane oxygenation.

material, combined with advances in the human genome project, has led to testing of greater numbers of genetic abnormalities prenatally. Increasingly, single nucleotide polymorphism arrays are being developed to genetically characterize diseases further and will clearly augment testing for aneuploidy in the future.[6]

## FETAL IMAGING

### Ultrasonography

Fetal anatomy, normal and abnormal, can be accurately delineated by US. This noninvasive technique appears to be safe for both the fetus and the mother and is now routinely applied in most pregnancies. Most anatomic surveys are performed in the middle of the second trimester between 18 and 20 weeks' gestation. The scope and reliability of the information obtained are directly proportional to the skill and experience of the ultrasonographer and ultrasonologist. For example management of a fetal defect requires a thorough evaluation of the fetus for other abnormalities because malformations often occur as part of a syndrome.

Real-time US may yield important information on fetal movement and fetal vital functions (heart rate, breathing movements) that reflect fetal well-being. Serial US evaluation is particularly useful in defining the natural history and progression of fetal disease. Further, US can stratify the severity of a disease. For instance details of the ultrasonogram that correlate with outcome include presence or absence of associated anomalies, presence or absence of hydrops fetalis, presence or absence of liver herniation into the chest, and relative lung size. The details of a complete anatomic survey are extensive and are covered elsewhere.[1] Finally, real-time US is critical for guidance during fetal interventions. It may be the only method of guidance in some procedures such as needle aspiration for fetal fluid or tissue sampling. For fetal endoscopic or open fetal procedures, US not only gives valuable information about the fetus but also gives information about the uterus, particularly placental location.

### Echocardiography

The field of echocardiography has seen rapid growth in the past 10 years because of advances in ultrasound technology and increasing experience with the assessment of the normal and abnormal fetal heart. Most structural cardiac anomalies can be detected prenatally.[7–9] Many abnormalities of interest to pediatric surgeons, such as congenital diaphragmatic hernia (CDH) and omphalocele, have a high incidence of associated structural cardiac anomalies, and the identification of these anomalies can affect postnatal outcome and prenatal counseling. The determination of cardiac function has played a significant role in predicting outcome for fetal anomalies that may cause cardiac dysfunction, such as sacrococcygeal teratoma and congenital pulmonary adenomatoid malformations, as well as twin anomalies that are less familiar to pediatric surgeons such as twin-twin transfusion syndrome (TTTS) and twin reversed arterial perfusion (TRAP) sequence. Further, fetal cardiac monitoring by perioperative echocardiography has been used to monitor the fetal response to surgery.[10] Finally, because the natural history of cardiac anomalies are now better understood,[9] ameliorating or reversing their progressive effects with fetal intervention by echocardiographic guidance has been attempted.[11–13]

### Magnetic Resonance Imaging

Although US remains the primary mode of imaging the fetus, magnetic resonance imaging (MRI) is used increasingly for a variety of abnormalities to evaluate the fetal spine, brain, and body. MRI has proved to be a valuable imaging technique because of the high resolution capabilities that are complementary to US, which is less costly and more accessible, and as a real-time modality that can show motion and changes over time. There are no known adverse effects of MRI on the fetus when it is performed with MRI scanners that are 1.5 T or less.[14] Figure 5-1 shows an ultrasonographic image of a CDH, and Figure 5-2 shows an MRI image of a CDH.

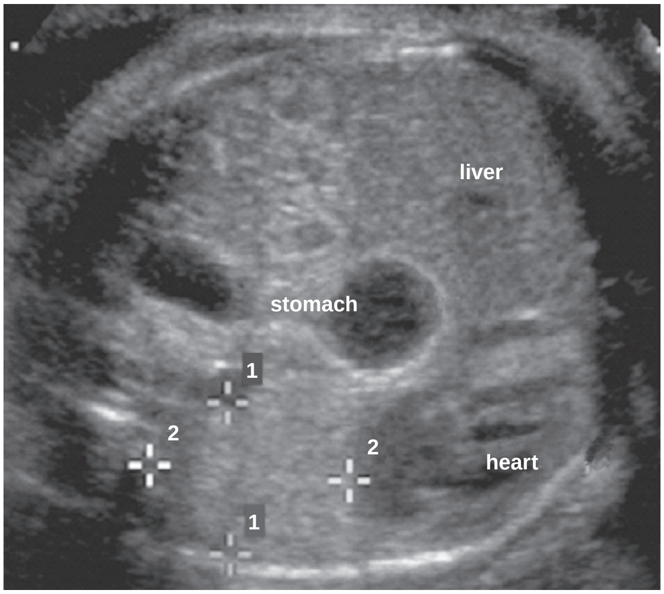



**FIGURE 5-1** Transaxial ultrasonographic image of the chest in a fetus with a left diaphragmatic hernia (liver, stomach, and heart labeled). Measurements of the right lung (*1* and *2*) are made using electronic calipers to calculate the LHR.

**TABLE 5-2**

**Fetal Conditions That May Require Prenatal Medical Treatment**

| *Defects* | *Treatment* |
|---|---|
| Erythroblastosis fetalis (erythrocyte deficiency) | Erythrocytes—intraperitoneal or intravenous |
| Pulmonary immaturity (surfactant deficiency) | Glucocorticoids—transplacental |
| Metabolic block (e.g., methylmalonic acidemia, multiple carboxylase deficiency) | Vitamin $B_{12}$—transplacental<br>Biotin—transplacental |
| Cardiac arrhythmia (supraventricular tachycardia) | Digitalis—transplacental<br>Propranolol—transplacental<br>Procainamide—transplacental |
| Endocrine deficiency (e.g., hypothyroidism, adrenal hyperplasia) | Thyroid—transamniotic<br>Corticosteroids—transplacental |
| Nutritional deficiency (e.g., intrauterine growth retardation) | Protein-calories—transamniotic or intravenous |

## Fetal Access

Although most prenatally diagnosed anatomic malformations are best managed by appropriate medical and surgical therapy after maternal transport and delivery, a few simple anatomic abnormalities that have predictable devastating developmental consequences may require correction before birth.[15] In the 1980s the developmental pathophysiology of several potentially correctable lesions was worked out in animal models; the natural history was determined by serial observation of human fetuses; selection criteria for intervention were developed; and anesthetic, tocolytic, and surgical techniques for hysterotomy and fetal surgery were refined.[1,15–20]

This investment in basic and clinical research has benefited an increasing number of fetal patients with a few relatively rare defects and will benefit many more as new forms of therapy—including stem cell transplantation, tissue engineering, and gene therapy—are applied to a wide variety of anatomic and biochemical defects. Some milestones in this development of fetal therapy appear in Table 5-2.

The technical aspects of hysterotomy for open fetal surgery that evolved over 30 years of experimental and clinical work are presented in Figure 5-3.[1] Because the morbidity of hysterotomy (particularly preterm labor) is significant, videoendoscopic fetal surgery (FETENDO) techniques that obviate the need for a uterine incision were developed (Fig. 5-4).[21] Percutaneous fetoscopic intervention has been applied clinically for diagnostic biopsies, laser ablation of

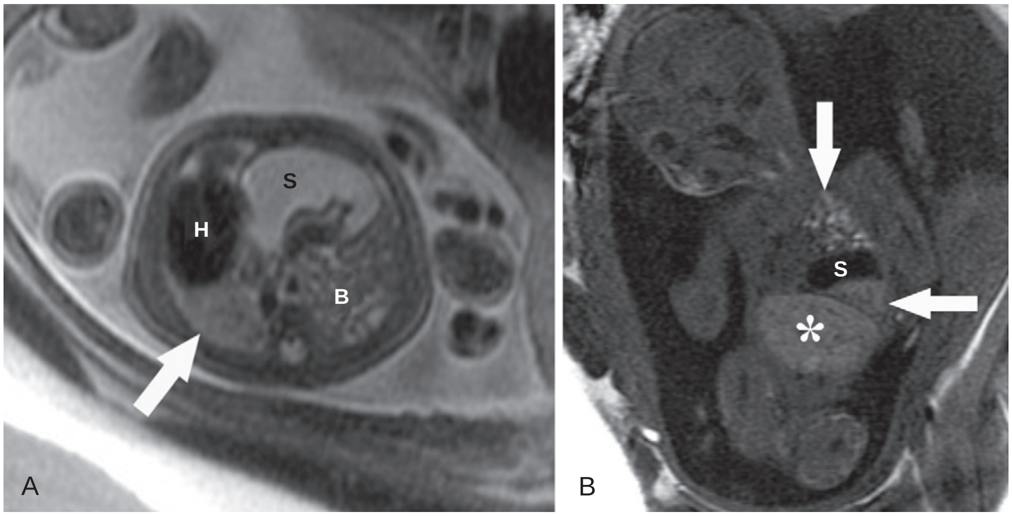



**FIGURE 5-2** **A,** Axial ssFSE T2-weighted image of a fetus at 24 weeks' gestation with a left-sided congenital diaphragmatic hernia (CDH). The heart *(H)* and right lung *(arrow)* are displaced to the right. The left lung is not visible, and instead the left side of the chest contains herniated stomach *(S)* and bowel *(B)*. **B,** Sagittal spoiled gradient-echo T1-weighted magnetic resonance image shows the stomach *(s)* in the left side of the chest. Note the liver *(asterisk)* is of relatively high signal intensity, facilitating the identification of the herniated left lobe *(horizontal arrow)* in the left side of the chest. The herniated bowel loops *(vertical arrow)* in the left side of the chest are also of relatively high signal intensity.

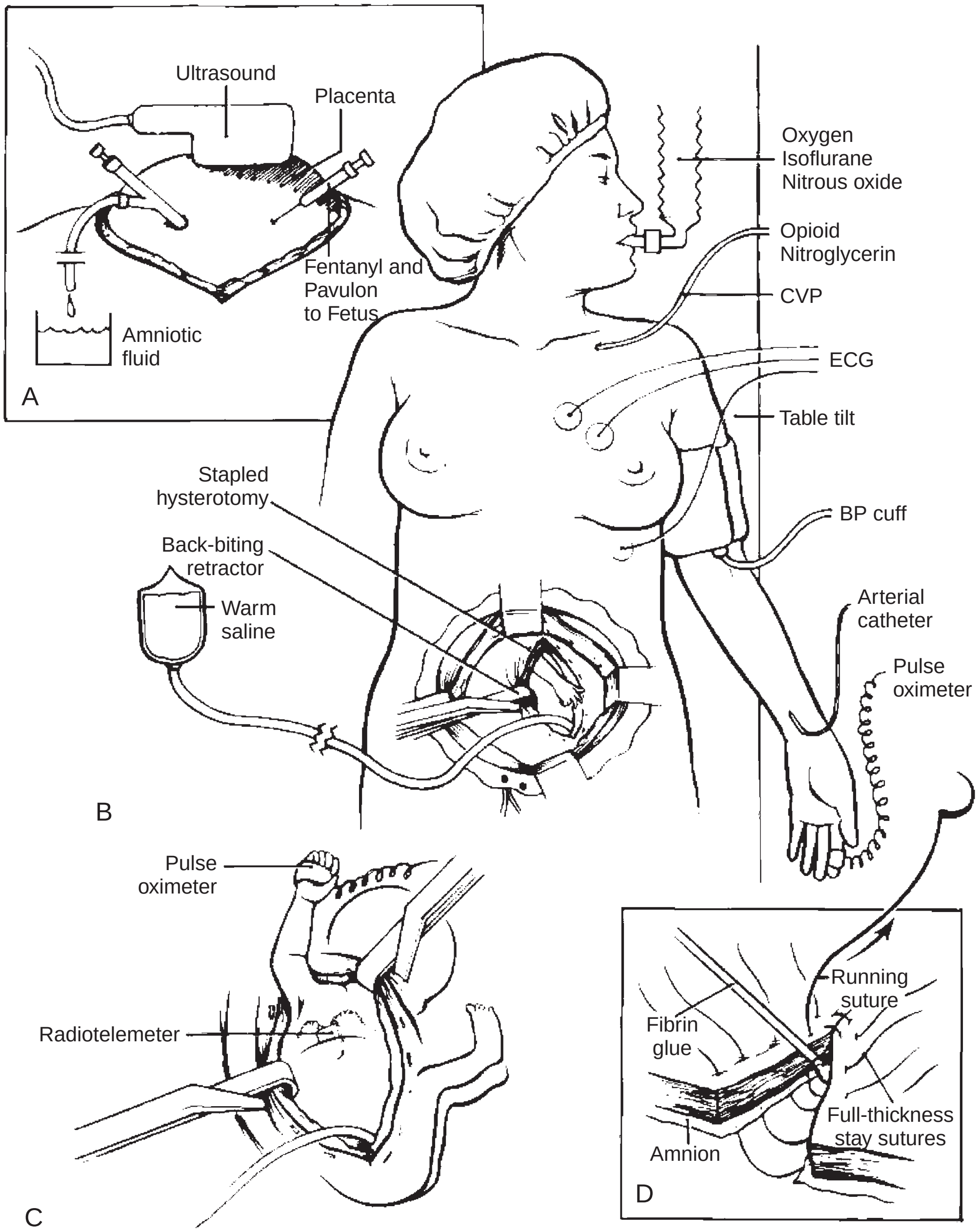



**FIGURE 5-3** Summary of open fetal surgery techniques. **A,** Uterus is exposed through a low transverse abdominal incision. Ultrasonography is used to localize the placenta, inject the fetus with narcotic and muscle relaxant, and aspirate amniotic fluid. **B,** The uterus is opened with staples that provide hemostasis and seal the membranes. Warm saline solution is continuously infused around the fetus. Maternal anesthesia, tocolysis, and monitoring are shown. **C,** Absorbable staples and back-biting clamps facilitate hysterotomy exposure of the pertinent fetal part. A miniaturized pulse oximeter records pulse rate and oxygen saturation intraoperatively. A radiotelemeter monitors fetal electrocardiogram *(ECG)* and amniotic pressure during and after operation. **D,** After fetal repair the uterine incision is closed with absorbable sutures and fibrin glue. Amniotic fluid is restored with warm lactated Ringer solution. BP, blood pressure; CVP, central venous pressure.

placental vessels in twin-twin transfusion syndrome,[22] fetal cystoscopy and urinary tract decompression,[23,24] cord ligature or division in anomalous twins,[25,26] division of amniotic bands, and tracheal occlusion for CDH.[27] Percutaneous ultrasonographically guided intervention has been applied to placement of catheter shunts (bladder, chest),[24,28] vascular access (heart,[29] umbilical vessels), radiofrequency ablation of large tumors or anomalous twins,[30] aspiration of fluid from fetal body cavities,[28] and administration of drugs or cells directly to the fetus.[31]

## Management of Mother and Fetus

Breaching the uterus, whether by puncture or incision, incites uterine contractions. Despite technical advances, disruption of membranes and preterm labor are the Achilles' heel of fetal therapy. Although halogenated inhalation agents provide satisfactory anesthesia for mother and fetus, the depth of anesthesia necessary to achieve intraoperative uterine relaxation

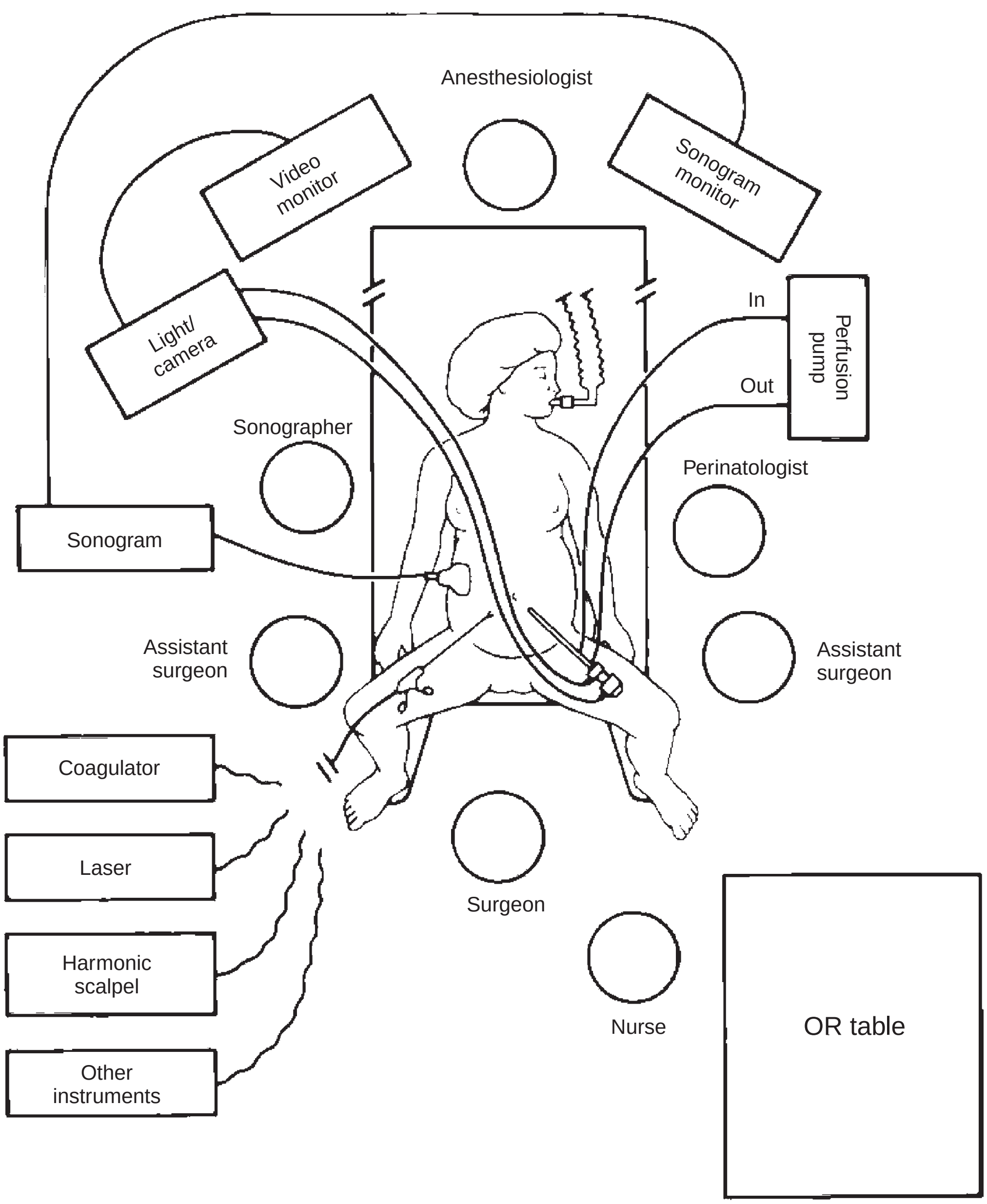



**FIGURE 5-4** Drawing of the operating room set-up. Note that there are two monitors at the head of the table: one for the fetoscopic picture and the other for the real-time ultrasonographic image.

can produce fetal and maternal myocardial depression and affect placental perfusion.[10] Indomethacin can constrict the fetal ductus arteriosus and the combination of magnesium sulfate and betamimetics can produce maternal pulmonary edema. The search for a more effective and less toxic tocolytic regimen led to the demonstration in monkeys that exogenous nitric oxide ablates preterm labor induced by hysterotomy.[32] Intravenous nitroglycerin is a potent tocolytic but requires careful control to avoid serious complications.[1]

Postoperative management is dictated by the degree of intervention. Open fetal surgery by maternal laparotomy and hysterotomy is usually performed with the patient under general anesthesia. Fetal well-being and uterine activity are recorded externally by tocodynamometer. Extensive monitoring, both fetal and maternal, continues postoperatively. Patient-controlled analgesia or continuous epidural analgesia, or both, ease maternal stress and aid tocolysis. After contractions are controlled, monitoring and tocolysis continue and fetal sonograms are obtained at least weekly. Open hysterotomy requires cesarean delivery in this and future pregnancies because of the potential for uterine rupture.[33,34] The most common immediate maternal complication is pulmonary edema due to the administration of perioperative tocolytic agents and intravenous fluids. The incidence was as high as 28% in previous experiences, but with refinement of surgical techniques and tocolytic management the incidence is now approximately 5%.[35] Bleeding that requires transfusion is an infrequent but significant complication of open fetal surgery. Preterm labor and membrane rupture are the most significant complications throughout the remainder of the pregnancy. Close monitoring for contractions, amount of amniotic fluid, membrane disruption,

and cervical shape and length must be performed throughout pregnancy.

Patients who undergo percutaneous procedures, performed either with fetoscopic guidance or with image guidance using 1- to 3-mm-diameter devices, usually receive regional or local anesthesia. The requirement for tocolytic therapy is significantly less than for open fetal surgery, and most patients can be safely discharged from the hospital within 24 to 48 hours after the procedure.[35] Maternal bleeding and pulmonary edema are rare. However membrane rupture and preterm labor remain significant complications,[22] and close monitoring is required throughout the remainder of pregnancy.

# Risks of Maternal-Fetal Surgery

The risk of the procedure for the fetus is weighed against the benefit of correction of a fatal or debilitating defect. The risks and benefits for the mother are more difficult to assess. Most fetal malformations do not directly threaten the mother's health, yet she must bear significant risk and discomfort from the procedure. She may choose to accept the risk for the sake of the unborn fetus and to alleviate the burden of raising a child with a severe malformation.

There is a paucity of published data on the maternal impact of fetal surgical interventions.[34] We analyzed maternal morbidity and mortality associated with different types of fetal intervention (open hysterotomy, different endoscopic procedures, and percutaneous techniques) to quantify this risk. We performed a retrospective evaluation of a continuous series of 187 procedures performed between July 1989 and May 2003 at the University of California, San Francisco (UCSF) Fetal Treatment Center.

Fetal surgery was performed in 87 patients by open hysterotomy, 69 patients underwent endoscopic techniques, and 31 patients underwent percutaneous techniques. There was no maternal mortality. Endoscopic procedures, even with laparotomy, showed statistically significantly less morbidity compared with the open hysterotomy group regarding cesarean section as the mode of delivery (94.8% versus 58.8%; $P < 0.001$), requirement for intensive care unit (ICU) stay (1.4% versus 26.4%; $P < 0.001$), length of hospital stay (7.9 days versus 11.9 days; $P = 0.001$), and requirement for blood transfusions (2.9% versus 12.6%; $P = 0.022$). It was not significant for premature rupture of membranes, pulmonary edema, abruptio placentae, postoperative vaginal bleeding, uncontrollable preterm labor leading to preterm delivery, or interval from fetal surgery to delivery. In more recent series, however, the incidence of pulmonary edema after percutaneous fetal endoscopic surgery has been low.[22] The group that had percutaneous procedures had the least morbidity.[35]

Our study of maternal outcome confirmed that fetal surgery can be performed without maternal mortality. Short-term morbidity can be serious, with impact on maternal health, length of pregnancy, and survival of the fetus.

Because midgestation hysterotomy is not performed in the lower uterine segment, delivery after fetal surgery and all future deliveries should be by cesarean section. In our series uterine disruptions occurred in subsequent pregnancies; uterine closure and neonatal outcome were excellent in both cases. Finally, the ability to carry and deliver subsequent infants does not appear to be jeopardized by fetal surgery.[33]

### PRENATAL DIAGNOSIS DICTATES PERINATAL MANAGEMENT

The nature of the defect determines perinatal management (see Table 5-1).[1] When serious malformations that are incompatible with postnatal life are diagnosed early enough, the family has the option of terminating the pregnancy. Most correctable malformations that can be diagnosed in utero are best managed by appropriate medical and surgical therapy after delivery near term; prenatal diagnosis allows delivery at a center where a neonatal surgical team is prepared. Elective cesarean delivery rather than a trial at vaginal delivery may be indicated for fetal malformations that cause dystocia or that will benefit from immediate surgical repair in a sterile environment.

Early delivery may be indicated for fetal conditions that require treatment as soon as possible after diagnosis, but the risk of prematurity itself must be carefully considered. The rationale for early delivery is unique to each anomaly but the principle remains the same: continued gestation will have progressive ill effects on the fetus. In some cases the function of a specific organ system is compromised by the lesion (e.g., hydronephrosis) and will continue to deteriorate until the lesion is corrected. In some malformations, the progressive ill effects on the fetus result directly from being in utero (e.g., the bowel damage in gastroschisis from exposure to amniotic fluid).

Some fetal deficiency states may be alleviated by treatment before birth (Table 5-3). For example blood can be transfused into the fetal peritoneal cavity or directly into the umbilical artery, and antiarrhythmic drugs can be given transplacentally to convert fetal supraventricular tachycardia. When the necessary substrate, medication, or nutrient cannot be delivered across the placenta, it may be injected into the amniotic fluid from which it can be swallowed and absorbed by the fetus. In the future it is possible that deficiencies in cellular function will be corrected by providing the appropriate stem cell graft or the appropriately engineered gene.[31,36]

# Fetal Anomalies

The only anatomic malformations that warrant consideration are those that interfere with fetal organ development and that if alleviated would allow normal development to proceed (Table 5-4). Initially a few life-threatening malformations were studied intensively and successfully corrected. Over the past two decades an increasing number of fetal defects have been defined and new treatments devised.[1,18] As less invasive interventional techniques are developed and proved safe, a few nonlethal anomalies (e.g., myelomeningocele) have become candidates for fetal surgical correction.[37–39] Finally, stem cell transplantation, gene therapy, and tissue engineering should open the door to treatment of a variety of inherited disorders.[31,36,40,41] In the next section of this chapter, we give an overview of fetal anomalies that may be amenable to fetal intervention as well as fetal anomalies that are of specific interest to pediatric surgeons.

### URINARY TRACT OBSTRUCTION

Fetal urethral obstruction produces pulmonary hypoplasia and renal dysplasia, and these often-fatal consequences can be ameliorated by urinary tract decompression before birth.[24]

The natural history of untreated fetal urinary tract obstruction is well documented, and selection criteria based on fetal urine electrolyte and ß$_2$-microglobulin levels and the ultrasonographic appearance of fetal kidneys have proved reliable.[24] Of all fetuses with urinary tract dilatation, as many as 90% do not require intervention. However fetuses with bilateral hydronephrosis due to urethral obstruction in whom oligohydramnios subsequently develops require treatment. If the lungs are mature the fetus can be delivered early for postnatal decompression. If the lungs are immature the bladder can be decompressed in utero by a vesicoamniotic shunt placed percutaneously using ultrasonographic guidance or by fetoscopic vesicostomy.[24,28] Fetal cystoscopic ablation of posterior urethral valves has also been reported, with the potential benefit of maintenance of the normal physiologic state of fetal bladder filling and emptying.[23,42]

Experience treating several hundred fetuses in many institutions suggests that selection is good enough to avoid inappropriate intervention and that restoration of amniotic fluid can prevent the development of fatal pulmonary hypoplasia. It is not yet clear how much renal function damage can be reversed by decompression. In one retrospective series of fetuses treated with vesicoamniotic shunting for lower urinary tract obstruction, survival at 1 year was 91%, with two neonatal deaths from pulmonary hypoplasia. There was a 39% incidence of prune belly syndrome, more than 50% demonstrated some renal dysfunction, and 33% required renal replacement. Approximately half of the children had persistent respiratory problems, musculoskeletal problems, and frequent urinary tract infections. Nearly two thirds of them had poor growth.[43] Identifying fetuses who may consistently have renal benefit from fetal intervention is likely contingent on the development of more sensitive biomarkers for early fetal renal dysfunction.

**TABLE 5-3**
**Milestones**

| | | |
|---|---|---|
| Intrauterine transfusion (IUT) for Rh disease | Women's National Hospital, Auckland, NZ | 1961 |
| Hysterotomy for fetal vascular access—IUT | University of Puerto Rico | 1964 |
| Fetoscopy—diagnostic | Yale | 1974 |
| Experimental pathophysiology (sheep model) | UCSF | 1980 |
| Hysterotomy and maternal safety (monkey model) | UCSF | 1981 |
| Vesicoamniotic shunt for uropathy | UCSF | 1982 |
| Open fetal surgery for uropathy | UCSF | 1983 |
| International Fetal Medicine and Surgery Society founded | Santa Barbara | 1982 |
| CCAM resection | UCSF | 1984 |
| First edition of *Unborn Patient: Prenatal Diagnosis and Treatment* | UCSF | 1984 |
| Intravascular transfusion | King's College, London University | 1985 |
| CDH open repair | UCSF | 1989 |
| Anomalous twin—cord ligation, RFA, and so on | King's College, London University | 1990 |
| NIH Trial: Open repair CDH | UCSF | 1990 |
| Aortic balloon valvuloplasty | King's College, London University | 1991 |
| SCT resection | UCSF | 1992 |
| Laser ablation of placental vessels | St Joseph's Hospital, Milwaukee; King's College, London University | 1995 |
| EXIT procedure for airway obstruction | UCSF | 1995 |
| Stem cell treatment for SCIDS | Detroit | 1996 |
| EXIT for CHAOS | CHOP | 1996 |
| Eurofetus founded | University Hospital Leuven, Belgium | 1997 |
| Myelomeningocele—open repair | Vanderbilt | 1997 |
| NIH Trial: FETENDO balloon CDH | UCSF | 1998 |
| Mediastinal teratoma resection | CHOP | 2000 |
| Eurofetus trial for twin-twin transfusion syndrome | University Hospital Gasthuisberg, Belgium; Universite Paris-Ouest Versailles, France | 2001 |
| NIH Trial: open repair myelomeningocele | UCSF, CHOP, Vanderbilt | 2002 |
| Balloon dilation for hypoplastic heart | Harvard | 2003 |
| NAFTNet founded | North America | 2005 |
| Percutaneous temporary tracheal occlusion for CDH | University Hospital Leuven, Belgium | 2006 |

CCAM, cystic adenomatoid malformation; CDH, congenital diaphragmatic hernia; CHAOS, congenital high airway obstruction syndrome; CHOP, Children's Hospital of Philadelphia; EXIT, ex utero intrapartum treatment; NIH, National Institutes of Health; RFA, radiofrequency ablation; SCIDS, severe combined immunodeficiency disease; SCT, sacrococcygeal teratoma; UCSF, University of California, San Francisco.

## AIRWAY OBSTRUCTION

The tracheal occlusion strategy for fetal CDH required development of techniques to safely reverse the obstruction at birth. The ex utero intrapartum treatment (EXIT) procedure is a technique in which the principles of fetal surgery (anesthesia for mother and fetus, complete uterine relaxation, and maintenance of umbilical circulation to support the fetus) are used during cesarean delivery to allow the airway to be secured while the fetus remains on maternal bypass. The EXIT procedure has been used successfully to reverse tracheal occlusion, repair the trachea, secure the airway by tracheotomy, resect large cervical tumors, place vascular cannulas for immediate extracorporeal membrane oxygenation (ECMO) (EXIT to ECMO), and manage laryngeal obstruction in congenital high airway obstruction syndrome (CHAOS).[44–46]

The EXIT procedure provides a wonderful opportunity for surgeons, perinatologists, neonatologists, and anesthesiologists to learn to work together, and this should be one of the first procedures done in developing a fetal treatment center.

## CONGENITAL PULMONARY AIRWAY MALFORMATION

Although congenital pulmonary airway malformation (CPAM), traditionally referred to as congenital cystic adenomatoid malformation (CCAM), often presents as a benign pulmonary mass in infants and children, some fetuses with large lesions die in utero or at birth from hydrops and pulmonary hypoplasia. The pathophysiologic characteristics of hydrops and the feasibility of resecting the fetal lung have been studied in animals. Experience managing more than 200 patients suggests that

**TABLE 5-4**

**Fetal Conditions That May Benefit from Treatment Before Birth**

***Effect on Development***

| | Rationale for Treatment | Result Without Treatment | Recommended Treatment |
|---|---|---|---|
| **Life-threatening defects** | | | |
| Urinary obstruction (urethral valves) | Hydronephrosis | Renal failure | Percutaneous vesicoamniotic shunt |
| | Lung hypoplasia | Pulmonary failure | Fetoscopic ablation of valves |
| | | | Open vesicostomy |
| Cystic adenomatoid malformation | Lung hypoplasia-hydrops | Hydrops, death | Open pulmonary lobectomy |
| | | | Ablation (laser/RFA) |
| | | | Steroids |
| Congenital diaphragmatic hernia | | | Open complete repair |
| | Lung hypoplasia | Pulmonary failure | Temporary tracheal occlusion |
| | | | Tracheal clip (open and fetoscopic) |
| | | | Fetoscopic balloon (percutaneous/reversible) |
| Sacrococcygeal teratoma | High-output failure | Hydrops, death | Open resection of tumor |
| | | | Vascular occlusion—RFA, alcohol |
| | | | RFA |
| Twin-twin transfusion syndrome | Donor-recipient steal through placenta | Fetal hydrops, death, neurologic damage to survivor | Fetoscopic laser ablation of placental vessels |
| | | | Amnioreduction |
| | | | Selective reduction |
| Acardiac/anomalous twin (TRAP) | Vascular steal | Death/damage to surviving twin | Selective reduction |
| | Embolization | | Cord occlusion/division |
| | | | RFA |
| Aqueductal stenosis | Hydrocephalus | Brain damage | Ventriculoamniotic shunt |
| Valvular obstruction | Hypoplastic heart | Cardiac failure | Balloon valvuloplasty |
| Congenital high airway obstruction (CHAOS) | Overdistention by lung fluid | | Fetoscopic tracheostomy |
| | | Hydrops, death | EXIT |
| Cervical teratoma | Airway obstruction | Hydrops, death | Open resection |
| | High-output failure | | EXIT |
| | | | Vascular occlusion—alcohol/RFA |
| **Non-life-threatening defects** | | | |
| Myelomeningocele | Spinal cord damage | Paralysis, neurogenic bladder/bowel, hydrocephalus | Open repair (NIH trial) |
| | | | Fetoscopic coverage |
| Gastroschisis | Bowel damage | Malnutrition/short bowel | Serial amnioexchange |
| Cleft lip and palate | Facial defect | Persistent deformity | Fetoscopic repair* |
| | | | Open repair |
| **Metabolic and cellular defects** | | | |
| Stem cell enzyme defects | Hemoglobinopathy | Anemia, hydrops | Fetal stem cell transplant<br>Fetal gene therapy* |
| | Immunodeficiency | Infection/death | |
| | Storage diseases | Retardation/death | |
| Predictable organ | Agenesis/hypoplasia heart/lung/kidney | Neonatal heart/lung/kidney failure | Induce tolerance for postnatal organ transplant*<br>Tissue engineering* |

*Not yet attempted in human fetuses.

CHAOS, congenital high airway obstruction syndrome; EXIT, ex utero intrapartum treatment; NIH, National Institutes of Health; RFA, radiofrequency ablation; TRAP, twin reversed arterial perfusion.

most lesions can be successfully treated after birth and that some lesions resolve before birth. Although only a few fetuses with very large lesions experience hydrops before 26 weeks of gestation, these lesions may progress rapidly and the fetuses die in utero.[47]

Careful ultrasonographic surveillance of large lesions is necessary to detect the first signs of hydrops because fetuses in whom hydrops develops can be successfully treated by emergency resection of the cystic lobe in utero.[48] Size of the CPAM is an important determinant of outcome and the most commonly used metric is the CCAM volume ratio (CVR). CVR is a ratio of the volume of CPAM/fetal head circumference, and higher CVR has been shown to produce a higher incidence of

the development of hydrops fetalis and perinatal mortality.[49] That study also found that microcystic CPAMs tend to plateau in size at 26 to 28 weeks of gestation, whereas macrocystic CPAMs may grow rapidly throughout gestation. Fetal pulmonary lobectomy for fetuses with microcystic CPAM and hydrops fetalis has proved surprisingly simple and quite successful at two large fetal surgery centers, although there is a high likelihood for preterm labor and premature delivery.[44] In 2003, we reported our initial experience with maternal corticosteroid administration for fetuses with microcystic CPAM lesions and hydrops, showing reversal of hydrops and survival in patients.[50] The cumulative data for treatment of 37 fetuses with large microcystic CPAMs at three centers showed 87% overall survival and 80% survival for those with hydrops (16/20 patients).[51] The effect of the steroids on the CPAM is unclear and difficult to elucidate as there is no sufficient animal model for microcystic CPAM. However some have speculated that CPAM represents an arrested state of normal lung development that has been characterized by increased cell proliferation and decreased apoptosis.[52]

We hypothesized that administration of maternal corticosteroids may drive maturation of microcystic CPAM tissue into more mature pulmonary tissue, decreasing proliferation of the lesions. The experience of treating large fetal macrocystic CPAM with maternal steroid administration has not been successful.[53] For lesions with single large cysts thoracoamniotic shunting has been the best option.[54]

## CONGENITAL DIAPHRAGMATIC HERNIA

The history of the evolution of fetal diagnosis and therapy for CDH outlines many of the successes and disappointments of the field. Prenatal diagnosis is now made routinely for CDH.

CDH can now be diagnosed accurately by midgestation, and the severity can be reasonably stratified by fetal US, MRI, and echocardiography. The diagnosis of fetal CDH is usually made by second-trimester anatomic ultrasonographic survey. Typical findings include mediastinal shift with abdominal viscera in the thorax. Careful attention is paid to the presence of other anomalies that can significantly affect the outcome for patients with CDH, including cardiac anomalies, aneuploidy, and other genetic syndromes such as Fryns syndrome. The most consistent prognostic factor for isolated CDH is presence or absence of liver herniation into the chest.[55] For prenatally diagnosed CDH, the presence of liver herniated into the chest is correlated with decreased survival compared with patients without liver herniation. Attempts at further stratifying the severity of CDH by determining relative lung size have met with variable success. The primary ultrasonographic measurement is lung/head ratio (LHR). To determine LHR a two-dimensional measurement of the lung is made at the level of the four-chambered view of the heart (numerator) and is compared with the head circumference to control for differences in gestational age and fetal size. LHR in the presence of liver herniated into the chest has been shown to have close correlation to survival in several single-institution series as well several multi-institutional series.[55,56] LHR shows substantial variability among ultrasonologists and requires an ultrasonologist with extensive experience in evaluating fetuses with CDH. LHR without liver herniation has not been shown to correlate with outcome.

Lung volume on MRI is the other primary measurement to determine severity of fetal CDH. Three-dimensional interpretation of fetal MRI data is performed and compared with nomograms for fetal lung volume to calculate the percentage of expected lung volume.[57] Some centers have found ultrasonographic measurements to be more predictive of outcome, whereas others have found MRI measurements to be more predictive.

Fetuses without liver herniation and with a favorable LHR (>1.4) have low mortality after term delivery at tertiary centers. However fetuses with liver herniation and a low LHR have high mortality and morbidity despite recent advances in intensive neonatal care, including ECMO, nitric oxide inhalation, high-frequency ventilation, and delayed operative repair of the diaphragmatic hernia.[19,58–63] The fundamental problem in newborns with CDH is pulmonary hypoplasia. Research in experimental animal models and later in human patients over 2 decades has aimed to improve growth of the hypoplastic lungs before they are needed for gas exchange at birth. Anatomic repair of the hernia by open hysterotomy proved feasible but did not decrease mortality and was abandoned.[64,65] Fetal tracheal occlusion was developed as an alternative strategy to promote fetal lung growth by preventing normal egress of lung fluid. Occlusion of the fetal trachea was shown to stimulate fetal lung growth in a variety of animal models.[66–68] Techniques to achieve reversible fetal tracheal occlusion were explored in animal models and then applied clinically, evolving from external metal clips placed on the trachea by open hysterotomy or fetoscopic neck dissection to internal tracheal occlusion with a detachable silicone balloon placed by fetal bronchoscopy through a single 5-mm uterine port.[69–71]

Our initial experience suggested that fetal endoscopic tracheal occlusion improved survival in human fetuses with severe CDH.[71–73] To evaluate this novel therapy we conducted a randomized controlled trial comparing tracheal occlusion with standard care.[74] Survival with fetal endoscopic tracheal occlusion (73%) met expectations (predicted 75%) and appeared better than that of historical controls (37%) but proved no better than that of concurrent randomized controls. The higher than expected survival in the standard care group may be because the study design mandated that patients in both treatment groups be delivered, resuscitated, and intensively managed in a unit experienced in caring for critically ill newborns with pulmonary hypoplasia.[74]

Attempts to improve outcome for severe CDH by treatments either before or after birth have proved double-edged swords. Intensive care after birth has improved survival but has increased long-term sequelae in survivors and is expensive.[19,59–61,63] Intervention before birth may increase lung size but prematurity caused by the intervention itself can be detrimental.[65,72,75–77] In our study newborns with severe CDH who had tracheal occlusion before birth were born on average at 31 weeks as a consequence of the intervention. The observation that their rates of survival and respiratory outcomes (including duration of oxygen requirement) were comparable to infants without tracheal occlusion who were born at 37 weeks suggests that tracheal occlusion improved pulmonary hypoplasia, but the improvement in lung growth was affected by pulmonary immaturity related to earlier delivery.[74]

The current results underscore the role of randomized trials in evaluating promising new therapies. This is the second National Institutes of Health (NIH)-sponsored trial studying a new prenatal intervention for severe fetal CDH. The first trial showed that complete surgical repair of the anatomic defect (which required hysterotomy), although feasible, was no better than postnatal repair in improving survival and was ineffective when the liver as well as the bowel were herniated.[65] That trial led to the abandonment of open complete repair at our institution and subsequently around the world. Information derived from that trial regarding measures of severity of pulmonary hypoplasia (including liver herniation and the development of the LHR) led to the development of an alternative physiologic strategy to enlarge the hypoplastic fetal lung by temporary tracheal occlusion[73,76,77] and to the development of less invasive fetal endoscopic techniques that did not require hysterotomy to achieve temporary reversible tracheal occlusion.[21,69,71]

Our ability to accurately diagnose and assess severity of CDH before birth has improved dramatically. Fetuses with CDH who have associated anomalies do poorly, whereas fetuses with isolated CDH, no liver herniation, and an LHR greater than 1.4 have an excellent prognosis (100% in our experience). In this study fetuses with an LHR between 0.9 and 1.4 had a chance of survival greater than 80% when delivered at a tertiary care center. The small number of fetuses with an LRH less than 0.9 had a poor prognosis in both treatment groups and should be the focus of ongoing study.[74] Further, animal models have shown that reversal of tracheal occlusion before delivery may minimize the damage to type II pneumocytes and surfactant production that prolonged tracheal occlusion may cause.[78]

With the advent of further miniaturized fetoscopic equipment, the group in Leuven, Belgium has led efforts to perform percutaneous temporary fetoscopic tracheal occlusion for isolated severe (liver herniation into chest, LHR <1.) CDH. They have reported 50% survival with gestational age at delivery of 34 weeks in fetuses undergoing temporary tracheal occlusion compared with survival of less than 15% in a cohort of fetuses with similar prenatal variables.[79] The European experience now consists of more than 200 patients with temporary tracheal occlusion, and a prospective randomized trial comparing that strategy to standard postnatal care is under way in Europe.[80] The low survival of patients with standard postnatal care in Europe has been criticized, as survival in that cohort in the United States at certain tertiary centers has been significantly higher. UCSF currently is conducting a safety and feasibility trial for temporary percutaneous fetoscopic tracheal occlusion for severe CDH with oversight by the US Food and Drug Administration (FDA).

## Myelomeningocele

Myelomeningocele is a devastating birth defect with sequelae that affect both the central and peripheral nervous systems. Altered cerebrospinal fluid dynamics result in the Chiari II malformation and hydrocephalus. Damage to the exposed spinal cord results in lifelong lower extremity neurologic deficiency, fetal and urinary incontinence, sexual dysfunction, and skeletal deformities. This defect carries enormous personal, familial, and societal costs, as the near-normal life span of the affected child is characterized by hospitalization, multiple operations, disability, and institutionalization. Although it has been assumed that the spinal cord itself is intrinsically malformed in children with this defect, recent work suggests that the neurologic impairment after birth may be due to exposure and trauma to the spinal cord in utero and that covering the exposed cord may prevent the development of the Chiari malformation.[37,39,81]

Since 1997 more than 200 fetuses have undergone in utero closure of myelomeningocele by open fetal surgery. Preliminary clinical evidence suggests that this procedure reduces the incidence of shunt-dependent hydrocephalus and restores the cerebellum and brainstem to a more normal configuration.[39] However clinical results of fetal surgery for myelomeningocele are based on comparisons with historical controls, examine only efficacy not safety, and lack long-term follow-up.

The NIH has funded a multicenter randomized clinical trial (Management of Myelomeningocele Study [MOMS]) of 200 patients that will be conducted at three fetal surgery units: the University of California, San Francisco; the Children's Hospital of Philadelphia; and Vanderbilt University Medical Center, along with an independent data and study coordinating center, the George Washington University Biostatistics Center. Since the inception of the trial Vanderbilt has dropped out as a surgical site.

Primary objectives of this randomized trial are (1) to determine if intrauterine repair of fetal myelomeningocele at 19 to 26 weeks' gestation using a standard multilayer closure improves outcome, as measured by death or the need for ventricular decompressive shunting by 1 year of life, compared with standard postnatal care and (2) to determine if intrauterine repair of myelomeningocele can improve motor function as well as cognitive function as measured by the Bayley Scales of Infant Development mental development index at 30 months' corrected age.[82] The study was closed to new patient enrollment on December 7, 2010, after 183 patients had been randomized because of the efficacy of prenatal repair. Specifically, prenatal repair of spina bifida reduced the need for ventricular shunting to treat hydrocephalus and improved motor outcomes including the ability to walk at 30 months of age.[98] Prenatal repair of MMC was also associated with significant maternal and neonatal risks, including premature birth and uterine scar issues.

### SACROCOCCYGEAL TERATOMA

Most neonates with sacrococcygeal teratoma survive and malignant invasion is unusual. However the prognosis of patients with sacrococcygeal teratoma diagnosed prenatally (by ultrasonography or elevated AFP levels) is less favorable. There is a subset of fetuses (fewer than 20%) with large tumors in whom hydrops develops from high-output failure secondary to extremely high blood flow through the tumor. Because hydrops progresses rapidly to fetal death, frequent ultrasonographic follow-up is mandatory. Excision of the tumor reverses the pathophysiology if it is performed before the mirror syndrome (maternal eclampsia) develops in the mother.[1,83] Attempts to interrupt the vascular steal by ablating blood flow to the tumor by alcohol injection or embolization have not been successful. Ultrasonographically guided radiofrequency ablation of the vascular pedicle has worked but with unacceptable damage to adjacent structures.

## Gastroschisis

Patients born with gastroschisis require immediate surgical intervention after birth with either primary or staged closure of the abdominal wall. Despite closure of the abdominal wall defect, many infants face prolonged difficulty with nutrient absorption and intestinal motility. At birth, the intestines of these patients are frequently thickened and covered by a fibrinous "peel." Mesenteric shortening and intestinal atresia may also be present. The bowel damage may be due to constriction of the mesentery (like a napkin ring), causing poor lymphatic and venous drainage from the bowel, or to an inflammatory reaction to various substances in the amniotic fluid bathing the bowel.[84]

With advances in neonatal care, survival for gastroschisis is now more than 90% in most series.[84–86] Serial amniotic fluid exchange has been used to dilute putative inflammatory mediators and thus prevent bowel damage.[87] However our ability to select fetuses with damaged bowels is limited, and the volume of exchange may be inadequate to alter outcome.

Despite high survival rates the complications of gastroschisis remain severe. Gastroschisis is one of the leading causes of short-bowel syndrome and one of the leading indications for small bowel transplantation. The main challenge in fetal treatment of gastroschisis has been identifying biomarkers to distinguish the small subset of fetuses who will have poor outcomes for both counseling and potential treatment. Unfortunately most attempts at predicting outcome by prenatal markers have been unsuccessful. The only prenatal marker that has been reproducible has been multiple intra-abdominal dilated loops of intestine on prenatal US.[88,89]

## INTESTINAL ABNORMALITIES

Nearly all abnormalities of fetal intestines are best managed postnatally. However pregnant women are frequently referred to pediatric surgeons for consultation. A common ultrasonographic finding is that of echogenic bowel, seen in up to 1.4% of all second-trimester ultrasonograms.[90] The vast majority of fetuses with echogenic bowel as an isolated anomaly have no clinical sequelae. However the presence of echogenic bowel does increase the risk of aneuploidy. Further, echogenic bowel can herald the presence of bowel injury from a variety of causes. The workup for echogenic bowel may include a detailed ultrasonogram of the fetus and an amniocentesis for karyotype for evidence of cytomegalovirus, toxoplasmosis, and parvovirus. Cystic fibrosis (CF) carrier testing for both parents and maternal serologic testing for recent cytomegalovirus and toxoplasmosis may also be performed. Follow-up with serial growth scans is recommended because these fetuses are potentially at risk for poor growth.

Evidence of frank bowel perforation is suggested by prenatal ultrasonographic findings of ascites, abdominal calcifications, pseudocysts, dilated loops of intestine, or polyhydramnios. The causes of bowel perforation in utero are similar to postnatal causes and are familiar to pediatric surgeons. They include intestinal atresias, meconium ileus, midgut volvulus, and intestinal ischemia. The majority of fetuses with evidence of bowel perforation usually require no surgery postnatally. However fetuses with pseudocysts or diffuse ascites are at higher risk for postnatal surgery and the possibility of long-term intestinal complications.[91]

Dilatation of intestine as an isolated finding usually indicates jejunal-ileal atresia. Without evidence of perforation, volvulus, or other complications, postnatal management results in excellent outcome.[92]

## ANOMALIES OF MONOCHORIONIC TWINS

Identical twins may have separate placentas (dichorionic) or share a placenta (monochorionic). Monochorionic twins may have unequal blood flow or unequal shares of the placenta and are at risk for discordant growth or more severe anomalies such as TTTS and TRAP sequence, two of the anomalies of monochorionic twinning that frequently require fetal surgery. Consultation for complications in monochorionic twins represents the most frequent consultation to fetal diagnosis and treatment centers. Further, the laser treatment for TTTS described later on is the most common fetal surgery performed both in the United States and worldwide.

## TWIN-TWIN TRANSFUSION SYNDROME

Branches of umbilical arteries and veins from one twin connect with branches of umbilical arteries and veins from the other twin on the surface of the placenta in all monochorionic twin pregnancies. In normal monochorionic twin pregnancies, the flow of blood is relatively balanced from one twin to the other.

TTTS is a complication of monochorionic multiple gestations resulting from an imbalance in blood flow through these vascular communications, or chorioangiopagus. This net imbalance in flow results in one twin (the "recipient") getting too much blood and becoming at risk for high-output cardiac failure and the other twin (the "donor) getting too little blood flow and becoming at risk for hypovolemia and hypoperfusion. Further, vascular mediators such as endothelin may exacerbate cardiac dysfunction in the recipient twin and cause progressive cardiac failure.[93]

It is the most common serious complication of monochorionic twin gestations, affecting between 4% and 35% of monochorionic twin pregnancies, or approximately 0.1 to 0.9 per 1000 births each year in the United States. Yet despite the relatively low incidence, TTTS disproportionately accounts for 17% of all perinatal mortality associated with twin gestations. Previously, standard therapy was limited to serial amnioreduction, which appears to improve the overall outcome but has little impact on the more severe end of the spectrum in TTTS. In addition survivors of TTTS treated by serial amnioreduction have an 18% to 26% incidence of significant neurologic and cardiac morbidity. Selective fetoscopic laser photocoagulation of chorioangiopagus has emerged as the gold standard for treatment of TTTS as demonstrated in a randomized trial in Europe.[22] This prospective randomized controlled trial compared fetoscopic laser coagulation of intertwin vessels to amnioreduction for severe TTTS, with the main outcome variable being survival of at least one twin. Survival of at least one twin was higher in the laser group compared with the amnioreduction group (76% versus 56%), with a decreased incidence of neurologic complications in the laser group. The authors concluded that laser coagulation for severe TTTS was superior to amnioreduction.[22]

## TWIN REVERSED ARTERIAL PERFUSION SEQUENCE

Acardiac/acephalic twinning is a rare anomaly in which a normal "pump" twin perfuses an acardiac twin, resulting in TRAP sequence. TRAP sequence in acardiac monochorionic twin gestations compromises the viability of the morphologically normal pump twin. Selective reduction and obliteration of blood flow in the acardiac twin has been accomplished by a variety of techniques, including fetectomy; ligation, division, and cauterization of the umbilical cord; and obliteration of the circulation in the anomalous twin by alcohol injection, electrocautery, or radiofrequency ablation.[25,26] We have pioneered a technique using radiofrequency technology with ultrasonographic guidance. We have used a 14-gauge or 17-gauge radiofrequency ablation (RFA) probe placed percutaneously into the body of the acardiac twin with real-time ultrasonographic guidance, which effectively obliterates the blood supply of the acardiac fetus and protects the pump twin.[26,94] Using this technique survival in monochorionic diamniotic TRAP pregnancies was 92%, with a mean gestational age of 36 weeks. The natural history of TRAP sequence has been reported at greater than 50% mortality.[95] Recently the North American Fetal Therapy Network presented a national registry of 98 pregnant women with TRAP sequence treated by RFA and found an 80% overall survival from 12 centers.[96]

## INHERITED DEFECTS CORRECTABLE BY FETAL STEM CELL TRANSPLANTATION

Various inherited defects that are potentially curable by hematopoietic stem cell (HSC) transplantation (e.g., immunodeficiencies, hemoglobinopathies, and storage diseases) can now be detected early in gestation. Postnatal bone marrow transplantation is limited by donor availability, graft rejection, graft-versus-host disease, and patient deterioration before transplantation, which often begins in utero. Transplantation of fetal HSCs early in gestation may circumvent these difficulties.[36,40,41]

The rationale for in utero rather than postnatal transplantation is that the preimmune fetus (<15 weeks) should not reject the transplanted cells, and the fetal bone marrow is primed to receive HSCs that migrate from the fetal liver. Thus myeloablation and immunosuppression may not be necessary. In addition in utero transplantation allows treatment before fetal health is compromised by the underlying disease. The disadvantage of treatment in utero is that the fetus is difficult to access for diagnosis and treatment. Definitive diagnosis using molecular genetic techniques requires fetal tissue obtained by transvaginal or transabdominal chorionic villus sampling, amniocentesis, or fetal blood sampling. Delivering even a small volume (<1 mL) of cells to an early-gestation fetus by intra-abdominal or intravenous injection requires skill and carries significant risks. The greatest potential problem with in utero transplantation of HSCs is that the degree of engraftment or chimerism may not be sufficient to cure or palliate some diseases. In diseases such as chronic granulomatous disease and severe combined immunodeficiency, relatively few normal donor cells can provide sufficient enzyme activity to alleviate symptoms. However a significantly higher degree of donor cell engraftment and expression in the periphery might be necessary to change the course of diseases such as ß-thalassemia or sickle cell disease. For diseases that require a high percentage of donor cells, a promising strategy is to induce tolerance in utero for subsequent postnatal booster injections from a living relative. The optimal source of donor HSCs for in utero transplantation is not known. Donor cells can be obtained from adult bone marrow or peripheral blood, from neonatal umbilical cord blood, or from the liver of an aborted fetus.

Clinical experience with fetal HSC transplantation is limited. Although engraftment has been successful in cases of severe combined immunodeficiency syndrome, for most other diseases low levels of engraftment after injection have limited clinical efficacy.[31,40,41]

## PAST AND FUTURE OF FETAL INTERVENTION

Although only a few fetal defects are currently amenable to surgical treatment, the enterprise of fetal surgery has produced some unexpected spin-offs that have interest beyond this narrow therapeutic field. For pediatricians, neonatologists, and dysmorphologists, the natural history and pathophysiologic features of many previously mysterious conditions of newborns have been clarified by following the development of the disease in utero. For obstetricians, perinatologists, and fetologists, techniques developed during experiments in lambs and monkeys will prove useful in managing other high-risk pregnancies. For example an absorbable stapling device developed for fetal surgery has been applied to cesarean sections; radiotelemetric monitoring has applications outside fetal surgery; and videoendoscopic techniques have allowed fetal manipulation without hysterotomy. These techniques will greatly extend the indications for fetal intervention. Finally, the intensive effort to solve the vexing problem of preterm labor after hysterotomy for fetal surgery has yielded new insight into the role of nitric oxide in myometrial contractions and has spawned interest in treating spontaneous preterm labor with nitric oxide donors.

Fetal surgical research has yielded advances in fetal biology with implications beyond fetal therapy. The serendipitous observation that fetal incisions heal without scarring has provided new insights into the biological characteristics of wound healing and has stimulated efforts to mimic the fetal process postnatally. Fetal tissue seems biologically and immunologically superior for transplantation and gene therapy, and fetal immunologic tolerance may allow a wide variety of inherited nonsurgical diseases to be cured by fetal HSC transplantation.

The great promise of fetal therapy is that for some diseases the earliest possible intervention (before birth) produces the best possible outcome (the best quality of life for the resources expended). However the promise of cost-effective preventive fetal therapy can be subverted by misguided clinical applications—for example, a complex in utero procedure that only half saves an otherwise-doomed fetus for a life of intensive (and expensive) care. Enthusiasm for fetal interventions must be tempered by reverence for the interests of the mother and her family, by careful study of the disease in experimental fetal animals and untreated human fetuses, and by a willingness to abandon therapy that does not prove both therapeutically effective and cost-effective in properly controlled trials. Advances must be achieved in a thoughtful manner that balances the potential benefits with the attendant risks, including those to the most important patient, the pregnant woman.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 6

# Neonatal Physiology and Metabolic Considerations

Agostino Pierro, Paolo De Coppi, and Simon Eaton

Advances in neonatal intensive care and surgery have significantly improved the survival of neonates with congenital or acquired abnormalities. This has been matched by an improvement in our understanding of the physiology of infants undergoing surgery and their metabolic response to starvation, anesthesia, operative stress, and systemic inflammation.[1] Newborn infants who undergo surgery are not just small adults; their physiology in terms of thermoregulation and fluid and caloric needs can be very different, particularly if the neonate is premature or has intrauterine growth retardation (IUGR). This chapter focuses on the physiology and metabolism of newborn infants undergoing surgery, with particular emphasis on the characteristics of preterm neonates. In this chapter we discuss fluid and electrolyte balance, neonatal energy metabolism and thermoregulation, and the metabolism of carbohydrate, fat, and protein. In addition, we present the current knowledge on the neonatal response to operative trauma and sepsis, which represent two of the major factors that alter their physiology.

## Premature, Small for Gestational Age, and Neonates with Intrauterine Growth Retardation

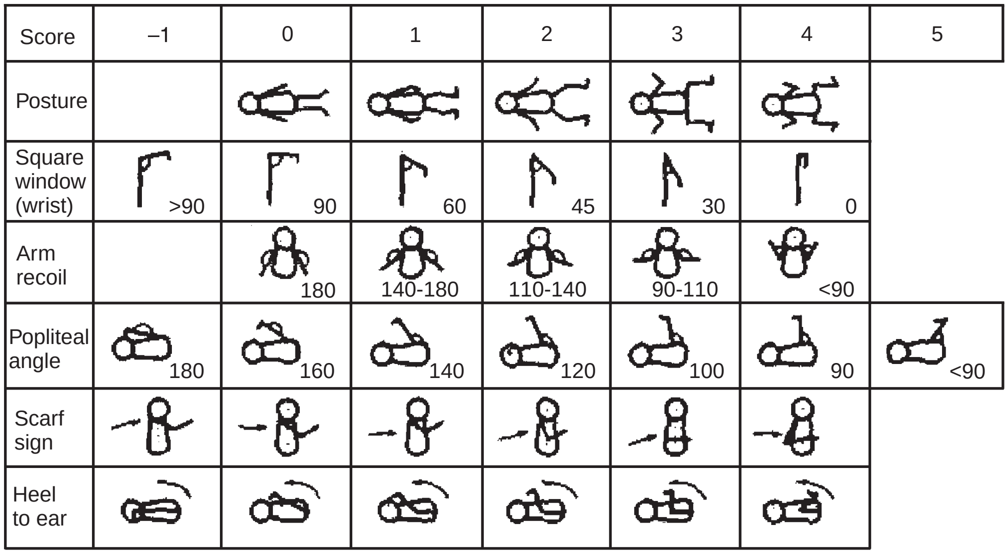
The greatest growth rate occurs during fetal life. In fact the passage from one fertilized cell to a 3.5-kg neonate encompasses an increase in length of 5000-fold, an increase in surface area of $61 \times 10^6$, and an increase in weight of $6 \times 10^{12}$. The greatest postnatal growth rate occurs just after birth. It is not unusual in neonates undergoing surgery to notice a period of slow or arrested growth during critical illness or soon after surgery.

Neonates can be classified as premature, term, or postmature according to gestational age. Any infant born before 37 weeks of gestation is defined as premature, term infants are those born between 37 and 42 weeks of gestation, and post-term neonates are born after 42 weeks of gestation. Previously any infant weighing less than 2500 g was termed premature. This definition is inappropriate because many neonates weighing less than 2500 g are mature or postmature but are small for gestational age (SGA); they have different appearance and different problems than do premature infants. The gestational age can be estimated antenatally or in the first days after birth using the Ballard score (Fig. 6-1).[2] By plotting body weight versus gestational age (Fig. 6-2),[3] newborn infants can be classified as small, appropriate, or large for gestational age. Head circumference and length are also plotted against gestational age to estimate intrauterine growth (Fig. 6-3).[3] Any infant whose weight is below the 10th percentile for gestational age is defined as SGA. Large for gestational age infants are those whose weight is above the 90th percentile for gestational age (see Fig. 6-2).[3] In general preterm infants weigh less than 2500 g, have a crown-heel length less than 47 cm, a head circumference less than 33 cm, and a thoracic circumference less than 30 cm. The preterm infant has physiologic handicaps due to functional and anatomic immaturity of various organs. Body temperature is difficult to maintain, there are commonly respiratory difficulties, renal function is immature, the ability to combat infection is inadequate, the conjugation and excretion of bilirubin is impaired, and hemorrhagic diathesis is more common.

Premature infants are usually further assigned to subgroups on the basis of birth weight as follows:

1. Moderately low birth weight (birth weight between 1501 and 2500 g): This group represents 82% of all premature infants. The mortality rate in this group is 40 times that in term infants.
2. Very low birth weight (birth weight between 1001 and 1500 g): This group represents 12% of premature infants. The mortality rate in this group is 200 times that in full-term newborns.
3. Extremely low birth weight (birth weight less than 1000 g): These neonates represent 6% of premature births but account for a disproportionate number of newborn deaths. The mortality rate is 600 times that in term infants.

The definition of IUGR is often confused and unclear in the medical literature. IUGR is usually defined as a documented decrease in intrauterine growth noted by fetal ultrasonography. IUGR can be temporary, leading to a normal-sized neonate at birth. There are two types of IUGR: symmetric and




Physical Maturity

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Skin | Sticky, friable, transparent | Gelatinous, red, translucent | Smooth, pink, visible veins | Superficial peeling and/or rash; few veins | Cracking, pale areas; rare veins | Parchment, deep cracking; no vessels | Leathery, cracked, wrinkled |
| Lanugo | None | Sparse | Abundant | Thinning | Bald areas | Mostly bald | |
| Plantar surface | Heel-toe 40-50 mm: –1 <40 mm: –2 | >50 mm, no crease | Faint red marks | Anterior transverse crease only | Creases anterior $^2/_3$ | Creases over entire sole | |
| Breast | Imperceptible | Barely perceptible | Flat areola, no bud | Stippled areola, 1–2 mm bud | Raised areola, 3–4 mm bud | Full areola, 5–10 mm bud | |
| Eye/ear | Lids fused loosely: –1 lightly: –2 | Lids open; pinna flat; stays folded | Slightly curved pinna; soft; slow recoil | Well-curved pinna; soft but ready recoil | Formed and firm, instant recoil | Thick cartilage, ear stiff | |
| Genitals (male) | Scrotum flat, smooth | Scrotum empty, faint rugae | Testes in upper canal, rare rugae | Testes descending, few rugae | Testes down, good rugae | Testes pendulous, deep rugae | |
| Genitals (female) | Clitoris prominent, labia flat | Clitoris prominent, small labia minora | Clitoris prominent, enlarging minora | Majora and minora equally prominent | Majora large, minora small | Majora cover clitoris and minora | |

Maturity Rating

| Score | Weeks |
|---|---|
| –10 | 20 |
| –5 | 22 |
| 0 | 24 |
| 5 | 26 |
| 10 | 28 |
| 15 | 30 |
| 20 | 32 |
| 25 | 34 |
| 30 | 36 |
| 35 | 38 |
| 40 | 40 |
| 45 | 42 |
| 50 | 44 |

**FIGURE 6-1** Ballard score for gestational age. (From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants. J Pediatr 1991;119:417–423.)

asymmetric. Symmetric IUGR denotes normal body proportions (small head and small body) and is considered a more severe form of IUGR.[4] Asymmetric IUGR denotes small abdominal circumference, decreased subcutaneous and abdominal fat, reduced skeletal muscle mass, and head circumference in the normal range. Infants with asymmetric IUGR show catch-up growth more frequently than do infants with symmetric IUGR, although 10% to 30% of all infants with IUGR remain short as children and adults. Premature infants are expected to have catch-up growth by 2 years of age. Those born after 29 weeks of gestation usually exhibit catch-up growth, whereas those born before 29 weeks of gestation are more likely to have a decreased rate of length and weight gain, which may be noted in the first week after birth and last up to 2 years.[5–7]

## Predicting Neonatal Mortality

Various factors contribute to the mortality of neonates. The most common factors are listed in Table 6-1. Although neonatal mortality decreased markedly as a result of improvements in care, it appears to have reached a plateau[8] at which small improvements in neonatal care may be offset by other secular trends such as increases in premature birth. Birth weight and gestational age are strong indicators of mortality, but ethnicity is also a factor (Fig. 6-4).[9] The survival of neonates of 500 g and 22 weeks' gestational age approaches 0%. With increasing gestational age, survival rates increase to approximately 15% at 23 weeks, 56% at 24 weeks, and 79% at 25 weeks of gestation. Scoring systems to predict mortality would be particularly useful in neonatal surgery to plan treatment, to counsel parents, and to compare outcomes between different centers.

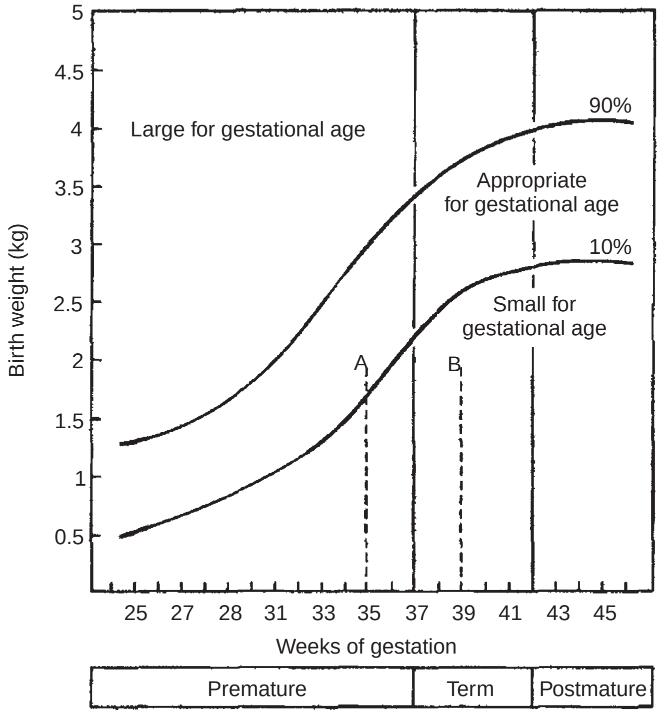



**FIGURE 6-2** Level of intrauterine growth based on birth weight and gestational age of live-born, single white infants. (From Disturbances in newborns and infants. In Beers MF, Berkow R [eds]: The Merck Manual of Diagnosis and Therapy, 17th ed. White House Station, NJ, Merck Research Laboratories, 1999, pp 2127–2145.)

However these scoring systems have not been developed and validated in neonatal surgery. Generic scoring systems for neonates are available but these do not take into consideration the anatomic abnormality requiring surgery. They are based on physiologic abnormalities such as hypotension-hypertension, acidosis, hypoxia, hypercapnia, anemia, and neutropenia (Score for Neonatal Acute Physiology [SNAP]) or clinical parameters such as gestational age, birth weight, anomalies, acidosis, and fraction of inspired oxygen ($F_{IO_2}$) (Clinical Risk Index for Babies [CRIB]).[10,11] CRIB includes 6 parameters collected in the first 12 hours after birth, and SNAP has 26 variables collected during the first 24 hours, and there have been various modifications to these scoring systems (e.g., CRIB-II, SNAP-II).[12] The authors have recently used[13] a modified organ failure score (Table 6-2) based on the Sepsis-related Organ Failure Assessment (SOFA) in use in adults and children to monitor the clinical status of neonates with acute abdominal emergencies who require surgery. Combining the surgeon's judgment and an objective score may produce an accurate assessment of the clinical progress of critically ill neonates and estimate their risk of mortality.

**TABLE 6-1**
**Major Causes of Mortality in Neonates Undergoing Surgery**

| *Preterm Neonates* | *Term Neonates* |
|---|---|
| Necrotizing enterocolitis | Congenital anomalies |
| Congenital anomalies | Infection |
| Severe immaturity | Persistent pulmonary hypertension |
| Respiratory distress syndrome | Meconium aspiration |
| Intraventricular hemorrhage | Birth asphyxia, trauma |
| Infection | |
| Bronchopulmonary dysplasia | |

# Fluid and Electrolyte Balance

## BODY WATER COMPOSITION

The content and distribution of intracellular and extracellular water in the human body is defined as total body water (TBW) and it changes with age. TBW also varies with body fat content. Fat cells contain very little water; therefore children with more body fat have a lower proportion of body water than

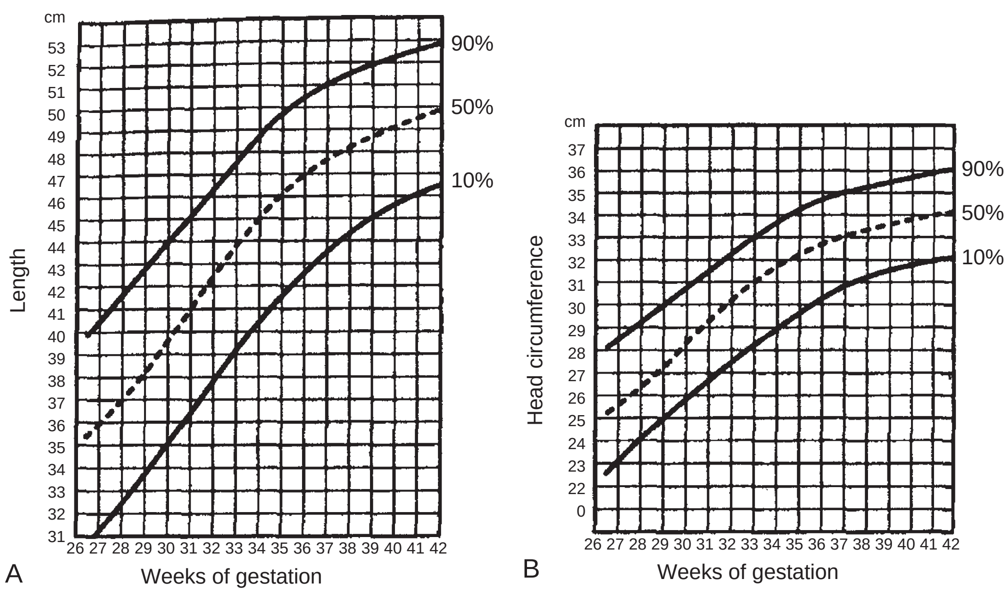



**FIGURE 6-3** Level of intrauterine growth based on gestational age, body length **(A)**, and head circumference **(B)** at birth. (From Disturbances in newborns and infants. In Beers MF, Berkow R [eds]: The Merck Manual of Diagnosis and Therapy, 17th ed. White House Station, NJ, Merck Research Laboratories, 1999, pp 2127–2145.)

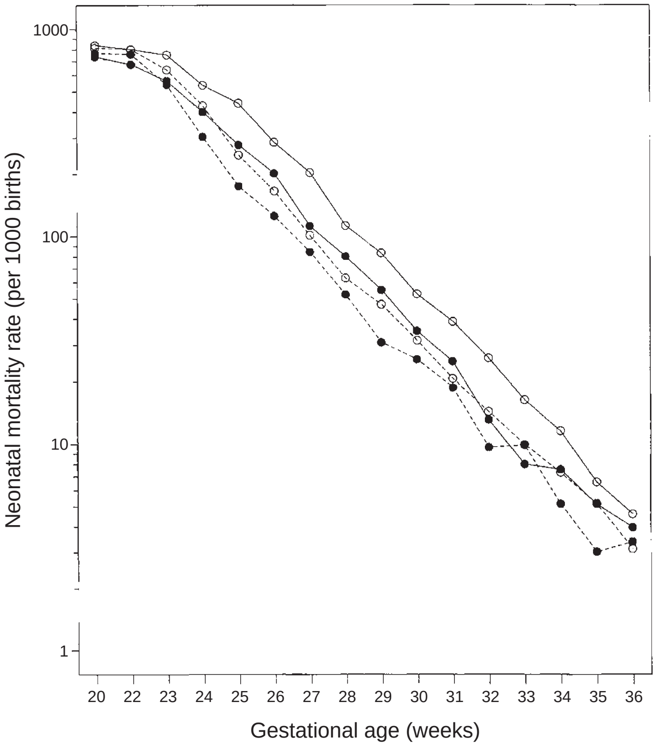



**FIGURE 6-4** Neonatal mortality, by gestational age, for black (•) and white (○) infants in the United States. Solid lines denote data for 1989; dashed lines are for 1997. Data shown are for less than 37 weeks' gestation only. (From Demissie K, Rhoads GG, Ananth CV, et al: Trends in preterm birth and neonatal mortality among blacks and whites in the United States from 1989 to 1997. Am J Epidemiol 2001;154:307-315.)

children with less fat. The water in body tissues includes the intracellular fluid, which represents the water contained within the cells, and extracellular fluid. Extracellular fluid is further subdivided into intravascular fluid (plasma), interstitial fluid (fluid surrounding tissue cells), and transcellular fluid (e.g., cerebrospinal, synovial, pleural, peritoneal fluid). During the first trimester, when only 1% of body mass is fat, 90% of body mass is TBW, with 65% of body mass made up of extracellular fluid.[14] However these ratios alter throughout gestation as the amount of body protein and fat increases. TBW as a proportion of body mass declines and is approximately 70% to 80% by term.[15] TBW continues to decline during the first year of life reaching 60% of total body mass, which is consistent with adult age. This is accompanied by a decrease in the extracellular compartment fluid (ECF)/intracellular compartment fluid (ICF) ratio. The ECF is 60% of total body mass at 20 weeks' gestation, declining to 40% at term, whereas ICF increases from 25% at 20 weeks' gestation to 35% of body mass at term and then to 43% at 2 months of age. Because extracellular fluid is more easily lost from the body than intracellular fluid and infants have a larger surface area/body mass ratio, they are more at risk of dehydration than are older children and adults.

Among preterm infants, those who are SGA have a significantly higher body water content (approximately 90%) than appropriate for full-term infants (approximately 80%).[16] Blood volume can be estimated as 106 mL/kg in preterm infants, 90 mL/kg in neonates, 80 mL/kg in infants and children and about 65 mL/kg in adults.[17,18] Adequate systemic perfusion depends on adequate intravascular volume, as well as many other factors. However infants and children can compensate for relatively large losses in circulating volume, and signs and symptoms of shock may be difficult to detect if a child has lost less than 25% of the circulating volume. The movement of fluid between the vascular space and the tissues depends on osmotic pressure, oncotic pressure, hydrostatic pressure, and changes in capillary permeability. Understanding these factors is important when trying to anticipate changes in the child's intravascular volume.[19]

## NEONATAL FLUID BALANCE

Before labor, pulmonary fluid production decreases while existing fluid is reabsorbed, and efflux through the trachea increases and accelerates during labor, thereby drying out the lungs. During labor, arterial pressure increases and causes shifts in plasma from the vascular compartment and a slight rise in hematocrit values. Placental transfusion can occur if

**TABLE 6-2**
**Modified Organ Failure Score***

To calculate the aggregate score, the worst value of each parameter in each time interval will be recorded. MAP = Mean Arterial Pressure

| | Score | | | | |
|---|---|---|---|---|---|
| ***Organ System*** | ***0*** | ***1*** | ***2*** | ***3*** | ***4*** |
| Respiratory $Pa_{O_2}/F_{IO_2}$ | >400 | ≤400 | ≤300 | ≤200 with respiratory support | ≤100 with respiratory support |
| Renal (urine output) | | | <1 mL/kg /hr for 6 hours | <0.5 mL/kg /hr for 6 hours | Anuria |
| Hepatic (serum bilirubin in µmol/L and [in mg/dL]) | | 20-32 [1.17-1.9] | 33-101 [2.0-5.9] | 102-204 [6.0-12.0] | >204 [> 12.0] |
| Cardiovascular (hypotension) | No hypotension | MAP < gestational age + age (weeks) mmHg | Dopamine ≤5 or dobutamine any dose | Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1 | Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 |
| Coagulation (platelet count) | >150 | ≤150 | ≤100 | ≤50 | ≤20 or platelet transfusion |

*$P$ < .05 vs. preoperative sample.
From Hall NJ, Eaton S, Peters MJ, et al: Mild controlled hypothermia in preterm neonates with advanced necrotizing enterocolitis. Pediatrics 2010;125:e300-e308.

there is delayed clamping of the cord and the neonate is placed at or below the level of the placenta, resulting in up to 50% increase in red blood cells and blood volume. This polycythemia may have severe consequences such as neurologic impairment, thrombus formation, and tissue ischemia.[20] One day postpartum the neonate is oliguric. Over the following 1 to 2 days, dramatic shifts in fluid from the intracellular to extracellular compartment result in a diuresis and natriuresis that contributes to weight loss during the first days of life. This is approximately 5% to 10% in the term neonate and 10% to 20% in the premature newborn. The proportion of contributions from ECF and ICF to fluid loss is controversial and the mechanism is yet to be determined. This diuresis occurs regardless of fluid intake or insensible losses and may be related to a postnatal surge in atrial natriuretic peptide.[21] Limitations in the methodology of measuring ECF and ICF have limited our understanding of the processes. It has been demonstrated however that large increases in water and calorie intake are required to reduce the weight loss. Higher caloric intake alone reduces weight loss but the ECF still decreases. Subsequent weight gain appears to be the result of increases in tissue mass and ICF per kilogram of body weight but not ECF per kilogram of body weight. By the fifth day postpartum, urinary excretion begins to reflect the fluid status of the infant.

## RENAL FUNCTION

The kidneys in neonates have small immature glomeruli and for this reason the glomerular filtration rate (GFR) is reduced (about 30 mL/min/1.73m$^2$ at birth to 100 mL/min/1.73m$^2$ at 9 months). Eventually renovascular resistance decreases, resulting in a rapid rise in GFR over the first 3 months of life followed by a slower rise to adult levels by 12 to 24 months of age. Premature and low-birth-weight infants may have a lower GFR than term infants, and the initial rapid rise in GFR is absent.

Urine osmolality is controlled by two mechanisms. Urine is concentrated in the loop of Henle using a countercurrent system dependent on the osmolality of the medullary interstitium. In neonates, the low osmolality in the renal medulla means the countercurrent system is less effective and urine concentration capacity is between 50 and 700 mOsm/kg compared with 1200 mOsm/kg in the adult kidney; therefore there is less tolerance for fluid imbalance.

## COMMON FLUID AND ELECTROLYTE DISTURBANCES AND THEIR TREATMENT

### Sodium

Serum sodium is the major determinant of serum osmolality and therefore extracellular fluid volume. Urinary sodium excretion is dependent on the GFR and therefore is low in neonates when compared with adults. Normal neonatal serum sodium levels are 135 to 140 mmol/L, controlled by moderating renal excretion. During the period of oliguria on the first day of life, sodium supplementation is not normally required. The normal maintenance sodium requirement after normal diuresis is 2 to 4 mmol/kg/day.

***Hyponatremia*** Hyponatremia is defined when serum sodium concentrations are less than 135 mmol/L. Treatment depends on the fluid status of the patient and in case of hypovolemia or hypervolemia, fluid status should be corrected first. When normovolemic, serum sodium levels should be gradually corrected with NaCl infusion, but at a rate not exceeding 0.8 mEq/kg/hr. Symptoms are not reliable for clinical management because they are not often apparent until serum sodium levels fall to less than 120 mmol/L, and their severity is directly related to the rapidity of onset and magnitude of hyponatremia. If not promptly recognized, hyponatremia may manifest as the effects of cerebral edema: apathy, nausea, vomiting, headache, fits, and coma. Urine sodium concentrations can be useful to help determine the underlying cause of hyponatremia because the kidneys respond to a fall in serum sodium levels by excreting more dilute urine, but the secretion of antidiuretic hormone (ADH)/vasopressin in response to hypovolemia affects this. Urine sodium concentrations less than 10 mmol/L indicates an appropriate renal response to euvolemic hyponatremia. However if the urinary sodium concentration is greater than 20 mmol/L this can indicate either sodium leakage from damaged renal tubules or hypervolemia.

***Hypernatremia*** Hypernatremia (serum sodium concentrations >145 mmol/L) may be due to hemoconcentration/excessive fluid losses (e.g., diarrhea). Symptoms and clinical signs include dry mucous membranes, loss of skin turgidity, drowsiness, irritability, hypertonicity, fits, and coma. Treatment is again by correction of fluid status with appropriate electrolyte-containing solutions. Other causes of hypernatremia are renal or respiratory insufficiency, or it can be related to drug administration.

### Potassium

In the 24 to 72 hours postpartum, a large shift of potassium from intracellular to extracellular compartments occurs, resulting in a rise in plasma potassium levels. This is followed by an increase of potassium excretion until the normal serum concentration of 3.5 to 5.8 mmol/L is achieved. Therefore supplementation is not required on the first day of life, but after neonatal diuresis a maintenance intake of 1 to 3 mmol/kg/day is required.

***Hypokalemia*** Hypokalemia is commonly iatrogenic, either due to inadequate potassium intake or use of diuretics but can also be caused by vomiting, diarrhea, alkalosis (which drives potassium intracellularly) or polyuric renal failure. As a consequence, the normal ion gradient is disrupted and predisposes to muscle current conduction abnormalities (e.g., cardiac arrhythmias, paralytic ileus, urinary retention, and respiratory muscle paralysis). Treatment employs the use of KCl.

***Hyperkalemia*** Hyperkalemia can be iatrogenic or due to renal problems but can also be caused by cell lysis syndrome (e.g., from trauma), adrenal insufficiency, insulin-dependent diabetes mellitus, or severe hemolysis or malignant hyperthermia. As in hypokalemia, hyperkalemia alters the electrical gradient of cell membranes and patients are vulnerable to cardiac arrhythmias, including asystole. Treatment is with insulin (plus glucose to avoid hypoglycemia) or with salbutamol.

### Calcium

Calcium plays important roles in enzyme activity, muscle contraction and relaxation, the blood coagulation cascade, bone metabolism, and nerve conduction. Calcium is

maintained at a total serum concentration of 1.8 to 2.1 mmol/L in neonates and 2 to 2.5 mmol/L in term infants and is divided into three fractions. Thirty percent to 50% is protein bound and 5% to 15% is complexed with citrate, lactate, bicarbonate, and inorganic ions. The remaining free calcium ions are metabolically active and concentrations fluctuate with serum albumin levels. Hydrogen ions compete reversibly with calcium for albumin-binding sites and therefore free calcium concentrations increase in acidosis. Calcium metabolism is under the control of many hormones but primarily 1,25-dihydroxycholecalciferol (gastrointestinal absorption of calcium, bone resorption, increased renal calcium reabsorption), parathyroid hormone (bone resorption, decreased urinary excretion), and calcitonin (bone formation and increased urinary excretion). Calcium is actively transported from maternal to fetal circulation against the concentration gradient, resulting in peripartum hypercalcemia. There is a transient fall in calcium postpartum to 1.8 to 2.1 mmol/L and a gradual rise to normal infant levels over 24 to 48 hours.

***Hypocalcemia*** In addition to the physiologic hypocalcemia of neonates which is usually asymptomatic, other causes of hypocalcemia are hypoparathyroidism, including DiGeorge syndrome, and parathyroid hormone insensitivity in infants of diabetic mothers, which may also be related to hypomagnesemia. Clinical manifestations are tremor, seizures, and a prolonged QT interval on electrocardiography.

***Hypercalcemia*** This is less common than hypocalcemia but can result from inborn errors of metabolism such as familial hypercalcemic hypocalcuria or primary hyperparathyroidism. Iatrogenic causes are vitamin A overdose or deficient dietary phosphate intake. Less common causes in children are tertiary hyperparathyroidism, paraneoplastic syndromes, and metastatic bone disease.

### Magnesium

As an important enzyme cofactor, magnesium affects adenosine triphosphate (ATP) metabolism and glycolysis. Only 20% of total body magnesium is exchangeable with the biologically active free ion form. The remainder is bound in bone or to intracellular protein, RNA, or ATP, mostly in muscle and liver. Gastrointestinal absorption of magnesium is controlled by vitamin D, parathyroid hormone, and sodium reabsorption. As previously stated, hypomagnesemia is often related to hypocalcemia and should be considered.

### Acid-Base Balance

Acidosis (pH <7.35) and alkalosis (pH >7.45) can be generated by respiratory or metabolic causes. When the cause is respiratory—$Pa_{CO_2}$ >45 mm Hg (acidosis) or <35 mm Hg (alkalosis)—treatment is with appropriate respiratory support. In case of metabolic causes—bicarbonate <21 mmol/L (acidosis) or > 26 mmol/L (alkalosis)—it is useful to check the anion gap $[Na^+ - (Cl^- + HCO_3^-)$, which is normally 12 ± 2 mEq/L] to understand the underlying cause. Treatment should be directed toward any underlying cause, for example, metabolic acidosis caused by dehydration or sepsis. The slow infusion of buffers such as sodium bicarbonate or tris-hydroxymethylaminomethane (THAM, a sodium-free buffer) should be used as therapeutic adjuncts. The amount of sodium bicarbonate required can be calculated using the following equation:

$$NaHCO_3 \text{ (mmol)} = \text{base excess} \times \text{body weight (kg)}$$

Acid-base balance is maintained by a complex system achieved by intracellular and extracellular buffer systems, respiration, and renal function. Intracellular systems consist of conjugate acid-base pairs in equilibrium as shown by the following equation (A = acid, H = proton):

$$HA \leftrightarrow H^+A^-$$

The pH can be derived from the Henderson-Hasselbalch equation:

$$pH = \frac{pK + \log[A^-]}{[HA]}$$

where pK is the dissociation constant of the weak acid, $[A^-]$ is the concentration of the dissociated acid, and [HA] is the concentration of the acid. The most important of these systems is the carbonic anhydrase system:

$$CO_2 + H_2O \leftrightarrow H^+ + HCO_3{}^-$$

Extracellular buffer systems are similar but the proton is loosely associated with proteins, hemoglobin, or phosphates and take several hours to equilibrate.

Respiratory compensation occurs through the carbonic anhydrase system, ridding the body of carbon dioxide and thereby shifting equilibrium to the left of the reaction and reducing the number of protons. The extent of the shift is influenced by the active transport of bicarbonate across the blood-brain barrier, thereby triggering central respiratory drive.

Normal extracellular pH is maintained at 7.35 to 7.45. Normal metabolic processes produce carbonic acid, lactic acid, ketoacids, phosphoric acid, and sulfuric acid, all of which are either excreted or controlled by a number of buffer systems.

In the neonate, loss of the contribution of the fetomaternal circulation and maternal respiratory and renal compensation mechanisms force adaptation and maturation. There is a suggestion that increased sensitivity of the respiratory centers to fluctuations in pH changes allow the neonate to control acid-base balance more. Increases in the intracellular protein mass allow greater intracellular buffering. The extracellular buffer systems are already functional.

Respiratory compensation becomes active as respiration is established. It relies on pulmonary function and lung maturity, and therefore neonates with lung disease may have impaired respiratory compensation. Carbon dioxide passes freely across the blood-brain barrier, allowing almost immediate response to respiratory acidosis from respiratory drive centers. The response to metabolic acidosis is delayed because interstitial bicarbonate requires a few hours to equilibrate with the cerebral bicarbonate.

Renal compensation is the most important mechanism available to the neonate for acid-base balance. Adjustments in urine acidity have been seen as soon as a few hours postpartum but it takes 2 to 3 days for it to fully mature. Consequent to the changes in renal function and perfusion described previously, the ability of the neonate to handle acid-base balance is limited in the first few days of life. Proximal tubules are responsible for the reabsorption of 85% to 90% of filtered bicarbonate but function less efficiently in

the premature neonate. Reabsorption can also be affected by some drugs used in neonates. Dopamine inhibits sodium/proton pump activity in the proximal tubules and therefore decreases the amount of bicarbonate that is reabsorbed. The remaining bicarbonate reabsorption takes place in the distal tubules, but they differ from the proximal tubules in their absence of carbonic anhydrase. Aldosterone is the most important hormone affecting distal tubular function and stimulates proton excretion in the distal tubules. However the distal nephrons of the premature infant are developmentally insensitive to aldosterone. Protons are excreted in the urine as phosphate, sulfate, and ammonium salts. This increases with age and gestation. However the introduction of phosphate-containing drugs increases phosphate delivery to the distal tubules and therefore can increase the capacity to excrete $H^+$. Dopamine decreases the reabsorption of protons in the distal tubules thereby increasing proton excretion.

### Intravenous Fluid Administration

***Fluid Maintenance*** Fluid administration varies with age as a consequence of the variation of TBW composition and the different compensatory mechanisms. Newborns can have a very wide range of maintenance requirements, depending on clinical conditions. In addition, especially in preterm infants, fluid administration should also allow for physiologic weight loss over the first 7 to 10 days of life (up to a maximum of 10% of birth weight), always maintaining a urine output of greater than or equal to 0.5 mL/kg/hr (Table 6-3).

Not only the amount of fluids but also the type of fluid administered varies according to age. In newborns, 10% dextrose solution is recommended. Sodium supplementation is not usually required in the first 24 hours (low urine output), and after that time can be given at 2 to 4 mmol/kg/day (adjusted primarily based on serum sodium values and changes in weight). Potassium (1 to 3 mmol/kg/day) and calcium (1 mmol/kg/day) are usually added after the first 2 days of life. In infancy and childhood various intravenous solutions are used (Table 6-4); probably the most common is 5% dextrose with one-half normal saline. Potassium is not usually necessary, except if intravenous fluid is given for a longer time. Fluids can be administered intravenously with peripherally or centrally placed catheters. In newborns, or in other situations in which dextrose is administered at more than 10%, peripheral administration is not recommended because of complications due to hyperosmolar solutions.

**TABLE 6-3**
**Normal Maintenance Fluid Requirements**

| | | |
|---|---|---|
| Premature infant | 1st day of life | 60-150 mL/kg/day |
| | 2nd day of life | 70-150 mL/kg/day |
| | 3rd day of life | 90-180 mL/kg/day |
| | >3rd day of life | Up to 200 mL/kg/day |
| Term infant | 1st day of life | 60-80 mL/kg/day |
| | 2nd day of life | 80-100 mL/kg/day |
| | 3rd day of life | 100-140 mL/kg/day |
| | >3rd day of life | Up to 160 mL/kg/day |
| Child > 4 weeks of age, up to 10 kg | | 100 mL/kg/day |
| Child from 10-20 kg | | 1000 mL + 50 mL/kg/day for each kg over 10 |
| Child >20 kg | | 1500 mL + 20 mL/kg/day for each kg over 20 |

## Energy Metabolism

Energy provides the ability to do work and is essential to all life processes. The unit of energy is the calorie or joule (J). One calorie = 4.184 J. One calorie equals the energy required to raise 1 g of water from 15° to 16° centigrade. The most widely used medical unit of energy is the kilocalorie (kcal), which is equal to 1000 calories. One joule equals the energy required to move 1 kilocalorie the distance of 1 meter with 1 newton of force. The first law of thermodynamics states that energy cannot be created or destroyed. Thus:

$$\text{Energy in} = \text{Energy out} + \text{Energy stored}$$

In the case of a neonate this can be expressed as:[22]

$$\begin{aligned}\text{Energy intake} = {} & \text{Energy losses in excreta} + \text{Energy stored} \\ & + \text{Energy of tissue synthesis} \\ & + \text{Energy expended on activity} \\ & + \text{Basal metabolic rate}\end{aligned}$$

### ENERGY INTAKE

The principal foodstuffs are carbohydrates, fats, and proteins (see later). The potential energy that can be derived from these foods is energy that is released when the food is completely absorbed and oxidized. The metabolizable energy is somewhat less than the energy intake, since energy is lost in the feces in the form of indigestible elements and in the urine in the form of incompletely metabolized compounds such as urea from amino acids or ketone bodies from fats.

**TABLE 6-4**
**Common Intravenous Fluids**

| *Intravenous fluid* | *Glucose (g/100 mL)* | *$Na^+$ (mEq/L)* | *$K^+$ (mEq/L)* | *$Cl^-$ (mEq/L)* | *Osmolality (mOsm/L)* |
|---|---|---|---|---|---|
| 5% dextrose | 5 | — | — | — | 252/277 |
| 10% dextrose | 10 | — | — | — | 505/556 |
| Normal saline (0.9% NaCl) | — | 154 | — | 154 | 308 |
| ½ Normal saline (0.45% NaCl) | — | 77 | — | 77 | 154 |
| 5% dextrose with ½ normal saline | 5 | 77 | — | 77 | 406 |
| 5% dextrose with ¼ normal saline | 5 | 34 | — | 34 | 329 |
| Lactated Ringer solution | 0 | 130 | 4 | 109 | 273 |
| Hartmann's solution | 0 | 131 | 5 | 111 | 278 |

Thus metabolizable energy can be calculated as the following equation:

$$\text{Metabolizable energy} = \text{Energy intake} - \text{Energy losses in urine and stool}$$

The foodstuffs are metabolized through a variety of complex metabolic pathways. Complete metabolism of a food requires that it be oxidized to carbon dioxide, water, and in the case of proteins urea and ammonia. This metabolism takes place according to predictable stoichiometric equations.[23] The energy liberated by oxidation is not used directly but is used to create high-energy intermediates, from which the energy can be released where and when it is required. The main intermediates are ATP (all cell types) and creatine phosphate (muscle and brain) but there are others.

These intermediates store the energy in the form of a high-energy phosphate bond. The energy is released when the bond is hydrolyzed. Formation of these high-energy intermediates may result directly from a step in a metabolic pathway. More often however they are created indirectly as the result of oxidative phosphorylation in mitochondria, the process by which a compound is oxidized by the sequential removal of hydrogen ions, which are then transferred through a variety of flavoproteins and cytochromes until they are combined with oxygen to produce water. This process releases large amounts of energy, which is used to form the high-energy phosphate bonds in the intermediates. Thus the energy in food is used to produce high-energy intermediates, the form of energy that is used for all processes of life. This process is the main oxygen-consuming process in the body, and the continual requirement for ATP for all energy requiring processes explains why oxygen delivery to the mitochondria of every cell is crucial for survival of these cells and ultimately the body as a whole.

Respiratory quotient is calculated as carbon dioxide production divided by oxygen consumption and varies with the substrate that is being oxidized. It has a numeric value of 1.0 for glucose oxidation and 0.70 to 0.72 for fat oxidation, depending on the chain length of fat oxidized. Thus the respiratory quotient, measured by indirect calorimetry, reflects the balance of substrate use. This situation is complicated however by partial oxidation of, for example, fats to ketone bodies or carbohydrate conversion to lipids, which will give a respiratory quotient greater than 1. Tables of precise respiratory quotient values for individual carbohydrates, fats, and amino acids are available.[23]

Birth represents a transition from the fetal state, in which carbohydrate is the principal energy substrate (approximately 80% of energy expended) to the infant state, in which both carbohydrate and fat are used to provide energy.[24] This transition is evidenced by the change in respiratory quotient, which declines from 0.97 at birth to 0.8 by 3 hours of age,[25,26] such that fat provides around 60% to 70% of energy expenditure. This is probably due to the fact that newborns have some initial difficulty in obtaining enough exogenous energy to meet their energy needs and are thus more dependent on their endogenous energy stores. Thereafter the respiratory quotient has been shown to increase slightly during the first week of life,[26–28] which suggests that newborns may preferentially metabolize fat in the first instance. Low-birth-weight infants have a respiratory quotient higher than 0.9 because of their limited fat stores and dependence on exogenous glucose.[29]

## ENERGY STORAGE

Although glucose is an essential source of energy, the circulation only contains approximately 200 mg glucose at birth in a term infant, which is only enough to support whole-body requirements for 15 minutes. The body does not store glucose directly because of osmotic problems, but glucose can be indirectly stored in the liver, kidneys, and muscles (and to a lesser degree in other cells) as glycogen. Muscle glycogen can only be used in situ, but liver and kidney glycogen can be used to produce glucose for metabolism in other sites. Glycogen stores in a term infant approximate 35 g (~140 kcal), enough to sustain energy requirements for between 12 and 24 hours. Energy is stored mainly as fat, which has two advantages. First, there is more energy stored per gram of fat (9 kcal/g) than glycogen (4 kcal/g). Second, although fat is stored as globules in adipose tissue and requires little hydration (~15% of its own mass in water), glycogen is stored as a hydrated polymer and so requires four times its own mass in water. Taking both these factors into consideration, 9.4 times as much glycogen mass (with its associated water) would need to be stored as the equivalent caloric amount of fat. A term infant has about 460 g of fat, which is capable of yielding 4140 kcal of energy on oxidation, enough energy for a 21-day fast. Protein largely performs functions other than energy storage, although some of the 525 g of protein (~60% intracellular; ~40% extracellular) in a term infant can be used as a source of energy during severe fasting, yielding 4 kcal/g. The serious consequences of oxidizing protein include wasting, reduced wound healing, edema, failure of growth/neurologic development, and reduced resistance to infection. The relative amounts of fat and carbohydrate stored as a proportion of body mass alter in the last trimester of gestation as the relative hydration decreases, so preterm infants have much lower caloric reserves than do term infants (Fig. 6-5).

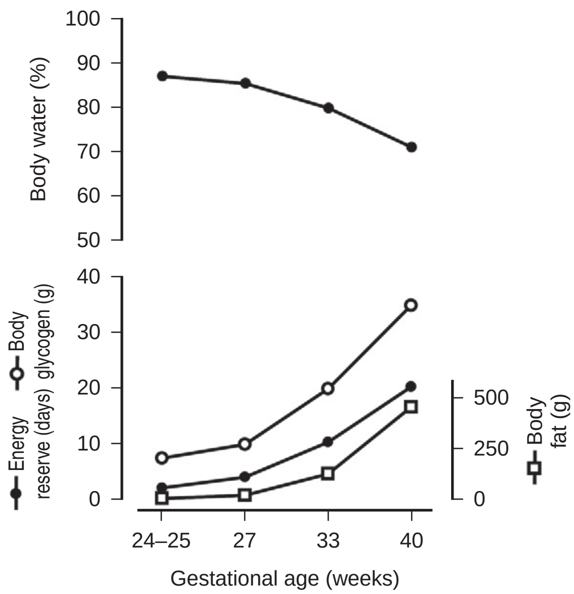



**FIGURE 6-5** Body water and energy stores according to gestational age.

## ENERGY OF GROWTH AND TISSUE SYNTHESIS

In stable mature adults little energy is needed for growth. However in neonates the energy requirements for growth are considerable. In infants up to 50% of the energy intake can be used for growth.[22,30] The energy required to lay down tissue stores includes two components: (1) the energy stored within the tissue itself (i.e., 9 kcal/g of fat, 4 kcal/g of carbohydrate or protein) and (2) the energy investment needed to convert the food into storable and usable substrates. Studies have shown this additional investment to be on the order of 5% to 30% of the energy value of the tissue.[31] The rate of growth of premature infants is on the order of 17 to 19 g/kg/day,[32] whereas that of full-term infants is 4 to 8 g/kg/day.[33] In addition, in rapidly growing premature infants more of the weight gain is as protein. Although protein has a lower energy value per unit weight than does fat, it requires a greater energy investment. Thus the energy cost of growth is much greater in the premature infant largely due to the rate of protein accretion.[34–37] In rapidly growing premature infants, this metabolic cost of growth has been estimated to be 1.2 kcal/g of weight gained, which represents about 30% of total energy expenditure.[34,37]

## ENERGY LOSSES

Infants lose energy in the excreta. Because of the immaturity of the gut and kidney and potentially inadequate supply of bile acids, stool and urine losses may be proportionally higher than in adults. This is especially true for infants undergoing surgery or those with gastroenterologic problems. Conversely parenterally fed infants have low or absent energy losses in stools, although there may be urinary losses.

## ENERGY USED IN ACTIVITY

Studies have shown that energy expenditure varies considerably with changes in the activity of the infant. Vigorous activity such as crying may double energy expenditure,[36] but because most of the time is spent sleeping,[36] the energy expended on activity is less than 5% of the total daily energy expenditure.[22] Studies have shown that daily energy expenditure is related to both the duration and level of activity.[27,35]

## BASAL METABOLIC RATE AND RESTING ENERGY EXPENDITURE

Basic metabolic rate represents the amount of energy used by the body for homeostasis: maintaining ion gradients, neurologic activity, cell maintenance, synthesis of extracellular proteins such as albumin, and so on. Because of ethical considerations, it is not possible to completely starve a newborn for the 14 hours required for a measurement of basal metabolic rate. As a result resting energy expenditure (REE) is much more commonly used as the basis of metabolic studies. REE is influenced by a number of factors, including age, body composition, size of vital organs, and energy intake.

### Age

The REE of a full-term, appropriate-for-gestational-age infant increases from 33 kcal/kg/day at birth, to 48 kcal/kg/day by the end of the first week of life.[38,39] It then remains constant for 1 month before declining. REE is higher in premature and SGA infants than in full-term and appropriate-for-gestational age infants.[40] The differences discussed probably reflect changes in body composition,[38] although it has been suggested that the increase in basal metabolism during the first week of life may represent increased enzyme activity in functioning organs.[41]

### Body Composition

During the first weeks of life infants lose body water. This is accompanied by a well-recognized loss of body weight.[25] Immediately before birth, a term infant is approximately 75% water, but by 1 month of age the water content has reduced to 45%.[42,43] Thus the increase in REE observed during the first weeks of life may reflect the relative increase in body tissue and the relative decrease in body water. These differences in body composition also result in an alteration in the ratio of basal metabolic rate/nonprotein energy reserve (Fig. 6-6).

### Size of Vital Organs

The brain, liver, heart, and kidneys account for up to 66% of basal metabolic rate in adults yet make up only 7% of total body weight. In infants these organs, particularly the brain, account for a greater proportion of body weight. It is believed that the brain alone may account for 60% to 65% of basal metabolic rate during the first month of life. In premature and SGA infants, the vital organs are less affected by intrauterine and extrauterine malnutrition than are other organs.[38,40] Thus their contribution to basal metabolism is even greater.[32] The brain alone may account for up to 70% of basal metabolism.[44] Premature and SGA infants also tend to have a greater proportion of metabolically active brown adipose tissue than relatively inactive white adipose tissue.[36] By contrast full-term appropriate-for-gestational age infants may have only 40 g of brown adipose tissue yet have 520 g of white adipose tissue.[38]

### Dietary Intake

REE of infants is related to caloric intake and weight gain. A significant linear correlation of increasing REE with increasing energy intake has been demonstrated.[30] REE increased by 8.5 kcal/kg/day after a meal, which was equivalent to 5.7% of the gross energy intake, which correlates well with the energy cost of growth.[30] Salomon and colleagues[45]

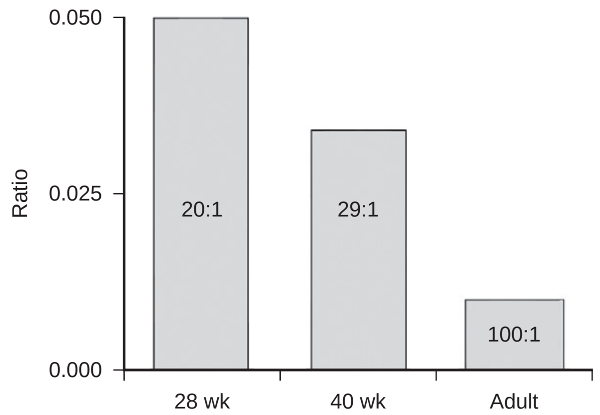



FIGURE 6-6 Ratio of basal metabolic rate/nonprotein energy reserve.

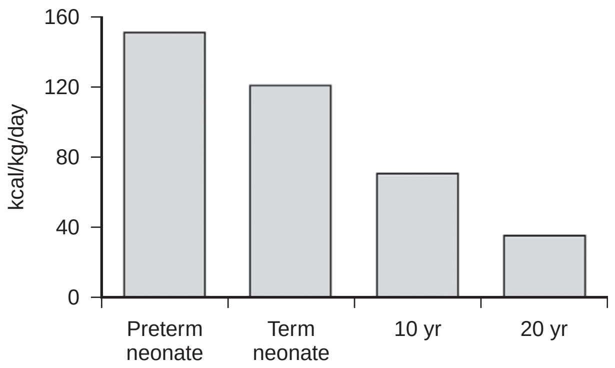



FIGURE 6-7 Energy requirements from the neonatal period to adulthood.

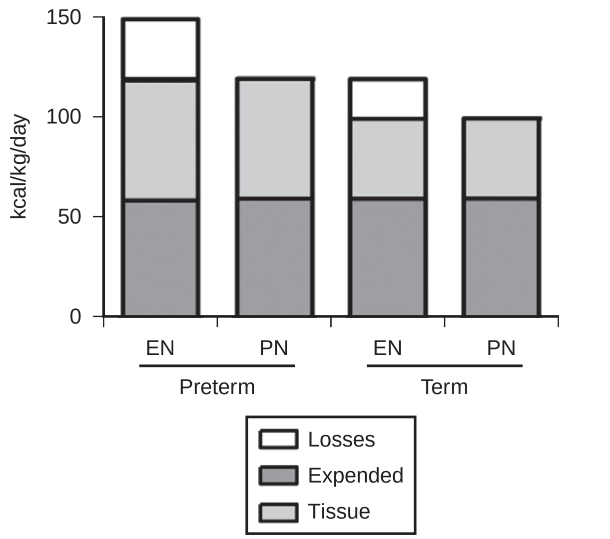



FIGURE 6-8 Partition of energy metabolism in preterm and term infants receiving enteral nutrition (EN) or parenteral nutrition (PN). *Expended* includes basal metabolic rate, activity, the energy expended in laying down new tissue, and thermoregulation, *tissue* is the amount of energy actually stored in new tissue, *losses* include losses in stool and so on. Data from references 22, 36, 48, 49 and 52.

measured the diet-induced thermogenesis of each dietary constituent in infants. They found that amino acids increased REE by 11% (4.4% of caloric intake), fat increased REE by 8% (3% of caloric intake), and glucose did not increase REE at all. This study is somewhat at odds with the results of other studies that have shown that REE increases considerably after a glucose load, particularly at high doses.[46,47]

The energy metabolism of neonates is different from that of adults and children and this reflects the special physiologic status of the neonate. Newborns have a significantly higher metabolic rate and energy requirement per unit body weight than do children and adults: the total energy requirement for an extremely low-birth-weight (i.e., <1000 g) preterm infant fed enterally is 130 to 150 kcal/kg/day[48] and that of a term infant is 100 to 120 kcal/kg/day compared to 60 to 80 kcal/kg/day for a 10-year old child and 30 to 40 kcal/kg/day for a 20-year old individual (Fig. 6-7).[49–51] The partition of this energy is also different from that of adults. Of the 100 to 120 kcal/kg/day required by the term infant, approximately 40 to 70 kcal/kg/day is needed for maintenance metabolism, 50 to 70 kcal/kg/day for growth (tissue synthesis and energy stored), and up to 20 kcal/kg/day to cover energy losses in excreta.[22,35,36] Newborns receiving total parenteral nutrition require fewer calories (110 to 120 kcal/kg/day for a preterm infant and 90 to 100 kcal/kg/day for a term infant[52]) because of the absence of energy losses in excreta and the fact that energy is not required for thermoregulation when the infant is in an incubator. These data are summarized in Fig. 6-8.

Several equations have been published to predict energy expenditure in adults.[53] In stable neonates undergoing surgery, REE can be predicted from parameters such as weight, heart rate, and age using the following equation:[54]

$$\begin{aligned}\text{Resting energy expenditure (cal/min)}\\ &= -74.436 + (34.661 \times \text{body weight in kilograms})\\ &\quad + (0.496 \times \text{heart rate in beats/minute})\\ &\quad + (0.178 \times \text{age in days})\end{aligned}$$

$$(r = 0.92; F = 230.07; \text{significance } F < 0.00001).$$

The major predictor of REE in the preceding equation is body weight, which is also the strongest individual predictor of REE and represents the total mass of living tissue. The other predictors are heart rate, which provides an indirect measure of the hemodynamic and metabolic status of the infant, and postnatal age, which has been shown to influence REE in the first few weeks of life.

# Thermoregulation

After delivery the relatively low ambient temperature and evaporation of the residual amniotic fluid from the skin further increase the heat loss from the newborn. Neonates are homeotherms. They are far more susceptible to changes in environmental temperature than are adults[28] because they have a small mass and relatively large surface area, they possess relatively little insulating tissue such as fat and hair, they are unable to make significant behavioral alterations such as increasing the central heating or putting on extra clothing, and they have limited energy reserves. The thermoneutral zone is of critical importance to infants[38] and is higher (32 to 34° centigrade for full-term appropriate-for-gestational age infants) than it is for adults.[55] There are a number of published tables giving the optimum environmental temperature for infants of different weights and ages.[55] Numerous studies have shown that the morbidity and mortality of infants nursed outside the thermoneutral zone, is significantly increased. There are however indications such as hypoxic ischemic encephalopathy in which therapeutic moderate hypothermia is used,[56] and the difference between iatrogenic hypothermia (potentially with rapid uncontrolled rewarming) and therapeutic controlled hypothermia (with slow controlled rewarming) should be emphasized.

## RESPONSE TO COLD

Heat is lost through radiation/conduction/convection (70%), evaporation (25%), raising the temperature of feedings (3%), and with the excreta (2%).[38] The response of the infant to cooling depends on the maturation of hypothalamic regulatory centers and the availability of substrates for thermogenesis.[38] The initial response, which is mediated through the sympathetic nervous system, is to reduce heat losses by

vasoconstriction[28] and to increase heat production by shivering and nonshivering thermogenesis. The most important site of nonshivering thermogenesis is the brown adipose tissue. This is well established by 22 weeks of gestation and makes up 90% of the total body fat by 29 weeks of gestation.[57] Other sites include the brain, liver, and kidneys. Studies have shown that the preferred fuels for nonshivering thermogenesis are free fatty acids.[58] The energy cost of thermoregulation in a cold environment is considerable. Even within the thermoneutral zone, thermoregulation can account for up to 8% of total energy expenditure.[59] The REE can double when full nonshivering thermogenesis is taking place.

Neonates undergoing major operations under general anesthesia frequently become hypothermic.[60,61] Compared with adults newborns experience greater difficulties in the maintenance of physiologic body temperature in the presence of a cold environmental challenge.[62] Hypothermia may increase the incidence of postoperative complications such as acidosis, impaired immune function, and delayed wound healing.[63] Newborns are not able to respond to cold exposure by shivering but have a highly specialized tissue, brown fat, capable of generating heat without the presence of shivering (nonshivering thermogenesis). As environmental temperature decreases, an increased blood flow to brown fat stores is observed and heat is produced in brown fat mitochondria. During an operation the neonate is exposed not only to a cool environment but also to a wide variety of anesthetic and paralytic agents that may have detrimental effects on heat production (energy expenditure) and core temperature.[64,65] Nonshivering thermogenesis is inhibited by anesthetic agents in experimental animals.[62,66] Albanese and associates[62] have shown that termination of general anesthesia during cold exposure causes a rapid and profound increase in nonshivering thermogenesis in rabbits. This may explain the sudden and rapid increase in energy expenditure observed in young infants at the end of an operation.[64,67]

It has long been known that brown adipose tissue is responsible for heat production, containing a protein (uncoupling protein 1) that dissipates the proton gradient formed across the mitochondrial inner membrane during substrate oxidation.[58] However it is only in recent years that a contribution of the proton leak to thermogenesis in liver has been postulated.[68] The magnitude of the proton leak may be a major determinant of metabolic rate.[69] Oxidative breakdown of nutrients releases energy, which is converted to usable chemical fuel (ATP) in the mitochondria of cells by oxidative phosphorylation. This is used to drive energy-consuming processes in the body. During oxidative phosphorylation, protons are pumped from the mitochondrial matrix to the intermembrane space. Proton pumping is directly proportional to the rate of oxygen consumption and generates and maintains a difference in electrochemical potential of protons across the inner membrane. Protons return to the matrix by one of two routes: the "phosphorylation pathway," which generates ATP, or by the "leak pathway," which is nonproductive and releases energy as heat. A significant proportion (20% to 30%) of oxygen consumed by resting hepatocytes in adult rats is used to drive the heat-producing proton leak.[70] This leak pathway in liver and other organs is a significant contributor to the reactions that compose the standard REE and therefore results in significant resting heat production.[71,72] The proton permeability of the inner mitochondrial membrane that is present in rat liver mitochondria is high in fetuses and is significantly reduced during early neonatal life and reaches the lowest maintained level in adults.[73] These authors suggest that this could provide a physiologic protective mechanism for thermal adaptation of newborn rats during the perinatal period before the establishment of brown adipose tissue thermogenesis.[73] It is conceivable that human newborns are "preprogrammed" with similar protective mechanisms that allow them to survive the stresses of birth (cold adaptation), surgery (cord division), and starvation (transient hypoglycemia).

## Carbohydrate, Fat, and Protein Metabolism of the Neonate

The profound physiologic changes that take place in the perinatal period are reflected by equally dramatic changes in nutrition and metabolism. The fetus exists within a thermostable environment in which nutrition is continually supplied "intravenously" and waste products are equally efficiently removed. At birth, this continual nutrient supply ceases abruptly, resulting in a brief period of starvation. At the end of this period of starvation, nutrition also changes from the placental supply of glucose to milk, which is high in fat and low in carbohydrate. In addition the kidney and lung of the neonate have to become much more active metabolically and the neonate must maintain its own body temperature by activating both metabolic and physiologic mechanisms of thermogenesis and heat conservation, as described previously. The successful adaptation of the neonate to extrauterine life requires carefully regulated changes in glucose and fat metabolism, together with the use of stored protein reserves, until adequate nutritional supply of protein or amino acids, or both, is established. Toward the end of the neonatal period nutrition again changes as the infant is weaned onto a diet that is higher in carbohydrate and lower in fat than the milk diet of the neonatal period. Hence a healthy neonate is in a state of metabolic flux, and these changes must be carefully regulated in order to maintain growth and brain development in this "critical epoch." It is now known that nutrition and growth during the neonatal period are important later determinants of cardiovascular disease[74] and neurodevelopment.[75] Additional physiologic stresses caused by prematurity, infection, gastrointestinal dysfunction, anesthesia, and surgical stress present a considerable challenge to the neonate to maintain metabolic homeostasis. Careful management of nutrition and metabolism by surgeons and physicians is necessary to avoid additional morbidity and mortality caused by malnutrition and the neurologic sequelae of hypoglycemia or hyperglycemia.[76] The long-term metabolic, neurologic, and cardiovascular sequelae of surgery, parenteral nutrition, or sepsis during the neonatal period are unknown, but given the importance of this period on subsequent development, nutritional management of the neonate undergoing surgery is also likely to play a role in adult health.

### NEONATAL GLUCOSE METABOLISM

Most of the energy supply (approximately 70% of total calories as carbohydrate, $<10\%$ as fat[24]) of the fetus comes from maternally supplied glucose. At birth the switch from a high-carbohydrate diet to a diet that is high in lipid and lower

in carbohydrate (approximately 40% of calories as carbohydrate, 50% as fat[24]) means that the neonate must not only adapt to a difference in timing and magnitude of carbohydrate supply but also must regulate its own level of glycemia by insulin/glucagons, gluconeogenesis, and the other mechanisms of glucose homeostasis. The brain can use only glucose or ketone bodies; it is not able to oxidize lipids directly, so maintenance of euglycemia during the neonatal period is particularly important for favorable neurologic outcomes. Despite the greater supply of fats as a fuel source in neonates than in adults, glucose turnover is greater in neonates (3 to 5 mg/kg/min) than in adults (2 to 3 mg kg/min) partly due to the relatively increased brain/body mass ratio. Premature infants have an even greater glucose turnover rate (5 to 6 mg/kg/min).[77] In the premature and term infant, 90% of glucose is used by the brain, whereas this decreases to about 40% in adults.[78] The term infant has two important means of glucose production to maintain euglycemia: glycogenolysis and gluconeogenesis. Glucose production in term neonates originates from glycogenolysis (approximately 40%) and gluconeogenesis from glycerol (20%), alanine and other amino acids (10%), and lactate (30%).[79]

### Glucagon/Insulin Axis in the Perinatal Period

Although the fetus is capable of synthesizing and releasing glucagon and insulin, the function of insulin during pregnancy is probably its promotion of anabolism and enhancing growth rather than regulating circulating glucose.[77] Glucagon is important for the induction of gluconeogenic enzymes during pregnancy, and the surge in glucagon at birth, which results from cord clamping, is probably responsible for the rapid postnatal increase in gluconeogenic capacity.[80] Islet cell function is relatively unresponsive for the first 2 weeks of neonatal life so that increases in insulin secretion and decreases in glucagon secretion are relatively slow in response to increased glucose concentration.[77] There is a similarly slow response to hypoglycemia in the neonate so that if a neonate starts to become hypoglycemic, it may be some time before insulin secretion is decreased and glucagon secretion is increased to stimulate gluconeogenesis. In addition insulin sensitivity is lower in end organs of neonates than in those of adults so that plasma insulin is less closely linked with blood glucose, whereas plasma glucagon is more closely linked to glycemia.[81,82] The maturation of the response to glucose is even slower in preterm infants than in term neonates.[83]

### Glycogen and Glycogenolysis in the Perinatal Period

During the third trimester of pregnancy, storage of maternal glucose as glycogen takes place. Most fetal storage is in the liver, although some glycogen is stored in fetal skeletal muscle, kidney, and intestine, and only to a small degree in brain. Hepatic and renal glycogen is mobilized at and immediately after birth to maintain circulating glucose concentration; however the hepatic glycogen stores are exhausted within 24 hours of birth, or even sooner in premature neonates (who have had an abbreviated or no third trimester), SGA neonates, or neonates who have experienced extensive perinatal stress and have therefore had early catecholamine-stimulated mobilization of hepatic glycogen. Other tissues such as heart, skeletal muscle, and lung can metabolize stored glycogen intracellularly but cannot mobilize it to the circulation because of a lack of the enzyme glucose-6-phosphatase. Mobilization and use of glycogen stores takes place in response to the perinatal surge in glucagon or catecholamine, or both.

### Gluconeogenesis in the Neonate

Key enzymes of gluconeogenesis are present in the fetus from early in gestation and increase throughout gestation and during the neonatal period. However in vivo fetal gluconeogenesis has not been demonstrated and it is not known whether cytosolic phosphoenolpyruvate carboxykinase (necessary for gluconeogenesis from amino acids or lactate) or glucose-6-phosphatase (necessary for gluconeogenesis from all substrates and for glucose export after glycogenolysis) is expressed adequately to support gluconeogenesis by fetal liver. Glucose-6-phosphatase expression is low in the fetus but increases in activity within a few days of birth in term neonates.[84] Studies measuring gluconeogenesis from glycerol in preterm infants have suggested that some gluconeogenesis from glycerol can occur[85] but can only partly compensate a decrease in exogenous glucose supply in preterm infants, probably because of limitation at the level of glucose-6-phosphatase.[86] Parenteral glycerol[87] supports enhanced rates of gluconeogenesis in preterm infants, whereas no increase in gluconeogenesis was observed by provision of mixed amino acids[88] or alanine[89] to preterm neonates, supporting the hypothesis that gluconeogenesis from amino acids or lactate is limited by lack of phosphoenolpyruvate carboxykinase activity in preterm infants. Parenteral lipids stimulate gluconeogenesis in preterm infants,[88] probably by providing both carbon substrate (glycerol) and fatty acids. Fatty acid oxidation is indispensable for gluconeogenesis; although fatty acid carbon cannot be used for glucose, fat oxidation provides both an energy source (ATP) to support gluconeogenesis and acetyl coenzyme A (acetyl-CoA) to activate pyruvate carboxylase. In experimental animals the increase in the glucagon/insulin ratio at birth stimulates maturation of the enzymes of gluconeogenesis, particularly phosphoenolpyruvate carboxykinase, although little is known about the induction of gluconeogenesis in human neonates. Gluconeogenesis is evident within 4 to 6 hours after birth in term neonates.[90,91]

### Neonatal Hypoglycemia

Blood glucose levels fall immediately after birth but rise either spontaneously from glycogenolysis/gluconeogenesis or as a result of feeding. This period of hypoglycemia is not considered of clinical significance, but the appearance of hypoglycemia subsequent to this should be avoided. However there is considerable controversy as to which blood glucose level should be considered the cutoff below which infants are considered hypoglycemic. It is also debated what the duration of hypoglycemia should be before preventive or investigational measures, or both, are instigated,[92] particularly as glucose concentrations fluctuate significantly during this period of massive metabolic, physiologic, and nutritional change. In addition the symptoms of neonatal hypoglycemia are nonspecific and may include the signs and symptoms shown in Table 6-5, many of which are subjective. Current recommendations for operational thresholds of circulating glucose levels are less than 45 mg/dL (2.5 mmol/L) for the term neonate with abnormal clinical signs, persistently less than 36 mg/dL (2.0 mmol/L) for the term neonate with risk factors for compromised metabolic adaptation, 47 mg/dL

**TABLE 6-5**
**Signs and Symptoms of Neonatal Hypoglycemia**

| | |
|---|---|
| Jitteriness | Abnormal cry |
| Tremors | Cardiac arrest |
| Apnea | Hypothermia |
| Cyanosis | Tachypnea |
| Limpness/apathy/lethargy | Seizures |

(2.6 mmol/L) for preterm neonates (although data is limited), and maintenance of blood glucose greater than 45 mg/dL (2.5 mmol/L) at all times in parenterally fed infants because of the likelihood of increased insulin (and therefore suppressed lipolysis and ketogenesis) in these neonates.[93] Causes of hypoglycemia in the neonatal period are shown in Table 6-6. Glucose metabolism is particularly important for the brain during this critical growth period, and hypoglycemia less than 2.6 mmol/L has been found to be associated with short-term neurophysiologic changes[94] and poor neurodevelopmental outcome.[95,96] However in these studies it is difficult to reliably delineate hypoglycemia as a risk factor independent from those of comorbidities and causes of hypoglycemia—such as prematurity, congenital hyperinsulinism,[97] SGA status,[96] or a diabetic mother[98]—and there is uncertainty concerning the frequency, degree, and duration of hypoglycemia that may cause neurologic problems.[99] Recent advances in neonatal cerebral imaging modalities have suggested a wide spectrum of features that may result from neonatal hypoglycemia.[100] However there is remarkably little strong evidence regarding which blood glucose levels are the thresholds below which adverse neurodevelopmental sequelae are likely to result, and many normal healthy infants experience glucose levels below these thresholds without adverse effects.[101,102] It is likely that duration of hypoglycemia and other metabolic factors such as ketone body levels (see later) are important as determinants of outcome. Treatment of hypoglycemia in the neonate depends on the feeding route and whether risk factors have been identified. Frequent monitoring of blood glucose levels is necessary and treatment/investigation algorithms combine increased enteral feeds with intravenous administration of glucose if clinical signs of hypoglycemia are present.[92]

**TABLE 6-6**
**Causes of Hypoglycemia in the Neonate**

| |
|---|
| **Associated with Changes in Maternal Metabolism** |
| Intrapartum administration of glucose |
| Drug treatment |
| Terbutaline, ritodrine, propranolol |
| Oral hypoglycemic agents |
| Diabetes in pregnancy/infant of diabetic mother |
| Severe Rh incompatibility |
| **Associated with Neonatal Problems** |
| Idiopathic condition or failure to adapt |
| Perinatal hypoxia-ischemia |
| Infection/sepsis |
| Hypothermia |
| Hyperviscosity |
| Erythroblastosis fetalis, fetal hydrops |
| Exchange transfusion |
| Other |
| Iatrogenic causes |
| Congenital cardiac malformations |
| **Intrauterine Growth Restriction** |
| **Endocrinology and Metabolism** |
| Hyperinsulinism (e.g., congenital hyperinsulinism, Beckwith-Weidemann syndrome) |
| Other endocrine disorders |
| Panhypopituitarism |
| Isolated growth hormone deficiency |
| Cortisol deficiency |
| Inborn errors of metabolism |
| Glycogen storage diseases types 1a and 1b |
| Fructose 1,6-diphosphatase deficiency |
| Pyruvate carboxylase deficiency |
| Fatty acid oxidation disorders |

### Neonatal Hyperglycemia

Neonatal hyperglycemia can also occur and has been recognized as representing several distinct clinical entities. Diabetes mellitus can present in the neonatal period, although the condition is rare, representing approximately 1 in 400,000 to 1 in 500,000 live births.[103,104] Both permanent and transient neonatal diabetes occurs. Transient neonatal diabetes mellitus, which usually resolves within 3 to 6 months but may lead to the development of permanent diabetes in childhood or adolescence, represents about 50% of cases and permanent neonatal diabetes mellitus represents the other 50%. Transient neonatal diabetes mellitus is due to paternal imprinting[105,106] and one of the molecular causes of the permanent form has been elucidated.[107] However most hyperglycemia in neonates is self-limiting, resolves spontaneously, and has few features in common with diabetes. Its frequency appears to be increasing in parallel with increased survival of extremely low-birth-weight infants who are fed parenterally and receive corticosteroids. The etiology of neonatal hyperglycemia is not well understood, but possible causes[92] include inability to suppress gluconeogenesis in response to glucose infusion, excessive glucose infusion rates, end-organ insulin resistance, low plasma insulin levels in combination with high catecholamine levels (e.g., due to corticosteroid administration), infection, or response to pain or surgery (see later). The management of hyperglycemia in the neonate is to manage the cause, for example, treat infection or pain or decrease excessive glucose infusion rates. There is still controversy regarding insulin administration:[108] on the one hand insulin infusion allows maintenance of high glucose infusion rates (and may therefore increase weight gain), whereas on the other hand there are reports of adverse effects. Neither the acute nor the long-term sequelae of hyperglycemia in the neonate are well understood. Ketosis or metabolic acidosis does not occur as a result of hyperglycemia, but osmotic diuresis and glycosuria may lead to dehydration. Hyperglycemia has been found to be associated with increased mortality in premature infants.[109–111] Hyperglycemia has also been associated with increased morbidity and mortality in neonates with necrotizing enterocolitis.[112] However, except for a study linking hyperglycemia with white matter injury in premature infants,[109] evidence for a cerebral pathologic cause and adverse neurodevelopmental outcome as a result of neonatal hyperglycemia is scant, although there is a risk of increased

cerebral bleeds from osmotic shifts. There has been a great deal of interest in the tight control of blood glucose in patients in adult intensive care units after the study of Van Den Berghe and colleagues.[113] In very-low-birth-weight infants, insulin therapy to maintain normoglycemia was not found to improve outcomes,[114] whereas a recent study (including some neonates) in glucose control in a pediatric intensive care unit suggested that intensive insulin therapy improved short-term outcomes.[115] Hence it remains uncertain whether tight control of blood glucose concentration is beneficial in neonates or in specific subgroups of neonates.

## NEONATAL LIPID AND FAT METABOLISM

Fat is the main energy source of the neonate, providing 40% to 50% of calories in milk or formula. As discussed earlier, fat oxidation becomes a major fuel used within 3 hours after birth.[25,26] In addition fat is the main store of energy within the body. Although most chain lengths of fatty acids can be used for energy, fatty acids, in the form of phospholipids and other fat-derived lipids, are extremely important structural components of cell membranes, and the function of these membranes is critically dependent on the availability of the correct chain length and degree of unsaturation of fatty acids. Thus throughout the period of growth of the neonate, an array of different fatty acids, either supplied by the diet or metabolized by the body, is essential to support growth, particularly that of the brain, which is rich in complex lipids.

### Fatty Acid Oxidation and Ketogenesis in Neonates

Fatty acid beta oxidation is the major process by which fatty acids are oxidized, by sequential removal of two-carbon units from the acyl chain, providing a major source of ATP for heart and skeletal muscle. Hepatic beta oxidation serves a different role by providing ketone bodies (acetoacetate and β-hydroxybutyrate) to the peripheral circulation and supporting hepatic gluconeogenesis by providing ATP and acetyl-CoA to activate pyruvate carboxylase activity. In addition kidney,[116] small intestine,[117] white adipose tissue,[118] and brain astrocytes[119] may be ketogenic under some conditions. Ketone bodies are another significant fuel for extrahepatic organs, especially the brain, when blood glucose levels are low. Consequently, ketogenesis is extremely important to provide an alternative fuel for the brain when glucose levels may be fluctuating because of alterations in feeding pattern and adaptation of physiologic and metabolic homeostasis. For oxidation of the acyl groups of stored, ingested, or infused triacylglycerol to take place, nonesterified fatty acids must be released. This can take place distant from the site of use by the action of hormone-sensitive lipase (HSL) in the adipocyte or locally by the action of endothelial lipoprotein lipase (LPL).[120,121] Nonesterified fatty acids (NEFA) bound to albumin provide the main substrate that is taken up and oxidized by tissues. In addition intracellular triacylglycerol stores can also provide a significant source of acyl moieties for beta oxidation in the heart and skeletal muscle, again through the action of HSL. HSL and LPL are under control of the hormonal and nutritional milieu so that fatty acid oxidation is partly controlled by the supply of NEFA to the tissue.[122] In the immediate postnatal period the plasma levels of NEFA increase rapidly in response to the glucagon/catecholamine surge that stimulates lipolysis and the fall in insulin that occurs as a result of birth and cord division.[123,124] This lipolysis also results in the release of glycerol, which can be used as a gluconeogenic precursor (see previous discussion).[123,124] Ketone bodies are formed fairly soon after birth, [24,125–129] reaching 0.2 to 0.5 mmol/L in the first 1 postnatal day, and 0.7 to 1.0 mmol/L between 5 and 10 days,[125] although this may be impaired in premature or SGA infants.[126,128,130] During hypoglycemia, ketone body concentrations can raise to 1.5 to 5 mmol/L.[125] The enzymes of fatty acid oxidation and ketogenesis all increase in activity postnatally in experimental animals, accounting for this increase in capacity for fatty acid oxidation and ketogenesis,[24] although little is known about the induction of fatty acid oxidation enzymes in humans. Hydroxymethylglutaryl-CoA synthase is thought to be particularly important in the control of ketogenesis and is subject to short-term activation by glucagon, which may account for the rapid surge in ketogenesis at birth.[131]

### Ketone Body Use

Little is known about the ontogeny of the enzymes of ketone body use in human tissues. Heart, muscle, kidney, and brain are all capable of ketone body use and the enzymes required have been shown in human tissue.[132–134] In rats the activities of the ketone body use enzymes are very active in neonatal brain and decrease at weaning, whereas they are lower than adult levels in neonatal muscle and kidney, suggesting preferential use by the brain.[24]

### Neonatal Protein and Amino Acid Metabolism

In contrast to healthy adults who exist in a state of neutral nitrogen balance, infants need to be in positive nitrogen balance in order to achieve satisfactory growth and development. Infants are efficient at retaining nitrogen and can retain up to 80% of the metabolizable protein intake on both oral and intravenous diets. [34,135,136] Protein metabolism is dependent on both protein and energy intake. The influence of dietary protein is well established. An increased protein intake has been shown to enhance protein synthesis,[137,138] reduce endogenous protein breakdown,[139] and thus enhance net protein retention.[139,140] The influence of nonprotein energy intake on protein metabolism is more controversial. Protein retention can be enhanced by giving carbohydrate or fat,[141–146] which are thus said to be protein sparing. Although some studies have suggested that the protein-sparing effect of carbohydrate is greater than that of fat,[142,143,146] others have suggested that the protein-sparing effect of fat may be either equivalent to or greater than that of carbohydrate.[141,144,145] The addition of fat calories to the intravenous diet of newborns undergoing surgery reduces protein oxidation and protein contribution to the energy expenditure and increases protein retention.[144] In order to further investigate this positive effect on protein metabolism we studied the various components of whole protein metabolism by the combined technique of indirect calorimetry and stable isotope ($^{13}$C-leucine) tracer technique. Two groups of neonates receiving isonitrogenous and isocaloric total parenteral nutrition were studied: one group received a high-fat diet and the other a high-carbohydrate diet.[65] There was no significant difference between the two groups with regard to any of the components of whole-body protein metabolism: protein synthesis, protein breakdown, protein oxidation/excretion, and total protein flux. This study confirms previous observations that infants have high rates of protein turnover, synthesis, and breakdown, which may be

up to eight times greater than those reported in adults. In newborn infants receiving parenteral nutrition, synthesis and breakdown of endogenous body protein far exceed intake and oxidation of exogenous protein. Infants are avid retainers of nitrogen, and carbohydrate and fat have an equivalent effect on protein metabolism. This supports the use of intravenous fat in the intravenous diet of newborns undergoing surgery.

The protein requirements of newborns are between 2.5 and 3.0 g/kg/day. Amino acids, the building blocks of protein, can be widely interconverted so that several are described as dispensable (or nonessential). These are alanine, aspartate, asparagine, glutamate, and serine. Others are described as indispensable (or essential): histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. There are yet other amino acids (arginine, cysteine, glycine, glutamine, proline, and tyrosine) that are not usually essential but can become limiting during metabolic stress such as sepsis. Sulfur amino acids (i.e., cysteine, methionine) and tyrosine, in particular, are abundant in acute-phase proteins, so their supply becomes particularly important during acute-phase responses. Human milk provides amino acids in the form of protein and as free amino acids. However milk proteins are not just important for their nutritive value but also possess other important properties such as antiinfective activity (IgA, IgM, IgG, lactoferrin, lysozyme).[147] Platelet-activating factor acetylhydrolase, a minor component of human milk, has been suggested to be responsible for some of the protective effects of breast milk against necrotizing enterocolitis.[148] The amino acid glutamine is of particular interest in premature neonates and neonates undergoing surgery.

The nitrogen source of total parenteral nutrition is usually provided as a mixture of crystalline amino acids. The solutions commercially available contain the eight known essential amino acids plus histidine, which is known to be essential in children.[140] Complications like azotemia, hyperammonemia, and metabolic acidosis have been described in patients receiving high levels of intravenous amino acids.[149] These complications are rarely seen with amino acid intake of 2 to 3 g/kg/day.[150] In patients with severe malnutrition or with additional losses (i.e., in those who have undergone jejunostomy or ileostomy) the protein requirements are higher.[140] The ideal quantitative composition of amino acid solutions is still controversial. Cysteine, taurine, and tyrosine seem to be essential amino acids in newborns. However the addition of cysteine in the parenteral nutrition of neonates does not cause any difference in the growth rate and nitrogen retention.[136] The essentiality of these amino acids could be related to the synthesis of neurotransmitters, bile salts, and hormones. The consequences of failure to supply these amino acids may be poor long-term neurologic or gastrointestinal function.[151] The incidence of abnormalities of plasma aminograms during parenteral nutrition is low. There are no convincing data at the moment to support the selection of one crystalline amino acid solution over another in newborns. Glutamine is a nonessential amino acid that has many important biologic functions, such as being a preferential fuel for the immune system and the gut. Various authors have postulated that glutamine may become "conditionally essential" during sepsis and that addition of glutamine to parenteral feedings of premature neonates or those undergoing surgery may help to preserve mucosal structure, prevent bacterial translocation, and hence reduce the number of infections and the time before full enteral feeding can be established.

# Metabolic Response to Stress

The body has developed a system of responses to deal with various noxious stimuli that threaten survival. In some respects these responses are stereotypical and lead to the so-called stress response. Stress can be defined as "factors that cause disequilibrium to an organism and therefore threaten homeostasis."[152] Initiators of the stress response in newborns include operative trauma and sepsis. In this section we discuss the response to operative trauma. The physiologic changes due to sepsis are discussed in another chapter.

## OPERATIVE TRAUMA

The stress response that follows operative procedures is initiated and coordinated by several messengers and affects whole body systems. The insult of operative trauma can be considered a form of "controlled" injury.

After surgery there are alterations in metabolic, inflammatory, endocrine, and immune system responses. These responses have evolved to enhance survival to trauma and infection in the absence of iatrogenic intervention. They limit patient activity in the area of injury to prevent secondary damage and start the healing process through the inflammatory signals produced. Changes in metabolism increase the availability of substrates needed by regenerating and healing tissue. The immune stimulation allows for the swift eradication of any causal or secondary opportunistic microbial invasion, whereas the subsequent immune paresis may allow for a dampening of this immune stimulation to allow for healing to ensue.

In contrast to adults the energy requirement of infants and children undergoing major operations seems to be modified minimally by the operative trauma per se. In adults trauma or surgery causes a brief "ebb" period of a depressed metabolic rate followed by a "flow phase" characterized by an increase in oxygen consumption to support the massive exchanges of substrate between organs (Fig. 6-9).[153] In newborns major abdominal surgery causes a moderate (15%) and immediate (peak at 4 hours) elevation of oxygen consumption and REE and a rapid return to baseline 12 to 24 hours postoperatively (see Fig. 6-9).[64] There is no further increase in energy expenditure in the first 5 to 7 days after an operation.[64,154] The timing of these changes corresponds with the postoperative increase in catecholamine levels described by Anand and associates.[155] The maximum endocrine and biochemical changes are observed immediately after the operation and gradually return to normal over the next 24 hours. It is of interest that infants who have a major operation after the second day of life have a significantly greater increase in REE than infants who undergo surgery within the first 48 hours of life. A possible explanation for this may be the secretion of endogenous opioids by the newborn. It has been suggested that nociceptive stimuli during the operation are responsible for the endocrine and metabolic stress response and that these stimuli may be inhibited by opioids.[155,156] This is supported by studies showing that moderate doses of opioids blunt the endocrine and metabolic responses to operative stress in infancy.[155,156] The levels of endogenous opioids in the cord blood of newborn infants are five times higher than plasma levels in resting adults.[157] Thus, it is possible that

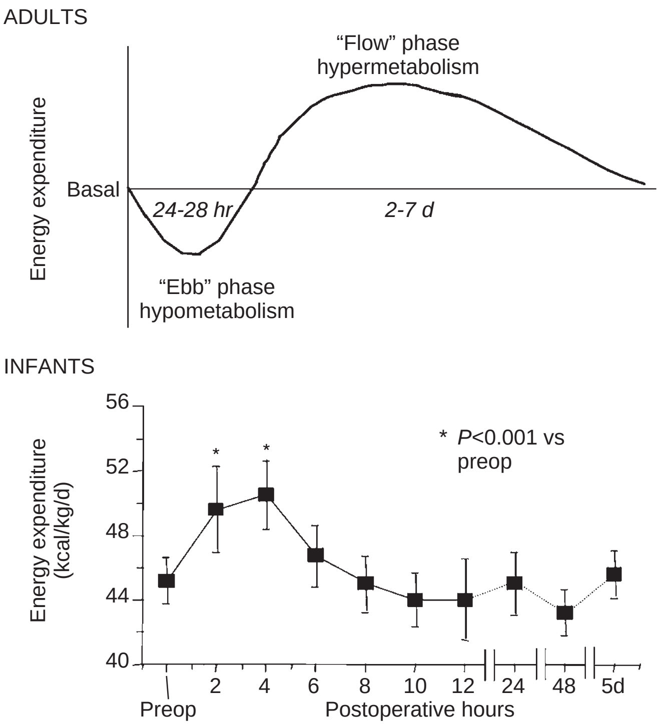



**FIGURE 6-9** Postoperative variations in energy expenditure in adults and neonates undergoing major operations. Data for infants are expressed as mean ± SEM. (Adapted from Jones MO, Pierro A, Hammond P, et al: The metabolic response to operative stress in infants. J Pediatr Surg 1993;28:1258-1262; and Pierro A: J Pediatr Surg 2002;37:811-822.)

the reduced metabolic stress response observed in neonates less than 48 hours old is related to higher circulating levels of endogenous opioids. This may constitute a protective mechanism blunting the response to stress in the perinatal period. Chwals and colleagues[158] demonstrated that the postoperative increase in energy expenditure can result from severe underlying acute illness, which frequently necessitates surgery (i.e., sepsis or intense inflammation). REE is directly proportional to growth rate in healthy infants, and growth is retarded during acute metabolic stress. These authors suggest that energy is used for growth recovery after the resolution of the acute injury response in neonates undergoing surgery. The authors indicate that serial measurement of postoperative REE can be used to stratify injury severity and may be an effective parameter to monitor the return of normal growth metabolism in neonates undergoing surgery.

Operative trauma initiates a constellation of inflammatory pathways that regulate a whole-body response to operative stress, which is similar to that seen after injury. The responses can be initiated and controlled by both chemical/hormonal signals and afferent nervous signals. Some of the chemical signals responsible for the responses originate in the operative wound in response to cellular injury.

## Cytokines

One of the key chemical messenger systems in the control and the coordination of the response to injury are cytokines. Cytokines are a group of low-molecular-weight polypeptides or glycoproteins, which act to regulate the local and systemic immune function and modulation of the inflammatory response. They are active at very low concentrations, found usually at the picogram level, and their production is usually transient. Cytokines bring about their action by altering gene expression in target cells. They act in a paracrine and autocrine manner at concentrations in the picomolar to nanomolar range, but can have systemic effects if there is spill over into the circulation.

Cytokines generally have a wide range of actions in the body. Cytokines are not usually stored intracellularly and must therefore be synthesized de novo and released into the tissues on appropriate stimulation and gene transcription. One of the crucial controllers of cytokine gene regulation is nuclear factor kappa B (NFκB),[159,160] a protein transcription factor that enhances the transaction of a variety of cytokine genes. Lymphocytes are activated at the site of injury. The first cells to be recruited to the site of inflammation are monocytes and neutrophils, where they produce cytokines in the first few hours after the onset of a surgical or traumatic wound.[161] These cytokines are chemoattractant to other white cells.

Cytokines are divided into proinflammatory and antiinflammatory types on the basis of whether they stimulate the immune system or decrease or dampen the immune response. Although most cytokines have a clear proinflammatory or antiinflammatory response, a few have dual properties. Some cytokines may exhibit a proinflammatory action in a particular cell or certain conditions but an antiinflammatory response in a different cell or under different conditions.[162] The presence of antiinflammatory cytokines is of importance in abating the immune response to prevent excessive tissue destruction and death. The presence of naturally occurring inhibitors helps abate the otherwise catastrophic positive feedback loop that could lead to widespread tissue destruction from excessive inflammation. The cytokines that are commonly released after trauma include the proinflammatory interleukins (ILs) IL-1 and IL-6 and tumor necrosis factor-α (TNF-α) and the antiinflammatory IL-1ra and IL-10.

Both proinflammatory and antiinflammatory cytokines are produced in response to operative stress. The actual cytokine cascade is heterogeneous and is determined by various factors, which include the type and magnitude of the operation. The cytokine cascade in response to operations in adults has been well characterized.[163] There have been limited studies in neonates. Cytokines bond to specific membrane receptors of target organs. Their actions in the acute stress response include (1) changes in gene expression and proliferation, thereby affecting wound healing and immunocompetence; (2) release of counterregulatory hormones; and (3) facilitation of cell-to-cell communication.[164] Substrate use is also affected by cytokine release. Glucose transport is increased by TNF, hepatic gluconeogenesis is stimulated by IL-1, and hepatic lipogenesis is stimulated by IL-1, IL-6, and TNF. IL-1 and TNF also appear to promote muscle proteolysis. In neonates IL-6 increases maximally 12 hours after major surgery and the increase is proportional to the degree of operative trauma,[165] indicating that this cytokine is a marker of stress response in neonates. IL-1 and TNF may have a synergistic effect in producing the metabolic manifestations seen after injury and infection.[153] However systemic cytokine release cannot account for all the metabolic changes seen after injury because cytokines are not consistently found in the bloodstream of injured patients and systemic cytokine administration does not produce all the metabolic effects observed in injured adult individuals.

Other mediators of the response to tissue injury include *histamine*, a well-known chemical mediator in acute inflammation that causes vascular dilatation and the immediate transient phase of increased vascular permeability; *5-hydroxytryptamine (serotonin)*, a potent vasoconstrictor; *lysosomal compounds* released from activated neutrophils, monocytes, and macrophages; *lymphokines,* chemicals involved in the inflammatory cascade with vasoactive or chemotactic properties; the *complement system*, and the *kinin system*. These mediators cause vasodilation, increased vascular permeability, and emigration and stimulation of white blood cells. The postoperative changes that occur also affect the immune system. There is a period of immune stimulation that is often followed by a period of immune paresis. There is a proinflammatory response that is balanced by an antiinflammatory response. The balance often determines and predicts the development of complications and outcome in terms of morbidity and mortality.

Other responses may be initiated by peripheral and central nervous system stimulation. Peripheral efferent from pain receptors, for instance, can feed back to the central nervous system and produce some of the clinical signs of inflammation and the responses seen after operative stress. Indeed blockage of this afferent stimulus is associated with dampening of the stress response.[155] Fentanyl and morphine are commonly used in pediatric anesthesia for pain relief. Studies in preterm infants and neonates have shown that fentanyl blunts the metabolic response to operative stress.[155,156,166]

### Endocrine Response

Various studies have characterized the endocrine response to surgery in infants and children.[167–169] These studies have revealed that the response lasts between 24 and 48 hours postoperatively. The response differs in some respects to that of adults, which usually lasts longer.[170,171] Compared with values seen after an overnight fast, there is an increase in insulin levels in the early postoperative period. However this increase in insulin levels is not proportional to the increase in glucose. There is a change in the insulin/glucose ratio in the postoperative period,[167,172] which lasts more than 24 hours postoperatively. Anand and colleagues[167] found that neonates exhibited an initial decrease in the insulin/glucose ratio in the immediate postoperative period that was restored by 6 hours. Ward-Platt and associates[172] found an instantaneous and continuous rise in the ratio in older infants and children.

Cortisol is significantly elevated and remains elevated for the first 24 hours postoperatively and is accompanied by a rise in catecholamines.[173,174] Both the hormones have antiinsulin effects. The rise in cortisol and catecholamines partially drives the postoperative hyperglycemic response and may be responsible for the relative insulin insensitivity in the postoperative period. Anand and colleagues found a very significant correlation between glucose and adrenaline levels in neonates at the end of abdominal surgery.[167] There is an increase in lactate levels in the postoperative period in both adults and infants/children.[156,175,176] The increase in lactate in the postoperative period is related to the alteration in glucose metabolism[167] and more acutely the presence of tissue hypoperfusion related to surgery.[176] The increase in lactate may represent a means of discriminating the magnitude of operative stress. Altogether the changes in hormone levels are related to the magnitude of the operative stress and have been shown in some but not all procedures to be lessened by laparoscopic surgery.

### Effect of Surgery on Glucose Metabolism in Neonates

Surgery in adults is well known to cause hyperglycemia, and a hyperglycemia response to surgery has also been well documented in neonates,[155,156,166,167,177–181] with the degree of hyperglycemia being negatively correlated with age.[181] In contrast to adults, however, in whom blood glucose concentration may remain high for several days postoperatively, the rise in glucose levels in neonates is short-lived, lasting only up to 12 hours. In an elegant study, Anand and Aynsley-Green showed a strong correlation between the degree of surgical stress and the increase in glucose levels.[168] In the same study stress scores were also strongly positively correlated with plasma levels of adrenalin, noradrenalin, glucagon, insulin, and less strongly with cortisol.[168] The hyperglycemic response to surgery is probably multifactorial, including increased glycogenolysis and gluconeogenesis in response to increases in plasma catecholamine and subsequently glucagon. In addition the insulin response to hyperglycemia may be inappropriately low, especially in preterm neonates undergoing surgery,[167] and tissues may become relatively refractory to insulin. Support for the hypothesis that these effects are driven by catecholamine release are provided by Anand's group, who in a series of studies showed that blunting of the catecholamine response to surgery by modulation of the anesthetic regimen led to a blunting of the hyperglycemic/endocrine response to surgery.[155,156,166] The timing of the adrenaline, noradrenaline, and glucose response to neonatal surgery is shown in Figure 6-10.

Carbohydrate conversion to fat (lipogenesis) occurs when glucose intake exceeds metabolic needs. The risks associated with this process are twofold: accumulation of the newly synthesized fat in the liver[182] and aggravation of respiratory acidosis resulting from increased carbon dioxide production, particularly in patients with compromised pulmonary function.[183] Jones and coworkers[184] have shown that there is a negative linear relationship between glucose intake (grams per kilogram per day) and fat use (oxidation and conversion to fat) expressed in grams per kilogram per day ($y = 4.547 - 0.254x$; $r = -0.937$; $P = <0001$) in infants undergoing surgery who receive parenteral nutrition. From this equation it was calculated that "net fat synthesis from glucose" exceeds "net fat oxidation" when the glucose intake is greater than 18 g/kg/day. Jones and colleagues[184] also found a significant relationship between glucose intake and carbon dioxide production (milliliters per kilogram per minute) ($y = 3.849 + 0.183x$; $r = 0.825$; $P = <0001$). The slope of this relationship was steeper when glucose intake exceeded 18 g/kg/day ($y = 2.62 + 0.244x$; $r = 0.746$; $P = <05$) than when glucose intake was less than 18 g/kg/day ($y = 5.30 + 0.069x$; $r = 0.264$; $P = .461$). Thus the conversion of glucose to fat results in a significantly increased production of carbon dioxide. Glucose intake exceeding 18 g/kg/day is also associated with a significant increase in respiratory rate and plasma triglyceride levels. In summary:

1. Glucose intake is the principal determinant of carbohydrate and fat use.
2. The maximal oxidative capacity for glucose in infants undergoing surgery is 18 g/kg/day, which is equivalent to the energy expenditure of the infant.

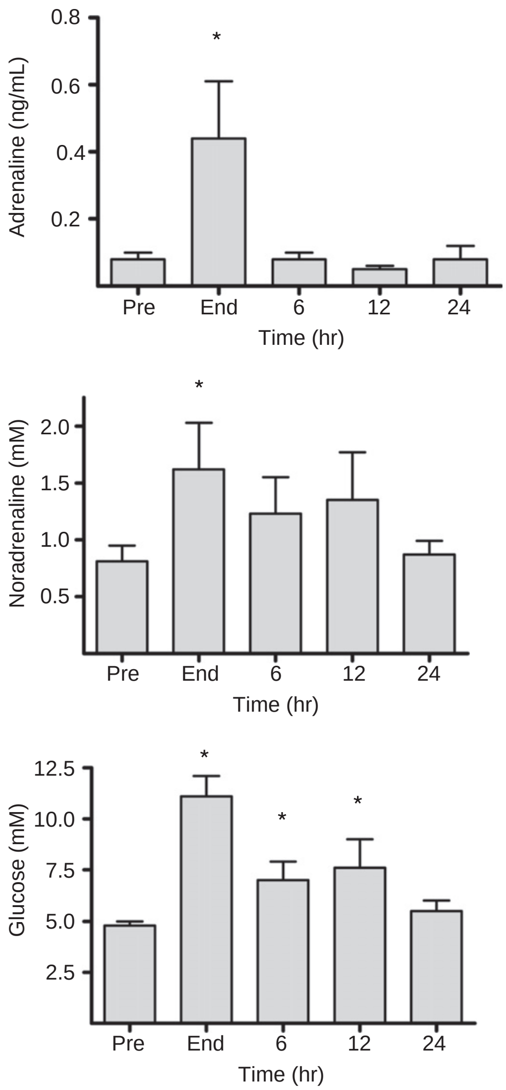



**FIGURE 6-10** Response of adrenaline, noradrenaline, and glucose to surgery in neonates. (Data from Anand KJS, Brown MJ, Causon RC, et al: Can the human neonate mount an endocrine and metabolic response to surgery? J Pediatr Surg 1985;20:41-48.)

3. If glucose is given in excess of maximal oxidative capacity: (a) net fat oxidation ceases; (b) net fat synthesis begins; (c) the thermogenic effect of glucose increases and the efficiency with which glucose is metabolized decreases; (d) carbon dioxide production and respiratory rate increase; (e) plasma triglyceride levels increase.

It is advisable therefore in stable newborns undergoing surgery and requiring parenteral nutrition not to exceed 18 g/kg/day of intravenous glucose intake.[184,185]

### Effect of Surgery on Fat Metabolism in Neonates

Surgery in neonates causes an increase in NEFA and ketone body levels,[156,166,167,180] which can be decreased by modulating the catecholamine release,[156,166] suggesting that catecholamine stimulation of lipolysis is responsible for this increase. Pierro and colleagues have studied intravenous fat use by performing an "Intralipid use test."[185] This consisted of infusing for 4 hours Intralipid 10% in isocaloric and isovolemic amounts to the previously given mixture of glucose and amino acids. Gas exchange was measured by indirect calorimetry to calculate the patient's oxygen consumption and carbon dioxide production, and net fat use. The study showed that (1) infants undergoing surgery adapt rapidly (within 2 hours) to the intravenous infusion of fat; (2) more than 80% of the exogenous fat can be oxidized; and (3) carbon dioxide production is reduced during fat infusion as a consequence of the cessation of carbohydrate conversion to fat.[185] This study did not measure the rate of fat use during a mixed intravenous diet including carbohydrate, amino acids, and fat. More recent studies on stable newborns undergoing surgery receiving fixed amounts of carbohydrate and amino acids and variable amounts of intravenous long-chain triglycerides (LCTs) fat emulsion have shown that at a carbohydrate intake of 15 g/kg/day (56.3 kcal/kg/day) the proportion of energy metabolism derived from fat oxidation does not exceed 20% even with a fat intake as high as 6 g/kg/day. At a carbohydrate intake of 10 g/kg/day this proportion can be as high as 50%.[186] This study seems to indicate that during parenteral nutrition in neonates undergoing surgery the majority of the intravenous fat infused is not oxidized but deposited. Net fat oxidation seems to be significantly influenced by the carbohydrate intake and by the REE of the neonate. When the intake of glucose calories exceeds the REE of the infant, net fat oxidation is minimal regardless of fat intake.[186] In order to use intravenous fat as an energy source (i.e., oxidation to carbon dioxide and water), it is therefore necessary to maintain carbohydrate intake at less than basal energy requirements.

Commonly used fat emulsions for parenteral nutrition in pediatrics are based on LCTs. The rate of intravenous fat oxidation during total parenteral nutrition can theoretically be enhanced by the addition of L-carnitine or medium-chain triglycerides (MCTS), or both, to the intravenous diet. Important differences have been observed between MCTS and LCTS with respect to physical and metabolic properties. MCTs are cleared from the bloodstream at a faster rate and are oxidized more completely for energy production than are LCTs. Therefore they seem to serve as a preferential energy source for the body. We have investigated the effects of MCTs on intravenous fat use during total parenteral nutrition in stable newborns undergoing surgery.[187] Two groups of neonates undergoing surgery and receiving total parenteral nutrition were studied: one group received LCT-based (100% LCTs) fat emulsion and the other group received an isocaloric amount of MCT-based (50% MCTs + 50% LCTs) fat emulsion. In newborns receiving carbohydrate calories in excess of measured REE (56 kcal/kg/day), net fat oxidation was not enhanced by the administration of MCT-based fat emulsion. Conversely in infants receiving carbohydrate calories less than REE (41 kcal/kg/day), the administration of MCT fat emulsion increased net fat oxidation from 0.6 ± 0.2 to 1.7 ± 0.2 g/kg/day. The administration of MCT-based fat emulsion did not increase the metabolic rate of the infants. Fats that are not used can become the substrates for free-lipid peroxidation and free-radical production. Peroxidation has been specifically linked with lipids in parenteral nutrition[188,189] and has been shown to be dependent on the amount of carbohydrate given: If net fat oxidation is not taking place because carbohydrate intake is high, more lipid is present to be peroxidized.[190]

### Effect of Surgery on Protein and Amino Acid Metabolism in Neonates

Major operative stress in adults results in a negative nitrogen balance due to muscle protein catabolism. The neonate is already in a more precarious position regarding nitrogen balance, so if major protein catabolism were to take place in the neonate who undergoes surgery, growth and other important functions would be impaired. Nitrogen losses are increased after surgery in neonates,[191–194] and muscle protein breakdown has also been demonstrated by increased 3-methylhistidine excretion in these neonates.[155,166] However these changes are relatively short-lived and can be overcome by provision of additional dietary nitrogen or calories, or both. Powis and associates[195] investigated protein metabolism kinetics in infants and young children who had undergone major operations. Patients were studied for 4 hours preoperatively and for the first 6 hours after surgery. There were no significant differences in the rates of whole-body protein flux, protein synthesis, amino acid oxidation, and protein degradation between the preoperative and postoperative times, indicating that infants and children do not increase their whole-body protein turnover after major operations. It is possible that infants and children are able to convert energy expended on growth to energy directed to wound repair and healing, thereby avoiding the overall increase in energy expenditure and catabolism seen in the adult.[195] However little is known about the components of protein turnover in neonates who have surgery. The only available study, in six neonates with necrotizing enterocolitis, showed no differences in protein turnover between acute and recovery phases of the disease.[196]

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 7

# Respiratory Physiology and Care

Jay M. Wilson and John W. DiFiore

"The body is but a pair of pincers set over a bellows and a stewpan and the whole fixed upon stilts."[1] This chapter discusses the bellows. In doing so we examine normal lung development, pulmonary physiology, devices (invasive and noninvasive) for patient monitoring, and devices designed to provide ventilatory support. Finally we discuss how to apply this information to the management of infants and children with respiratory failure in the modern intensive care unit.

The primary function of the respiratory system is the continuous absorption of oxygen and the excretion of carbon dioxide. This is achieved by bringing into close proximity massive amounts of air and blood while simultaneously humidifying inspired gas and filtering out contaminants. Ordinarily this process requires a minimal amount of work, but stressful conditions and disease can ultimately overwhelm the system. Since a reasonable understanding of the normal anatomy and physiology of the respiratory system is essential to the understanding and management of pulmonary diseases, we briefly review it here.

## Lung Development

Lung development is divided into five phases: embryonic, pseudoglandular, canalicular, saccular, and alveolar. The boundaries between these phases are not sharp; they blend into one another with considerable overlap at any given time between areas within the lung, and they vary from person to person.[2]

### EMBRYONIC PHASE

The human fetal lung originates in the 3-week-old embryo as a ventral diverticulum that arises from the caudal end of the laryngotracheal groove of the foregut.[3] This diverticulum grows caudally to form the primitive trachea. By 4 weeks the end of the diverticulum divides, forming the two primary lung buds. The lung buds develop lobar buds, which correspond to the mature lung lobes (three on the right side and two on the left side). By the sixth week of gestation the lobar buds have further subdivided to form the bronchopulmonary segments. During this time the vascular components of the respiratory system also begin their development. The pulmonary arteries form as a branch off the sixth aortic arch and the pulmonary veins emerge from the developing heart.

The primitive lung bud is lined by an epithelium derived from endoderm; it differentiates into both the respiratory epithelium that lines the airways[4] and the specialized epithelium that lines the alveoli and permits gas exchange.[5] The lung bud grows into a mass of mesodermal cells from which blood vessels, smooth muscle, cartilage, and other connective tissues that form the framework of the lung will differentiate.[6] Ectoderm contributes to the innervation of the lung (Fig. 7-1, *A*).[7]

### PSEUDOGLANDULAR PHASE

From the seventh to sixteenth weeks of gestation, conducting airways and the associated pulmonary vasculature are formed by repeated dichotomous branching, resulting in 16 to 25 generations of primitive airways.[3] During this phase the lung has a distinctly glandular appearance (hence the term *pseudoglandular*) created by small epithelium-lined tubules surrounded by abundant mesenchyma (Fig. 7-1, *B*).[6] By the sixteenth week of gestation all the bronchial airways have been formed.[8–10] After this time further growth occurs only by elongation and widening of existing airways and not by further branching. During this period the respiratory epithelium begins to differentiate, cilia appear in proximal airways, and cartilage begins to develop from the surrounding mesoderm to support airway structures. The amount of cartilage supporting the airway decreases, moving distally from the trachea as smooth muscle cells increase. Alterations in the development of smooth muscle, cartilage, and vascular structures are responsible for many pulmonary disorders.

### CANALICULAR PHASE

The canalicular phase takes place from the sixteenth to twenty-fourth weeks of gestation. During this time the basic structure of the gas-exchanging portion of the lung is formed and vascularized.

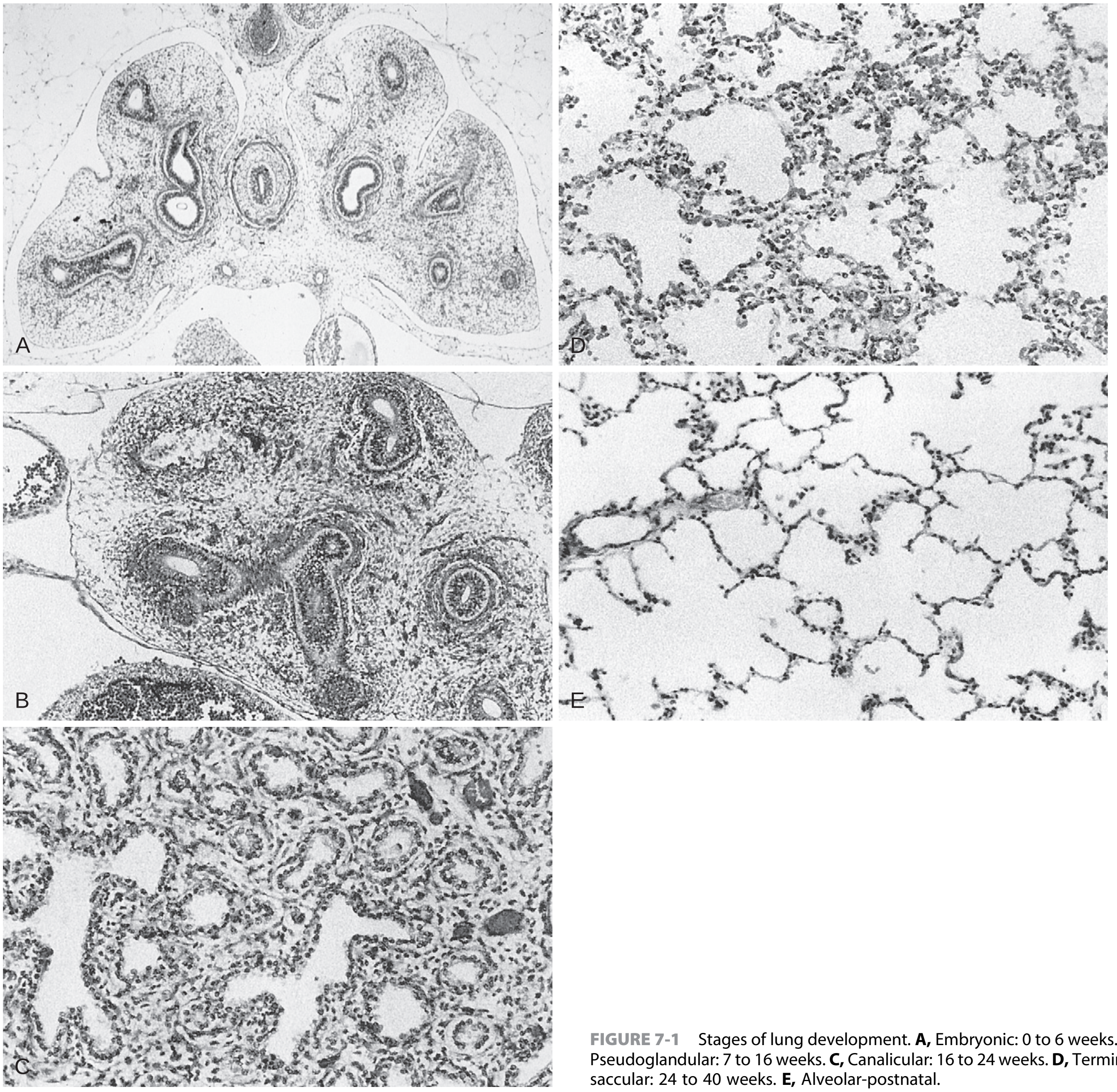


**FIGURE 7-1** Stages of lung development. **A,** Embryonic: 0 to 6 weeks. **B,** Pseudoglandular: 7 to 16 weeks. **C,** Canalicular: 16 to 24 weeks. **D,** Terminal saccular: 24 to 40 weeks. **E,** Alveolar-postnatal.

Early in the canalicular period the lungs have a simple airspace configuration. Potential gas-exchanging structures are smooth-walled blind-ending channels that are lined by cuboidal epithelium and supported by abundant loose interstitium and scattered small blood vessels. As the canalicular period progresses interstitial tissue decreases, capillary growth increases, and these "channels" assume a more complex irregular pattern (Fig. 7-1, *C*).

At approximately 20 weeks' gestation differentiation of the primitive epithelial cells begins. The first morphologic evidence of this phase of differentiation is the growth of capillaries beneath the epithelial cells that line the primitive gas-exchanging channels. In one population of overlying epithelial cells, capillary ingrowth results in thinning of the cytoplasm, narrowing of the air-blood interface, and differentiation into type I pneumocytes—the cells ultimately responsible for gas exchange. In other overlying epithelial cells, the lamellar bodies that are associated with surfactant synthesis begin to appear; these bodies identify the type II cells that will ultimately produce surfactant. Although some investigators have concluded that the progenitor of type I cells is an undifferentiated epithelial cell, a more convincing body of evidence suggests that type I cells develop from differentiated type II cells.[11–15] By the end of the canalicular period, structural development of the lung has progressed to the point that gas exchange is possible.

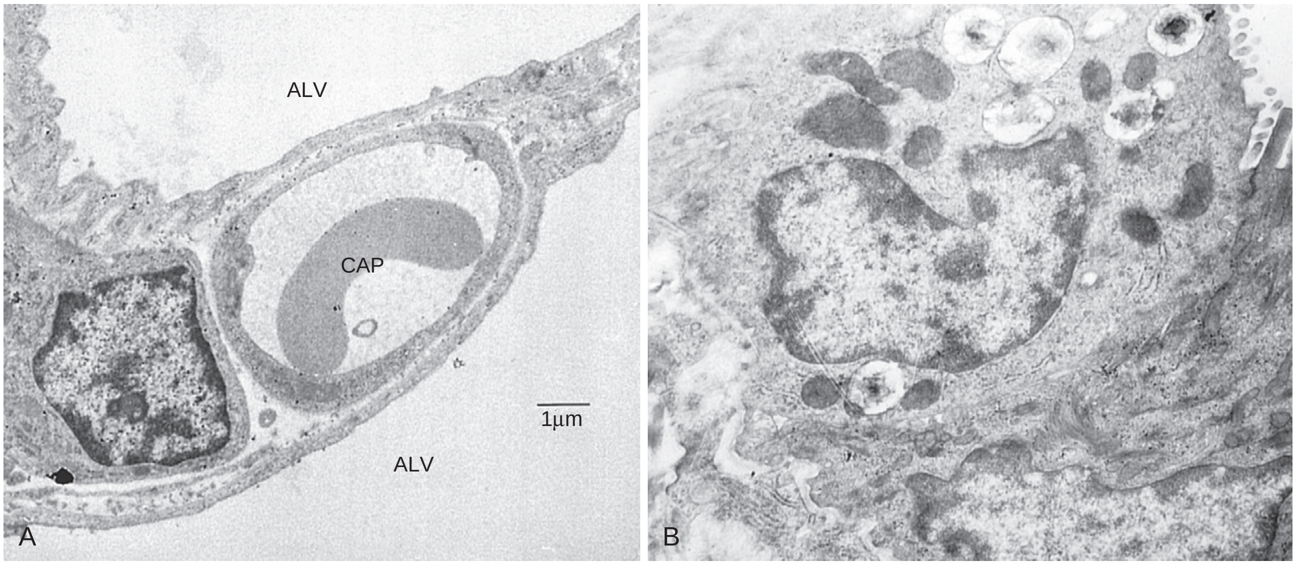


**FIGURE 7-2** **A,** Electrophotomicrograph of a type I pneumocyte. Note the thin alveolar-arterial interface. **B,** Electrophotomicrograph of a type II pneumocyte. Note the lamellar bodies filled with surfactant. ALV, alveolar; CAP, capillary.

## TERMINAL SACCULAR PHASE

The terminal saccular phase of lung development takes place from 24 weeks' gestation until term and is associated with remarkable changes in the appearance of the lung. Interstitial tissue becomes less prominent and airspace walls demonstrate marked thinning. Tissue projections into the distal airspace regions divide the distal airspaces into saccules, where capillaries are generally exposed to only one respiratory surface (Fig. 7-1, *D*). Later in the mature alveolus, each capillary is simultaneously exposed to at least two alveoli.[16]

The cells that line the terminal saccules of the human fetal lung at this stage of development are recognizable type I and type II pneumocytes. Morphologically they are indistinguishable from the corresponding cells described in neonatal or adult human lung tissue. However the surfactant produced by the early fetal lung differs biochemically from that produced later in gestation. Although no apparent morphologic differences in the lamellar bodies exists, immature lungs produce surfactant that is rich in phosphatidylinositol, whereas the surfactant produced by lungs late in gestation is rich in phosphatidylglycerol.[17]

## ALVEOLAR PHASE

An alveolus is defined as an open outpouching of an alveolar duct lined almost exclusively by the thin processes of type I pneumocytes. Its interstitial capillaries are simultaneously exposed to at least two alveoli, and because the nuclei of all cells are located away from the gas-exchange surface, the barrier to gas exchange is usually only a few nanometers thick.[18] The barrier between the gas in the alveoli and the blood in the capillaries is composed of three layers: the thin processes of the type I cells, a basement membrane that appears to be common to the endothelial and alveolar cells, and the thin extensions of the endothelial cells (Fig. 7-2, A). The type I cell is responsible for gas exchange and the type II cell synthesizes and secretes surfactant.

At birth the lung has no mature alveoli but instead contains approximately 20 million primitive terminal sacs.[19–22] These sacs are lined by mature alveolar epithelium; they resemble large shallow cups.[9,19–22] At approximately 5 weeks after birth, these 20 million primitive terminal sacs begin to develop into the 300 million alveoli that will be present by 8 years of age, with the fastest multiplication occurring before 4 years of age (Fig. 7-1, *E*).[21–23] After age 8 years, increases in lung volume result from increases in alveolar size but not number.[21]

## ARTERIAL GROWTH

The pattern of growth of pulmonary arteries differs depending on the location of the artery relative to the acinus. The preacinar region refers to the conducting airways and includes the trachea, major bronchi, and bronchial branches to the level of the terminal bronchiolus. The acinus refers to the functional respiratory unit of the lung and includes structures that are distal to the terminal bronchiolus (specifically the respiratory bronchioli, alveolar ducts, and alveoli). In the preacinar region the pulmonary artery gives off a branch to accompany each airway branch—a "conventional" artery that ultimately provides terminal branches to the acini. Many additional branches arise from the conventional arteries and pass directly into adjacent respiratory tissue to supply the peribronchial parenchyma; these are called *supernumerary* arteries.[8,24]

Mirroring the branching of bronchial airways, the development of all preacinar conventional and supernumerary arteries is complete by 16 weeks' gestation.[24,25] Subsequent changes in the preacinar arteries involve only size not number. In the intra-acinar region terminal branches of the conventional pulmonary arterioles supply the capillary bed. Concurrent with alveolar development these small vessels of the lung

multiply rapidly after birth to keep pace with alveolar multiplication.

In adults complete muscularization of pulmonary arteries is found throughout the acinus, even in the walls of alveoli immediately under the pleura. In the fetus, however, complete muscularization of the arteries occurs only proximal to or at the level of the terminal bronchioli. Consequently only partially muscular or nonmuscular arteries are found within the acinus itself. New alveoli appear during early childhood simultaneously with the accompanying intra-acinar arteries. However muscularization of these arteries is a slow process.[9]

### MEDIATORS OF FETAL LUNG DEVELOPMENT

Although a complete discussion of the genetics of lung development is beyond the scope of this chapter, some of the basic pathways are becoming better understood and are thus worthy of mention. Early lung bud development and airway branching involves the genes *GATA*6, HNF-3, *FGF*-10, *SHH*, and TGF-b. Alveolar development involves *platelet-derived growth factor, tropoelastin,* and glucocorticoids. Pulmonary vascular development involves *TGF-b*, *VEGF-A*, *FOX*, and *integrin*.[26] So far not enough is known about the genetics of lung development for it to be exploited clinically, but that day is probably not far off.

The distribution of fetal lung fluid has been exploited clinically. There is a large body of evidence supporting the role of lung liquid in normal and experimental fetal lung growth. Fetal lung fluid is a combination of plasma ultrafiltrate from the fetal pulmonary circulation, components of pulmonary surfactant, and other fluids from pulmonary epithelial cells. This fluid is produced constantly to keep the fetal lung inflated and at slightly positive pressure, which is essential to stimulate normal lung development. Naturally occurring airway occlusions in humans have resulted in large fluid-filled lungs that histologically have either normal or slightly distended alveoli.[27–31] In other instances intrauterine airway occlusion results in large lungs despite the presence of other anatomic abnormalities, such as Potter syndrome or congenital diaphragmatic hernia, that would normally lead to pulmonary hypoplasia.[32–34]

Experimental studies of normal fetal lambs have confirmed that retention of lung liquid leads to pulmonary hyperplasia, whereas drainage of liquid leads to hypoplasia. Fetal tracheal occlusion has also been shown to prevent pulmonary hypoplasia associated with fetal diaphragmatic hernia.[35–38] Since these initial studies, multiple experimental animal models of fetal tracheal occlusion have shown dramatic increases in lung growth. Subsequently several clinical trials of tracheal occlusion in association with congenital diaphragmatic hernia have shown some progress in alleviating the associated pulmonary hypoplasia, but preterm labor has continued to limit its application.[39,40] Postnatal intrapulmonary distention with perfluorocarbon liquid has also been shown to accelerate neonatal lung growth, but randomized clinical trials have been thwarted by regulatory issues.[26]

Although increased intrapulmonary pressure has been cited as the primary stimulus for lung growth in tracheal occlusion models, it is likely only a trigger for more complex downstream regulatory changes. Tracheal occlusion has been associated with increased expression or production of multiple growth factors, including keratinocyte growth factor, vascular endothelial growth factor, transforming growth factor-β2, insulin-like growth factor I, and many others, all of which may participate in a complex regulatory pathway for lung development enhanced by tracheal occlusion.[41–44]

## Pulmonary Physiology

Shortly before birth epithelial cells cease production of lung fluid and begin to actively absorb it back into the fetal circulation. This process is facilitated by active sodium transport and is stimulated by thyroid hormone, glucocorticoids, and epinephrine.

At birth as the lung expands with the first few breaths, pulmonary arterial $P_{O_2}$ increases and $P_{CO_2}$ decreases. This results in pulmonary vasodilation, lowered pulmonary vascular resistance, and constriction of the ductus arteriosus. The loss of maternal prostaglandins further stimulates ductus arteriosus closure. Cessation of umbilical blood flow results in closure of the ductus venosus and a rise in the systemic vascular resistance, which in turn results in an increase in left-sided heart pressures above the pressure in the right side of the heart, resulting in closure of the foramen ovale. With this final right-to-left shunt closure, the transition from fetal to postnatal circulation is complete. Failure of any of these events can lead to persistence or recurrence of fetal circulation and respiratory failure.

The process of breathing is complex and involves contraction of the inspiratory muscles to generate negative pressure in the trachea to bring fresh air into the lungs. In the lungs the process of oxygen uptake and carbon dioxide elimination occurs by means of diffusion across the ultrathin alveolar capillary membrane. This process is critical not only to fuel the cells of the body with oxygen for metabolism but also to maintain appropriate acid-base status by careful regulation of carbon dioxide. Dysfunction in any part of this process can lead to respiratory failure and the need for mechanical ventilatory support.

### LUNG VOLUMES

To understand the process of respiration, it is necessary to understand the terminology associated with the assessment of pulmonary function. The total volume of the lung is divided into subcomponents, defined as follows (Fig. 7-3):

- Functional residual capacity (FRC): The volume of gas in the lung that is present at the end of a normal expiration when airflow is zero and alveolar pressure equals ambient pressure
- Expiratory reserve volume: The additional gas that can be exhaled beyond FRC to reach residual volume
- Residual volume: The minimum lung volume possible; this is the gas that remains in the lung after all exhalable gas has been removed
- Total lung capacity: The total volume present in the lung
- Inspiratory capacity: The difference in inhaled volume between FRC and total lung capacity
- Vital capacity: The amount of gas inhaled from FRC to total lung capacity

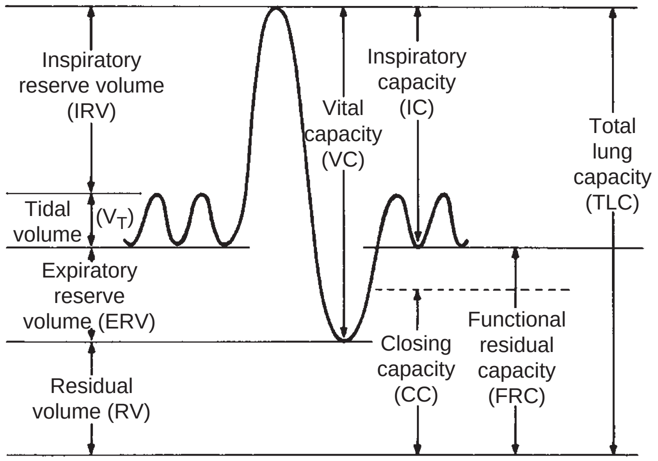


**FIGURE 7-3** Functional components of lung volume.

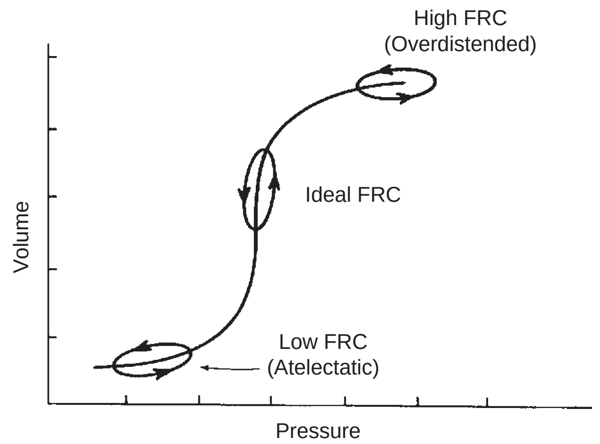


**FIGURE 7-4** Static compliance curve with superimposed dynamic flow-volume loops for high, low, and ideal functional residual capacities (FRCs).

- Inspiratory reserve volume: The amount of gas inhaled from peak normal inspiratory volume to total lung capacity
- Tidal volume: The volume of a normal inspiration

Tidal volume, vital capacity, inspiratory capacity, inspiratory reserve volume, and expiratory reserve volume can be measured directly by spirometry. Conversely total lung volume, FRC, and residual volume cannot be measured by spirometry, and one of the following techniques must be used: (1) the nitrogen washout test, in which the nitrogen eliminated from the lungs while breathing pure oxygen is measured; (2) the helium dilution test, which measures the equilibration of helium into the lung; or (3) total-body plethysmography, which measures changes in body volume and pressure to calculate FRC using Boyle's law.[45]

## CLOSING CAPACITY

Inspiratory pressure within the airway decreases as gas travels in a distal direction. Eventually the intraluminal pressure stenting the airway open equals the surrounding parenchymal pressure; this is called the *equal pressure point*.[46] Downstream of the equal pressure point, intraluminal pressure drops to less than surrounding parenchymal pressure, and airway closure occurs leading to unventilated alveoli and a physiologic shunt. In normal lungs little or no unventilated area exists at FRC. However any reduction in FRC (which frequently occurs in diseased lungs) will cause more areas of the lung to reach closing volume and become atelectatic and increase the shunt.[47] Conversely an increase in FRC (achieved by positive-pressure ventilation) may open some areas that were closed, thereby reducing the physiologic shunt.

## PULMONARY COMPLIANCE

Pulmonary compliance is defined as the change in lung volume per unit change in pressure.[48] Dynamic compliance is the volume change divided by the peak inspiratory transthoracic pressure. Static compliance is the volume change divided by the plateau inspiratory pressure.[49] With the initiation of an inspiratory breath the transthoracic pressure gradient increases to a peak value. This increase is a function of elastic resistance of the lung and chest wall as well as airway resistance. The pressure then falls to a plateau level as the gas redistributes in alveoli. Consequently dynamic compliance is always lower than static compliance. Figure 7-4 demonstrates a standard static compliance curve.[50] Ventilation normally occurs in the steep portion of the curve, whereas large changes in volume occur in response to small changes in pressure. However at low and high volumes, large changes in pressure result in minimal changes in volume. In diseased lungs in which compliance has dropped into the flat portion of the curve, the goal of mechanical ventilation is to return it to the steep portion. Excessive pressure applied by the ventilator results in ventilation at the top of the curve where the process once again becomes inefficient.[51]

Changes in lung volume and pleural pressure during a normal breathing cycle, which reflect the elastic and flow-resistant properties of the lung, are displayed as a pressure-volume loop in Figure 7-5. The slope of the line that connects the end-expiratory and end-inspiratory points in the figure provides a measure of the dynamic compliance of the lung. The area that falls between this line and the curved lines to the right and left represents the additional work required to overcome flow resistance during inspiration and expiration, respectively.

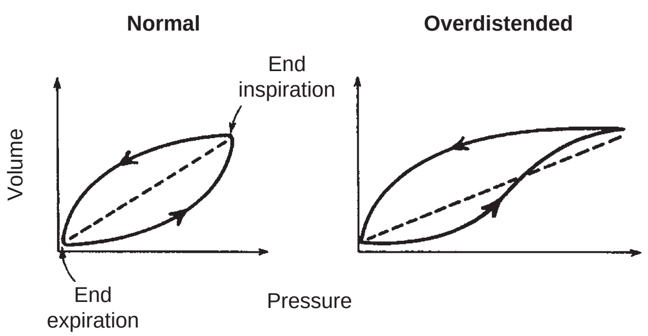


**FIGURE 7-5** Dynamic pressure-volume loop demonstrating an idealized ventilatory cycle and overdistention during positive-pressure ventilation.

## AIRWAY RESISTANCE

Resistance to gas flow is a function of the physical property of the gas (molecules interact with one another and with airway walls) as well as the length of the tube through which the gas travels. Most important, resistance is a function of the internal diameter of the tube. Because the airways in small children are narrow, a slight change in diameter secondary to airway swelling can result in a dramatic increase in resistance. Because airways are smaller at the base of the lung, resistance is greater there than in the apical region.[52] In addition the velocity of flow affects resistance because below critical velocity gas flow is laminar. However above critical velocity there is turbulent flow and resistance increases.

## TIME CONSTANTS

The time constant is a product of the compliance and resistance of the lung and calculates how quickly exhalation can occur. Consequently increases in compliance or resistance of individual alveolar units or areas of the lung increase the time constant. One time constant is defined as the time required to complete 63% of tidal volume expiration (two, three, and four time constants = 87%, 95%, and 99%, respectively).[53] Because the resistance of the airways leading to individual alveoli varies depending on alveolar location, and because the compliance of individual alveoli also varies, the measured time constant is actually an average of many different time constants throughout the lung. The importance of understanding time constants becomes apparent when assisted mechanical ventilation is contemplated. In a lung with high compliance or high resistance the time constant is prolonged. Mechanical ventilator settings would consequently need to be adjusted to allow for near-complete expiration (three time constants, or 95% expiration) to avoid breath stacking and overdistention. Conversely in lungs with low compliance or low resistance, the time constant is less; under these circumstances an increase in minute ventilation should be accomplished with increases in respiratory rate rather than increases in tidal volume. Because of low compliance, tidal volume would be more likely to lead to high pressure and barotrauma.

## PULMONARY CIRCULATION

Mixed venous blood from the systemic circulation collects in the right atrium, passes into the right ventricle, and then travels into the pulmonary capillary bed where gas exchange occurs. Blood subsequently drains into the left atrium where it is pumped into the left ventricle and ultimately into the systemic circulation. Desaturated blood that originates from systemic sources through the bronchial and pleural circulation represents 1% to 3% of the total volume of blood that exits the left atrium. In pathologic situations this anatomic right-to-left shunting can approach 10%.[54] In addition under any circumstance in which pressure in the right atrium exceeds that of the left atrium, the foramen ovale (which is anatomically patent in all neonates and in 20% to 30% of older children) becomes another major area for extrapulmonary right-to-left shunting.

Because blood is a fluid and is affected by gravity, in an upright individual blood pressure and thus blood flow in the pulmonary capillary bed are lowest at the apex of the lung and greatest at the base. Under normal circumstances pulmonary artery pressure is adequate to deliver some blood to the apex of the lung; however in pathologic situations such as hemorrhage or shock, blood flow to the apex can fall to zero, resulting in an area that is ventilated but not perfused; such areas are referred to as dead space. The lung can be divided into four regions designated progressively in a caudal direction from apex to base. In zone 1 (the apex) the alveolar pressure exceeds pulmonary artery pressure and little or no flow occurs. In zone 2 the arterial pressure exceeds alveolar pressure, but alveolar pressure exceeds venous pressure. In this region flow is determined by arterial-alveolar pressure differences. In zone 3 the pulmonary venous pressure exceeds alveolar pressure and flow is determined by the arterial-venous pressure differences. In zone 4 (the base) pulmonary interstitial pressure exceeds both pulmonary venous and alveolar pressure and flow in this region is determined by arterial interstitial pressure differences.[55]

Because oxygen is a pulmonary vasodilator, hypoxemia is a potent stimulus for vasoconstriction in the pulmonary vascular bed. In addition because acidosis is a pulmonary vasoconstrictor and alkalosis is a vasodilator, the partial pressure of carbon dioxide ($P_{CO_2}$) indirectly affects the capillary bed because of its effect on pH.

## PULMONARY GAS EXCHANGE

### Diffusion

Oxygen and carbon dioxide pass between the alveolus and the pulmonary capillary bed by passive diffusion from higher to lower concentration.[56] Because diffusion in a gaseous environment is a function of molecular weight, oxygen diffuses more rapidly through air than carbon dioxide does. However because diffusion across the capillary alveolar membrane involves a shift from the gaseous phase to the liquid phase, solubility of the gas in liquid becomes rate limiting, so carbon dioxide (being far more soluble than oxygen) diffuses 20 times more rapidly.[57]

Diffusion is driven not only by differences in solubility but also by differences in partial pressure of the gases across the capillary alveolar membrane. Gas exchange is consequently most rapid at the beginning of the capillary where the differences in the partial pressure of oxygen ($P_{O_2}$) and $P_{CO_2}$ between the alveoli and the capillaries are greatest; gas exchange is virtually complete one third of the way across the pulmonary capillary bed.[58] Consequently in normal individuals the principal limiting factor for oxygen uptake at rest or during exercise is pulmonary blood flow.[59] Although the rate of diffusion is not rate limiting in the healthy state, when the alveolar capillary membrane is thickened, diffusion may become sufficiently impaired to prevent complete saturation of available hemoglobin. Carbon monoxide, which has diffusion characteristics similar to those of oxygen, is used to measure diffusion capacity.

### Dead Space

Minute ventilation, which is defined as the total volume of air inspired each minute, is calculated as the product of the tidal volume and the respiratory rate. However the entire volume of gas does not participate in gas exchange; the portion of each tidal

breath that ventilates only the oropharynx, larynx, trachea, and major conducting bronchi (the anatomic dead space) does not participate in gas exchange.[60] In addition to the anatomic dead space, a certain volume of gas ventilates unperfused alveoli and consequently does not participate in gas exchange. This is known as alveolar dead space and is minimal in the absence of disease. The combination of anatomic and alveolar dead space, known as physiologic dead space, is equal to approximately one third of the normal tidal volume; dead space that exceeds this amount is considered pathologic.[61]

### Ventilation-Perfusion Matching

For optimal gas exchange, the ventilation (V) and perfusion (Q) to a given segment of the lung should be matched.[62] The V/Q ratios of different lung units are not identical,[58] but the averaged ratio of alveolar ventilation/blood flow in the lung is approximately 0.8. At the apex of the lung the V/Q ratio is higher; at the base of the lung the ratio is lower. Under normal circumstances V/Q mismatching is minimal and inconsequential. However in disease states mismatching can contribute significantly to the impairment of gas exchange. When blood flows through regions of the lung with no ventilation, a right-to-left shunt that can significantly decrease the arterial oxygen saturation is created.

### Oxygen Transport

Oxygen is transported through the bloodstream in one of two ways. It may be transported in aqueous solution in the plasma or in chemical combination within hemoglobin in erythrocytes. The amount of oxygen transported in solution is negligible. Thus most oxygen is carried bound to hemoglobin in erythrocytes. At full saturation, 1 g of hemoglobin is capable of carrying 1.34 mL of oxygen. However the actual amount of oxygen carried by hemoglobin varies and is defined by a sigmoid-shaped curve referred to as the oxyhemoglobin dissociation curve (Fig. 7-6). Under normal circumstances hemoglobin is 100% saturated with oxygen; however the sigmoid shape of this curve ensures that the oxygen carrying capacity of hemoglobin remains relatively high, even at a $P_{O_2}$ as low as 60. As a result mild pulmonary disorders do not interfere with oxygen delivery. At the same time the steep area of the dissociation curve ensures that a large quantity of oxygen can be unloaded into the peripheral tissues as $P_{O_2}$ drops. The oxyhemoglobin dissociation curve can be shifted to the left or right by changes in the affinity of hemoglobin for oxygen. A shift to the left results in a higher affinity of hemoglobin for oxygen and is caused by alkalosis,[63] hypothermia, decreased erythrocyte 2,3-diphosphoglycerate[64] (which often occurs in old banked blood),[65] or fetal hemoglobin.[66] In this situation, at a given $P_{O_2}$, the hemoglobin is more saturated than normal and tissue perfusion should therefore be increased to deliver the same amount of oxygen for metabolic needs. A shift to the right is the result of a lowered affinity of hemoglobin for oxygen and is caused by acidosis,[63] hyperthermia, and an increased red blood cell 2,3-diphosphoglycerate content.[64] This rightward shift results in hemoglobin that is less saturated at a given $P_{O_2}$ thereby allowing the unloading of more oxygen at lower rates of flow to the peripheral tissues.

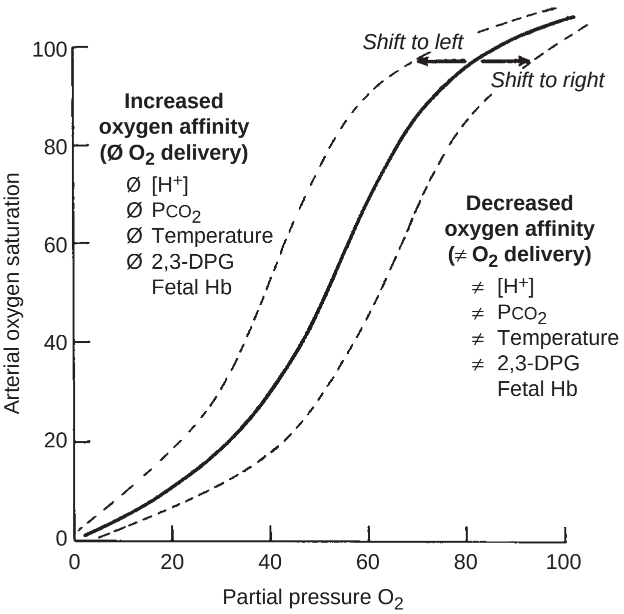


**FIGURE 7-6** Oxyhemoglobin dissociation curve. DPG, diphosphoglycerate; Hb, hemoglobin.

### Carbon Dioxide Equilibrium and Acid-Base Regulation

Because carbon dioxide is produced as an end product of metabolism, its rate of production is a function of metabolic rate. Under normal circumstances the amount of carbon dioxide produced is slightly less than the amount of oxygen consumed. This is defined by the respiratory quotient (R):

$$R = \frac{\text{Rate of } CO_2 \text{ output}}{\text{Rate of } O_2 \text{ uptake}}$$

Under normal circumstances, the respiratory quotient is 0.8, but it can vary from 1.0 to 0.7, depending on whether carbohydrate or fat is used as the principal source of nutrition. The lungs are primarily responsible for the elimination of carbon dioxide, and the rate of elimination depends on pulmonary blood flow and alveolar ventilation. Carbon dioxide is carried in the bloodstream in several forms. In aqueous solution it exists in a state of equilibrium as dissolved carbon dioxide and carbonic acid ($CO_2 + H_2O \rightleftharpoons H_2CO_3$). This equation normally is shifted markedly to the left. In erythrocytes, however, the enzyme carbonic anhydrase catalyzes the reaction, which shifts the equation to the right.[67,68] The ability of carbonic acid to dissociate and reassociate ($H_2C_3 \rightleftharpoons H^+ + HCO_5$) is an important factor in buffering plasma to maintain a physiologic pH. The relationship is defined using the Henderson-Hasselbalch equation. A small amount of carbon dioxide is also carried combined with hemoglobin in the form of carbaminohemoglobins.[67]

## Monitoring

Because the condition of acutely ill infants and children can deteriorate rapidly, continuous surveillance of their physiologic status is necessary to provide ideal care. Many options for physiologic monitoring are available to the clinician in the modern intensive care unit; the most useful are discussed in this section.

## NONINVASIVE MONITORING

### Pulse Oximetry

Pulse oximetry provides continuous noninvasive monitoring of hemoglobin saturation. The principle of pulse oximetry is based on spectrophotometry and relies on the fact that oxygenated and deoxygenated hemoglobin transmits light at different frequencies. Oxygenated hemoglobin selectively absorbs infrared light (940 nm) and transmits red light (660 nm), whereas deoxyhemoglobin absorbs red light and transmits infrared light. The pulse oximeter probe contains two light-emitting diodes that pass light at the wavelengths noted through a perfused area of tissue to a photodetector on the other side. The photodiode compares the amounts of infrared, red, and ambient light that reach it to calculate the oxygen saturation in arterial blood ($SaO_2$).[69,70]

The advantages of pulse oximetry are that it is noninvasive and has a rapid response time, making changes in clinical status immediately apparent. Disadvantages of oximetry are that it is insensitive to large changes in arterial $PO_2$ at the upper end of the oxygenated hemoglobin dissociation curve. In addition at an oxygen saturation less than 70%, the true $SaO_2$ is significantly underestimated by most oximeters. When $SaO_2$ measurements are routinely less than 85%, determination of its correlation with actual partial pressure of oxygen in arterial blood ($PaO_2$) through the use of indwelling arterial catheters is necessary. Errors can also occur when other forms of hemoglobin exist.[71] The presence of carboxyhemoglobin and methemoglobin results in falsely elevated $SaO_2$ readings.[65] Conversely certain dyes such as methylene blue result in a marked decrease in measured $SaO_2$.[72] The presence of fetal hemoglobin, which has an absorption spectrum similar to that of adult hemoglobin, has no impact on the accuracy of $SaO_2$ measurements. Physical factors—including poor peripheral perfusion, abnormally thick or edematous tissue at the site of sensor placement, the presence of nail polish, and excessive ambient light—also lead to inaccurate readings.[73–75]

### Capnometry

Capnometry is a noninvasive method that measures the end-tidal partial pressure of carbon dioxide in the expired gas.[76] As with pulse oximetry capnometry is based on the principle that carbon dioxide absorbs infrared light. Exhaled gas passes through a sampling chamber that has an infrared light source on one side and a photodetector on the other side. Based on the amount of infrared light that reaches the photodetector, the amount of carbon dioxide present in the gas can be calculated. Depending on the equipment, data can be reported as the maximum concentration of carbon dioxide (end-tidal carbon dioxide) or it can provide a display of the entire exhaled carbon dioxide waveform; this display is known as a capnogram.[77]

Two categories of carbon dioxide monitors exist: mainstream monitors and sidestream monitors.[78] Mainstream monitors, in which the sampling cell is connected to the airway between the ventilator and the endotracheal tube, respond faster to changes in carbon dioxide but must be heated to prevent water condensation. These chambers are consequently heavy and hot and must be supported to avoid contact with the patient. Sidestream monitors draw a continuous sample of gas from the respiratory circuit into the measuring cell. This system is lightweight and can theoretically be used in nonintubated patients[79]; however because of the longer transit time to the sampling chamber, this unit is slow in responding to changes in carbon dioxide.

Because the carbon dioxide that is measured in expired gases is a product of metabolic rate, pulmonary circulation, and alveolar ventilation, these variables must all be considered when interpreting changes in end-tidal carbon dioxide measurements.

### Transcutaneous Measurement of Gas Tension

Measurement of $PO_2$ and $PCO_2$ at the skin surface is possible by means of transcutaneous monitoring.[80] The principle of this device is based on the fact that $PO_2$ and $PCO_2$ approximate arterial values in areas where blood flow exceeds the metabolic requirements of the tissue. To increase blood flow the devices used to measure transcutaneous $PO_2$ and $PCO_2$ contain a sampling electrode and a warming device to increase local blood flow.[81] The advantage of transcutaneous monitoring is that it may reduce the number of (but not eliminate the need for) arterial blood gas determinations required in a sick individual. One limitation of the device is that the measured transcutaneous $PO_2$ and $PCO_2$ are not equal to arterial blood gas tensions and can frequently be 5 to 10 mm Hg higher or lower than the arterial counterpart. Changes in peripheral perfusion caused by shock or vasopressors can make these values even more inaccurate.[82] Another disadvantage is that burns or blisters may occur at the electrode site because of the warming component. This requires frequent changing of the monitoring site, at which time recalibration is necessary.

## INVASIVE MONITORING

### Mixed Venous Oxygen Monitoring

Measurement of mixed venous oxygen saturation ($SvO_2$) may be the single most useful measurement in determining critical impairment in oxygen delivery to the tissues (usually interpreted as an $SvO_2$ <60%). Because the $SvO_2$ is a function of arterial saturation, cardiac output, and hemoglobin concentration, any deviation in these values is detected in the $SvO_2$.

Although a lowered $SvO_2$ does not identify the cause of the impairment, it provides several hints to solving the problem. Increasing the fractional concentration of oxygen in inspired gas ($FIO_2$) to elevate $SaO_2$, using pressors or volume expansion to increase the cardiac output, or increasing the hemoglobin concentration with transfusions can all be used to correct a critically low $SvO_2$. The $SvO_2$ can be monitored by intermittent measurement of blood withdrawn from a pulmonary artery catheter or by continuous monitoring using a pulmonary artery catheter equipped with a fiberoptic bundle.[83]

### Arterial Catheterization

Indwelling arterial catheterization provides access for continuous monitoring of arterial blood pressure and intermittent arterial blood gas sampling. This method is indicated for patients who require frequent blood gas sampling or who are hemodynamically unstable.

In children the most common locations for arterial catheter placement are the radial, posterior tibial, or dorsalis pedis arteries. When placing a radial artery catheter, it is imperative to ascertain the patency of the ulnar artery by assessing blood

flow to the hand and fingers while the radial artery is compressed (Allen test).[84] Otherwise ischemic necrosis of the hand may occur.[85] In newborn infants the umbilicus provides two additional arteries for access. The catheter tip is generally placed at one of two positions. The high position (T6 through T8) places the tip below the ductus arteriosus but above the major abdominal tributaries. The low position (L3 through L4) places the catheter tip between the renal arteries and inferior mesenteric arteries. These positions have the advantage of minimizing the potential complications of thrombus or embolus into the tributary vessels.

The advantage of direct arterial catheterization is that it provides the most accurate continuous measurement of blood pressure as well as the most accurate assessment of $Pa_{O_2}$ and $Pa_{CO_2}$. The disadvantage is that the technique is invasive and therefore involves a risk of infection,[2,86] embolization,[87] and thrombosis[88]; this risk increases with time.[89] Another complication is the potential for anemia because the presence of indwelling arterial lines has been associated with excessive blood testing.[90] Consequently daily assessment of the necessity of direct arterial monitoring is essential and catheters should be removed as soon as the patient can be managed without them.

In infants the right radial artery is unique in that it provides peripheral arterial access to preductal blood (i.e., blood ejected from the left ventricle before being mixed in the aorta with blood from a patent ductus arteriosus). When pulmonary hypertension exists (e.g., congenital diaphragmatic hernia), significant differences in preductal and postductal arterial saturation may occur and monitoring of both sites is often useful in guiding therapy.

### Pulmonary Artery Catheterization

The pulmonary artery catheter enables the direct measurement of right atrial pressure, right ventricular end-diastolic pressure, pulmonary artery pressure, and $Sv_{O_2}$.[91–96] In addition calculation of cardiac output and left ventricular filling pressures can be calculated indirectly. Complications include cardiac arrhythmias in up to 50% of critically ill patients, conduction defects (6%), pulmonary infarction (<1%), pulmonary artery rupture (0.2%), catheter knotting, balloon rupture (5%), and infection.[97–102] Because of these safety concerns and the evolution of less invasive methods such as echocardiography, use of pulmonary artery catheters in noncardiac pediatric patients is now rare.

# Mechanical Ventilators

A basic knowledge of mechanical ventilators is important for pediatric surgeons because many surgical procedures result in transient respiratory failure, and respiratory failure is the most frequent diagnosis requiring admission to neonatal and pediatric intensive care units.[103] The goals of mechanical ventilation are to achieve adequate excretion of carbon dioxide by maintaining alveolar ventilation, maintain adequate arterial oxygenation, expand areas of atelectasis by increasing lung volume, and reduce the mechanical work of breathing. While achieving these goals, mechanical ventilation must also avoid inflicting further injury from barotrauma or oxygen toxicity, or both.[104]

The first-generation ventilator developed by O'Dwyer in 1968 was powered by a foot pump and was not significantly improved on until 1970, when Siemens introduced the 900A. Since then ventilators have evolved from simple devices delivering bulk volumes of air based on cycling pressure and time to more advanced devices. Microprocessor-driven models provide new functions such as pressure support ventilation (PSV), mandatory minute ventilation, airway pressure release ventilation, and more recently proportional assist ventilation and volume-assured PSV.

## CYCLING MECHANISMS

### Mechanical Breath Phases

All ventilators deliver mechanical breaths that cycle through four distinct phases: inspiration, cycling, expiration, and triggering. Inspiration is the point at which expiratory valves close and fresh gas is introduced under pressure into the lungs. Cycling is the point at which inspiration changes to expiration and can occur in response to elapsed time, delivered volume, or pressure met. At this point inflow of gas stops and expiratory valves open to allow passive release of gas from the lungs. Triggering is the changeover from expiration to inspiration and can occur in response to elapsed time (control mode) or in response to a patient-initiated event (assist mode), such as changes in airway pressure or gas flow. Most of the recent refinements in ventilator design are aimed at decreasing the mechanical lag time between patient effort and ventilator response, thereby increasing patient comfort and reducing the work of breathing.[105,106]

## VENTILATOR TYPES

Ventilators can be broadly classified into two groups: volume controlled and pressure controlled, based on the specific parameter by which the ventilator cycles are controlled.

### Pressure-Controlled Ventilation

Pressure-controlled ventilation uses pressure as the main parameter to define inspiration. With pressure control the inspiratory phase ceases when a preset peak inspiratory pressure (PIP) is reached. Some ventilators, known as time-cycled ventilators, use a preset inspiratory time to determine inspiration but are pressure limited and thus classified as pressure ventilators. A variation of this, intermittent positive pressure ventilation using a time-cycled pressure limited continuous-flow ventilator, is currently the most common form of ventilation used in infants. The major advantage of pressure ventilation is that it allows careful control of PIP and mean airway pressure thereby avoiding barotrauma. The disadvantage is that tidal volume is a function of not only the difference between PIP and PEEP but also the inspiratory time and compliance. Consequently as lung compliance changes during the course of an illness, tidal volumes may change dramatically. Therefore use of pressure-cycled ventilators requires careful attention to the tidal volume being delivered at a given setting to avoid underventilation as compliance worsens or overdistention and barotrauma as compliance improves (see Fig. 7-5).

### Volume-Controlled Ventilation

Volume-controlled ventilation uses a preset tidal volume to define inspiration. The major advantage of this type of ventilator is that a consistent tidal volume is delivered. However in reality, what is actually controlled is the volume of gas injected into the ventilator circuit not the volume of gas delivered into the patient's lungs. Humidification, compression of gas, distention of the compliant circuit, and the variable leak around an uncuffed endotracheal tube contribute to inaccurate control of delivered tidal volume. Frequently as the pathologic process progresses, adjustments in tidal volume and rate are necessary to maintain the desired minute ventilation and avoid high pressures and barotrauma. To avoid dangerously high PIPs most volume-cycled ventilators have a pressure-limit valve that prematurely interrupts inspiration when the preset limit is reached. Because this can lead to significant alveolar hyperventilation, a pressure-limit alarm sounds to alert the clinician that this is occurring. Volume-cycled ventilation is more commonly used in older children but can be used in infants.[104]

## MODES OF VENTILATION

Modes of mechanical ventilation are classified on the basis of three factors: How is each breath initiated? How is gas flow controlled during breath delivery? How it is the breath ended? The mode indicates how the ventilator interfaces with the patient's own breathing efforts. Most pressure- and volume-cycled ventilators are capable of providing several modes, which vary from total control of ventilation to simple maintenance of PEEP without ventilatory assistance.

### Control Mode

Total control is used when it is necessary to maintain complete control of the patient's ventilation.[79] Because the mechanisms for patient-triggered assist modes are disabled, it is generally necessary to paralyze and sedate the patient to eliminate asynchrony with the ventilator. The control mode is generally used when extremes of ventilation are necessary, such as very high minute ventilation requiring rapid respiratory rates.

### Assist-Control Mode

Assist-control mode is similar to the control mode in that the variables of volume pressure and inspiratory time are preset. However the patient is allowed to override the preset respiratory rate with patient-triggered breaths, which are then completely supported by the ventilator. In the assist-control mode, each breath, whether the patient or the ventilator triggers it, is fully supported by the ventilator. This method may be advantageous if the goal is to reduce the work of breathing or disadvantageous in situations such as weaning, when exercise of the patient's respiratory muscles is desirable.[91] Another disadvantage is that in small infants with high respiratory rates, hyperventilation and asynchrony with the ventilator are common.

### Intermittent Mandatory Ventilation

Intermittent mandatory ventilation (IMV) differs from the control and assist-control methods in that the ventilator controls are preset for mandatory inflations, but spontaneous unsupported ventilation is also allowed. The advantage of this method is that it allows exercise of the respiratory muscles. IMV is also an excellent weaning technique, and in infants with high respiratory rates it can avoid the hyperventilation seen with control modes. One disadvantage is the potential for asynchrony with the ventilator because a machine-driven inspiration may be stacked on top of a patient's spontaneous exhalation. This increases the work of breathing and may result in hypoventilation or even pneumothorax.[107]

### Synchronized Intermittent Mandatory Ventilation

Synchronized IMV allows the mandatory ventilator-delivered breaths to be synchronized with the patient's spontaneous efforts. The obvious advantage of this mode is synchronization of breaths, which should reduce the work of breathing.[108] However spontaneous breaths in excess of the set rate are not supported, which results in uneven tidal volumes and a higher work of breathing during weaning. Other disadvantages relate to the sensitivity of the synchronizing mechanisms because a spontaneous inspiratory effort (usually identified by a change in airway pressure) that is not immediately responded to with a synchronous breath can actually increase the work of breathing.[91]

### Pressure Support Ventilation

Pressure support ventilation (PSV) is a spontaneous mode of ventilation in which each breath is initiated by the patient but is supported by constant pressure inflation. This method has been shown to increase the efficiency of inspiration and decrease the work of breathing.[109,110] Like IMV, PSV is useful for weaning patients from mechanical ventilation. Unlike IMV, in which weaning involves decreasing the number of mandatory breaths with maintenance of inspiratory pressures, PSV involves steady decreases in the level of pressure support because the rate is controlled by the patient.

### Continuous Positive Airway Pressure and Positive End-Expiratory Pressure

With continuous positive airway pressure (CPAP), a predetermined positive airway pressure is administered to the patient throughout the respiratory cycle.[111] The patient however is responsible for generating the tidal volume. This method increases the FRC and usually improves oxygenation by preventing atelectasis.[112] However this technique can increase the work of breathing.

Positive end-expiratory pressure (PEEP) provides continuous positive pressure throughout the ventilatory cycle, which can prevent atelectasis, increase FRC, and improve oxygenation. PEEP is commonly administered in the range of 2 to 10 cm/$H_2O$ in neonates and 5 to 20 cm/$H_2O$ in older children, although most ventilators can provide PEEP at significantly higher levels.

### Inverse Ratio Ventilation

With inverse ratio ventilation, the inspiratory/expiratory time ratio is greater than 1 as opposed to the typical ratio of 1:2 to 1:5. It has been advocated for use in severe acute respiratory distress syndrome (ARDS) or acute lung injury to improve oxygenation while minimizing volutrauma or barotrauma.[1] This is because inverse ratio ventilation allows for increases in mean airway pressure without increases in tidal volume or PIP. Its use remains controversial; several small studies support its use but others report higher complication rates than

with more conventional modes of ventilation.[113–117] However it should be considered when traditional modes of ventilation have failed to reverse hypoxemia despite high airway pressures.[118]

### High-Frequency Ventilation

High-frequency ventilation (HFV) is defined as mechanical ventilation that uses a tidal volume less than or equal to dead space delivered at superphysiologic rates (>150 breaths per minute).[119] The potential advantages of HFV include smaller volume and pressure changes during the respiratory cycle, gas exchange at significantly lower pressures, and less depression of endogenous surfactant production. A large body of animal data suggests that ventilator-induced lung injury results from changes in pulmonary volume rather than from changes in pressure.[120] Large cyclic volume changes during conventional ventilation have been shown to disrupt the alveolar capillary interface, resulting in increased microvascular permeability and pulmonary interstitial edema.[121] This combination of fluid and protein in the interstitial and alveolar spaces results in surfactant inhibition, further reducing lung compliance. Conversely it has been shown that maintaining high lung volume with minimal changes in alveolar pressure or volume does not result in significant pulmonary injury.[122]

Several techniques of HFV exist. High-frequency positive-pressure ventilation is a modification of conventional pressure-limited ventilators, providing rates up to 150 breaths per minute.[123] High-frequency flow interrupters deliver high-pressure, short-duration breaths, with passive expiration.[40] High-frequency jet ventilators deliver short jet breaths at the distal end of the endotracheal tube; expiration is passive.[124] High-frequency oscillatory ventilation (HFOV) uses extremely small tidal volumes delivered at very high rates.[125,126] Unlike the other forms of HFV, the expiratory phase of oscillating ventilators is active.

The mechanism of gas exchange is poorly understood in HFV. With a tidal volume less than dead space volume, alveolar ventilation should equal zero, and the technique should not work. However the probable mechanisms are bulk axial flow, interregional gas mixing (pendelluft), and molecular diffusion.

Oxygenation is improved by recruiting or maintaining lung volume. Unlike conventional ventilation, which requires elevated peak pressure, mean lung volumes can be maintained with ventilation occurring around a relatively fixed intrapulmonary pressure.[127] Elimination of carbon dioxide is much more sensitive to changes in tidal volume than changes in rate.[128] Consequently when a lower $P_{CO_2}$ is desired, it can be accomplished by reducing breathing frequency because the benefit of the increased volume output per stroke exceeds the detriment of decreasing the rate.

Currently there are two strategies for applying HFV. The high-volume strategy is designed for patients with atelectasis-prone lungs. The mean airway pressure is steadily increased in small increments while oxygenation is monitored. Risks of this approach include using inadequate pressure, thereby worsening atelectasis, or using excessive pressure, leading to injury and air leak.[129] The low-volume strategy is for patients with pneumothorax or air trapping.[130] A higher $F_{IO_2}$ is frequently necessary with this strategy, and a higher $Pa_{CO_2}$ (50 to 60 mm Hg) is frequently tolerated.

The initial clinical experience with HFOV (the most widely used HFV at present) was in premature infants with hyaline membrane disease.[131] That initial study did not show a particular benefit of HFV over conventional ventilation, but its methods have been criticized and its conclusions have not been corroborated by subsequent studies. Later studies of HFOV in neonates demonstrated a significant reduction in the incidence of chronic lung disease,[126] improvement in oxygenation, and reduction in the incidence of air-leak syndrome.[125] Several other studies have shown HFOV to be a reasonable alternative to extracorporeal membrane oxygenation (ECMO) for infants who meet ECMO criteria.[132,133]

Clinical data in older children are sparse; however, a series from Children's Hospital in Boston demonstrated that HFOV has some efficacy as a rescue therapy for pediatric patients who meet ECMO criteria.[134] In this study the high-volume strategy was used to rapidly attain and maintain optimal lung volume. A multicenter prospective randomized trial has since been completed, comparing HFOV with conventional mechanical ventilation in pediatric patients with diffuse alveolar disease or air-leak syndrome.[135] Those data showed that HFOV offered rapid and sustained improvements in oxygenation, and despite the use of higher mean airway pressures, a lower incidence of barotrauma was seen with HFOV than with conventional mechanical ventilation. However a 2009 Cochrane database analysis reported that although early observational studies and randomized studies did not show benefit of HFOV, important other changes in the practice of medicine including surfactant and inhaled nitric oxide (INO) might affect that and therefore recommended new prospective randomized controlled trials.

### Extreme Modes of Gas Exchange

***Extracorporeal Life Support*** Extracorporeal life support (ECLS) sits at the extreme end of the gas exchange spectrum. It supports or temporarily replaces the function of the heart or the lungs, or both, with an extracorporeal mechanical device. Further details and indications for its use are discussed in Chapter 8.

***Intravascular Oxygenation*** Intravascular oxygenation involves an intracorporeal gas exchange device inserted into the inferior vena cava that functions similarly to the ECLS circuit. Space constraints in the inferior vena cava limit its use to a supportive role. This is discussed in greater detail in Chapter 8.

***Extracorporeal Carbon Dioxide Removal*** Extracorporeal removal of carbon dioxide is similar to that in ECLS, but it is used when carbon dioxide elimination is the principal problem. This is discussed further in Chapter 8.

***Liquid Ventilation*** Although the ability to provide gas exchange by means of a liquid medium was first demonstrated in the laboratory almost 30 years ago, liquid ventilation did not become a reality until 1990 when the first clinical evaluations were performed in moribund premature newborn infants with respiratory distress syndrome.[136] That study was the first to demonstrate that gas exchange could be supported clinically using a liquid medium. Since then additional clinical studies have been performed to assess the safety and efficacy of liquid ventilation in adults and children.[137–140]

To date the clinical trials of liquid ventilation have used perfluorocarbons as the liquid vehicle. Perfluorocarbons are clear, colorless, odorless fluids that have low surface tension and carry a large amount of oxygen and carbon dioxide. There are currently two methods of liquid ventilation: total liquid ventilation (TLV) and partial liquid ventilation (PLV). In TLV the lungs are completely filled with perfluorocarbon to FRC. Subsequently tidal volumes of additional perfluorocarbon are administered using a device similar to the ECMO circuit. The tidal volume of perfluorocarbon must pass through an external membrane oxygenator (where gas exchange occurs) before reentering the lungs. Because of the complexity of this process, to date TLV has been performed only in laboratory investigations. PLV in contrast is quite easy to perform and very similar to standard mechanical ventilation. In PLV the lungs are filled with the perfluorocarbon liquid to FRC. Tidal volume however is provided by a standard ventilator that uses gas.[138,141] The mixing of the liquid and the gas in the conducting airways of the lung allows the transfer of gases between the two mediums. Because of its ease of use, PLV has been used exclusively for all clinical trials to date.

The mechanism by which liquid ventilation improves gas exchange is probably a combination of a direct surfactant effect of the perfluorocarbon, resulting from its low surface tension, and a lavage effect that removes exudates in the peripheral airways. These two effects result in recruitment of atelectatic lung regions and better ventilation-perfusion matching.

After the initial clinical evaluation of perfluorocarbon liquid in newborns with respiratory distress, several other uncontrolled clinical studies were done in adults and children; these studies generally demonstrated improvement in pulmonary function with liquid ventilation.[137–139]

The only prospective randomized controlled trial of PLV in children was stopped prematurely; at the termination of the study the 28-day mortality rate was not significantly different between the control group and the PLV group.[142]

# Investigational Adjuncts to Mechanical Ventilation

## PRONE POSITIONING

Placing patients with ARDS in the prone position is purported to improve oxygenation by redistributing gravity-dependent blood flow into nonatelectatic areas of nondependent lung by placing them in a dependent position. Several small series have demonstrated at least transient improvements in oxygenation,[39] whereas another failed to show significant improvements in ventilator-free days or survival. In addition this latter study noted significant complications with this technique.[143] Most recently a Cochrane database review determined that compared with the supine position, the prone position improved oxygenation, including desaturation episodes, when used for short periods or when patients were stable and in the process of weaning.[144] The value of this adjunct continues to be investigated.

## INHALED NITRIC OXIDE

Nitric oxide is a potent short-acting pulmonary vasodilator that has been in clinical trial since the early 2000s. In neonates with primary pulmonary hypertension, it has been shown to improve oxygenation and decrease the use of ECLS. However despite a transient improvement in oxygenation, it has failed to improve ventilator weaning or survival in three large trials of patients with ARDS.[145,146]

In 2010 a Cochrane database report determined that there was insufficient evidence to support the use of INO in any category of ARDS in either adult or pediatric patients.[147] Despite these findings INO continues to be used widely in the pediatric and neonatal intensive care unit.

### Pharmacologic Adjuncts in Acute Respiratory Distress Syndrome

Several pharmacologic adjuncts have been proposed for patients with ARDS, including prostaglandin E, acetylcysteine, high-dose corticosteroids, surfactant, and a variety of antioxidants. Unfortunately despite encouraging results from several small series, a recent meta-analysis of all published trials demonstrated no effect on early mortality and a greater number of adverse events in the active therapy arm in the prostaglandin, surfactant, and steroid trials.[148] Consequently none of these agents can be routinely recommended as adjunctive measures in the treatment of respiratory failure or ARDS at this time. Investigation continues.

# Management of Respiratory Failure

The management of respiratory failure and infants and children is the subject of entire textbooks. Presented here will be the briefest of overviews. Respiratory failure is defined as inadequate oxygenation leading to hypoxemia or inadequate ventilation leading to hypercarbia. The first step in treating respiratory failure is to establish an adequate airway. Usually this is accomplished using an endotracheal tube, which can be placed either orally or nasally. However recent interest in noninvasive methods of respiratory support such as continuous positive airway pressure and bilevel positive airway pressure (BiPAP) occasionally allow mild respiratory distress or failure to be treated without intubation. If appropriate these methods can be evaluated first. The approximate internal diameter of the endotracheal tube can be estimated in children older than 2 years using the following formula:

$$\frac{16 + \text{age of child}}{4}$$

Traditionally in children older than 8 years, uncuffed tubes are often used, in which case there should be an air leak present when positive pressure between 20 and 30 cm $H_2O$ is achieved. If properly cared for, these uncuffed tubes can be left in place for several weeks without fear of tracheal injury. Recently however softer cuffed tubes have become available and are used almost exclusively even in neonates in some units.

The goal of mechanical ventilation is to restore alveolar ventilation and oxygenation toward normal without causing injury from barotrauma or oxygen toxicity. In general this correlates to maintaining $Pa_{O_2}$ between 50 and 80 mm Hg, $Pa_{CO_2}$ between 40 and 60 mm Hg, pH between 7.35 and 7.45, and mixed venous oxygen saturation at less than 70%.

Initial ventilator settings on pressure-cycled ventilators should be $FiO_2$ = 100%, rate = 20 to 30 breaths per minute, PIP = 20 to 30 mm Hg, PEEP = 3 to 5 mm Hg, and inspiratory-expiratory ratio = 1:2. The aim is to provide an initial tidal volume of 6 to 8 mL/kg. PEEP should be used in cases of diffuse lung injury to support oxygenation. Support should be started at 2.0 cm $H_2O$ and adjusted in increments of 1 to 2 cm $H_2O$. PEEP greater than 10.0 cm $H_2O$ in infants and 15.0 cm $H_2O$ in older children is rarely indicated. Sedation often enhances the response to mechanical support by allowing better synchrony between patient and machine. After the patient has been stabilized for a brief period, the ventilatory management must be individualized depending on the underlying physiologic condition.

## MANIPULATING THE VENTILATOR SETTINGS

Various parameters can be preset on most ventilators, including the respiratory rate, PIP, PEEP, inspiratory time, and gas flow rate. When adjusting these parameters it is necessary to consider the pathologic condition present in the lung. Infants with primary pulmonary hypertension have very compliant lungs that are easily overdistended. In these patients adequate minute ventilation may be achieved with low PIP and PEEP, a short inspiratory time, and a moderate respiratory rate. Conversely a child with ARDS has noncompliant lungs and may require a relatively high PIP and PEEP, a short inspiratory time, and a high respiratory rate to achieve adequate alveolar ventilation. Obstructive disorders such as meconium aspiration syndrome and asthma have a longer time constant and require ventilation at a slower rate. After determining the initial settings, however, the patient's response must be evaluated and adjustments must be made to stay abreast of dynamic changes in pulmonary compliance and resistance that occur over time.

## ADJUSTING THE PARTIAL PRESSURE OF CARBON DIOXIDE

The $PaCO_2$ is directly related to alveolar ventilation and consequently to minute ventilation (tidal volume × respiratory rate). An increase in minute ventilation can be achieved by adjusting either tidal volume or more frequently respiratory rate. However at high rates or in lungs with prolonged time constants, increases in respiratory rate can lead to breath stacking, overdistention, reduced alveolar ventilation, and a subsequent rise in $PCO_2$.

## ADJUSTING THE PARTIAL PRESSURE OF OXYGEN

In most conditions requiring mechanical ventilation, patchy atelectasis, caused by a drop in FRC toward closing capacity, results in a significant intrapulmonary shunt that is relatively insensitive to increases in $FiO_2$. Recruitment of the atelectatic areas by increasing the mean airway pressure is far more likely to be effective in increasing $PaO_2$. This can be achieved by increasing PIP, PEEP, or the inspiratory-expiratory ratio. High PIP has been shown to cause barotrauma, most likely as a result of overdistention of the more compliant (i.e., healthier) portions of the lung.[50] Consequently increases in PIP should be used sparingly. An increased PEEP is generally preferable to an increased PIP because the PEEP can recruit collapsed alveoli (by increasing FRC) thereby decreasing the intrapulmonary shunt without significant risk of barotrauma. However if a pressure-cycled ventilator is used, increases in PEEP without changes in PIP will result in a lower tidal volume and require adjustments in respiratory rate to maintain minute ventilation. Monitoring compliance also ensures that breaths are provided at the most compliant part of the ventilation curve.

## WEANING

Weaning is the process during which mechanical ventilation is slowly withdrawn, allowing the patient to assume an increasing amount of the work of breathing. The specific technique of weaning depends on which form of ventilation is being used. Weaning from mechanical ventilation should be attempted only when the patient is hemodynamically stable on acceptable ventilator settings and is able to spontaneously maintain an acceptable $PaCO_2$. In general this translates into an $FiO_2$ less than 0.4, PIP less than 30, PEEP less than 5, and ventilator-assisted breaths less than 15 per minute. The child should also have adequate nutrition and a ratio of dead space gas/tidal volume of less than 0.6 (normal = 0.3).

Weaning from IMV support involves a gradual decrease in the frequency of ventilator-delivered breaths. The rate of weaning depends on the patient's clinical condition and response. Monitoring the patient's spontaneous respiratory efforts and blood gas parameters can assist in this process. In older patients the IMV rate can be reduced to as low as 2 to 4 breaths per minute before the patient is extubated. Because of higher airway resistance in the smaller endotracheal tubes used in younger patients, extubation is generally attempted when the rate is reduced to 8 to 10 breaths per minute.

Weaning from PSV involves a slow decrease in the level of pressure support while monitoring the quality and quantity of the patient's spontaneous respiratory effort. In general this type of ventilation is withdrawn by reducing the pressure in increments of 1 to 2 cm $H_2O$.

## WEANING FAILURE

Despite multiple indicators that predict successful weaning, 10% of patients will fail extubation. In most cases this failure is due to excessive respiratory load. This is manifested clinically as the development of rapid shallow breathing, worsening of lung mechanics, and increase in respiratory muscle load.[149,150] Factors that contribute to this are increased ratio of dead space gas/tidal volume, which accompanies the onset of rapid, shallow breathing; excessive carbon dioxide production caused by increased work of breathing; and, sometimes, excessive carbohydrate calories. Respiratory muscle fatigue due to increased respiratory load can cause prolonged (>24 hours) impairment in diaphragmatic and respiratory muscle function.[151] Consequently time must be allowed for recovery before attempting to wean again. Metabolic abnormalities such as acute respiratory acidosis decrease the contractility and endurance of the diaphragm.[152] Imbalances in phosphate, calcium, potassium, and magnesium also impair respiratory muscle function[153–155] as does

hypothyroidism.[156] Correction of these variables toward normal ensures that the patient's best effort is being evaluated.

## Complications of Mechanical Ventilation

Barotrauma is the principal complication of mechanical ventilation. It is caused by overdistention of alveoli by inappropriately high PIP or PEEP or excessive tidal volumes. The consequences of barotrauma include pneumothorax, pneumomediastinum, and pulmonary interstitial emphysema.[157] In addition, because barotrauma seems to be more closely related to volume changes than to pressure changes, the incidence and severity of barotrauma can potentially be lowered by the use of lower tidal volumes (5 to 7 mL/kg) and by accepting a lower pH and a higher $P_{CO_2}$—a ventilatory technique known as permissive hypercapnea.[158]

Oxygen toxicity is another complication of mechanical ventilation. The mechanism of injury is purported to be damage to the capillary endothelium, as well as type I and type II pneumocytes, from oxygen free radicals.[159] Every attempt should be made to maintain the $F_{IO_2}$ at less than 0.6 by adjusting mean airway pressure to improve intrapulmonary shunting and by accepting marginal levels of $P_{O_2}$ (50 to 60 mm Hg) as long as $S_{VO_2}$ remains adequate.

Bronchopulmonary dysplasia is a progressive chronic condition that may occur in 15% of infants who require mechanical ventilation. It is unclear whether the cause of this dysplasia is related to barotrauma or oxygen toxicity, or both. Consequently bronchopulmonary dysplasia can best be avoided by paying careful attention to providing adequate ventilatory support at the lowest possible pressures and oxygen concentration.

These complications are all a direct consequence of positive-pressure inflation of an organ designed to function in a negative-pressure environment. Consequently it is unlikely that any current or future variation of positive-pressure ventilation will ever be completely safe.

Other common complications not directly related to the mechanics of ventilation itself include nosocomial pneumonia acquired because of the ubiquitous nature of pathogens in the intensive care unit and breach of upper airway defenses by the endotracheal tube. Deep vein thrombosis and pulmonary emboli are not uncommon in older pediatric patients, and these patients should receive prophylaxis. Laryngeal trauma during intubation, tracheal stenosis caused by ill-fitting tubes and prolonged intubation, and sinusitis principally associated with nasal intubation round out the list of the more common complications. Most can be avoided or treated by careful attention to detail.

*The complete reference list is available online at www.expertconsult.com.*

# CHAPTER 8

# Extracorporeal Life Support for Cardiopulmonary Failure

Ronald B. Hirschl and Robert H. Bartlett

Extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO) denotes the use of prolonged extracorporeal cardiopulmonary bypass, usually through extrathoracic cannulation, in patients with acute reversible cardiac or respiratory failure who are unresponsive to conventional medical or pharmacologic management.[1,2] It is important to recognize that ECLS is not a therapeutic intervention; it simply provides cardiopulmonary support so that the patient is spared the deleterious effects of high airway pressure, high oxygen fraction in inspired air ($FiO_2$), vasoactive drugs, and perfusion impairment while reversible pathophysiologic processes are allowed to resolve either spontaneously or by medical or surgical intervention. The technology of ECLS is similar for all applications, but the indications, management, and results are best considered separately for adults, children, and neonates with either respiratory or cardiac failure. This chapter is limited to neonates and children with respiratory or cardiac failure.

In 1989 the active ECLS centers formed the Extracorporeal Life Support Organization (ELSO), which standardized many aspects of ECLS. ELSO maintains a registry of all cases treated by the member centers. Much of the information provided here is based on reports from the ELSO Registry.[3] As of January 2011 the ELSO Registry database reported 44,824 adult, pediatric, and newborn patients with cardiorespiratory failure who were supported with ECLS, with an overall 62% survival rate.[3,4]

## Background

ECLS was first successfully applied in a newborn with respiratory failure in 1975.[5] By 1982 it had been used in 45 premature and full-term newborns with respiratory failure, demonstrating a survival of 55% and short-term normal growth and development in 80% of the survivors.[5–7] Three prospective, randomized trials compared the effectiveness of ECLS with that of conventional mechanical ventilation in full-term newborns with severe respiratory insufficiency. In 1985 our group used an adaptive design known as "play-the-winner," which weighted randomization toward the successful and away from the unsuccessful intervention.[8] The randomization scheme resulted in 11 patients who received ECLS and survived and 1 control patient who died. Although statistically significant in view of the 80% to 90% predicted mortality among the enrolled patients, this study was highly controversial and was not well accepted by the medical community. In 1989 O'Rourke and colleagues[9] conducted a randomized trial using a similar adaptive design. Survival in the control group was 6 of 10 patients (60%) and in the ECLS group 28 of 29 (97%) patients survived. A traditional randomized prospective study was performed in the United Kingdom that demonstrated a significant difference in survival between full-term newborns managed with ECLS (72%) and those managed by conventional means (41%).[10] Based on these studies ECLS is considered to be indicated in neonatal respiratory failure whenever the risk of mortality is high.[11] As of the beginning of 2011, 24,344 newborns had been managed with ECLS with a 75% survival rate.[3,12] Interestingly, the rate of use of ECLS in neonates has markedly decreased over the past two decades as newer ventilatory strategies have been developed and applied.

Timmons and associates[13] conducted a multicenter data collection study of pediatric respiratory failure in 1991. The only treatment variable that correlated with improved outcome was ECLS. This large database was further evaluated by Green and colleagues.[14] They did a matched-pair study of patients who were managed with ECLS (74% survival) compared with those managed by conventional means (53% survival). As of January 2011 there were 4771 cases of respiratory failure in children more than 30 days old in the registry, with an overall survival of 56%.

ECLS has been used successfully for pediatric cardiac failure since 1972. Intraoperative or postoperative cardiac failure is the most common indication, although preoperative use of ECLS is effective as a bridge to surgical palliation or anatomic repair.[15] In the past ECLS was the only mechanical support system available to support cardiac failure in children, but now ventricular assist devices such as the Berlin Heart (Berlin Heart AG, Berlin, Germany) are available, increasing in use, and may be associated with enhanced outcome.[16–18] The ELSO Registry documents 9453 cases of cardiac failure in newborns and children with an overall survival of 44%.

## Indications

ECLS is indicated for acute severe respiratory or cardiac failure when recovery can be expected within 2 to 4 weeks. Severe cardiac or respiratory failure can be defined as any acute failure in which the mortality risk is greater than 50%; survival ranges from 50% to 90% in different categories of patients. In some cases the risk is easy to identify (e.g., cardiac arrest or inability to be removed from cardiopulmonary bypass in the operating room). In other cases it is more difficult to quantitate (e.g., a neonate with borderline oxygenation receiving 80% oxygen on moderate ventilatory settings with nitric oxide). Some scoring systems have been devised in these categories of patients to try to define high mortality risk:

1. Mortality risk in neonatal respiratory failure can be measured by an oxygen index (OI) that is based on arterial oxygenation ($PaO_2$) and mean airway pressure (MAP) despite and after all appropriate treatment. It is computed according to the following formula:

$$OI = (MAP \times FiO_2 \times 100)/PaO_2$$

2. In the early ECLS studies an OI greater than 40 in three of five postductal arterial blood gas measurements (each drawn 30 to 60 minutes apart) was predictive of a mortality rate greater than 80%.[19,20] A randomized controlled study performed by our group suggested that "early" initiation of ECLS based on an OI greater than 25, which is predictive of a 50% mortality rate, is associated with a trend toward higher mental developmental scores and a lower incidence of morbidity at 1 year of age when compared with a control group of patients in whom ECLS was initiated at an OI greater than 40.[21] We currently consider institution of ECLS when a series of postductal arterial blood gas measurements demonstrates an OI greater than 25, with mandatory application of ECLS when the OI is greater than 40.
3. Criteria for high mortality risk among older children with respiratory failure are based on the OI or alveolar-arterial oxygen ($PAO_2 - PaO_2$) gradient. Rivera and associates[22] suggest that a ventilation index (respiratory rate $\times$ $PaCO_2$ $\times$ peak inspiratory pressure/1000) greater than 40 and an OI greater than 40 are associated with a mortality rate of 77%, and a combination of peak inspiratory pressure of 40 cm $H_2O$ or greater and an $AaDO_2$ greater than 580 mm Hg are associated with a mortality of 81%. We consider $PAO_2 - PaO_2$ greater than 600 on $FiO_2$ 1.0—despite and after optimal treatment—an indication of high mortality risk in children.
4. Criteria for the initiation of ECLS in pediatric patients with cardiac failure include clinical signs of decreased peripheral perfusion, including oliguria (urine output <0.5 mL/kg per hour), metabolic acidosis, and hypotension despite the administration of inotropic agents and volume resuscitation.[23,24] ECLS is applied in pediatric cardiac patients in the setting of cardiogenic shock (20%), cardiac arrest (20%), and acute deterioration (10%); an additional 20% of patients are placed on ECLS directly in the operating room because of an inability to be weaned from heart-lung bypass.

Current relative contraindications for ECLS are as follows:

1. Prematurity. The lower limit for newborns is 1.5 kg and 30 weeks' gestational age because of a higher incidence of intracranial bleeding in smaller, younger infants.[25,26]
2. Pre-ECMO intracranial hemorrhage higher than grade 2.[27]
3. Prolonged mechanical ventilation. Mechanical ventilation for longer than 7 days in newborn and pediatric patients has been considered a contraindication to ECLS because of the high incidence of bronchopulmonary dysplasia and irreversible fibroproliferative pulmonary disease. However reviews of the ELSO Registry data suggest that the survival rate remains at approximately 50% to 60% after 14 days of pre-ECLS mechanical ventilation in neonatal and pediatric patients with respiratory failure.[28] We currently consider ECLS in any patient who has received mechanical ventilation for up to 14 days, keeping in mind that morbidity and mortality increase with time on the ventilator.
4. Cardiac arrest that requires cardiopulmonary resuscitation in the pre-ECLS period. This has been considered a contraindication to the institution of extracorporeal support. However survival rates of up to 60% have been observed among neonates who suffer cardiac arrest before or during cannulation.[12,29] Of those who survive at least 60% have a reasonable neurologic outcome. Similar survival rates (64%) without long-term sequelae were noted among pediatric patients with cardiac failure who endured cardiac arrest for 65 ± 9 minutes before the institution of ECLS.[30] Based on these data many centers now consider patients who sustain pre-ECLS cardiac arrest to be candidates for extracorporeal support.
5. Congenital diaphragmatic hernia (CDH) with severe pulmonary hypoplasia. Although CDH with severe pulmonary hypoplasia was originally a contraindication to ECLS,[31,32] it was subsequently demonstrated that a number of patients who met this exclusion criteria survived. Thus most centers now consider any patient with CDH a candidate for ECLS.[33–35] Other centers suggest that failure to generate a best preductal $PaO_2$ greater than 100 mm Hg and a $PaCO_2$ less than 50 mm Hg accurately identifies nonsalvageable newborns with CDH who should be excluded from ECLS.
6. Profound neurologic impairment, multiple congenital anomalies, or other conditions not compatible with meaningful life.

Additional relative contraindications for older children include the following:

1. Multiorgan system failure: In general organ system failure other than cardiac, pulmonary, and renal failure, which can be effectively supported with ECLS, are considered contraindications.
2. Major burns: Although thermal injury was previously considered a contraindication, ECLS has been applied in pediatric burn patients (mean of 46% of total body surface area burned), with survival in three of five patients.[36,37]
3. Immunodeficiency: Conditions associated with compromise of the immune system in the past have been considered contraindications to ECLS. Data from the ELSO Registry suggest however that survival is 31% with ECLS in pediatric patients with a diagnosis associated with immunocompromise although specific diagnoses such as bone marrow transplantation carry a poor outcome.[38]
4. Active bleeding.
5. An incurable disease process.

## Methods of Extracorporeal Support

The goal of ECLS is to perfuse warmed arterialized blood into the patient.[1] To achieve this goal the extracorporeal blood flow is used most commonly in venoarterial (VA) mode for cardiac support and venovenous (VV) mode for respiratory support. VA mode provides complete support, but there are significant disadvantages: (1) a major artery must be cannulated and at least temporarily sacrificed, (2) the risk of dissemination of particulate or gaseous emboli into the systemic circulation is substantial, (3) pulmonary perfusion may be markedly reduced, (4) left ventricular output may be compromised owing to the presence of increased ECLS circuit-induced afterload resistance, and (5) the coronary arteries are perfused predominantly by the relatively hypoxic left ventricular blood.[37] VV access, either by two vessels or by a single vessel through a double-lumen catheter, supports gas exchange without the disadvantages of VA support. VV or double-lumen VV ECLS is now the preferred method for patients of all age groups who do not require cardiac support (Fig. 8-1).[39] Data from the ELSO Registry and a nonrandomized multicenter study suggest that bypass performed with the double-lumen VV configuration may increase the survival rate and reduce the incidence of intracranial hemorrhage in neonates.[40] However a matched-pairs analysis that corrected for pre-ECLS severity of cardiopulmonary dysfunction revealed no difference in either parameter between patients undergoing bypass with a double-lumen VV or a VA configuration.[32] Femoral and jugular cannulation is used for most children, although recent availability of the Avalon double-lumen cannulas (Avalon Laboratories, LLC, Rancho Dominguez, Calif.) from 13 to 31 French has broadened the use of double-lumen VV ECLS.

Arteriovenous support, typically through cannulation of the femoral artery and vein, is being applied for arteriovenous carbon dioxide removal (AVCO2R). This technique has been shown to be reduce $Pa{CO_2}$ and ventilatory requirements in adults with acute respiratory distress syndrome (ARDS) and children with asthma.[41,42]

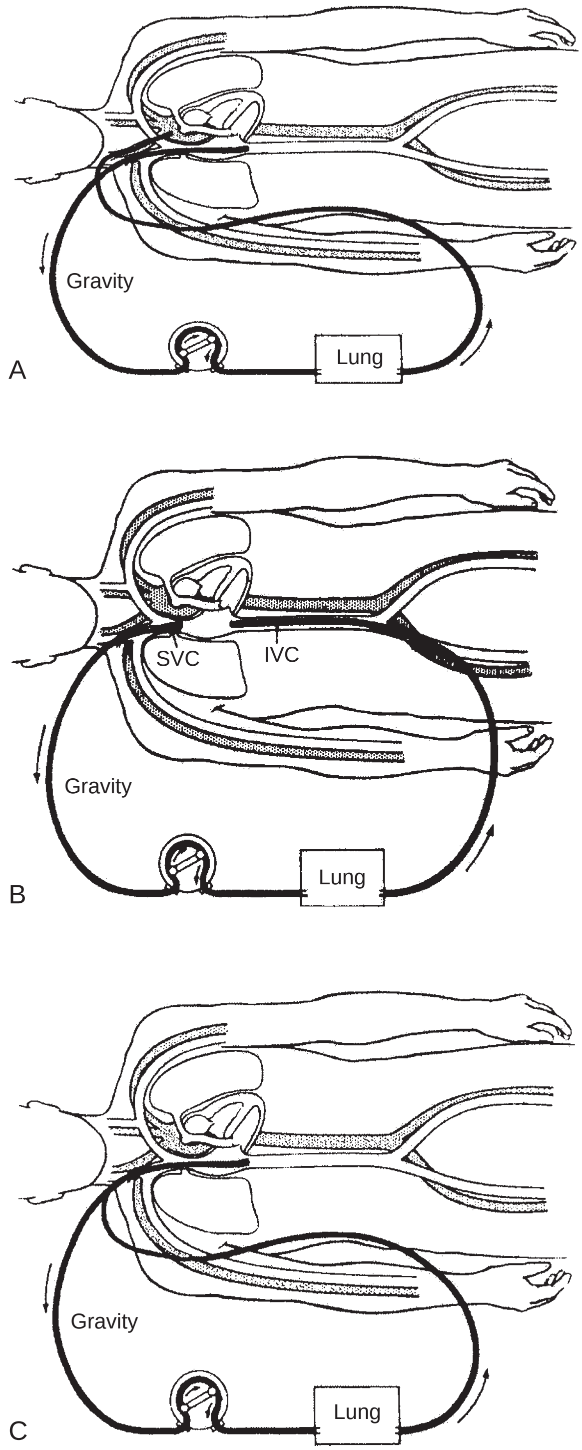


**FIGURE 8-1** Three most common extracorporeal bypass configurations. **A,** Venoarterial configuration with drainage from the internal jugular vein and reinfusion into the carotid artery. **B,** Venovenous configuration with drainage from the internal jugular vein and reinfusion into the femoral vein. **C,** Venovenous configuration with a double-lumen cannula placed into the internal jugular vein. IVC, inferior vena cava; SVC, superior vena cava.

## Extracorporeal Life Support Circuit

The ECLS circuit comprises a pump, a membrane lung, and a heat exchanger (Fig. 8-2), as well as other devices associated with safety and monitoring functions. A full description of the technology, including device function and malfunction, is published in the ELSO's textbook.[43] Right atrial blood is drained by gravity siphon by a cannula placed through the right internal jugular or right femoral vein. Roller pumps are the most common perfusion devices used and require continuous servoregulation and monitoring to prevent the application of high levels of negative pressure to the drainage circuit and high levels of positive pressure, with a risk of circuit disruption, to the infusion limb of the circuit if occlusion occurs.[44] Application of high negative pressures to the drainage circuit (e.g., with a centrifugal pump) results in hemolysis, damage to the endothelium of the right atrium or vena cava, and cavitation as air is drawn out of solution.

The artificial lung most commonly used is the Kolobow spiral coil (Medtronic, Minneapolis, Minn.) solid silicone

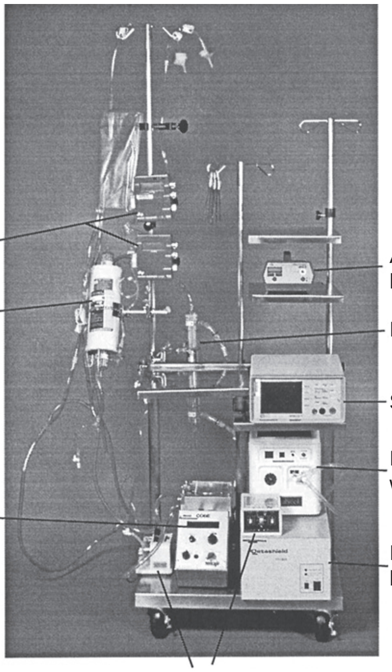


**FIGURE 8-2** Extracorporeal life support circuit. The essential components include the roller pump, the membrane lung, and the heat exchanger. The remainder of the devices shown perform monitoring and safety functions.

rubber membrane lung.[45] The size of the various ECLS components required as a function of patient weight is shown in Table 8-1. Hollow-fiber artificial lungs made of microporous materials are highly efficient with regard to gas exchange, have low resistance to blood flow, and are easy to prime. The disadvantage of the microporous membrane is the increased rate of condensation of water in the gas phase and the frequent need for replacement owing to the development of plasma leak.[46] Phospholipid adsorption onto the blood surface of the hollow fiber at the site of 5-μm pores is the mechanism by which the plasma leak occurs.[46] Artificial lungs with hollow fibers that do not have pores resolve this problem and are preferred for ECLS. These devices have been used in Europe and Japan but are not available in the United States. Plasma leak is retarded in artificial lungs that use polymethylpentene fibers; such artificial lungs are being used more frequently in the United States and other parts of the world.[44]

The volume of the neonatal circuit is approximately 400 to 500 mL, which is one to two times the newborn blood volume. The circuit must therefore be primed carefully to perfuse the neonate at the onset of bypass with blood containing the appropriate pH, hematocrit, calcium, clotting factors, and electrolytes and at the appropriate temperature. However, as shown in Table 8-1, ECLS may be instituted in patients weighing more than 35 kg without the addition of blood to the priming solution.

## Patient Management

Patient management is described in detail in the ELSO textbook.[43] The size of the venous cannula is the factor that determines the blood flow rate and therefore the level of extracorporeal support. The largest possible venous access cannula should be used; it should be of sufficient size to provide adequate blood flow (∼100 mL/kg per minute) with the assistance of 100-cm $H_2O$ gravity siphon pressure. The flow-pressure characteristics of a given cannula are determined by a number of geometric factors, including length, internal diameter, and side hole placement. The M number provides a standardized means for describing the flow-pressure relationships in a variety of vascular access devices.[47,48]

The first choice for venous access is the internal jugular vein because it is large and provides easy access to the right atrium through a short cannula. The femoral vein is the second choice for venous drainage access during ECLS and the first choice for drainage during VV support. In children younger than 5 years, the femoral vein is too small to function as the primary drainage site, and VV access is used in a jugular-to-femoral fashion or using a double-lumen VV cannula in young children. A proximal venous drainage cannula can be placed in the proximal internal jugular vein to enhance venous

**TABLE 8-1**
**Circuit Components and Prime for Patients of Different Sizes Receiving Venovenous Support**

| | Weight (kg) | | | | | |
|---|---|---|---|---|---|---|
| | *2-4* | *4-15* | *15-20* | *20-30* | *30-50* | *50+* |
| Drainage tubing (in) | ¼ | ¼ | ⅜ | ⅜ | ½ | ½ |
| Raceway (in) | ¼ | ¼ | ⅜-½ | ½ | ½ | ½ |
| Oxygenator ($m^2$) | 0.8-1.5 | 0.8-1.5 | 2.5-3.5 | 3.5-4.5 | 4.5 | 4.5 × 2 |
| Cannulas* (French) | 12-15 | 13-20 | Inf: 16-19 | Inf: 17-21 | Inf: 21 | Inf: 21 |
| | DLVV† | DLVV† | Dr: 14-19 | Dr: 17-21 | Dr: 19-23‡ | Dr: 21-23‡ |
| Prime | RBC: 1-2 U | RBC: 1-2 U | RBC: 3 U | RBC: 4 U | RBC: 4 U§ | RBC: 5 U§ |
| | FFP: 50-100 mL | FFP: 50-100 mL | FFP: ½ U | FFP: 1 U | FFP:1 U | FFP: 1 U |

*All cannulas are the shortest Biomedicus cannula available in the specified size. These are only guidelines, and individual patient variables must be considered.
†12 and 15 Fr DLVV cannulas are manufactured by Jostra. The 14 Fr DLVV cannula is manufactured by Kendall. Cannulas 13 to 31 Fr are manufactured by Avalon.
‡The M-number (2.4) of the 23 Fr Biomedicus (38 cm) custom cannula is nearly the same as that of the 29 Fr Biomedicus (50 cm) cannula.
§Normosol (3 L) with 12.5 g albumin and 1 g CaCl is usually used.
DLVV, double-lumen venovenous; Dr, drainage; ECLS, extracorporeal life support; FFP, fresh frozen plasma; Inf, infusion; NA, not applicable; RBC, red blood cells; U, units.

drainage to the extracorporeal circuit.[49] One study demonstrated a reduction in intracranial hemorrhage after initiation of the use of such a cannula when compared with historical controls.[50] An ELSO Registry study however failed to demonstrate an effect on intracranial hemorrhage or survival during routine use of a proximal venous drainage cannula. (F. L. Fazzalari, R. B. Hirschl, T. Delosh, R. H. Bartlett, oral communication, 1994).

The size of the reinfusion cannula is less critical than that of the venous drainage cannula, although it must be large enough to tolerate the predicted blood flow rate at levels of total support without generating a pressure greater than 350 mm Hg proximal to the membrane lung. When only respiratory support is required, the reinfusion cannula may be placed into the femoral vein to provide VV support. Rich and associates[52] demonstrated advantages in terms of reduced blood recirculation and overall oxygenation when the femoral cannula was used for drainage and the internal jugular cannula was used for reinfusion. When cardiovascular support is required, the first choice for placement of a cannula into the arterial circulation is the carotid artery in all age groups because it provides easy access to the aortic arch. Few complications have been associated with carotid artery cannulation and ligation in newborns and children.[53,54] The second choice for arterial access is the femoral artery. Distal perfusion of the lower extremity arterial circulation may be required when the femoral artery is cannulated and may be achieved through antegrade perfusion of the common femoral artery or retrograde perfusion of the posterior tibial artery.[55] However arch perfusion and oxygenation, and therefore heart and brain circulation, are poorly achieved with femoral artery reinfusion. This may be overcome and carotid artery cannulation-ligation avoided using the technique of venoarterial-venous (VAV) ECLS in which a drainage cannula is placed into the femoral vein and reinfusion cannulas into the femoral artery and internal jugular vein. Reinfusion into the femoral artery is limited to that required to maintain blood pressure, thus allowing a substantial portion of arterialized blood to reinfuse through the internal jugular vein, providing oxygenation of the blood perfusing the aortic arch.

The cannulation procedure is usually performed by direct cutdown using local anesthesia (Fig. 8-3). The tips of the arterial and venous cannulas (see Table 8-1 for sizes) are optimally located at the opening of the right brachiocephalic artery and the inferior aspect of the right atrium, respectively. The double-lumen VV cannula must be placed so that the tip is in the midright atrium, with the reinfusion ports oriented toward the tricuspid valve to minimize recirculation of reinfused blood. Percutaneous access to the internal jugular and femoral veins is the routine and preferred approach to cannulation in adults and children older than 3 years. Sequentially larger dilators are placed over a wire, and a Seldinger technique allows final access of the cannula itself into these large veins. A 12 or 15 French double-lumen VV cannula is amenable to percutaneous introduction into the internal jugular vein in neonates. The Avalon cannula can be placed by a percutaneous approach in patients of all ages. This cannula has distal and proximal drainage ports with a midcannula reinfusion lumen. As such the cannula design is intended for placement of the distal tip into the inferior vena cava with the reinfusion lumen opening positioned at the level of the tricuspid valve.

The cannulas are connected to the ECLS circuit and cardiopulmonary bypass is initiated. Flow is increased over the ensuing 10 to 15 minutes to levels of approximately 100 mL/kg. Once a patient is receiving extracorporeal support there is typically rapid cardiopulmonary stabilization. All paralyzing agents, vasoactive drugs, and other infusions are discontinued during VA support; some pressor or inotropic support may be necessary when VV bypass is used.[39] Ventilator settings are adjusted to minimal levels (peak inspiratory pressure <25 and $F_{IO_2}$ <0.4) to allow the lung to rest and any air leaks secondary to barotrauma to seal.[1] Application of positive end-expiratory pressure in the range of 12 to 14 cm $H_2O$ during the course on extracorporeal support has been demonstrated to decrease the duration of ECLS from 132 ± 55 hours to 97 ± 36 hours.[56] Because only partial bypass is used, oxygenation and carbon dioxide elimination are determined by a combination of native pulmonary function and extracorporeal flow. The mixed venous oxygen saturation ($S_{VO_2}$) is conveniently monitored by a fiberoptic Oximetrix catheter placed in the venous limb of the circuit, which allows one to determine the adequacy of oxygen delivery in relation to oxygen consumption, especially during VA ECLS. Pump flow is adjusted to maintain oxygen delivery so that the $S_{VO_2}$ is greater than 70% during VA support and, because of the effects of reinfusion into the venous system, greater than 85% during VV support. The $Pa_{CO_2}$ is inversely proportional to the flow rate of gas ventilating the membrane lung.

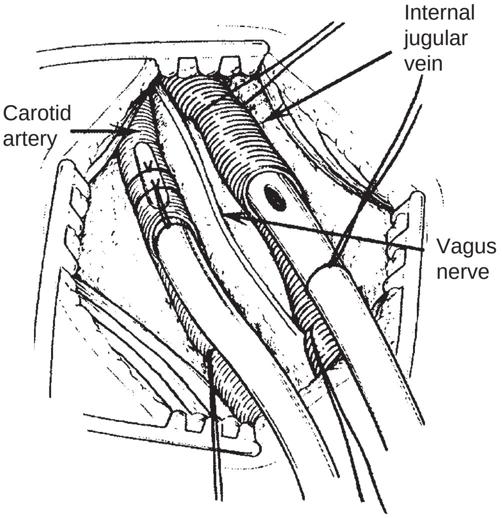


**FIGURE 8-3** Cannulation for venoarterial extracorporeal support. The transverse right supraclavicular incision is shown. In neonates the cannulas are placed 2.5 cm into the artery and 6.0 cm into the vein. They are secured using two circumferential 2-0 silk ligatures with a small piece of plastic vessel loop placed underneath to protect the vessels from injury during decannulation. One of the ends of the marking ligature is tied to the most distal circumferential suture for extra security.

## Cannulation for Cardiac Support

Deterioration in myocardial function is observed in approximately 7% of neonates after initiation of ECLS.[57–59] This "myocardial stun" usually occurs in patients with exaggerated levels of hypoxia, with more frequent episodes of cardiac arrest, and who required more frequent epinephrine pressor

support before ECLS. It typically resolves over the first 24 to 48 hours after initiation of ECLS.

If the left ventricle does not eject (no arterial pulse contour), the left ventricle and atrium will distend and cause pulmonary edema. If this occurs balloon or blade atrial septostomy may be required to decompress the left oximetry and allow the resolution of pulmonary edema and eventual improvement in cardiac function.[60]

Heparin is titrated to prevent thrombus formation throughout the course of ECLS. The level of anticoagulation is monitored hourly by the whole-blood activated clotting time (ACT).[1,2] The ACT is maintained at 50% to 60% above normal (180–220 seconds for the Hemochron device [ITC, Edison, NJ]).[61] Transfusion of red blood cells to maintain the hematocrit at greater than 45% and fresh frozen plasma to maintain the fibrinogen levels at greater than 200 mg/dL are frequently required. Platelets are transfused to maintain the platelet count at greater than 100,000/mm$^3$, although the decrease in platelet function and count associated with extracorporeal support appears to be only transiently corrected by platelet administration.[62] Stallion and colleagues[63] suggested that maintaining the platelet count at greater than 200,000/mm$^3$ appears to be associated with a decrease in bleeding complications. We continue to maintain the platelet count at greater than 100,000/mm$^3$, except in patients who are at high risk for or have ongoing hemorrhage, in which case the platelet count is maintained at greater than 150,000/mm$^3$.

Diuresis or hemofiltration is titrated to normal “dry” weight. Renal function may be transiently impaired during ECLS; therefore use of a hemofilter placed in the circuit to supplement urine output may be necessary in some patients.[64,65] Routine use of a hemofilter may reduce time on ECLS and mechanical ventilation.[66] Renal insufficiency that develops before or during ECLS can also be easily managed by a hemofilter or continuous renal replacement therapy placed in the extracorporeal circuit as necessary.[67] Nutrition remains a high priority in a critically ill patient requiring ECLS.

Most operative procedures performed during ECLS are carried out in the intensive care unit, although as comfort with ECMO transport increases, travel to the operating or cardiac catheterization suite is becoming more routine.[68] Either isoflurane gas anesthesia administered through the oxygenator of the ECLS circuit or intravenous anesthesia with fentanyl or sufentanil and vecuronium may be used. Nagaraj and associates[69] described 44 procedures performed in 37 neonates receiving ECLS. These procedures consisted of recannulation or repositioning of cannulas (14), tube thoracostomy (11), cardiac surgery (6), cardiac catheterization (4), repair of CDH (5), and thoracotomy (4). Hemorrhagic complications, which occurred in 46% to 55% of patients, were associated with a higher mortality. Therefore one should strongly consider whether the procedure is necessary (e.g., placement of thoracostomy tubes for small pneumothoraces) or whether the operation can be delayed until ECLS is discontinued. During procedures performed while the patient is receiving ECLS, electrocautery should be used generously, the ACT reduced to a maximum of 160 to 180 seconds, and the platelet count maintained at greater than 150,000/mm$^3$. One should also consider perioperative administration of aminocaproic acid (Amicar).[70]

Repair of CDH can be done before, during, or after ECLS. Practice changed when we realized that pulmonary dysfunction is caused by hypoplasia and vasospasm and not the hernia. Connors and colleagues[71] first described the repair of CDH in six newborns at a mean of 25 hours after initiation of ECLS, with four survivors. Lally and coworkers[72] reported a 43% survival rate among 42 newborns undergoing diaphragmatic hernia repair while receiving extracorporeal support. Vazquez and Cheu[73] reported that up to 48% of patients with CDH who require ECLS undergo repair while receiving extracorporeal support. Other studies suggest that operative repair in a newborn with CDH can be performed after discontinuation of ECLS, continued resolution of pulmonary hypertension, and ventilator weaning. Based on data from the ELSO Registry, Vazquez and Cheu[73] demonstrated that surgical hemorrhage requiring transfusion occurred in 38% of CDH repaired while the patient was receiving ECLS versus 18% and 6% of those repaired before and after, respectively. Wilson and coworkers[70,74] observed a reduction in blood loss and transfusion requirement in a group of 22 patients receiving ECLS in whom repair was performed electively before decannulation. In these patients the ACT was maintained at the 180- to 200-second level, and aminocaproic acid was administered continuously for 72 hours postoperatively or until decannulation in all patients. Reexploration for hemorrhage was not required.[75] Bryner and associates[75] suggested that survival is enhanced when repair is performed following discontinuation of ECLS. In general our current practice is to repair the hernia after weaning the patient from ECLS, although there is a trend across the United States toward early repair while the patient is receiving ECLS.

When pulmonary function improves, ECLS flow is decreased, leading to a “trial off” (without ECLS). During VV bypass, the gas phase of the membrane lung can simply be capped indefinitely so that the patient remains on extracorporeal blood flow but without the artificial lung’s contribution to gas exchange. Patients receiving VA bypass are tested by clamping the lines (no flow). Such trials are performed on a daily basis when cardiopulmonary physiology suggests improvement with optimal pressor support and are frequently accompanied by echocardiographic evaluation in patients with cardiopulmonary compromise.

Once it has been determined that ECLS can be discontinued, the cannulation site incisions are opened and the right carotid artery or internal jugular vein, or both, are ligated. The carotid artery can be repaired after a course of VA extracorporeal support, although there is no proven benefit and there is the potential risk of distal embolism, late stenosis or thrombosis, and development of atherosclerosis.[14,49,76,77] The internal jugular vein can be repaired as well, especially in patients with congenital heart disease who will require future percutaneous access.[78] A central line or Broviac catheter may be placed into the vein during decannulation with a surprisingly low risk of infection.[79] Percutaneously placed cannulas can simply be removed and pressure applied without concern about the patient’s anticoagulation status. The femoral artery, if used, is repaired and the femoral vein is ligated.

The duration of ECLS (mean ± standard deviation) is 170 ± 126 hours for neonates with respiratory failure, 260 ± 224 hours for children with respiratory failure, and 151 ± 140 hours for patients with heart failure. Reasons to discontinue extracorporeal support other than when indicated by improvement of cardiopulmonary function include the presence of irreversible brain damage, other lethal organ failure, and uncontrollable bleeding. Neonates with CDH or pneumonia

and pediatric patients with cardiac or pulmonary failure may require substantially longer periods on ECLS before resolution of the cardiopulmonary process is observed. On occasion a second course of ECLS is required and results in survival rates of 44% in children.[80]

## Complications

In general the complications associated with ECLS fall into one of three major categories: (1) bleeding associated with heparinization, (2) technical failure, and (3) neurologic sequelae, a majority of which are secondary to the hypoxia and hemodynamic instability that occur before the onset of extracorporeal support.

The average number of patient complications per ECLS case is 2.1.[81] Because of systemic heparinization, bleeding complications are the most common and devastating.[82] Intracranial hemorrhage occurs in approximately 13% of neonates, 5% of pediatric patients, and 4% of cardiac patients. It is the most frequent cause of death in newborns managed with ECLS.[83] Because of the associated heparinization, intracranial hemorrhage may be unusual in terms of both extent and location.[84,85] The mechanism by which it occurs in newborns receiving ECLS is multifactorial. In addition to heparin administration, platelet function and number are decreased for up to 48 hours after discontinuation of ECLS, as are coagulation factor levels.[86] Wilson and colleagues[77] noted a reduction in the incidence of intracranial hemorrhage, compared with historical controls, among a cohort of 42 newborns considered to be at high risk for bleeding complications who received 100 mg/kg of aminocaproic acid just before or after cannulation, followed by a continuous infusion of 30 mg/kg per hour until decannulation. The incidence of intracranial hemorrhage is clearly increased in patients who are premature, especially those less than 37 weeks' gestational age. Although carotid ligation and institution of ECLS in normal animals do not affect carotid artery or cerebral blood flow, initiation of ECLS in the setting of hypoxia results in augmentation of carotid artery and cerebral blood flow and loss of cerebral autoregulation.[87] In addition, decreases in $Pa{CO_2}$ result in marked decreases in cerebral blood flow.[88] Therefore carotid artery and internal jugular vein ligation along with rapid institution of ECLS in the setting of hypoxia or hypercarbia may result in alterations in cerebral blood flow and cerebral autoregulation, with the potential induction of intracranial hemorrhage in a patient who has undergone anticoagulation.

Bleeding at extracranial sites is observed in 21% of neonatal patients, 44% of pediatric respiratory patients, and 40% of neonatal and pediatric cardiac patients. These sites of bleeding include gastrointestinal hemorrhage (2% to 5%), cannulation site bleeding (up to 6%), bleeding at another surgical site (neonatal respiratory patients, 6%; pediatric respiratory patients, 24%, neonatal and pediatric cardiac patients, 28%), and a miscellaneous group of bleeding sites, including pericardial, intrathoracic, and retroperitoneal (7% to 15%). Bleeding during ECLS is managed by maintaining the platelet count at greater than 150,000/mm$^3$ and decreasing the ACT to a maximum of 160 to 180 seconds. Occasionally discontinuation of heparin or, if tolerated, temporary discontinuation of bypass with normalization of the coagulation status may be necessary to achieve resolution of the bleeding.[89] If hemorrhage persists, aggressive surgical intervention is indicated. Administration of recombinant factor seven may be effective when nonsurgical bleeding is present, although thrombotic complications, including development of ECLS circuit or systemic arterial clots, is a concern.[90–94] We have found that intra-abdominal or intrathoracic packing with planned daily reexploration allows control of hemorrhage in most situations. Only in extreme circumstances should permanent discontinuation of bypass be considered in a patient with persistent cardiopulmonary failure. Heparin-induced thrombocytopenia occurs occasionally and argatroban or lepirudin may be used to provide systemic anticoagulation.[95,96]

Neurologic injury induced either before or after the onset of ECLS is a constant concern. Many neonates must endure the insult of hypoxia or ischemia before the institution of bypass and it has been suggested that ligation of the carotid artery in the minutes before the onset of ECLS, at a time when hypoxemia and hemodynamic instability are maximized, results in a further decrease in cerebral tissue oxygenation, which in turn might exacerbate the neurologic injury.[97] However Streletz and colleagues[98] noted no increase in the electroencephalographic abnormalities present before and during ECLS among 145 neonates. In addition Walsh-Sukys and associates[99] in a prospective evaluation of 26 neonates managed with conventional mechanical ventilation and 43 neonates managed with ECLS, noted a similar 25% rate of neurodevelopmental impairment in both groups at 8 to 20 months of age. The incidence of any neurodevelopmental impairment at 1 year of age was 28% among survivors of both groups in the United Kingdom neonatal randomized study.[10]

Seizures have been noted in 10% to 13% of patients undergoing ECLS.[100] The presence of seizures in newborns during ECLS portends a poor prognosis: 50% to 65% with electrographic seizures during ECLS either died or were developmentally delayed at 1 to 2 years of age.

Hemolysis (serum hemoglobin >100 mg/dL) occurs in 6% to 12% of patients. This complication is likely due to red blood cell trauma during extracorporeal support, which is often related to clot formation within the circuit or overocclusion of the roller pump. Centrifugal pumps have been associated in the past with development of hemolysis over time, likely caused by heat generation.[101] Newer generation magnetically levitated centrifugal pumps, which are magnetically suspended and therefore associated with minimal friction, can be used without major concerns about hemolysis generation. Hyperbilirubinemia is noted in 8% of patients and renal insufficiency in 10%. Pneumothorax (occurring in 4% to 14%) and pericardial tamponade are life-threatening intrathoracic complications that manifest with increasing $Pa{O_2}$ and decreasing peripheral perfusion and $Sv{O_2}$, followed by decreasing ECLS flow and progressive deterioration. Initial emergent placement of a pleural or pericardial drainage catheter, followed by thoracotomy for definitive treatment of a pericardial tamponade, may be lifesaving.

Technical complications occurred in 15% of the neonatal and pediatric cases reported to the ELSO Registry.[102] The average number of mechanical complications per ECLS case was 0.71.[102] The most notable technical complications include the presence of thrombus in the circuit (26%), cannula problems (10%), oxygenator failure (9%), pump malfunction

**TABLE 8-2**
**Extracorporeal Life Support Organization Registry: Summary Data on Neonatal Respiratory Failure Cases Managed with Extracorporeal Life Support (as of January 2011)**

| *Primary Diagnosis* | *Number of Patients* | *Number Survived* | *Percent Survived* |
|---|---|---|---|
| Congenital diaphragmatic hernia | 6147 | 3139 | 51 |
| Meconium aspiration syndrome | 7743 | 7255 | 94 |
| Persistent pulmonary hypertension of the newborn/ persistent fetal circulation | 4043 | 3134 | 78 |
| Respiratory distress syndrome/ hyaline membrane disease | 1496 | 1263 | 84 |
| Sepsis | 2635 | 1967 | 75 |
| Other | 2606 | 1639 | 75 |
| Total | 24,670 | 18,397 | 75 |

**TABLE 8-3**
**Pediatric Respiratory Failure Cases Managed with Extracorporeal Life Support at the University of Michigan between November 1982 and January 2011**

| *Primary Diagnosis* | *Number of Patients* | *Number Survived* | *Percent Survived* |
|---|---|---|---|
| Viral pneumonia | 56 | 47 | 84 |
| Bacterial pneumonia or sepsis | 29 | 21 | 72 |
| Aspiration | 14 | 11 | 79 |
| Trauma | 7 | 7 | 100 |
| Acute respiratory failure | 57 | 34 | 60 |
| ARDS | 23 | 19 | 83 |
| Other | 76 | 59 | 78 |
| Total | 255 | 191 | 75 |

(2%%), and presence of air in the circuit (4%). The effect of technical complications on survival was not substantial, although there was a significant decrease among neonatal patients, from 84% without technical complications to 80% with them.

## Results and Follow-Up

A total of 44,824 cases have been reported to the ELSO Registry since 1975.[3,103] Of these, there have been 24,344 cases of neonatal respiratory failure, 4771 cases of pediatric respiratory failure, and 4232 cases of newborn cardiac failure, and 5221 of pediatric cardiac failure. The number and diagnosis of neonatal respiratory failure survivors are given in Table 8-2. Overall survival is 75%, with the best survival noted among neonatal patients with the diagnoses of meconium aspiration syndrome (94% survival), respiratory distress syndrome (84%), and persistent pulmonary hypertension of the newborn (78%). Patients with CDH continue to have the poorest survival among those who receive ECLS, likely because of the "irreversible" pulmonary hypoplasia associated with that condition. In fact the survival rate in patients with CDH who require ECLS has fallen from a high of 71% in 1987 to the current rate of 51%. The total number of neonatal respiratory ECLS cases peaked in 1992 with 1516 cases. There was a trend downward in the total number of neonatal cases to a low of 707 in 2009 owing to improved results with neonatal respiratory management, including the use of nitric oxide and high-frequency oscillatory ventilation.[3]

The experience with pediatric patients with respiratory failure who were managed with ECLS at the University of Michigan is shown in Table 8-3 and demonstrates an overall survival rate of 75% since 1982.[3,104] Patients in the younger age groups demonstrate greater survival rates, including 100% survival in infants younger than 1 year of age. The ELSO Registry demonstrates that pediatric respiratory cases are accumulating at a rate of 200 to 300 per year, with an overall survival rate of 56% (Table 8-4).[3] One of the most frequent diagnoses is viral pneumonia, which is dominated by respiratory syncytial virus, an entity associated with 49% to 58% survival.[23,105]

**TABLE 8-4**
**Extracorporeal Life Support Organization Registry: Summary Data on Pediatric Respiratory Failure Cases Managed with Extracorporeal Life Support (as of January 2011)**

| *Primary Diagnosis* | *Number of Patients* | *Number Survived* | *Percent Survived* |
|---|---|---|---|
| Bacterial pneumonia | 533 | 303 | 57 |
| Viral pneumonia | 989 | 623 | 63 |
| Aspiration | 205 | 136 | 66 |
| *Pneumocystis* | 30 | 15 | 50 |
| Acute respiratory failure | 817 | 417 | 51 |
| ARDS | 523 | 286 | 55 |
| Other | 1761 | 912 | 52 |
| Total | 4858 | 2692 | 55 |

ARDS, acute respiratory distress syndrome.

Other studies from individual centers also suggest that the survival rate of pediatric patients with respiratory failure managed with ECLS is 41% to 53%.[74,106] An approximately 50% survival rate is noted in pediatric patients with multiorgan system failure and in those with overwhelming septic shock who are managed with ECLS.[107] Green and colleagues,[108] analyzing data from the ELSO Registry, demonstrated that the survival rate in pediatric patients with respiratory failure who receive ECLS for longer than 2 weeks was similar to the survival rate of patients supported for shorter periods. However judgment must be used regarding the reversible nature of the respiratory dysfunction, the presence of associated organ system failure, and the development of complications associated with ECLS in determining whether continuation is warranted after prolonged periods on ECLS.

The ELSO Registry results for cardiac support cases are summarized in Table 8-5.[3] The number of pediatric cardiac cases reported to the registry is increasing steadily and currently is approximately 600 to 750 cases each year, the vast majority of which are pediatric cardiac surgical cases.[3]

**TABLE 8-5**

**Extracorporeal Life Support Organization Registry: Summary Data on Cardiac Failure Cases (Children Aged 1 Day to 16 Years) Managed with Extracorporeal Life Support (as of January 2011)**

| *Primary Diagnosis* | *Number of ECLS Runs* | *Number Survived* | *Percent Survived* |
|---|---|---|---|
| Congenital defect | 7243 | 2959 | 41 |
| Cardiac arrest | 221 | 82 | 37 |
| Myocarditis | 306 | 199 | 65 |
| Cardiomyopathy | 628 | 375 | 60 |
| Cardiogenic shock | 178 | 77 | 43 |
| Other | 1273 | 602 | 47 |
| Total | 9849 | 4294 | 44 |

The overall survival is 41%. Almost all patients are managed with VA bypass. The survival rate has been thought to be poor (0% to 25%) in patients with an anomaly that consists of a single ventricle, but Allan and colleagues[109,110] demonstrated a survival to discharge of 48% in patients with shunted single-ventricle physiology and 81% in patients who underwent cannulation for hypoxemia as opposed to hypotension-cardiovascular collapse. Although Ziomek and coworkers[111] demonstrated a 47% survival among 17 patients in whom ECLS was initiated in the operating room, other studies suggest a poor outcome when ECLS is initiated in the operating room, at a point more than 50 hours after operation, or when continued for more than 6 to 9 days.[111] Data from numerous centers demonstrate a survival rate ranging from 46% to 53%,[112,113] with Klein and colleagues[114] observing a survival rate of 61% among 39 infants and children. The cause of death was lack of improvement in cardiovascular function in 37% of patients and major central nervous system damage in 15%, suggesting that earlier intervention with ECLS could improve outcome.[113] In a large series from Children's Hospital of Philadelphia, ECLS was used for 3.4% of children undergoing cardiac operations; the overall survival was 39%.[115] Survival among patients in whom ECLS was a bridge to heart transplantation was 40% to 60%.[116] Using ECLS in pediatric patients with cardiac failure following cardiac transplantation is associated with a long-term survival of 46%.[117]

ECLS has been effective in other clinical situations such as blunt trauma in children and adults, with survival rates of approximately 65%.[118,119] ECLS has also been successfully applied to patients with tracheal anomalies requiring repair, those with alveolar proteinosis who require pulmonary lavage, and those with pulmonary hypoplasia due to in utero renal insufficiency, asthma, sickle cell disease, and pulmonary failure after lung transplantation.[120–127] ECLS has been successfully applied to the management of pediatric and adult patients with H1N1 pneumonia.[128] Another application of ECLS has been in the form of extracorporeal cardiopulmonary resuscitation in pediatric patients with cardiogenic shock, post-traumatic hypotension, hypothermia, arrhythmias, and cardiac arrest, with the ELSO Registry and the literature overall demonstrating an approximately 40% survival.[129–131] Patients with mediastinal malignancies and airway compromise may be stabilized on ECLS during operative biopsy in order to avoid the risk of cardiopulmonary collapse associated with general anesthesia.[132] Those with hypothermia due to cold water drowning or winter mishaps may also be successfully warmed using this technology.[133,134] Donation after cardiac death is a new approach in which patients in whom support is being withdrawn or those with irreversible cardiac arrest are placed on ECMO support after death is declared thus allowing organ support until harvest can be performed.[135] This management strategy has the promise of enhancing available organs for transplantation.

Multiple studies have involved the long-term follow-up of newborn and pediatric patients after a course of ECLS. Most documented normal neurologic function in 70% to 80% of patients, although at least two studies document that approximately 50% of school-aged patients undergoing ECMO have abnormalities on careful neurologic assessment.[136–141] Such studies demonstrate that neurologic morbidity is no different in ECLS-managed newborns than in those managed by conventional mechanical ventilation. Pulmonary function tests at 8 years of age after neonatal courses on ECMO document measurable pulmonary sequelae in approximately half of the patients, with newborns with CDH being most affected.[142]

Patients with CDH who are managed with ECLS demonstrate a high incidence of morbidity, including gastroesophageal reflux in up to 81%, the need for tube feeding in up to 69%, the development of chronic pulmonary disease in up to 62%, the development of extra-axial fluid collections or enlarged ventricles in 30%, and growth delay in 40% to 50%.[143–145] These problems tend to resolve with time. The neurodevelopmental outcome among newborns with CDH was not dissimilar to that of other ECLS-treated children. Although most patients with cardiac and pediatric respiratory failure demonstrate few sequelae at follow-up, long-term studies in these groups have been less complete.

Four studies have evaluated the relative cost of treating newborn patients with ECLS compared with more conventional means.[20] Pearson and Short[146] found that the average daily charge for neonates receiving ECLS was twice that for patients receiving conventional mechanical ventilation, but the mean hospital stay was decreased by 50% in the ECLS group. Hospital charges were 43% lower in the ECLS group compared with the conventionally treated group when only the survivors were considered. The most recent randomized controlled trial comparing the outcome and costs of ECLS and standard management in newborn respiratory failure revealed average total costs of £73,979 or the ECLS group when compared with £33,435 or those managed by conventional means (UK prices, 2005).[147]

Maintaining a patient on extracorporeal support for days or weeks requires a prepared, organized, well-trained, and highly skilled team of physicians, respiratory therapists, nurses, and ECLS technicians. It is not a technique to be undertaken in a haphazard fashion on the spur of the moment without prior preparation and organization. The current recommendations by the American Academy of Pediatrics Committee on the Fetus and Newborn suggest that neonatal ECLS centers be established only at recognized level III regional centers with appropriate educational programs, ongoing research activity, and infant follow-up programs.[148]

## Future of Extracorporeal Life Support

Although current devices allow safe and effective prolonged extracorporeal support, the future of ECLS depends on improvements in component technology, accompanied by circuit simplification and autoregulation. Safe nonocclusive pumps; leak-free low-resistance artificial lungs; circuit coatings that obviate the need for systemic anticoagulation, and simplified percutaneous single-cannulation systems are now either available or on the horizon. Once a compact servoregulated device is developed with the ability to provide extracorporeal support without anticoagulation, ECLS will be a simple technique rather than a complex labor-intensive intervention.[149] At that point the indications for extracorporeal support will broaden as the technique is applied to a wider population of patients with less severe cardiopulmonary insufficiency.

One of the major benefits of the ECLS experience may be the ability to explore the pathophysiology of cardiac and respiratory failure. Improved understanding of pulmonary and cardiac organ failure may lead to new preventive measures and improved treatment modalities that eventually eliminate the need for ECLS in patients with cardiorespiratory failure.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 9

# Neonatal Cardiovascular Physiology and Care

Albert P. Rocchini

To appropriately manage the cardiovascular needs of your patient, it is important to understand normal cardiovascular physiology. This chapter summarizes normal fetal and neonatal cardiovascular physiology and describes principles that are necessary for the medical management of common cardiovascular problems in neonates.

## Cardiovascular Physiology

Regardless of age, the major variables that affect cardiovascular function are preload (end-diastolic volume), heart rate, arterial pressure (afterload), and contractility (inotropic state of the heart).[1–3] At all ages, increasing myocardial muscle length, heart rate, and other factors that alter the inotropic state of the heart have a positive effect on cardiac function, whereas increasing afterload has a negative effect. However, in the intact animal or human, it is almost impossible to change one of these factors without also affecting another. The net physiologic response is the combined effect of the intervention. For example, in an isolated muscle preparation, increasing rate of stimulation of the muscle will always result in an increase in the force of contraction.[2] However, in animals and children, pacing the heart at a faster rate will cause a decrease in stroke volume and no change or even a slight decrease in cardiac output. These opposite effects result from the difficulty in controlling the interaction of venous return, end-diastolic volume, inotropic state, heart rate, and afterload.

In addition, the subject's age can affect cardiovascular function. For example, in the fetus, increases in systemic afterload have a much greater effect on fetal right ventricular function (decreasing it) than left ventricular function, whereas, in the infant, increases in systemic afterload have a much greater effect on left ventricular function (decreasing it) than on right ventricular function.[4] The following sections focus individually on heart rate, preload, afterload, and contractility in the fetus and neonate.

### HEART RATE

Changes in heart rate have the same effect on ventricular output in both the immature and the adult heart.[5] Increases in heart rate induced by atrial pacing also can result in a decrease of ventricular performance. Stroke volume falls with an increase in heart rate, a consequence of decreasing end-diastolic filling time and end-diastolic volume; however, because the decrease in stroke volume is usually proportional to the increase in heart rate, the net effect is either no change or a slight fall in cardiac output. In comparison with the adult, the fetus and neonatal infant have a relatively high resting heart rate. Because of the high basal heart rate, a neonate's cardiac output can rarely be increased by increasing heart rate. Similarly, in the neonate or fetus, decreases in heart rate to near adult levels, 60 beats/minute, are usually associated with marked decreases in cardiac output. Unlike pacing, a spontaneous increase in heart rate is usually associated with an increase in cardiac output. A spontaneous heart rate change differs from a similar change in heart rate resulting from atrial pacing, because the underlying stimuli that cause the spontaneous rate change also will affect inotropy, venous return, and/or afterload. For example, an increase in venous return that maintains end-diastolic volume, despite a rate-induced shortening of diastolic filling, can result in an increase in stroke volume. Similarly, if the stimulus to increase heart rate is associated with an increase in contractility, even though venous return may not increase, the increase in heart rate will still result in an increase in cardiac output. Exceptions to the positive effect of a spontaneous increase in heart rate on cardiac output can usually be explained by an increase in arterial pressure.[3] The negative effect of afterload on ventricular function results in a fall in stroke volume and cardiac output.

### PRELOAD

At all ages, ventricular output depends on end-diastolic volume. An increase in stroke volume or cardiac output occurs when end-diastolic volume is increased (the Frank-Starling relation).[1,6] This relation depends on both the number of cross-bridge attachments that can be made at a given sarcomere length, and the sarcomere length depends on myofilament sensitivity to calcium.[7] Although this relationship exists in

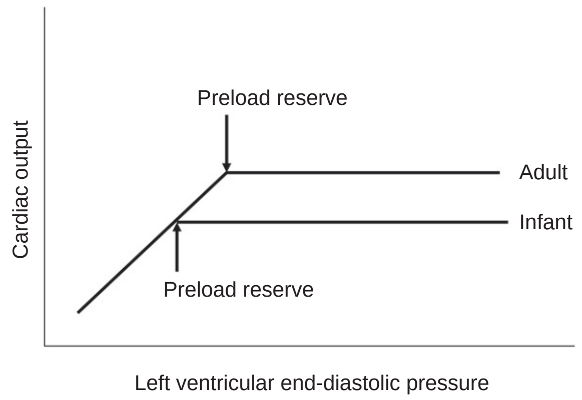


**FIGURE 9-1** The Frank-Starling relation between cardiac output and left ventricular end-diastolic pressure. The point at which further increases in end-diastolic volume result in no further increase in cardiac output is referred to as preload reserve *(arrow)*. Since the neonatal myocardium is stiffer and less compliant, the preload reserve occurs at lower pressure than in the mature adult heart.

both the newborn and the adult, the magnitude of the relationship is frequently diminished in the newborn. It is well known that when left ventricular end-diastolic pressure is high, only small increments in end-diastolic volume and stroke volume follow from a further increase in filling pressure. As can be seen in Figure 9-1, the end-diastolic pressure at which further increases result in little change in cardiac output is called preload reserve. In the newborn, because the myocardium is immature and has greater stiffness (reduced compliance), the preload reserve occurs at a lower pressure than in the adult.[8]

### AFTERLOAD

The cardiovascular function of both the immature and adult heart is negatively affected by an increase in afterload.[3,9,10] There is a maturational difference in the effect of afterload on myocardial function. The immature ventricle cannot eject against arterial pressures well-tolerated by the adult heart. This quantitative difference in response to afterload results from the weaker contraction of the immature myocardium (corrected for muscle cross-sectional area) and the thinner ventricular wall of the immature heart. Afterload also has a quantitatively different effect on right and left ventricular function. In both the neonate and the adult, increases in arterial pressure have a much greater negative effect on stroke volume of the right ventricle than that of the left. In the fetus and neonate with a widely patent ductus arteriosus, this difference is a consequence of the relatively larger right ventricular stroke volume, end-diastolic volume, and free wall curvature in the presence of similar right and left ventricular free wall thicknesses.[10] Because of Laplace's law, systolic wall stress of the right ventricle is greater than that of the left ventricle in the face of similar arterial pressures. This increase in right ventricular systolic wall stress causes the right ventricular ejection to be more negatively affected by an increase in arterial pressure.

### CONTRACTILITY

An intervention that does not alter preload or afterload yet increases the force of contraction or increases cardiac output is said to have a positive inotropic effect. This positive effect usually arises from either an increase in the sensitivity of the myofilaments to calcium or an increase in the cytosolic calcium transient. The immature heart responds to positive inotropic agents with an increase in left ventricular output; however, in comparison with the adult heart, this response is reduced. In cardiac muscle, the movement of calcium through the dihydropyridine-sensitive calcium channel is essential for calcium-induced calcium release from the sarcoplasmic reticulum.[11–15] Calcium-induced calcium release amplifies the effect of the calcium current on cytosolic calcium concentration.[15,16] In the absence of calcium-induced calcium release, trans-sarcolemmal calcium flow results in a contraction whose peak force is only a fraction of that achieved in the presence of the amplification system. Both the dihydropyridine-sensitive calcium channels and the sarcoplasmic reticulum calcium release channels (ryanodine receptors) are necessary for calcium-induced calcium release. Compared with the adult, the immature heart has a greater dependence on extracellular calcium, since it has reduced calcium-induced calcium release. The reduced dependence of the adult myocardium on extracellular calcium results from maturation of the sarcoplasmic reticulum. Both absolute and relative sarcoplasmic reticulum volume increases with age as does sarcoplasmic reticulum calcium release. For example, ryanodine has little effect on the force of contraction of the newborn myocardium. The immaturity of the sarcoplasmic reticulum and the greater dependence of the newborn heart on extracellular calcium concentrations are two explanations for why calcium channel blockers, such as verapamil, are poorly tolerated in the newborn.

## Fetal Circulation

In addition to understanding how preload, afterload, heart rate, and contractility effect neonatal cardiovascular function, it is important to understand how birth affects the cardiovascular system. The fetal circulation differs from the adult circulation in a number of ways. The adult circulation is characterized as blood flow in series, that is, blood returns to the heart from the venous system to the right atrium and ventricle and is then injected into the lungs for oxygenation. Oxygenated blood then returns through the pulmonary veins to the left atrium and ventricle and is then ejected into the arterial system. The right ventricle works against the low afterload of the pulmonary circulation, whereas the left ventricle works against the high afterload of the systemic circulation. In the fetus, oxygenation and carbon dioxide elimination take place in the placenta. Oxygenated blood flows to the fetus through the umbilical veins, which connect to the inferior vena cava through the ductus venous.[17–19] The oxygenated umbilical blood flow mixes with the poorly oxygenated portal blood from the gastrointestinal tract. Because of the eustachian valve in the right atrium, the higher saturated umbilical venous blood preferentially streams across the foramen ovale into the left atrium,[20,21] whereas the lower saturated blood from the distal inferior vena cava and from the superior vena cava enters the tricuspid valve and is directed to the right ventricle. Although there are preferential patterns of flow, some of the blood from the placenta does enter the tricuspid valve, and some of the blood from the distal inferior vena cava and

superior vena cava enters the foramen ovale. Both right and left ventricles pump to the systemic circulation. The right ventricular output is directed through the ductus arteriosus to the descending thoracic aorta, and the left ventricular output is directed although the aortic valve to the ascending aorta. Because of the preferential streaming of umbilical venous return, most oxygenated blood goes to the left ventricle and is distributed to the heart and cerebral circulations, whereas the lower oxygenated blood goes to the right ventricle and is distributed to the pulmonary arteries, abdominal organs, and placental arteries.[19]

Because of this unique fetal circulation, many types of congenital heart disease that are not compatible with life after birth are well tolerated in utero. For example, infants with hypoplastic or atretic left or right ventricular outflow tracts develop normally in utero, whereas after birth these lesions are fatal unless surgery is performed. With birth there is a rapid transformation from the fetal circulation to the adult circulation. This transformation involves elimination of the umbilical–placental circulation, establishment of an adequate pulmonary circulation, and separation of the left and right sides of the heart by closure of the ductus arteriosis and foramen ovale. Figure 9-2 depicts the fetal, immediate postbirth, and a few days postbirth hemodynamics.[22] Persistence of the fetal circulation after birth means that adequate pulmonary circulation is not achieved and fetal channels have not been closed. For example, infants with congenital diaphragmatic hernia have persistence of the fetal circulation because of high pulmonary resistance resulting from poor oxygenation and persistent patency of the foramen ovale and ductus arteriosus.

# Neonatal Management of Common Cardiovascular Problems

## CONGESTIVE HEART FAILURE

The common causes of heart failure in the neonate include rhythm disturbances and congenital cardiovascular malformations. Table 9-1 lists common congenital heart lesions and the age at which congestive heart failure is likely to occur. In the infant with cyanotic congenital heart disease, congestive heart failure usually occurs with lesions that have large amounts of pulmonary blood flow or regurgitant atrioventricular (AV) valves. The ultimate management of heart failure is to treat the underlying congenital malformation; however, medical management is essential to stabilize the infant and enable surgical correction to be performed with a reduced risk. The standard medical management includes the principles of rate control, preload control, afterload control, and improvement in contractility. Because of the high resting heart rate of the neonate, one cannot use increasing heart rate to increase cardiac output in the neonate. In fact, chronic supraventricular tachycardia, frequently the result of an atrial ectopic focus, is a cause of congestive cardiomyopathy.

Preload control is the mainstay of symptomatic therapy for heart failure. This is accomplished with the use of diuretics. The most common diuretic used to treat heart failure in the infant is furosemide (Lasix). Table 9-2 lists many of the commonly used diuretics and current dose recommendations. One diuretic that may have more benefit than just symptomatic therapy is spironolactone (Aldactone).[23,24] Recent evidence suggests that in addition to causing fluid retention aldosterone can cause myocardial fibrosis. There are now a number of clinical trials in adults that suggest that chronic blockade of mineralocorticoid receptors results in improved cardiac remodeling.[24] It is important when considering the use of diuretics to avoid too much diuresis. If the child's preload is reduced below their preload reserve, cardiac output will decrease (see Fig. 9-1).

Afterload agents work by decreasing ventricular loading, predominately by reducing systemic vascular resistance. The pharmacologic agents that are most useful in altering afterload are vasodilators (see Table 9-2). These agents are important therapeutic agents in the treatment of infants with heart failure secondary to a large left to right shunt, severe atrioventricular and semilunar valve regurgitation, dilated cardiomyopathy, and postoperative low-output states.[25–29] Angiotensin-converting enzyme inhibitors are the most commonly used class of afterload reducing agents.[30–33] In addition to reducing ventricular afterload, in adults with congestive cardiomyopathy, they have been shown to also improve cardiovascular remodeling.[24] Another means of afterload control is low-dose beta-receptor blockade. Low-dose beta-blockade has been used successfully in the treatment of congestive cardiomyopathy. This agent works by interfering with the deleterious effects of increased sympathetic activity.[34,35]

With gram-negative septic shock or anaphylactic shock, it may be necessary to increase systemic afterload. In this situation, although systemic blood flow is high, because of severe vasodilation, the cardiac output is not high enough to maintain arterial pressure. The pharmacologic agents that are used in this situation are epinephrine, norepinephrine, and vasopressin.[36,37]

The final group of agents used to treat congestive heart failure in infants and young children are agents that increase the inotropy of the heart (see Table 9-2). The oldest agent in this class is digitalis. Digoxin is still the most commonly used chronic inotropic agent. It increases contractility by inhibiting the sodium-potassium-ATPase pump, resulting in an increase in intracellular sodium, which, in turn, stimulates calcium entry into the cell by the sodium-calcium exchanger; the increased intracellular calcium leads to increased contractility. Recent studies have suggested that digitalis also helps heart failure by inhibiting sympathetic nerve traffic and thus decreasing cardiac metabolic demands.[38] In addition to digoxin, there are other intravenous inotropic agents, the majority of which stimulate the beta-adrenergic receptor in the heart, which, in turn, increases production of adenyl cyclase activity and ultimately contractility. These agents are especially useful in managing severe acute congestive heart failure and cardiogenic shock. Depending on the individual agent, blood pressure can be either increased or slightly decreased. For example, dopamine can cause alpha-receptor stimulation with some degree of vasoconstriction,[39] whereas dobutamine tends to produce more systemic vasodilatation and either slightly decreases or has no effect on systemic pressure.[38,40] Milrinone is another intravenous inotrope that is frequently used in the infant. Milrinone is a phosphodiesterase inhibitor and increases contractility by inhibiting the breakdown of cyclic 3′5′-adenosine monophosphate (c-AMP). Besides being a positive inotropic agent, it reduces afterload as well. Thus

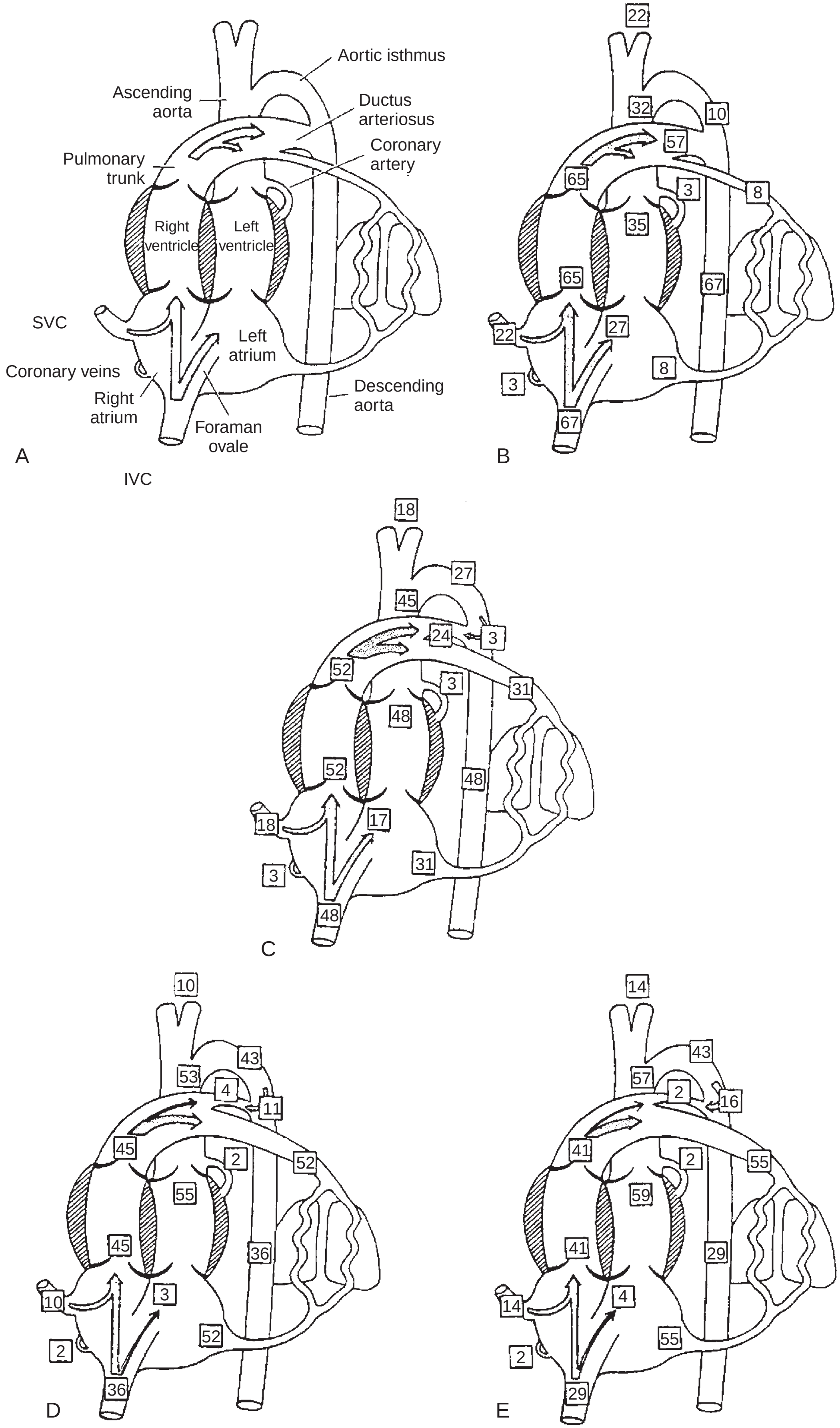


**FIGURE 9-2** Distribution of the circulation in the fetal lamb. Percentages of combined ventricular output are shown in boxes. **A,** Anatomy of the fetal circulation. **B,** Undisturbed state. **C,** After ventilation with 3% oxygen, so as not to alter fetal blood gases. **D,** After ventilation with oxygen. **E,** After ventilation with oxygen and umbilical cord occlusion. IVC, inferior vena cava; SVC, superior vena cava. (From Rudolph AM: The fetal circulation and its adjustments after birth. In Moller JH, Hoffman JIE [eds]: Pediatric Cardiovascular Medicine. Philadelphia, Churchill Livingstone, 2000, p 62.)

**TABLE 9-1**
**Causes of Congestive Heart Failure at Various Ages**

| *Fetus to Day 1 of Life* | *First Week to 6 Weeks of Life* | *6 Weeks to 3 Months of Life* | *Greater Than 6 Months of Life* |
|---|---|---|---|
| Tachyarrhythmias | Critical aortic stenosis | Ventricular septal defects | Myopericarditis |
| Anemia and/or hemolytic disease | Co-arctation of the aorta (simple or complex) | Patent ductus arteriosus | Endocarditis |
| Atrioventricular valve regurgitation | Hypoplastic left heart syndrome | Atrioventricular septal defects | Primary pulmonary hypertension* |
| Heart block | Interrupted aortic arch | Atrial septal defects* | Rheumatic heart disease |
| Cardiac or pericardial tumors* | Critical pulmonary stenosis | Tachyarrhythmias | Kawasaki disease |
| Arteriovenous malformations (usually brain or liver)* | Common mixing lesions (truncus, single ventricle, etc.) | Anomalous left coronary artery form the pulmonary artery | Postoperative congenital heart disease |
| Birth asphyxia | Tachyarrhythmias | Myocarditis or cardiomyopathy | Neuromuscular disease |
| Fetal–maternal or fetal–fetal transfusions | Obstructed or nonobstructed total anomalous pulmonary venous return | Nonobstructive total anomalous pulmonary venous return | Cardiomyopathies (restrictive, hypertrophic, and dilated) |
| Myocarditis | Myocarditis or cardiomyopathy | | Systemic hypertension |
| Hyperviscosity | Systemic hypertension* | | Collagen vascular disease* |
| Premature closure of the foramen ovale or patent ductus* | Endocrine disorders: thyroid disease, adrenal insufficiency, parathyroid disease* | | Drugs: anthracycline, ipecac, cocaine, heavy metal, etc. |
| Semilunar valve insufficiency (i.e., absent pulmonary valve, aortic to LV tunnel)* | Persistent pulmonary hypertension | | Anemia: sickle cell, thalassemia, hemolytic anemias, etc.* |
| | Patent ductus arteriosus (especially premature infants) | | |
| | Infant of diabetic mother | | |

*Rare causes of heart failure.
LV, left ventricle.

**TABLE 9-2**
**Medications Used to Treat Congestive Heart Failure**

| *Class* | *Drug* | *Dose* | *Dosing Interval* | *Comments* |
|---|---|---|---|---|
| Diuretic | Hydrochlorothiazide | 2.0-3.0 mg/kg up to 50 mg/day | bid | Will increase uric acid level |
| | Furosemide | 0.5-2.0 mg/kg up to 6 mg/kg/day | qd or bid | |
| | Spironolactone | 1.0-3.3 mg/kg | bid | Potassium-sparing, used with causing with CEI |
| | Metolazone | 0.2-0.4 mg/kg | qd | |
| ACE | Benazepril | 0.2 mg/kg up to 10 mg/day | qd | Contraindicated in pregnancy, check serum potassium, creatinine. Cough and angioedema are side effects |
| | Captopril | 0.3-0.5 mg/kg up to 6 mg/kg | tid | |
| | Enalapril | 0.08 mg/kg up to 5 mg/day | qd-bid | |
| | Lisinopril | 0.07 mg/kg up to 40 mg/day | qd | |
| ARB | Irbesartan | 6-12 years: 75-150 mg/day | qd | Contraindicated in pregnancy, check serum potassium, creatinine |
| | Losartan | 0.7 mg/kg/day up to 50 mg/day | qd | |
| Beta-blocker | Metoprolol | 1.0-2.0 mg/day up to 6.0 mg/kg/day | qd | |
| Vasodilator | Hydralazine | 0.75 mg/kg up to 7.5 mg/kg | qid | Tachycardia, fluid retention, lupus-like syndrome |
| | Prazosin | 0.05-0.1 mg/kg up to 0.5 mg/kg | tid | |
| Inotrope | Digoxin | Digitalizing dose 20-40 μg/kg depending on age<br>Maintenance dose 5-10 μg/kg | bid | |
| | Dobutamine | 2.0-20 μg/kg/min IV | | |
| | Dopamine | 2.0-20 μg/kg/min IV | | |
| | Milrinone | Loading dose 0.05-1 mg/kg then 0.5-0.75 μg/kg/min | | |
| | Epinephrine | 0.05-2 μg/kg/min IV | | |

ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CEI, converting enzyme inhibitor.

milrinone is likely to lower blood pressure slightly. It is also useful in producing some degree of pulmonary artery vasodilation and is therefore an ideal agent for the infant with severe congestive heart failure and pulmonary artery hypertension.[20]

If pharmacologic therapy is not enough to maintain adequate cardiac output, mechanical devices can be used to support the circulation. The most commonly used mechanical support device is extracorporeal membrane oxygenation. More recently ventricular assist devices have been used in infants with end-stage cardiomyopathy as a bridge to cardiac transplantation.[22,41,42]

## ABNORMALITIES IN CARDIAC RHYTHM

### Heart Block

Both slow and fast heart rates can severely compromise the cardiovascular circulation of an infant. Complete heart block may be either congenital or acquired and occurs in 1 per 20,000 live births.[43–45] There is a strong association between maternal connective tissue disease and congenital complete heart block. A mother with systemic lupus erythematosus has a 1 in 20 risk of having a child with complete heart block if she is anti-Ro positive.[46] Maternal immunoglobulin G antibodies to soluble ribonucleoprotein antigens (anti-Ro and anti-La) cross the placenta after the 12th to 16th week of gestation. This transfer of antibodies results in an inflammatory response in the fetal heart, particularly the conduction system, with destruction of the atrioventricular node.[45–51] Complete heart block in the neonate may or may not need treatment. The decision of whether to place a pacemaker in an infant with heart block depends on the presence of in utero heart failure (hydrops) or the development of postnatal congestive heart failure. Heart rate alone is usually not an indication for pacemaker placement; however, if the infant's heart rate remains at less than 50 beats/minute, a pacemaker is frequently required. Some forms of congenital heart disease also have a high incidence of heart block. These lesions include the Ebstein anomaly of the tricuspid valve and corrected transposition of the great arteries.

### Tachyarrhythmias

Tachyarrhythmias can also occur in the infant and young child and cause heart failure. The most common type of tachyarrhythmia is supraventricular tachycardia. The incidence of paroxysmal supraventricular tachycardia is 1 in 250 to 1000 children.[4] It occurs most commonly in males younger than 4 months of age and frequently is even present in the fetus. The pathologic mechanism underlying the tachycardia is usually either the result of Wolff-Parkinson-White (WPW) syndrome (an accessory pathway between the atria and ventricles) or atrioventricular nodal reentry (dual conduction pathways within the atrioventricular node). If the supraventricular tachycardia is sustained, heart failure will likely occur within 24 to 48 hours. The treatment for supraventricular tachycardia, regardless of cause, is similar. If the infant becomes acidotic or hypotensive, immediate synchronized direct-current cardioversion should be performed at a dosage of 1 to 2 watt-second/kg.[52] If the infant is stable and relatively asymptomatic, then in most situations any intervention that increases AV node refractoriness is likely to work. In the infant, application of ice or an ice-water bag directly to the center of the infant's face recruits the diving reflex and stops the tachycardia. A rapid intravenous infusion of adenosine is also very effective in terminating supraventricular tachycardia.[53] The usual dose is a 100 μg/kg bolus, increasing by 100 μg-increments to a maximum of 400 μg/kg. A few serious side effects associated with adenosine administration included atrial fibrillation, ventricular tachycardia, asystole, apnea, and bronchospasm. Because of these potential side effects, adenosine should be administered in an area where cardioversion and cardiopulmonary resuscitation can be performed.

Children with supraventricular tachycardia and mild to moderate congestive heart failure may be initially treated with adenosine; however, other pharmacologic agents, such as digoxin, amiodarone, and procainamide may be helpful if adenosine fails to convert the tachycardia. Table 9-3 lists many of the commonly used antiarrhythmic agents and current dose recommendations. In infants, the intravenous route is the preferred method for administration of digoxin. The digitalizing dose interval may be given as frequently as every 2 to 4 hours. If tachycardia persists after three doses, one more dose equivalent to one fourth of the total digitalizing dose may be given. If the tachycardia has still not converted vagal stimulation or adenosine may be effective in terminating the tachycardia after digitalization. The maintenance dose of digoxin should be determined according to the total digitalizing dose required to terminate the tachycardia and is one eighth of the total digitalizing dose twice daily. Digoxin should be avoided in patients with a wide QRS tachycardia and when WPW syndrome is considered as a possible cause. Digoxin in the presence of WPW with atrial fibrillation can result in an acceleration of the ventricular response and resultant ventricular fibrillation.

Esmolol or propranolol, which may further depress cardiac function, should be used with caution in the critically ill infant with congestive heart failure. Once the tachycardia has been terminated and the congestive heart failure controlled, beta blockers can be used as effective long-term antiarrhythmic therapy in infants with supraventricular tachycardia.

Amiodarone is now being used with increasing frequency for the emergency treatment of supraventricular tachycardia, especially in the postoperative patient. Intravenous administration of amiodarone has been reported to terminate the tachycardia within 2 hours of the initial bolus in more than 40% of patients.[54,55] The major side effects of amiodarone include hypotension, decreased ventricular function, and bradycardia.

Intravenous procainamide can be very effective in patients with refractory supraventricular tachycardia. The combination of procainamide and a beta blocker is especially effective in treating refractory atrial flutter in the neonate.

Verapamil, although an effective agent to treat supraventricular tachycardia in the adult, is contraindicated in the infant with congestive heart failure. Use of verapamil in infants has resulted in cardiovascular collapse and death.[56,57]

In our institution, we frequently use esophageal overdrive pacing to convert supraventricular tachycardia in the infant. Esophageal pacing has the advantage of not only treating the arrhythmia but also helping to make a definitive diagnosis of the tachycardia. Overdrive pacing involves pacing the atrium via the esophagus at a rate slightly higher than the rate of the tachycardia. With cessation of pacing, sinus rhythm will usually return. Esophageal pacing is effective in most forms of supraventricular tachycardia, including atrial flutter.[58,59]

**TABLE 9-3**

**Commonly Used Pharmacologic Agents to Treat Tachyarrhythmias**

| *Drug* | *Dosage* | *Onset of Action* | *Potential Adverse Effects* | *Drug Interactions* | *Cardiovascular Contraindications* | *Comments* |
|---|---|---|---|---|---|---|
| Adenosine | 100-150 μg/kg given rapid IV; double dose sequentially to maximum of 300 μg/kg | < 5 sec | Dyspnea, bronchospasm, headache, chest pains, AV block/asystole, PVCs, atrial fibrillation, torsades de pointes, hypotension | Theophylline-adenosine is less effective<br>Digoxin: increases risk of VT<br>Diazepam-potentiated effects of adenosine | Prolonged QT interval<br>Second- or third-degree AV block, except in the presence of pacemaker<br>Sick sinus syndrome | Have defibrillator available when administering, in the event of ventricular rate acceleration, torsade de pointes, or VF |
| Amiodarone | Bolus: 5 mg/kg during 10 min<br>Infusion of 10-15 μg/kg/day | Within 5 min of initial bolus | Hypotension, sinus arrest, or bradycardia, AV block | Digoxin: increases digoxin levels<br>Procainamide: causes increased levels of amiodarone<br>Warfarin: increases INR | Sick sinus syndrome or AV block, except if pacemaker present<br>Cardiogenic shock | Closely monitor blood pressure, heart rate and rhythm<br>Hypotension can be treated with volume and calcium |
| Esmolol | Load: 500 μg/kg during 1-2 min<br>Maintenance: 50-200 μg/kg/min | Within 1-2 min | Hypotension, dizziness, headache, nausea, bronchospasm, decreased cardiac output | Digoxin: increases level<br>Morphine: causes increased esmolol level | Sinus bradycardia, second- or third-degree heart block, cardiogenic shock, overt heart failure | Use with caution in patients with decreased renal function, diabetes, or asthma |
| Procainamide | Load: infants 7-10 mg/kg during 45 min, older children 12 mg/kg<br>Infusion 40-50 μg/kg/min, occasionally may need up to 100 μg/kg/min | Within 30 min | Hypotension, increased ventricular response with atrial flutter, bradycardia, asystole, depressed ventricular function, fever myalgia, AV block, confusion, dizziness and headache | Amiodarone: causes increased concentration of procainamide<br>Digoxin: causes increased digoxin levels | Second- and third-degree AV block without pacemaker<br>Congestive heart failure<br>Prolonged QT interval | Continuous ECG and BP monitoring<br>Monitor potassium levels; if potassium decreases arrhythmias may increase |

AV, atrioventricular; BP, blood pressure; ECG, electrocardiogram; INR, international normalization ratio; PVCs, premature ventricular contractions; VF, ventricular fibrillation; VT, ventricular tachycardia.

Ventricular tachycardia is extremely unusual in the newborn. It is most commonly seen in infants with intracardiac tumors, such as rhabdomyomas and in infants with long QT syndrome.

## MANAGEMENT OF SELECTIVE TYPES OF CONGENITAL HEART DISEASE

Certain types of congenital heart disease are frequently associated with other congenital lesions that require general surgical procedures to be performed in the newborn period. For example, tetralogy of Fallot and ventricular septal defects are common in infants with tracheoesophageal fistulas, anal atresia, and other lesions common to the VATER complex (vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia). Interrupted aortic arch, truncus arteriosus, and tetralogy of Fallot are frequently present in infants with the DiGeorge syndrome. Hypoplastic left heart syndrome has been reported to occur in infants with congenital diaphragmatic hernia. More than 60% of infants with Down syndrome have congenital heart disease (patent ductus arteriosus, ventricular septal defects, atrioventricular septal defects, and tetralogy of Fallot). Because of the strong association of congenital heart disease with other congential anomalies that require general surgery in the newborn period, a cardiology consultation and echocardiogram are frequently necessary prior to the surgical procedure. The exact management of the infant depends on the type of congential heart disease.

In infants with restricted pulmonary blood flow, such as seen with tetralogy of Fallot and/or pulmonary atresia, ductal patency is necessary in order to maintain adequate oxygenation. If a ductus was present in fetal life, it can usually be maintained patent with the administration of prostaglandin $E_1$, at a starting dose of 0.1 to 0.05 μg/kg/minute. If the ductus is patent, I use low-dose prostaglandin (0.02 to 0.03 μg/kg/minute) to maintain its patency; if the ductus is virtually closed, I start with a higher dose of prostaglandin until patency is achieved and then cut back to low-dose therapy. Side effects associated with prostaglandin administration include apnea, seizures, fevers, hypotension, and flushing. Once the infant has been stabilized, then more definitive therapy can be contemplated. At our institution, whenever possible, we choose complete repair of these lesions rather than palliation, with a systemic to pulmonary artery shunt.

In infants with hypoplastic left heart syndrome initial management requires that an atrial septal defect be present and that ductal patency be maintained. In these infants, systemic blood flow is directly related to pulmonary artery resistance, and oxygen saturation is inversely related to pulmonary

vascular resistance (i.e., as pulmonary resistance decreases, pulmonary blood flow increases, resulting in higher oxygen saturation and lower systemic blood flow). The ideal systemic oxygen saturation in an infant with hypoplastic left heart syndrome is about 80%. When oxygen saturations are in the high 80s to low 90s, the ratio of pulmonary to systemic blood flow is usually greater than 4:1, and systemic hypoperfusion is usually present; when oxygen saturation is in the high 70s to low 80s, the pulmonary to systemic flow ratio is nearly balanced. Ideally, I like to let these infants maintain spontaneous respirations, and I withhold supplemental oxygen. In some cases, it may be necessary to cause pulmonary vasoconstriction, which can be accomplished by placing the infant in a mixture of room air and nitrogen. The lower inspired oxygen concentration will cause pulmonary artery vasoconstriction, which will result in a reduction in pulmonary blood flow and maintenance of adequate systemic perfusion. Once the infant has been stabilized, it is my policy to perform Norwood palliation. In some selected cases, cardiac transplantation may be the best surgical option for the infant.

Infants with ventricular septal defects or atrioventricular septal defects usually have no symptoms from their heart disease during the first month of life. Congestive heart failure from a ventricular septal defect is usually the result of excess pulmonary blood flow. The two major determinants of left to right shunt flow across a ventricular septal defect are the size of the defect and the ratio of pulmonary arteriolar to systemic arteriolar resistance. In a term infant, it usually takes from 4 to 6 weeks for the pulmonary resistance to drop to normal levels; thus infants with large septal defects do not usually develop heart failure until the second month of life. Causes of early heart failure in an infant with a ventricular septal defect include prematurity and other associated cardiac lesions. The two lesions most often associated with the early development of congestive heart failure are the presence of a co-arctation of the aorta and, in the case of atrioventricular septal defect, the presence of significant atrioventricular valvular regurgitation.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 10

# Sepsis and Related Considerations

Allison L. Speer, Tracy C. Grikscheit, Jeffrey S. Upperman, and Henri R. Ford

Despite advances in neonatology and pediatric critical care, sepsis remains a challenging problem for the health care provider. Sepsis is a leading cause of morbidity and mortality in infants and children, and, unfortunately, its incidence continues to rise.[1,2] In their most recent reports, the Centers for Disease Control and Prevention and the National Center for Health Statistics cited septicemia as the tenth leading cause of death and bacterial sepsis of the newborn as the eighth leading cause of infant death in the United States.[3] In addition, sepsis-related health care costs represent a significant economic burden to society, with almost $17 billion spent annually in the United States alone.[4]

There are only a handful of epidemiologic studies of sepsis and even fewer regarding pediatric sepsis. One of the challenges to the study of sepsis has been the lack of standardized terminology. Consistent definitions may be crucial for early diagnosis and goal-directed therapies to improve mortality from sepsis. Furthermore, they may enhance the design and evaluation of future trials. The first part of this chapter outlines the evolution of sepsis terminology as well as its epidemiology. Emerging therapies for sepsis are typically aimed at enhancing or modulating the immune system or destroying the invading microbe. Therefore it is important to fully understand host defense mechanisms as well as microbial virulence. The second section covers the pathogenesis of sepsis, with a focus on the determinants of infection: host defense mechanisms and bacterial virulence. The third part of this chapter examines the diagnosis of sepsis, with a focus on the Goldstein consensus criteria[5] and the PIRO system (*P*redisposing conditions, the nature and extent of the *I*nsult or *I*nfection, the magnitude of the host *R*esponse, and the degree of concomitant *O*rgan dysfunction).[6] The fourth and final part discusses principles of management, with concentration on the Surviving Sepsis Campaign (SSC)[7,8] and the American College of Critical Care Medicine (ACCM)[9]/Pediatric Advanced Life Support (PALS)[10] guidelines for the management of pediatric and neonatal sepsis.

## Sepsis Terminology and Epidemiology

### TERMINOLOGY

Historically, confusing terminology and a lack of standardized definitions had obscured diagnosis and treatment as well as interpretation of clinical research trials on sepsis and its related syndromes. The American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) 1991 Consensus Conference established the current definitions of sepsis and its related syndromes with the goal of improving early diagnosis and thereby facilitating early therapeutic intervention.[11] They also reasoned that the ACCP/SCCM 1992 consensus criteria, or the Bone criteria, would help to standardize research protocols, which would enable improved application of information derived from clinical studies.

Sepsis is defined as the development of the systemic inflammatory response syndrome (SIRS) resulting from a confirmed infection. According to the Bone criteria, SIRS is characterized by the presence of two or more of the following: (1) temperature greater than 38° C or less than 36° C, (2) heart rate greater than 90 beats per minute, (3) respiratory rate greater than 20 breaths per minute or $Pa_{CO_2}$ less than 32 mm Hg, or (4) an alteration in the white blood cell count, such as greater than 12,000/mm$^3$, less than 4,000/mm$^3$, or greater than 10% immature neutrophils (bands). When sepsis is associated with acute organ dysfunction, it is referred to as severe sepsis.[11] Septic shock, by contrast, is defined as sepsis-induced hypotension (<90 mm Hg or reduction by 40 mm Hg or more from baseline in the absence of other causes) persisting despite adequate fluid resuscitation, along with signs of organ hypoperfusion, such as lactic acidosis, oliguria, or acute alteration in mental status. However, SIRS may also occur in the absence of infection as a result of trauma, burns, pancreatitis, or other triggers (Fig. 10-1). Septicemia and septic syndrome are confusing and ambiguous terms that should no longer be used.

According to Bone and colleagues,[11] detection of altered organ function in an acutely ill patient constitutes a syndrome that is termed multiple organ dysfunction syndrome (MODS). In contrast to organ failure, organ dysfunction is a dynamic process and a continuum of physiologic derangements that evolve with time. They argue that terms such as *sequential organ failure*[12] or *multiple systems organ failure*[13] are inadequate and should

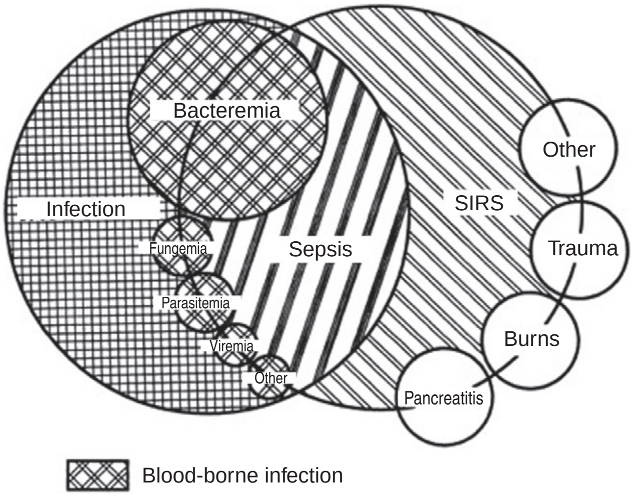


**FIGURE 10-1** The interrelationship between systemic inflammatory response syndrome (SIRS), sepsis, and infection. (Used with permission from Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644-1655.)

be eliminated from use. MODS develops by two relatively distinct, but not mutually exclusive, pathways that may be described as either primary or secondary. Primary MODS is the direct result of a well-defined insult in which organ dysfunction occurs early and can be directly attributed to the insult itself. Secondary MODS develops as a consequence of the host response (SIRS) in organs remote from the initial insult, typically after a latent period following the inciting injury.

The Bone criteria have been widely adopted in both clinical practice and research trials.[14–17] A MEDLINE search dated January 1992 to May 2010 yielded more than 50,000 publications using SIRS as a keyword. Despite this proliferation of articles, analysis of a recent physician attitudinal survey revealed that only 22% (114 of 529) of intensivists and 5% (26 of 529) of other physicians defined sepsis according to the ACCP/SCCM 1992 consensus criteria.[18] The failure to adopt these criteria and the concurrent growth of clinical trial data provided the impetus for a review of the 1992 definitions of sepsis and its related conditions. The 2001 International Sepsis Definitions Conference, sponsored by the SCCM, European Society of Intensive Care Medicine, ACCP, American Thoracic Society, and the Surgical Infection Society, undertook this task. These experts and opinion leaders ultimately upheld the ACCP/SCCM 1992 consensus criteria and expanded the list of signs and symptoms of sepsis to reflect clinical bedside experience (Table 10-1).[6]

## EPIDEMIOLOGY

The ACCP/SCCM 1992 consensus criteria have been applied in several epidemiologic surveys of sepsis during the last 15 years.[2,4,14,19–22] Although standardized terminology is now used, information on the incidence of sepsis and patient outcomes continues to be limited, and published results are conflicting. Two European studies reported the incidence of sepsis in adult intensive care units (ICUs) and drew some interesting conclusions regarding prognosis. Brun-Buisson and colleagues reported the incidence of severe sepsis in adult ICUs in French public hospitals to be 6.3%,[19] while Alberti and colleagues found a higher adult ICU-specific incidence of infection in Europe (21.1%). They stratified the data into the following categories: infection without SIRS (17.9%), sepsis (28.3%), severe sepsis (23.9%), and septic shock (29.9%), according to the ACCP/SCCM 1992 consensus criteria.[20] Alberti and colleagues identified the majority of infections to be gram-negative bacilli, followed by gram-positive cocci. However, even though the incidence of community-acquired (11.9%) versus hospital-acquired (9.2%) infection

**TABLE 10-1**
**Diagnostic Criteria for Sepsis**

| |
|---|
| Infection* documented or suspected, and some of the following†: |
| General variables |
| Fever (core temperature greater than 38.3° C) |
| Hypothermia (core temperature $<$ 36° C) |
| Heart rate $>$ 90 bpm or $>$ 2 SD above the normal value for age |
| Tachypnea |
| Altered mental status |
| Significant edema or positive fluid balance (>20 mL/kg over 24 hours) |
| Hyperglycemia (plasma glucose $>$ 120 mg/dL or 7.7 mmol/L) in the absence of diabetes |
| Inflammatory variables |
| Leukocytosis (WBC count $>$ 12,000 $\mu L^{-1}$) |
| Leukopenia (WBC count $<$ 4000 $\mu L^{-1}$) |
| Normal WBC count with $>$ 10% immature forms |
| Plasma CRP $>$ 2 SD above the normal value |
| Plasma procalcitonin $>$ 2 SD above the normal value |
| Hemodynamic variables |
| Arterial hypotension (SBP $<$ 90 mm Hg, MAP $<$ 70, or an SBP decrease $>$ 40 mm Hg in adults or $<$ 2 SD below normal for age) |
| $Svo_2$† $>$ 70%† |
| Cardiac index†,‡ $>$ 3.5 L $\times$ $min^{-1}$ $\times$ $M^{-23}$ |
| Organ dysfunction variables |
| Arterial hypoxemia ($Pao_2/Fio_2$ $<$ 300) |
| Acute oliguria (urine output $<$ 0.5 mL/kg/hr or 45 mmol/L for at least 2 hours) |
| Creatinine increase $>$ 0.5 mg/dL |
| Coagulation abnormalities (INR $>$ 1.5 or aPTT $>$ 60 seconds) |
| Ileus (absent bowel sounds) |
| Thrombocytopenia (platelet count $<$ 100,000 $\mu L^{-1}$) |
| Hyperbilirubinemia (plasma total bilirubin $>$ 4 mg/dL or 70 mmol/L) |
| Tissue perfusion variables |
| Hyperlactatemia (>1 mmol/L) |
| Decreased capillary refill or mottling |

Modified and used with permission from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250-1256.
*Infection is defined as a pathologic process induced by a microorganism.
†$Svo_2$ saturation $>$ 70% is normal in children (normally, 75% to 80%), and CI 3.5 to 5.5 is normal in children; therefore NEITHER should be used as signs of sepsis in newborns or children.
‡Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyperthermia or hypothermia (rectal temperature $>$ 38.5° C or $<$ 35° C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.
aPTT, activated partial thromboplastin time; BPM, beats per minute; CRP, C-reactive protein; INR, international normalized ratio; MAP, mean arterial blood pressure; SBP, systolic blood pressure; SD, standard deviation(s); $Svo_2$, mixed venous oxygen saturation; WBC, white blood cell.

was similar, nosocomially infected patients had poorer outcomes.[20] Interestingly, Brun-Buisson and colleagues demonstrated that patients with culture-negative, clinically suspected severe sepsis had the same 28-day mortality (60%) as patients with documented infection (56%).[19]

Before 2000, only two epidemiologic studies had been conducted in the United States that used the ACCP/SCCM 1992 consensus criteria.[21,22] Neither study provided accurate information on population incidence (including children) or the costs of care. In 1995, Rangel-Frausto and colleagues published a prospective epidemiologic study of the sequential progression of SIRS to sepsis, severe sepsis, and, finally, septic shock in a single institutional cohort.[21] They demonstrated a stepwise increase in positive blood cultures (17%, 25%, 69%, respectively) and in mortality rates along the hierarchy from SIRS (7%), to sepsis (16%), severe sepsis (20%), and septic shock (46%).[21] Interestingly, Rangel-Frausto and colleagues confirmed the findings of Brun-Buisson and colleagues that culture-negative patients had similar morbidity and mortality rates as culture-positive patients.[21] Another U.S. study by Sands and colleagues, however, reported very different results from the European epidemiologic studies. Their prospective, multi-institutional, observational study involving eight academic tertiary care centers, published in 1997, estimated the hospital-wide incidence of sepsis at 2.0%, with ICU patients accounting for 59%.[22] Bacteremia was documented in only 28% of the study population, with gram-positive organisms as the most frequent isolates. The 28-day mortality was 34%.[22] The lower incidence of sepsis, bacteremia, and the improved mortality rates compared with the European studies are likely due to the fact that this study enrolled patients hospital-wide, including healthier non-ICU patients in addition to sicker ICU patients. The differences in types of bacteria responsible for sepsis in the U.S. study by Sand and colleagues versus the European study by Alberti and colleagues may reflect geographic as well as institutional differences.

In an effort to better define the incidence, costs, and outcomes of sepsis in the United States, two important studies using the ACCP/SCCM 1992 consensus criteria were published in 2001[4] and 2003.[2] Angus and colleagues conducted a large observational cohort study to determine incidence, costs, and outcomes of severe sepsis.[4] Using 1995 state hospital discharge records from seven large states, they estimated 3.0 cases per 1,000 population, 2.26 cases per 100 hospital discharges (51.1% from the ICU),[4] and a national incidence of 751,000 cases per year. Major differences were identified between children and adults. The incidence of severe sepsis increased greater than100-fold with age (0.2/1000 in children to 26.2/1,000 in patients $>$ 85 years old). The annual total cost nationally was $16.7 billion, with an average cost per case of $22,100.[4] Costs were higher in infants, nonsurvivors, ICU patients, surgical patients, and those with more organ failure.[4] The mortality of severe sepsis also increased with age (10% in children to 38.4% in patients $>$ 85 years old, and 28.6% overall).[4]

Martin and colleagues published an epidemiologic study in the *New England Journal of Medicine* in 2003 that analyzed sepsis from 1979 to 2000 using a nationally representative sample of all nonfederal acute care hospitals in the United States.[2] They suggested that Angus and colleagues may have overestimated the incidence of severe sepsis by a factor of 2 to 4, because the estimated number of deaths exceeded the combined numbers of deaths reported in association with nosocomial bloodstream infections and septic shock. Martin and colleagues identified more than 10 million cases of sepsis occurring during approximately 750 million hospitalizations over the 22-year study period. The incidence of sepsis increased from 82.7 cases per 100,000 population to 240.4 cases per 100,000 population, for an increase of 8.7% per year. Martin and colleagues suggested that possible reasons for a true increase in the incidence of sepsis included increasing microbial resistance, the epidemic of human immunodeficiency virus (HIV) infection, and the increased use of invasive procedures, immunosuppressive drugs, chemotherapy, and transplantation.

Martin and colleagues[2] identified several other important changes that occurred during the 22-year study period. Gram-negative infections predominated until 1987, when gram-positive bacteria became more prevalent, increasing by an average of 26.3% per year. In 2000, gram-positive bacteria accounted for 52.1% of sepsis cases, whereas gram-negative bacteria were responsible for 37.6%. Of note, fungal organisms increased by 207% during the study period. Despite a decline in mortality rates from sepsis from 1979 to 2000, the increased incidence of sepsis resulted in a significant increase in the number of in-hospital deaths resulting from sepsis, increasing from 43,579 (21.9 per 100,000 population) to 120,491 (43.9 per 100,000 population). Racial disparities were also striking, with nonwhites having almost twice the risk of sepsis as whites. The highest risk was among African-American men, in whom sepsis occurred at the youngest age and resulted in the most deaths. Martin and colleagues did not focus on the pediatric population. The significant differences between pediatric and adult patients observed in the study by Angus and colleagues[4] and the scarce data on the epidemiology of sepsis in children became the incentive for a follow-up study by the University of Pittsburgh research group.

Using the same 1995 hospital discharge and population database that Angus and colleagues had studied, Watson and colleagues estimated 42,364 cases of pediatric severe sepsis per year nationally (0.56 cases per 1,000 population per year).[14] The incidence was 15% higher in boys than in girls and highest in infants (5.16/1000) compared with older children (0.20/1000 in those 10 to 14 years of age).[14] Half of all children had underlying comorbidity.[14] The majority of infectious causes were either respiratory (37.2%) or primary bacteremia (25.0%), although this varied by age, with bacteremia being more common in neonates and respiratory infections predominating in older children.[14] The mean length of stay (LOS) was 31 days with very-low-birth-weight (VLBW) newborns, weighing less than 1500 g at birth, accounting for 40% of the total hospital days.[14] Estimated annual total costs were $1.97 billion nationally, with a mean cost of $47,050, which is significantly more than the $22,100 cost per case for adults and children combined quoted by Angus and colleagues.[14] Thirty-one percent of the costs were incurred by VLBW newborns.[14]

Watson and colleagues demonstrated that hospital mortality was 10.3% (4,383 deaths nationally or 6.2 per 100,000 population), and more than one fifth were low-birth-weight newborns weighing less than 2500 g at birth.[14] Not surprisingly, hospital mortality was higher in children with neoplasms, HIV infection, and those undergoing surgical

procedures.[14] The risk of death increased with increasing number of dysfunctional organs (7.0% with single-organ failure to 53.1% for patients with greater than or equal to four-organ systems failing).[14] Although sepsis-associated mortality in children has fallen from 97% in 1966[23] to 10.3% in 1995[14] and remains lower than adult sepsis-associated mortality, without a doubt, sepsis is still a significant health problem in infants and children.

## Pathogenesis

The pathogenesis of sepsis is summarized in Figure 10-2. Bacterial invasion secondary to barrier failure leads to the local release of lipopolysaccharide (LPS), with consequent formation of an LPS–lipopolysaccharide binding protein (LBP)–CD14–Toll-like receptor-4 (TLR-4) complex on neutrophils, macrophages, and endothelial cells. Signaling via this complex results in activation of the complement system, clotting cascade, as well as various inflammatory cells. This process leads to the release of inflammatory mediators, which up-regulate adhesion molecules and promote chemotaxis of neutrophils and macrophages. The activated cells release microbicidal agents typically designed for bacterial killing but which may promote distant organ injury and SIRS if the inflammatory process is "uncontrolled." Predictably, immunocompromised infants and children, as well as preterm and term neonates who classically have significant host defense impairment, are particularly vulnerable to infections. Such infections may elicit an inflammatory response, which may be exaggerated at times and result in significant host tissue destruction. Failure to control either the infection itself or the host inflammatory response may follow a predictable course along the sepsis continuum: SIRS, sepsis, severe sepsis, septic shock, MODS, and, ultimately, death.[21]

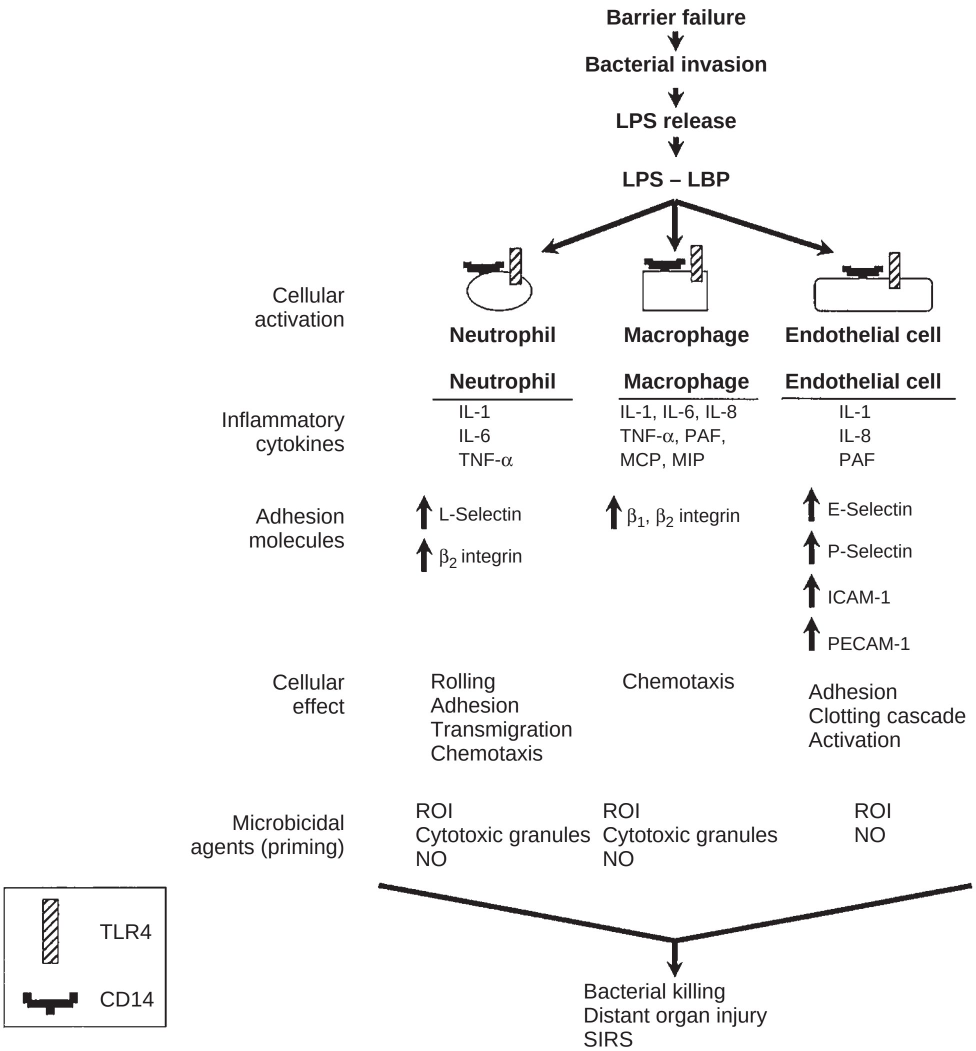


FIGURE 10-2 Pathogenesis of systemic inflammatory response syndrome (SIRS). Bacterial invasion secondary to barrier failure leads to the local release of lipopolysaccharide (LPS), with consequent formation of an LPS–lipopolysaccharide binding protein (LBP)–CD14–Toll-like receptor 4 (TLR-4) complex on neutrophils, macrophages, and endothelial cells, resulting in cellular activation. Inflammatory cytokines are released, up-regulate adhesion molecules, and promote chemotaxis of neutrophils and macrophages. (The complement system, clotting cascade, and lymphocyte population may also be activated, but this is not shown in the diagram.) The activated cells release microbicidal agents typically designed for bacterial killing, but they may be injurious and promote distant organ injury and SIRS if the inflammatory process is uncontrolled. ICAM, intercellular adhesion molecule; IL, interleukin; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; NO, nitric oxide; PAF, platelet-activating factor; PECAM, platelet-endothelial cell adhesion molecule; ROI, reactive oxygen intermediate (or species); TNF, tumor necrosis factor.

This section on pathogenesis examines the determinants of infection: host defense mechanisms and bacterial virulence. Host defense mechanisms include barriers to infection and host immunity. The host immune system classically mounts a well-orchestrated response aimed at destroying the invading microbe. Both cellular immunity (neutrophils, monocyte-macrophages, and lymphocytes) and humoral factors (immunoglobulins, complement, and cytokines) will be discussed, because they represent the final common pathway for the development of SIRS. Bacterial virulence is then examined in detail. Impairment or failure of the intrinsic host defense mechanisms and significant virulence of invading microbes increase the likelihood of successful establishment of infection and development of sepsis. This section ends with a separate discussion of impaired neonatal host defense mechanisms.

## HOST DEFENSE MECHANISMS

### Barriers to Infection

Host defense mechanisms begin with anatomic barriers to infection: the presence of indigenous microbial flora on the skin, oropharynx, respiratory, gastrointestinal, and genitourinary tracts. These ubiquitous host bacteria prevent colonization by foreign or pathogenic microbes by blocking adherence to the epithelial barrier or by competing for nutrients. Each organ system has additional local protective mechanisms as well. The largest organ in the body, the skin, limits bacterial replication by maintaining a relatively acidic environment as well as undergoing regular desquamation, which severely hinders bacterial adherence. Gastric acidity impedes bacterial replication and colonization. Intestinal mucus and peristalsis as well as the cilia of the respiratory epithelium prevent bacterial adherence. Immunoglobulin A (IgA)-rich secretions in the oropharynx, nasopharynx, and tracheobronchial tree also impair bacterial adherence to the mucosa. For infection to occur, there must be either a breach in the integrity of the normal protective barrier or a sufficiently virulent microbe must penetrate the barrier (Fig. 10-3). Barrier failure may be caused by trauma or direct tissue injury, surgery, malnutrition, burns, immunosuppression, shock, and reperfusion injury following ischemia.[24] For example, during ischemia, consumption of adenosine triphosphate results in the accumulation of adenosine diphosphate, adenosine monophosphate, inosine, and hypoxanthine. Xanthine oxidase activity is also increased, but its effect is initially blunted because oxygen is required to oxidize hypoxanthine to xanthine. However, during reperfusion, oxygen is supplied, hypoxanthine is oxidized,

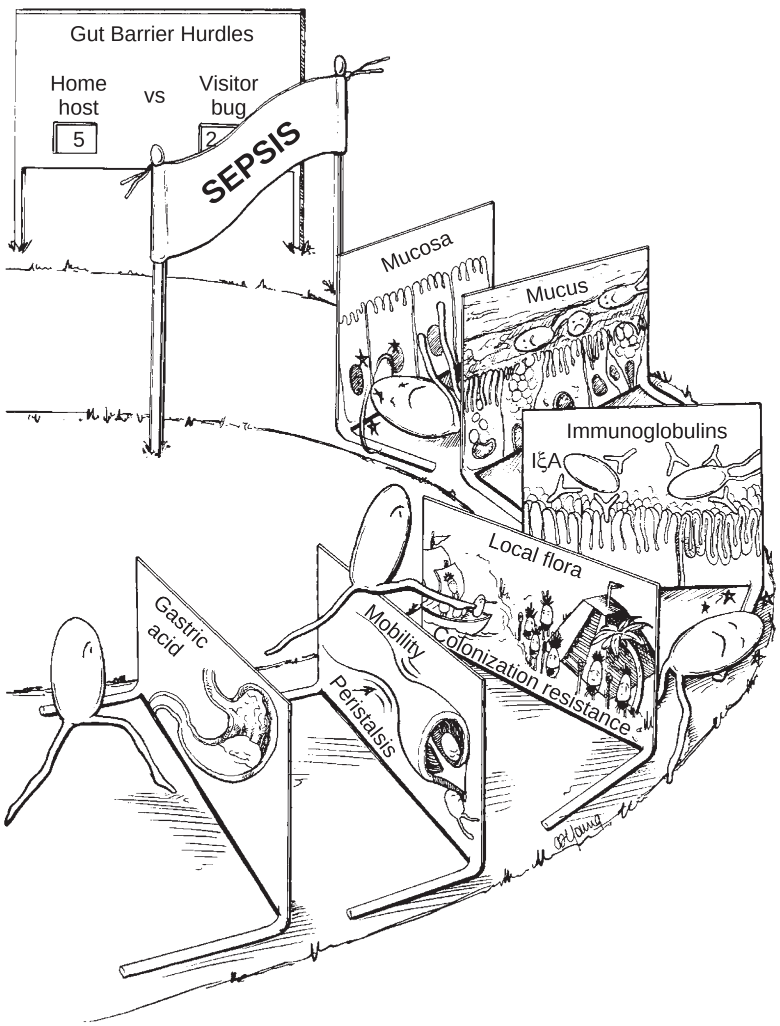


**FIGURE 10-3** The gut barrier is envisioned as a series of hurdles that bacteria must overcome to penetrate the epithelial layer and disseminate systemically. First hurdle: Gastric acid lowers intragastric pH, promoting a hostile environment for bacterial growth. Second hurdle: Coordinated peristalsis continually sweeps bacteria downstream, thus limiting their attachment to the mucosal surface. Third hurdle: Indigenous microbial flora (aerobes and anaerobes) prevent the overgrowth of pathogenic Gram-negative aerobic bacteria. Fourth hurdle: IgA, a nonbactericidal immunoglobulin, coats and aggregates bacteria, preventing their attachment to the mucosal surface. Fifth hurdle: Intestinal mucus forms a weblike barrier to prevent bacterial attachment to the enterocyte.

and toxic reactive oxygen intermediates (ROIs), or species such as superoxide ($O_2^-$) and hydrogen peroxide ($H_2O_2$), are formed. These ROIs can mediate direct tissue injury and thus result in gut barrier failure.[25–28] This results in adherence of bacteria, with subsequent penetrance and internalization. The development of clinical infection (bacterial survival and replication within the host) is dependent on the virulence of the microbe and its ability to evade both the local cellular and humoral host defense mechanisms.

## Cell-Mediated Immunity

***Neutrophils*** Neutrophils constitute the first line of defense in response to infection, tissue injury, or other triggers of inflammation. Egress from the circulation into the tissues is a highly regulated process that involves complex interactions between receptors on the phagocytes and the vascular endothelial cells. These interactions are partially governed by cytokines or other inflammatory mediators. The sequence of events occurs as follows: (1) neutrophil adherence to the endothelium, (2) migration of the neutrophil through the endothelium to the site of injury or inflammation (diapedesis), and (3) stimulation or priming of the neutrophil for killing.

Neutrophil adherence is regulated by adhesion molecules on both the neutrophil and the endothelial cell. There are three classes: selectins, integrins, and the immunoglobulin superfamily. Selectins direct the first step in the adhesion cascade, which involves the rolling of the neutrophil along the vascular endothelium. Specifically, leukocyte (L)-selectin binds endothelial (E)-selectin and platelet (P)-selectin, which are both present on activated endothelial cells.[29]

Migration of the neutrophil to the site of inflammation requires the formation of a firm adhesion between the neutrophil and endothelial cell. This step is governed by the $\beta_2$ integrin CD11b/CD18 on the neutrophil and the intercellular adhesion molecule-1 (ICAM-1) on the endothelial cell.[30] Interestingly, patients with leukocyte adhesion deficiency are susceptible to recurrent bacterial infections, because they lack the $\beta_2$ integrin receptor CD11b/CD18. Their neutrophils fail to adhere to the endothelium and therefore diapedesis cannot occur.[31]

Lipopolysaccharide released by bacteria enhances neutrophil–endothelial interactions directly and indirectly. LPS stimulates the release of inflammatory mediators, such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukin-1 (IL-1), and interferon-$\gamma$ (IFN-$\gamma$), which upregulate E-selectin and ICAM-1 expression on endothelial cells.[29,32] In addition, LPS forms a complex with LBP, which then binds to the CD14 molecule and TLR-4 on the neutrophil (and monocyte) and leads to up-regulation of the $\beta_2$ integrin CD11b/CD18. Thus LPS plays an important role in neutrophil adhesion and migration.[33,34]

After the firm adhesion step, neutrophil diapedesis is regulated by platelet-endothelial cell adhesion molecule-1 (PECAM-1), which normally maintains the vascular permeability barrier and modulates transendothelial migration of neutrophils and monocytes.[35–38] Antibodies to PECAM-1 lead to leaky barriers and inhibit neutrophil transmigration.[39] In addition to PECAM-1, neutrophil egress requires the presence of a chemotactic gradient through the extracellular matrix. A wide variety of chemotaxins abound at sites of inflammation, such as small bacterial peptides, monocyte chemotactic protein-1 (MCP-1), platelet-activating factor (PAF), and leukotriene $B_4$. Probably the two most important chemotaxins for neutrophil diapedesis are IL-8 and C5a. Interaction between specific receptors on the neutrophil and the chemotaxin evokes a cascade of secondary intracellular signaling events: translocation of protein kinase C from the cytoplasm to the cell membrane, protein kinase C–dependent phosphorylation, and an increase in free calcium in the cytosol. This results in conformational changes in the cytoskeleton of the neutrophil that allow its transendothelial egress and rapid movement toward the chemotactic gradient.[40] As one would expect, specific monoclonal antibodies against adhesion molecules disrupt the neutrophil–endothelial cell interaction and inhibit neutrophil chemotaxis, thus potentially impairing the ability to fight bacterial infection.[41]

The final step in the neutrophil response to infection is the phagocytosis of the microbe with subsequent intracellular killing. Phagocytosis is greatly enhanced by prior opsonization of the bacteria with specific immunoglobulins. This results in complement activation, the deposition of additional ligands or receptors on the bacterial surface, and the facilitation of neutrophil adherence to the microbe. This interaction results in the complete internalization of the microbe into endosomal compartments known as phagosomes. Prior stimulation or priming of the neutrophil by inflammatory cytokines or chemotaxins activates it for more efficient killing. Bacteria are then killed by the fusion of lysosomes containing potent microbicidal agents with the phagosome. In the phagolysosome, both oxygen-dependent and oxygen-independent pathways facilitate microbial killing.

The major oxygen-dependent mechanisms involve the formation of ROIs by the enzyme nicotinamide adenine dinucleotide phosphate oxidase. The active form of the enzyme is assembled in the cell membrane and catalyzes the reduction of molecular oxygen ($O_2$) to superoxide ($O_2^-$), the so-called respiratory burst. Superoxide is converted to hydrogen peroxide ($H_2O_2$) by superoxide dismutase. $H_2O_2$, in turn, can react with superoxide in the presence of iron or other metals to give the potent ROI hydroxyl radical ($^\circ OH$). Alternatively, $H_2O_2$ can react with chloride ($Cl^-$) in the presence of myeloperoxidase, an enzyme found in the cytoplasmic granules, to give the highly reactive hypochlorous acid (HOCl). HOCl, in turn, reacts with endogenous nitrogen-containing compounds to form the powerful oxidizing agents chloramines, which account for much of the neutrophil's cytotoxicity.[42,43]

The principal oxygen-independent microbicidal pathway is affected mainly by a number of peptides contained in specific cytoplasmic granules, including lysozyme, elastase, lactoferrin, cathepsin, and defensins. Many of these peptides act synergistically to promote microbial killing. For instance, defensins and elastase increase bacterial membrane permeability, allowing penetration by other microbicidal peptides or ROIs.

***Monocytes-Macrophages*** The monocyte-macrophage shares many similarities with the neutrophil in host defense mechanisms because it arises from the same stem cell as the granulocyte. The stem cell gives rise to the monoblast, which differentiates into a promonocyte, and then the monocyte. Once released into the bloodstream, monocytes migrate to various tissues and organs, where they terminally differentiate into macrophages. These mature macrophages are characterized by the acquisition of specific granules containing enzymes as well as receptors for growth factors and complement.[44–46]

Macrophages play an important role in the host defense against intracellular pathogens. Like neutrophils, they migrate to sites of inflammation in response to various chemotaxins, such as C5a, bacterial peptides, foreign antigens, and cytokines (IL-1, TNF-$\alpha$, and MCP-1). They also express adhesion molecules, such as L-selectin as well as $\beta_2$ and $\beta_1$ integrins. The latter is an important distinction from the neutrophil, because it allows the macrophage to migrate to sites of inflammation in patients lacking the $\beta_2$ integrin receptor (i.e., leukocyte adhesion deficiency). Macrophages can phagocytose and kill many common bacteria, though less efficiently than the neutrophil. The macrophage's mechanisms of intracellular killing closely resemble those of the neutrophil, with both oxygen-dependent and oxygen-independent pathways. However, in addition to the production of ROIs, macrophages make a substantial amount of the potent molecule nitric oxide (NO), which is also microbicidal.

NO is the product of the conversion of arginine to citrulline by nitric oxide synthase (NOS). There are three isoforms of NOS: NOS-1 (neuronal NOS) and NOS-3 (endothelial NOS) are calcium dependent and are expressed constitutively at low levels. NOS-2 (inducible NOS or iNOS) is usually absent except when induced in response to inflammatory mediators (e.g., LPS, cytokines) and is the principal isoform found in macrophages.[47,48] NO has been shown to have both cytotoxic and cytostatic activity against a wide range of microorganisms in vitro and in vivo; these include bacteria, viruses, fungi, mycobacteria, parasites, and *Chlamydia*.[49] However, there is no clear evidence that human phagocytes produce sufficient amounts of NO to account for its antimicrobial activity.[48] In fact, data suggest that NO must react with ROIs to exert cytotoxicity.[50] The precise nature of this reaction is not completely understood. Under certain conditions NO may be cytostatic or cytotoxic, while under others, it may be cytoprotective.[48,51,52]

Following the phagocytosis of bacteria and intracellular killing, antigenic fragments derived from these microbes are processed by the macrophage and then presented to T lymphocytes in the context of major histocompatibility complex (MHC) class II molecules. This interaction elicits specific immune responses that amplify the cytokine (and cellular) response to further enhance microbicidal activity. This highly specialized function is one of the key distinguishing features of the macrophage in the host defense against microbes.

***Lymphocytes*** Although neutrophils and monocytes-macrophages represent the major effectors of the host defense against microbes, certain microorganisms are able to evade their cytotoxic arsenal. These organisms must be eliminated through different means. The lymphocytes, and, to a lesser extent, the natural killer (NK) cells form the secondary line of defense against invading microbes.

Lymphocytes arise from a hematopoietic stem cell in the bone marrow. Early in the differentiation pathway, the lymphoid progenitor cell undergoes maturation in one of two distinct compartments, where it acquires its phenotypic and functional characteristics. Certain cells leave the bone marrow to undergo a process of "education" or maturation in the thymus. These mature T cells migrate from the thymus to reside in peripheral lymphoid organs, such as the spleen, lymph nodes, and intestinal Peyer patches. Other cells undergo maturation either in the bone marrow or fetal liver, where they become committed to immunoglobulin synthesis (B cells).

Both B cells and T cells play an important role in the elimination of microbes. B cells, in particular, produce opsonizing antibodies that facilitate phagocytosis of encapsulated organisms. They also secrete other immunoglobulins, such as IgA, that play a central role in mucosal immunity by preventing bacterial adherence and invasion. In addition, B cells participate in antibody-dependent cell-mediated cytotoxicity. T lymphocytes, in contrast, are the principal effectors of cell-mediated immunity against intracellular pathogens. T-cell–mediated killing requires: (1) recognition of the inciting antigen or microbe, (2) cellular activation, (3) clonal expansion, and (4) targeted killing.

Antigen presentation and recognition are governed in part by a family of normally occurring cell surface proteins known as major histocompatibility proteins. There are two classes of MHC proteins: class I, which is expressed in virtually all nucleated cells, and class II, which is expressed primarily in antigen-presenting cells (APCs), such as macrophages, dendritic cells, and B lymphocytes. These cells phagocytose bacteria, processing or breaking down the organism into smaller fragments or peptides that are then bound to the MHC class II proteins and inserted into the cell membrane of the APCs. T cells bearing the same MHC molecules are then able to recognize this MHC-peptide complex on the APC. Interaction between this complex and specific ligands on T helper (TH) cells (CD4+) leads to cytokine production, recruitment of additional phagocytic cells, and proliferation of different classes of lymphocytes: B cells, TH cells, and CD8+ cytotoxic T lymphocytes (CTLs). Ultimately, microbial killing is promoted primarily by the CTLs. Infected cells that cannot process antigen in the context of an MHC class II protein form a complex between MHC class I molecules in the cell and antigenic peptides derived from the invading pathogen. This complex is readily recognized and targeted for destruction by the CTLs. Thus although only APCs can process antigen in the context of MHC class II molecules and elicit a TH response, all cells infected by an intracellular pathogen can present foreign antigen in association with MHC class I molecules, which serve as the target for the CTLs.

T-cell activation is dependent on two important events: stimulation by the T-cell receptor signal-transducing protein complex CD3 and simultaneous cross-linking of the CD4 or CD8 ligand to the appropriate MHC peptide complex on an APC or infected cell (CD4–MHC class II–APC and CD8–MHC class I–infected cell). T-cell activation initiates a cascade of events leading to calcium mobilization, activation of protein kinases, and transcription/translation of specific genes encoding proteins that will help to eliminate the pathogen. These proteins include perforins and serine proteases in CTLs and various cytokines in TH cells. Activated CTLs bind to cells expressing the MHC peptide complex and release cytotoxic granules, such as perforin, which can "perforate" the cell membrane creating a hole that leads to osmotic lysis. Alternatively, CTLs may release serine proteases that induce apoptosis in the infected cell without affecting the effector cell.[53–55] Similar to the CTL, NK cells, which are a variant of the lymphocyte family, can also use granule exocytosis to kill infected target cells. In addition, these cells possess Fc receptors for immunoglobulin and therefore can participate in antibody-dependent cell-mediated cytotoxicity. Two classes of TH cells have been described based on their cytokine profile: TH1

cells produce IL-2 and IFN-γ, while TH2 cells produce IL-4, IL-5, IL-10, and IL-13. Other cytokines, such as IL-3 and granulocyte-macrophage colony-stimulating factor, are produced by both TH1 and TH2 cells. TH1 cells evoke primarily a T-cell–mediated response characterized in part by recruitment of macrophages to the site of infection, followed by macrophage activation by IFN-γ.[56,57] In contrast, TH2 cytokines shift the balance toward a humoral (B-cell) response.

### Humoral Factors

Thus far, we have emphasized the importance of cell-mediated immunity in the host defense against microbes. However, this cellular response is a highly complex phenomenon that is often initiated and optimized by diverse humoral factors, including immunoglobulins, complement activation, and cytokines, which is discussed in this section.

***Immunoglobulins*** Immunoglobulins or antibodies represent a class of proteins that are synthesized by mature B lymphocytes or plasma cells, mainly as a result of cognate interaction between a TH cell and an antigen-presenting cell bearing an MHC-plus-peptide complex. This interaction may lead to cytokine synthesis and B-cell proliferation and maturation, with production of distinct classes of immunoglobulin. The primary role of antibodies in the host defense against microbes is to prevent bacterial adherence to, and subsequent invasion of, susceptible host cells. The mechanisms involved in this process include opsonization of the microbe to facilitate phagocytosis and complement activation with deposition of complement fragments on bacterial membranes to further enhance phagocytosis and subsequent bacterial killing. Neutralization of intrinsic microbial toxins or virulence factors to impede bacterial attachment to cell surfaces also occurs. There are five major classes of immunoglobulins: IgA, IgG, IgM, IgD, and IgE. Among these groups, IgG, IgM, and IgA are the predominant antibodies that mediate the host defense against microbes.

IgM is the largest of the immunoglobulins. It is the main component of the initial response to infection or antigenic stimulus. As such, it has a half-life of only 5 to 6 days, and its level declines steadily as IgG levels increase. Because of its size, IgM is found exclusively in the intravascular space, serving as an efficient bacterial agglutinin and as a potent activator of the complement system.

IgG is perhaps the most abundant antibody, constituting nearly 85% of serum immunoglobulins. It is found in both intravascular and extravascular (tissue) spaces. It is the only immunoglobulin that crosses the placenta from the mother to the fetus. IgG is the predominant class of antibody directed against bacteria and viruses. The biological potency of the molecule resides in its ability to opsonize bacteria by binding the antigen with its Fab component, while simultaneously binding the Fc receptor on the neutrophil, monocyte, or macrophage with its own Fc component. Moreover, IgG aggregates can activate the complement system.

Antibodies of the IgA isotype play a critical role in local mucosal immunity. They are synthesized by plasma cells within lymphoid tissue situated subjacent to the epithelial surfaces where they are secreted. IgA is released as a dimer and acquires a secretory component as it passes through the epithelial cell to exit at the mucosal surface in the form of secretory IgA. The latter serves as an antiseptic paint that binds pathogenic microbes and thus prevents their attachment, colonization, and subsequent invasion of tissue. Note, however, that IgG, IgM, and, to a lesser extent, IgE can also play a role in local mucosal immunity, especially in patients with congenital IgA deficiency.

***Complement System*** Although antibodies are effective at recognizing antigenic determinants on microbial pathogens, they are unable to independently kill the microorganisms. Following opsonization, they must rely on phagocytes to ingest the microbe and on complement activation to further enhance or augment their opsonic ability to neutralize and ultimately kill the ingested pathogen. There are two distinct pathways for complement activation: classical and alternative. Antigen-antibody complexes are the predominant initiators of the classical pathway. In contrast, bacterial cell wall fragments, endotoxin (or LPS), cell surfaces, burned and injured tissue, and complex polysaccharides are capable of activating the alternative (properdin) pathway. Stimulation through either pathway initiates a cascade of events that can lead to marked complement activation as a result of an elaborate amplification process. The most critical point in this cascade occurs at C3, where both pathways converge to form C3a and C3b. C3a is both a vasodilator and a chemotaxin for phagocytes. The C3b molecule, in contrast, is the most critical component of the complement cascade, because this enzyme permits dramatic amplification of the system by facilitating further cleavage of C3 to C3a and C3b, as well as enhanced C3b production by the alternative pathway. Moreover, C3b is the most potent biologic opsonin, with cell surface receptors present on most phagocytes. Deposition of C3b on the surface of bacteria can promote its lysis by activating the distal components of the complement cascade (C8 and C9), which insert into and damage the cell membrane, resulting in osmotic lysis. In the process, another even more potent chemotaxin, C5a, is released, a molecule that is also capable of inducing a respiratory burst in the phagocyte and thus facilitates bacterial killing.

***Cytokines*** The mediators that regulate the complex interactions among the various cellular effectors in the cytotoxic arsenal against microbes are generally known as cytokines. They represent a heterogeneous class of glycoproteins that are secreted by a variety of cells, including neutrophils, monocytes-macrophages, B and T lymphocytes, NK cells, endothelial cells, and fibroblasts. In general, there is extensive pleiotropy and redundancy in cytokine function. Some cytokines serve to amplify the inflammatory response, while others function to limit its extent.

Proinflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-8, IL-11, and IL-18 share a number of similar properties; other cytokines that confer more specific immunity against certain pathogens, such as IL-2, IL-4, IL-12, and IL-13, also exhibit a number of similarities. Anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β, neutralize the biological activities of the proximal mediators of inflammation——the monocytes-macrophages and their secretory products.

Tumor necrosis factor-α is one of the earliest inflammatory mediators released in response to infection. The predominant source of TNF-α is the monocyte-macrophage, although NK

cells, mast cells, and some activated T cells also produce it, but to a lesser extent. TNF-α exerts a number of important functions in the inflammatory response. At low levels, it may (1) enhance endothelial cell adhesiveness for leukocytes; (2) promote neutrophil chemotaxis or recruitment to sites of inflammation; (3) stimulate the production of other proinflammatory cytokines that mimic TNF function, such as IL-1, IL-6, and IL-8; (4) prime neutrophils and monocytes-macrophages for microbial killing; and (5) up-regulate the expression of MHC class I molecules on target cells to facilitate killing. However, excess or uncontrolled TNF production, as occurs in overwhelming sepsis, may contribute to profound hemodynamic instability because of cardiovascular collapse, depressed myocardial contractility, and disseminated intravascular coagulation.

Interleukin-1 is released relatively early during the inflammatory response to infection or injury. It is produced by monocytes-macrophages and by epithelial, endothelial, and dendritic cells in response to endotoxin challenge or TNF stimulation. There are two biologically active forms of the molecule: IL-1α, which may be membrane associated, and IL-1β, which is active in soluble form. They share similar properties with TNF-α, including induction of other cytokines, such as IL-2, IL-6, and IL-8. However, unlike TNF-α, they exert little or no effect on MHC class I expression, nor do they play a role in hemodynamic collapse.

Interleukin-6 is the most important regulator of hepatic production of acute phase reactants, such as C-reactive protein. It is produced by a variety of cells, including mononuclear phagocytes, TH2 cells, and fibroblasts, in response to tissue injury, infection, TNF, and IL-1. It stimulates B-cell differentiation and enhances CTL maturation. IL-6 acts through a membrane-bound receptor that can shed and continue to regulate IL-6 activity away from the site of production.[58]

Interleukin-8 is secreted by monocytes-macrophages, T cells, endothelial cells, and platelets in response to inflammation, IL-1, and TNF. It is one of the most potent chemotactic and activating factors for neutrophils. IL-8 belongs to a family of chemoattractants that includes other chemokines, such as MCP-1, MCP-2, and MCP-3; macrophage inflammatory protein (MIP-1a, MIP-1b); and RANTES (regulated on activation, normal T expressed and secreted). These mediators are released early in inflammation, mainly by monocytes-macrophages but also by neutrophils and platelets. MIP-1a and MCP-1 may act in an autocrine fashion to recruit additional mononuclear phagocytes to sites of inflammation, thus potentially amplifying the inflammatory response. Another proinflammatory macrophage product, migration inhibitory factor, appears to be induced by TNF at sites of inflammation and serves to trap macrophages at those sites and elicit further TNF-α production by them.[59] RANTES is a lymphocyte-derived chemoattractant that promotes macrophage chemotaxis, up-regulates adhesion molecules, and enhances the release of inflammatory mediators.[59] Other chemoattractants include PAF, which is secreted by endothelial cells and macrophages, and leukotriene B4. In addition to serving as a chemoattractant for neutrophils, PAF up-regulates CD11b/CD18 ($\beta_2$ integrin) on the neutrophil.[60] In general, the chemoattractants not only recruit phagocytes to sites of inflammation but also appear to prime these cells for subsequent cytotoxic effector function.[61–63]

Other cytokines that play an important role in the elimination of invading microbial pathogens include products of TH1 cells, such as IL-2 and IFN-γ, as well as products of TH2 cells, such as IL-4 and IL-13. In general, TH1 cytokines are produced in response to bacterial, viral, or protozoan infections, and TH2 cytokines are secreted mostly in response to metazoa or allergens.[64,65] IL-2, the prototypical T-cell growth factor, directly amplifies the immune response by inducing cellular proliferation. It also augments killing by activating NK cells.

Interferon-γ is perhaps one of the most important macrophage activating factors. It stimulates the macrophage to express MHC class II molecules, which is necessary for antigen processing and for amplification of the immune response. In addition, it induces NOS activity (NOS-2), which is critical for intracellular killing of invading pathogens.[49,66] IFN-γ may enhance microbial killing by inducing TNF-α production and TNF-α receptor expression by macrophages and by activating NK cells. IFN- γ is also produced by activated CTLs in response to IL-2 and antigen expressed in the context of MHC class I molecules and by NK cells in response to IL-12.

Interleukin-12, primarily a macrophage product, is the most potent inducer of IFN-γ production by NK cells. In addition, it influences the uncommitted TH cell to differentiate into the TH1 phenotype, secreting IL-2 and IFN-γ.[60] IL-12 can support most of the functions performed by IL-2, except perhaps its proliferative effect. Therefore IL-12 plays an important role in the elimination of intracellular organisms.

The role of TH2 cytokines, such as IL-4 and IL-13, is less clear. Although they partly promote monocyte differentiation and may induce the expression of adhesion molecules in the endothelium, they are mostly responsible for immunoglobulin isotype switching in B cells, leading predominantly to IgG4 and IgE production.

Cytokine production and signaling are central to the sepsis response. Yet, under similar clinical and demographic circumstances, individuals may exhibit distinct responses to an identical stimulus. One possible explanation is differential protein expression between the two patients. For example, whereas a traumatic insult in one patient may lead to overwhelming sepsis and result in admission to the intensive care unit, another individual may exhibit a more attenuated response characterized by fever and tachycardia for a couple of hours, followed by resolution of the symptoms. Proteins may be expressed differently for a number of reasons, but one significant factor may be the genetic makeup of the individual. Gene polymorphisms or single nucleotide polymorphisms are differences in nucleic acid base pairs that occur every 100 bases. The change in base pairs that occurs in the promoter region of the gene may lead to overproduction or underproduction of a gene product. Recent evidence suggests that the presence of one gene polymorphism may serve as a marker for additional protective gene polymorphisms.[67] Cytokine gene polymorphisms may explain differences in the inflammatory response among individuals.[68]

### Bacterial Virulence

Microbial pathogens possess unique biochemical properties known as virulence factors, which permit the successful establishment of infection within the host. If these virulence factors escape the host immune system, the net result will be sufficient multiplication or persistence of the microorganism within the host to cause significant damage to local tissue or

allow transmission of the microorganism to other susceptible hosts.

The first and perhaps the most critical step in the process of microbial infection is adherence of the pathogenic microorganism to the cell surface. Some organisms multiply at the site of attachment, while others use this attachment as a prerequisite for microbial invasion. Elimination of this first step may completely abrogate colonization and invasion by microbial pathogens.

The process of microbial adherence requires specific interaction between specific molecules on the surface of the bacteria, known as adhesins, and specialized receptors on the host cell. Bacterial fimbriae or pili are perhaps the best studied adhesins that have been shown to promote bacterial adherence to mucosal surfaces. Members of the Enterobacteriaceae family exhibit prominent, morphologically similar pili—type I fimbriae—that permit their attachment to the d-mannose receptor sites on epithelial cells.[69,70] Further, certain bacteria, such as *Escherichia coli,* can simultaneously express different types of adhesins—type I, X, and P fimbriae—a property that clearly enhances the microbe's ability to attach to host surfaces.[71] Other adhesins include invasins, proteins that not only mediate bacterial attachment but also facilitate entry into the host, and hemagglutinin, which is expressed on pathogens such as *Bordetella pertussis, Salmonella typhimurium,* and influenza virus.[71] The host also secretes proteins that indirectly facilitate bacterial adherence; these include proteins of the extracellular matrix, namely, fibronectin, laminin, collagen, and vitronectin. These proteins share a common peptide sequence, Arg-Gly-Asp (RGD), which is also found on many microbial pathogens that bind to mammalian cells.[72] For instance, *Staphylococcus aureus* and *Streptococcus pyogenes* are known to bind fibronectin on epithelial surfaces.[71] Fortunately, bacterial binding to extracellular matrix proteins is usually of low affinity and rarely leads to microbial invasion.

Bacterial adherence allows microorganisms to penetrate the intact epithelial barrier of the host and eventually replicate. However, the mere adherence of the bacteria may not be sufficient for subsequent entry into the host cell. Bacterial internalization requires a high-affinity interaction between adhesins and specific receptors on the cell surface. The integrin receptors appear to be the primary targets on the cell surface for these interactions, because they can bind bacterial adhesins as well as extracellular matrix proteins, such as fibronectin, laminin, collagen, and vitronectin. It is the affinity of this interaction that determines whether the microbe becomes internalized or remains adherent to the host cell surface.[72]

Other bacterial virulence factors may also facilitate internalization. For instance, the cell surface protein invasin, found on *Yersinia* species, serves a dual purpose as an adhesin and an enhancer of bacterial invasion. It binds to $\beta_1$ integrins on the cell surface, resulting in internalization of *Yersinia*. Transfer of the invasin gene to nonpathogenic *E. coli* renders the organism capable of internalization and host tissue invasion.[72,73] Another variant of the invasin gene, termed the attachment invasion locus, has been identified in *Yersinia* species that cause clinical disease but not in those species that do not cause clinical infection. This molecule may serve as a potential marker of bacterial virulence.

Once bacterial internalization has occurred, the microbe is now located in an endosomal compartment, known as a phagosome, and must escape the intracellular host defense mechanisms to multiply. For internalized bacteria to survive, (1) fusion of the host cell lysosome with the phagosome to form a phagolysosome must be avoided, (2) acidification of the phagolysosome must be prevented, or (3) the antibacterial activity of the phagolysosome must be neutralized. Successful avoidance of these host defense mechanisms permits the establishment and multiplication of the organisms within the host. Bacterial toxins may play an important role in this process either by causing direct damage to host cells or by interfering with host defense mechanisms. For instance, diphtheria toxin creates a layer of dead cells that serves as a medium for bacterial growth. *Clostridium difficile* secretes both an enterotoxin (toxin A) and a cytotoxin (toxin B) that can damage the mucosal epithelium. *Clostridium perfringens* secretes numerous exotoxins with well-defined roles in the microbe's virulence. These toxins are enzymes with specific targets; they include hyaluronidase, collagenase, proteinase, deoxyribonuclease, and lecithinase. Several organisms, such as *Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis,* and other bacteria that infect the oral cavity produce proteases that are capable of neutralizing local host defense mechanisms.[74] *S. aureus* is able to neutralize ROIs, such as hydrogen peroxide, through the production of catalase.

Likewise, bacterial endotoxins have potent biological properties. LPS consists of three regions: an O-specific side chain, a core polysaccharide, and an inner lipid A region. Most of the biological properties of LPS (also known as endotoxin) are attributed to the lipid A region. In fact, lipid A is believed to be the principal mediator of septic shock. LPS (especially the lipid A component) triggers an inflammatory cascade, leading to the release of various inflammatory mediators, including arachidonic acid derivatives, leukotrienes, and proinflammatory cytokines, and complement activation. Endotoxin interacts with inflammatory cells by binding to a complex consisting of soluble and membrane-bound receptors; this leads to a cascade of signaling events that result in increased expression of proinflammatory cytokines. These inflammatory mediators are responsible for the hemodynamic and metabolic events that characterize SIRS.

Another method of evading the host defense mechanisms is for the bacteria to avoid phagocytosis or engulfment by the professional phagocytes, such as the neutrophils and macrophages. Streptococci secrete a streptolysin that inhibits neutrophil migration or chemotaxis and impairs phagocyte cytotoxicity. Encapsulated organisms cannot be eliminated unless specific opsonizing antibodies that bind to the surface of the bacteria and facilitate their attachment to the Fc receptors on the neutrophil are present. These organisms are virulent pathogens in splenectomized patients, especially those younger than 4 years, with 50% mortality for overwhelming postsplenectomy sepsis found in some studies. Finally, certain microbial pathogens may avoid phagocytosis by binding the Fc receptor of IgG with the bacterial cell wall protein A, which is found in many bacteria, including virulent strains of staphylococci. This interaction prevents binding of the Fc receptor of the IgG antibody to the Fc receptor of the neutrophil.

### Neonatal Host Defense

In general, neonates, especially premature infants, show increased vulnerability to bacterial infections and sepsis. This predisposition is closely linked to intrinsic deficiencies in the neonatal host defense apparatus. For term neonates,

production of neutrophils is near the maximal level. Neutrophils constitute approximately 60% of circulating leukocytes; 15% of these neutrophils are immature (bands). These percentages are substantially lower in premature infants. Perhaps one of the most important factors in neonates' increased propensity for bacterial infections is their relative inability to significantly increase the levels of circulating neutrophils in response to stress or infection, resulting primarily from a limited neutrophil storage pool (20% to 30% that of adults) and, to a lesser extent, to increased margination of neutrophils.[75,76] Therefore systemic infections in neonates often lead to severe neutropenia. In fact, the relative degree of depletion of the neutrophil storage pool is a predictor of fatal outcome in neonatal sepsis.[75]

In addition to an already diminished storage pool, neonatal neutrophils show decreased adhesion to activated endothelium.[77,78] This process may be due to decreased L-selectin expression on the surface of neonatal neutrophils and an inability to up-regulate cell surface $\beta_2$ integrin.[69,70] Consequently, the neutrophils are unable to form the high-affinity adhesion to the endothelium that is necessary to effectively respond to a chemotactic gradient and migrate into tissues at sites of inflammation. In fact, several studies have shown that chemotaxis of neonatal neutrophils is substantially less than that of adult neutrophils.[79,80] Further, accumulating evidence suggests that abnormal signal transduction following the binding of chemotactic receptors to membrane receptors on neonatal neutrophils may also contribute to impaired chemotaxis.

Under normal conditions, neonatal neutrophils bind, ingest, and kill bacteria as effectively as adult neutrophils do. However, in the presence of a suboptimal concentration of opsonins, neonatal neutrophils are less efficient at phagocytosis,[81] an important consideration, because neonatal serum is deficient in opsonins. Neonatal neutrophils show normal production of superoxide but a relative decrease in the amount of hydroxyl radical and in the number of specific granules (defensins).[82] Therefore they may exhibit decreased oxygen-dependent and oxygen-independent microbial killing.[82] However, the deficiencies in microbicidal activity appear to be less critical than the substantial reduction in the neonatal neutrophil storage pool and the impairment in neutrophil chemotaxis, except perhaps in the presence of a high bacterial load, when efficient microbial killing becomes crucial.

Although the neonatal neutrophil storage pool may be diminished, the number of monocytes per blood volume in term infants appears to be equal to or greater than that of adults.[83] However, migration of these monocytes to sites of inflammation is significantly delayed compared with adults. Possible explanations for this relative delay in migration include decreased generation of chemoattractant factors for monocytes, impaired monocyte chemotaxis (as has been shown for neutrophils), and inability to up-regulate adhesion molecules on the surface of neonatal monocytes. Yet numerous studies have shown that neonatal monocytes have normal chemotaxis; others suggest that they may have normal migratory capacity but fail to properly orient toward the chemotactic gradient. Similarly, there are several conflicting reports regarding the expression of adhesion molecules on the surface of neonatal monocytes. Some studies show increased expression of $\beta_2$ integrins, while others suggest that these molecules are down-regulated in activated and resting neonatal monocytes. Nevertheless, once they reach the site of active inflammation, neonatal monocytes phagocytose and kill bacteria as effectively as adult monocytes do. They probably use microbicidal mechanisms similar to adult monocytes because they can generate comparable levels of ROIs. However, data on NO production by neonatal monocytes relative to adult monocytes are scant. Activated neonatal monocytes and macrophages produce substantially less IL-6 and TNF-$\alpha$ than their adult counterparts. IL-1 production, in contrast, is equivalent.

Term neonates have a substantially greater number of circulating T lymphocytes than adults do. They also have a greater proportion of CD4+ versus CD8+ T cells compared with adults. These T cells express predominantly a virgin phenotype secondary to their relative lack of exposure to foreign antigens. However, they proliferate effectively in response to mitogenic stimuli. Stimulated neonatal T cells produce large quantities of IL-2. In contrast, production of other cytokines, such as TNF-$\alpha$, IFN-$\gamma$, IL-3, IL-4, IL-5, and IL-10, is either moderately or significantly suppressed.[84–86] Neonates show decreased T-cell–mediated (CTL) cytotoxicity; this phenomenon may be due in part to the relative lack of prior antigenic exposure and the deficiency in cytokine production. Alternatively, the relative decrease in T-cell function may be the result of impaired monocyte-macrophage chemotaxis, resulting in diminished MHC-restricted cognate interactions between antigen-presenting cells and TH cells. Thus cytokine production is significantly reduced, and the inflammatory response is not amplified.

Term neonates also show relative immaturity of B-cell function and development. Although neonatal B cells can differentiate into IgM-secreting plasma cells, they do not differentiate into IgG- or IgA-secreting plasma cells until much later. IgM is more abundant in neonatal than in adult secretions. In contrast, virtually all circulating neonatal serum IgG is derived from maternal placental transfer. In fact, it is not until the third or fourth month of life that neonatal IgG production begins to account for a greater proportion of circulating IgG. As a result, the fetus is protected against most infectious agents for which the mother has adequate levels of circulating IgG antibodies, but not against those microbes that elicit a different immunoglobulin isotype, such as *E. coli* and *Salmonella*. Premature neonates are particularly vulnerable to such infections, because they do not receive sufficient maternal IgG. IgM and secretory IgA, which is detected in neonatal secretions within the first week of life and is abundant in breast milk, may provide compensatory protection against bacterial infection.

In term neonates, the percentage of NK cells, which play an important role against intracellular pathogens by promoting target cell lysis in a non–MHC-restricted fashion, is similar to that of the adult. However, they are functionally and phenotypically immature (CD56−).[87,88] At birth, their lytic potential is only 50% of that of adult NK cells, and they do not reach mature levels until late in infancy. This phenomenon may be partly due to decreased cytokine production (especially IFN-$\gamma$) in neonates, as previously discussed.

In general, because of their reduced levels of immunoglobulins, neonates rely primarily on the alternative (antibody-independent) pathway of complement activation. However, a substantial proportion of term and preterm neonates exhibit a significant reduction in components of both the classic and the alternative pathways of complement activation. The level of C9, a terminal component of the complement system that is critical for killing gram-negative organisms, is diminished,

especially in preterm infants. The relative opsonic capacity of both term and preterm neonates is also impaired. This observation may be the result of inefficient cross-linking of the opsonin C3b after it has been deposited on the microorganism. Alternatively, it may reflect diminished levels of fibronectin, which plays an important role in cell adhesion and facilitates the binding of certain bacteria to phagocytes. Neonates also show decreased production of the potent chemotactic factor C5a. These defects further predispose term and preterm neonates to bacterial infections, because in addition to their already reduced neutrophil storage pool and their depressed levels of immunoglobulin, they cannot effectively use the most potent biologic opsonin, C3b, which is also responsible for amplification of the complement pathway. In addition, they have a decreased influx of phagocytes and impaired killing at the sites of infection owing to the decrease in C5a and in C9.

# Diagnosis

## GOLDSTEIN CRITERIA

Although definitions of the sepsis continuum have been published for adults,[6,11] no such work had been done for the pediatric population until 2002, when an international panel of 20 experts in sepsis convened to modify the published adult consensus definitions for children.[5] Physiologic and laboratory variables used to define SIRS, sepsis, severe sepsis, and MODS required modification for the different developmental stages in children. In addition, comparing pediatric sepsis studies had been very difficult because of the disparity in inclusion criteria and the myriad of pediatric definitions for the sepsis continuum in the literature before 2004. Therefore establishment of age group specific consensus definitions of the pediatric sepsis continuum should facilitate the interpretation and comparison of pediatric clinical trials. The following definitions and guidelines published by Goldstein and colleagues provide a uniform basis for diagnosing sepsis in children (Tables 10-2 to 10-4).

### Age Group–Specific Definitions for Abnormal Vital Signs and Leukocyte Count

Specific definitions for abnormal vital signs and leukocyte count were established in six clinically and physiologically meaningful age groups (see Table 10-2). Premature infants were excluded, because their care occurs primarily in neonatal intensive care units; diagnosis in this group of unique patients will be discussed later. Age groups were defined as newborn (0 days to 1 week), neonate (1 week to 1 month), infant (1 month to 1 year), toddler and preschool (2 to 5 years), school-age child (6 to 12 years), and adolescent and young adult (13 to <18 years).

### Definitions of the Pediatric Sepsis Continuum

Definitions of the pediatric sepsis continuum were established (see Table 10-3). There are several key differences in the terminology of sepsis and its related syndromes between adults and children. The major distinction is that the diagnosis of pediatric SIRS requires that a temperature or leukocyte abnormality be present. This requirement reflects the fact that tachycardia and tachypnea are common presenting symptoms of many pediatric disease processes and are not specific to SIRS or sepsis. A core temperature measured by rectal, bladder, oral, or central catheter probe is required. Temperatures taken through the tympanic, toe, or axillary route are not sufficiently accurate. Notably, bradycardia may be a sign of SIRS in the newborn age group. Although a positive culture confirms the presence of infection, the definition of infection in children also includes specific clinical examination findings, such as petechiae and purpura in the setting of hemodynamic instability; fever, cough, and hypoxemia in the setting of leukocytosis and pulmonary infiltrates; or a distended tympanitic abdomen with fever and leukocytosis associated with perforated bowel.

### Pediatric Organ Dysfunction Criteria

The definition of pediatric septic shock remains problematic, because children typically maintain their blood pressure until they are gravely ill. Thus, unlike adults, there is no requirement for systemic hypotension to make the diagnosis of septic shock, because shock may occur long before hypotension is present in children. Pediatric septic shock is defined as sepsis and cardiovascular organ dysfunction, as noted in Table 10-4. Although adult organ dysfunction criteria have been applied to various pediatric populations, they may be inappropriate for children. Thus the consensus conference established pediatric organ dysfunction criteria (see Table 10-4) based on those used in the Pediatric Logistic Organ Dysfunction, Pediatric-MODS, and Multiple Organ System Failure scores as well as the criteria used in the open-label recombinant human activated protein C study.[5]

**TABLE 10-2**
**Age Group Specific Definitions for Abnormal Vital Signs and Leukocyte Count**

| *Age Group* | *HR (Beats/Minute)* | *RR (Breaths/Minute)* | *SBP (mm Hg)* | *WBC count (WBCs × $10^3$/mm)* |
|---|---|---|---|---|
| Newborn (0 day-1 week) | >180 or <100 | >50 | <65 | >34 |
| Neonate (1 week-1 month) | >180 or <100 | >40 | <75 | >19.5 or <5 |
| Infant (1 month-1 year) | >180 or <90 | >34 | <100 | >17.5 or <5 |
| Toddler/preschool (2-5 years) | >140 | >22 | <94 | >15.5 or <6 |
| School-age child (6-12 years) | >130 | >18 | <105 | >13.5 or <4.5 |
| Adolescent/young adult (13 to <18 years) | >110 | >14 | <117 | >11 or <4.5 |

Modified and used with permission from Goldstein B, Giroir B, Randolph A, et al: International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2-8.
HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; WBC, white blood cell.

**TABLE 10-3**
**Definitions of the Pediatric Sepsis Continuum**

**Systemic Inflammatory Response Syndrome (SIRS)***

The presence of at least two of the following four criteria, **one of which must be abnormal temperature or leukocyte count:**

1. Core† temperature of > 38.5° C or < 36° C.
2. Tachycardia, defined as a mean heart rate > 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hour time period **OR for children < 1 year old: bradycardia, defined as a mean heart rate < 10th percentile for age in the absence of external vagal stimulus, beta-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hour time period.**
3. Mean respiratory rate > 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or > 10% immature neutrophils.

**Infection**

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)

**Sepsis**

SIRS in the presence of or as a result of suspected or proven infection.

**Severe Sepsis**

Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions. Organ dysfunctions are defined in Table 10-4.

**Septic Shock**

Sepsis and cardiovascular organ dysfunction as defined in Table 10-4.

Modified and used with permission from Goldstein B, Giroir B, Randolph A, et al: International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2-8.
*See Table 10-2 for age group specific definitions for abnormal vital signs and leukocyte count.
†Core temperature must be measured by rectal, bladder, oral, or central catheter probe.
Modifications from the adult definitions are in **boldface**; SD, standard deviation(s).

## DIAGNOSIS OF NEONATAL SEPSIS

The diagnosis of neonatal sepsis, particularly in premature newborns and VLBW infants, remains a challenge. As previously discussed, the neonate's host defense mechanism is markedly impaired, and this problem is even more pronounced in the preterm neonate. These infants may not manifest the same clinical signs as older patients. Sepsis should be suspected in any newborn with temperature instability, apnea, respiratory distress or tachypnea, cardiovascular instability (including tachycardia, bradycardia, and hypotension), reduced perfusion or poor color, feeding intolerance or diarrhea, and poor tone or lethargy, particularly in the presence of a maternal history of premature onset of labor, prolonged (>24 hours) rupture of membranes, clinically proven chorioamnionitis, colonization of the genital tract with pathogenic bacteria (e.g., group B *Streptococcus* or *E. coli*), urinary tract infection, or sexual intercourse near the time of delivery, because these are all independent risk factors for the development of neonatal infection. In fact, these risk factors increase the rate of systemic infection more than 10-fold.[89]

**TABLE 10-4**
**Pediatric Organ Dysfunction Criteria**

**Cardiovascular Dysfunction**

Despite administration of isotonic intravenous fluid bolus ≥ 40 mL/kg in 1 hour:

Decrease in BP (hypotension) < 5th percentile for age or systolic BP < 2 SD below normal for age*

OR

Need for vasoactive drug to maintain BP in normal range (dopamine > 5 μg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)

OR

Two of the following:

Unexplained metabolic acidosis: base deficit > 5.0 mEq/L
Increased arterial lactate > 2 times upper limit of normal
Oliguria: urine output < 0.5 mL/kg/hr
Prolonged capillary refill: >5 seconds
Core to peripheral temperature gap > 3° C

**Respiratory**†

$Pao_2/Fio_2$ < 300 in absence of cyanotic heart disease or preexisting lung disease

OR

$Paco_2$ > 65 torr or 20 mm Hg over baseline $Paco_2$

OR

Proven need‡ or >50% $Fio_2$ to maintain saturation ≥ 92%

OR

Need for nonelective invasive or noninvasive mechanical ventilation§

**Neurologic**

Glasgow Coma Score ≤ 11

OR

Acute change in mental status with a decrease in Glasgow Coma Score ≥ 3 points from abnormal baseline

**Hematologic**

Platelet count < 80,000/mm$^3$ or a decline of 50% in platelet count from highest value recorded during the past 3 days (for chronic hematology/oncology patients)

OR

International normalized ratio > 2

**Renal**

Serum creatinine ≥ 2 times upper limit of normal for age or twofold increase in baseline creatinine

**Hepatic**

Total bilirubin ≥ 4 mg/dL (not applicable for newborn)

OR

ALT 2 times upper limit of normal for age

Modified and used with permission from Goldstein B, Giroir B, Randolph A, et al: International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2-8.
*See Table 10-3.
†Acute respiratory distress syndrome must include a $Pao_2/Fio_2$ ratio ≤ 200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically, except the $Pao_2/Fio_2$ ratio must be ≤ 300 mm Hg.
‡Proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required.
§In postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.
ALT, alanine transaminase; BP, blood pressure; SD, standard deviation(s).

## BIOCHEMICAL MARKERS

Although the Goldstein consensus criteria establish important and useful definitions for the sepsis continuum in children, these are largely based on clinical and some laboratory findings.

Current research targets to improve the diagnosis of pediatric sepsis include various biochemical inflammatory markers. These may prove to be objective criteria and perhaps more reliable than some physiologic variables. Investigators have reported elevated sedimentation rate, C-reactive protein, base deficit, IL-6, procalcitonin level, adrenomedullin, soluble CD14, soluble endothelial cell/leukocyte adhesion molecule 1, MIP, and extracellular phospholipase $A_2$ as potential biochemical markers of SIRS.[90–104] Although some of these markers are sensitive, most lack specificity, and none of them is sufficiently robust to add to the consensus definition of SIRS at this time. However, in the future, it may be possible to incorporate biochemical and immunologic markers in the diagnostic criteria for pediatric SIRS.

## PIRO SYSTEM

An emerging concept in sepsis research is the PIRO system, which stratifies patients on the basis of their *P*redisposing conditions, the nature and extent of the *I*nsult or *I*nfection, the magnitude of the host *R*esponse, and the degree of concomitant *O*rgan dysfunction.[6] The PIRO system is analogous to the tumor-node-metastasis (TNM) system for oncology in that it can be used to assess risk and predict outcome in septic patients, assist with enrollment of patients into clinical trials, and determine the likely patient response to specific therapies. Specifically, the PIRO system should be able to discriminate morbidity arising from infection and morbidity arising from the response to infection based on a patient's I and R scores and their outcomes. Thus the PIRO system has the potential to help researchers develop and clinicians choose the most appropriate treatments for septic patients, because therapeutics that modulate the host response may adversely affect the body's ability to contain an infection.

A recent retrospective analysis of two large global databases of patients with severe sepsis (PROWESS-840 patients and PROGRESS-10,610 patients) was undertaken to generate and validate the PIRO system. In PROWESS, the correlation between the PIRO total score and in-hospital mortality rates was 0.974 ($P < 0.0001$), and in PROGRESS it was 0.998 ($P < 0.0001$). The investigators concluded that the PIRO system appears to accurately predict mortality, can develop into an effective model for staging severe sepsis, and may prove useful in future sepsis research.[105] Brilli and colleagues suggest that a modified PIRO system for pediatric sepsis should be developed and applied to future clinical pediatric sepsis trials, assuming the adult PIRO system is proven to be successful and adds a useful new dimension to clinical trials.[106,107]

# Management

## PREVENTION

Given the rising incidence of sepsis and growing health care burden, management of pediatric sepsis should begin with prevention. In neonates, early onset sepsis can potentially be prevented or reduced with appropriate prenatal and peripartum management, especially in complicated pregnancy. Active management of early postpartum newborns based on their risk profile with antibiotic prophylaxis is also important. Prevention of neonatal late onset sepsis and sepsis in older children is dependent on infection control practices that reduce hospital-acquired infection, such as frequent handwashing, contact precautions, invasive device care, sterilization of equipment, and epidemic control methods. Although good outcome studies of individual interventions are difficult because of power restrictions, intervention bundle studies indicate that combined implementation of infection control techniques reduces the risk of nosocomial infection.[108,109] One pediatric study by Costello and colleagues found that an intervention bundle in their pediatric cardiac ICU reduced the central-line–associated bloodstream infection rate from 7.8 infections per 1000 catheter-days to 2.3 infections per 1000 catheter-days.[110] Furthermore, Brilli and colleagues were the first to demonstrate a significant, sustained reduction in pediatric ventilator-associated pneumonia (VAP) rates following the use of an intervention bundle. After implementation of their VAP prevention bundle, VAP rates decreased from 7.8 cases per 1,000 ventilator days in fiscal year 2005 to 0.5 cases per 1,000 ventilator days in 2007.[111]

## EARLY GOAL-DIRECTED THERAPY

### Surviving Sepsis Campaign

After prevention, the cornerstone of treatment is early diagnosis and goal-directed therapeutic interventions. In 2002, the European Society of Intensive Care Medicine, International Sepsis Forum, and SCCM launched the surviving sepsis campaign (SSC) in an effort to improve sepsis outcomes by establishing evidence-based guidelines to standardize care. These internationally accepted guidelines (endorsed by 11 professional societies) were published in 2004 and updated in 2008.[7,8] Previous studies have found that the development and publication of guidelines are infrequently integrated into bedside practice in a timely fashion and may not change clinical behavior.[112–117] Recognizing that guideline implementation is a significant challenge, Levy and colleagues conducted the SSC performance improvement initiative at 165 sites internationally to assess the impact of guideline compliance on the hospital mortality of 15,022 patients. Compliance increased linearly over the 2-year study period and unadjusted hospital mortality decreased from 37% to 30.8% in the same period. The adjusted odds ratio for mortality improved the longer a site participated in the campaign. The authors commented that the campaign was associated with a sustained, continuous quality improvement in sepsis care and a reduction in reported hospital mortality rates, although these findings do not necessarily reflect cause and effect.[118] Although the SSC guidelines primarily pertain to the adult population, both the 2004 and 2008 publications address pediatric considerations in sepsis.

### American College of Critical Care Medicine/ Pediatric Advanced Life Support Guidelines

The same year the SSC was launched, the ACCM published their clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock.[9] Multiple

studies have reported that these guidelines are useful, effective, and improve outcomes in infants and children with sepsis.[10] For instance, Han and colleagues demonstrated that although resuscitation practice among community physicians was consistent with the ACCM/PALS guidelines in only 30% of patients, when practice was in agreement with guideline recommendations, a lower mortality was observed (8% vs. 38%). Notably, every hour that went by with persistent shock was associated with a greater than twofold increase in odds of mortality.[119] In a retrospective study of the 2003 Kids' Inpatient Database, including nearly 3 million pediatric discharge records, overall hospital mortality from severe sepsis was estimated to be 4.2%, 2.3% in previously healthy children, and 7.8% in children with comorbidities.[120] This lower mortality rate is distinct from the previous estimate of 10.3% by Watson and colleagues, using 1995 hospital discharge and population data. Survival from severe sepsis in 2003 may have improved, in part, as a result of guideline implementation.[14] In a randomized controlled trial, de Oliveira and colleagues reported that treatment adhering to the ACCM/PALS guidelines with central venous oxygen saturation ($Scvo_2$) goal-directed therapy resulted in reduced 28-day mortality for severe sepsis and septic shock (11.8% vs. 39.2%, $P = 0.002$).[121] These studies support the implementation of the early, goal-directed therapy recommended by the ACCM/PALS guidelines.

The ACCM/PALS guidelines were updated in 2007 with continued emphasis on (1) first-hour fluid resuscitation and inotrope drug therapy directed to restore threshold heart rate (HR), normal blood pressure (BP), and capillary refill less than or equal to 2 seconds and (2) subsequent intensive care unit hemodynamic support directed to achieving $Scvo_2$ greater than 70% and cardiac index (CI) of 3.3 to 6.0 L/minute/m$^2$. The changes recommended were few but include the following: (1) the use of peripheral inotropes (not vasopressors) until central access is attained is recommended, because mortality increased with delay in establishing central access and subsequent inotrope use. (2) Etomidate is not recommended for children with septic shock unless it is used in a randomized controlled trial; atropine and ketamine may be used for invasive procedures in children with septic shock, but no recommendation is made for sedative/analgesic use in newborns with septic shock. (3) Cardiac output (CO) may be measured not only with a pulmonary artery catheter, but also with Doppler echocardiography, a pulse index contour CO catheter, or a femoral artery thermodilution catheter. Therapy should be directed to maintain a CI 3.3 to 6.0 L/min/m$^2$ or superior vena cava (SVC) flow greater than 40 mL/min/kg in VLBW infants. (4) Several new potential rescue therapies, including enoximone, levosimendan, inhaled prostacyclin, and intravenous (IV) adenosine, should be further evaluated in the appropriate patient settings. (5) Fluid removal is recommended using diuretics, peritoneal dialysis, or continuous renal replacement therapy in adequately fluid resuscitated patients who cannot maintain fluid balance by native urine output, which can be identified by the development of new-onset hepatomegaly, rales, or greater or equal to 10% body-weight fluid overload.

## SURVIVING SEPSIS CAMPAIGN AND AMERICAN COLLEGE OF CRITICAL CARE MEDICINE/PEDIATRIC ADVANCED LIFE SUPPORT RECOMMENDATIONS AND MANAGEMENT ALGORITHMS

The recommendations of both the updated SSC and ACCM/PALS guidelines for the management of pediatric and neonatal sepsis are summarized in two algorithms: the time-sensitive, goal-directed stepwise management of hemodynamic support for infants and children (Fig. 10-4) and for newborns (Fig. 10-5) in septic shock. These recommendations and management algorithms are discussed in detail below.

### Initial Resuscitation

Once the diagnosis of sepsis is made, aggressive early intervention should ensue. The principal objective is to restore oxygen delivery to the tissues in view of the decreased peripheral oxygen utilization and the increased oxygen demand. This goal can be achieved by ensuring that the patient is adequately resuscitated. Evidence suggests that children who present with sepsis are often grossly underresuscitated.[119,122] Contrary to adult septic shock, low CO, not low systemic vascular resistance (SVR), is associated with mortality in pediatric septic shock.[123–132] Therefore children frequently respond well to aggressive volume resuscitation, with attainment of the therapeutic goal of a CI 3.3 to 6.0 L/minute/m$^2$.[124,132] Ceneviva and colleagues demonstrated that outcome can be significantly improved when aggressive fluid resuscitation is used for fluid-refractory, dopamine-resistant septic shock.[124,132] Additionally, they make an important point: Unlike adults, children with fluid-refractory shock are frequently hypodynamic and respond to inotrope and vasodilator therapy; because hemodynamic states are heterogeneous and change with time, an incorrect cardiovascular therapeutic regimen should be suspected in any child with persistent shock.[132]

***Airway, Breathing, and Circulation*** During the first 15 minutes of the initial resuscitation, the airway, breathing, and circulation, or ABCs, should be maintained or restored. The airway must first be secured followed by establishment of oxygenation and ventilation. Finally, assessment of perfusion and blood pressure should be performed. Hypoglycemia and hypocalcemia should also be corrected during these first 15 minutes.[10] Missed hypoglycemia can result in neurologic devastation. It is crucial to rapidly diagnose and promptly treat hypoglycemia with appropriate glucose infusion in the septic patient.[10] A 10% dextrose-containing isotonic intravenous (IV) solution can be run at maintenance rate and titrated as needed to provide age appropriate glucose delivery to prevent hypoglycemia. The target plasma glucose concentration is greater than or equal to 80 mg/dL. Hypocalcemia is a frequent, reversible cause of cardiac dysfunction.[133,134] Calcium replacement therapy should be aimed at normalizing ionized calcium concentration, because serum calcium is often bound to albumin and may appear falsely low in malnourished patients.[10]

***Crystalloid Versus Colloid*** Fluid infusion is best begun with boluses of 20 mL/kg isotonic saline or colloid, and initial volume resuscitation commonly requires 40 to 60 mL/kg but

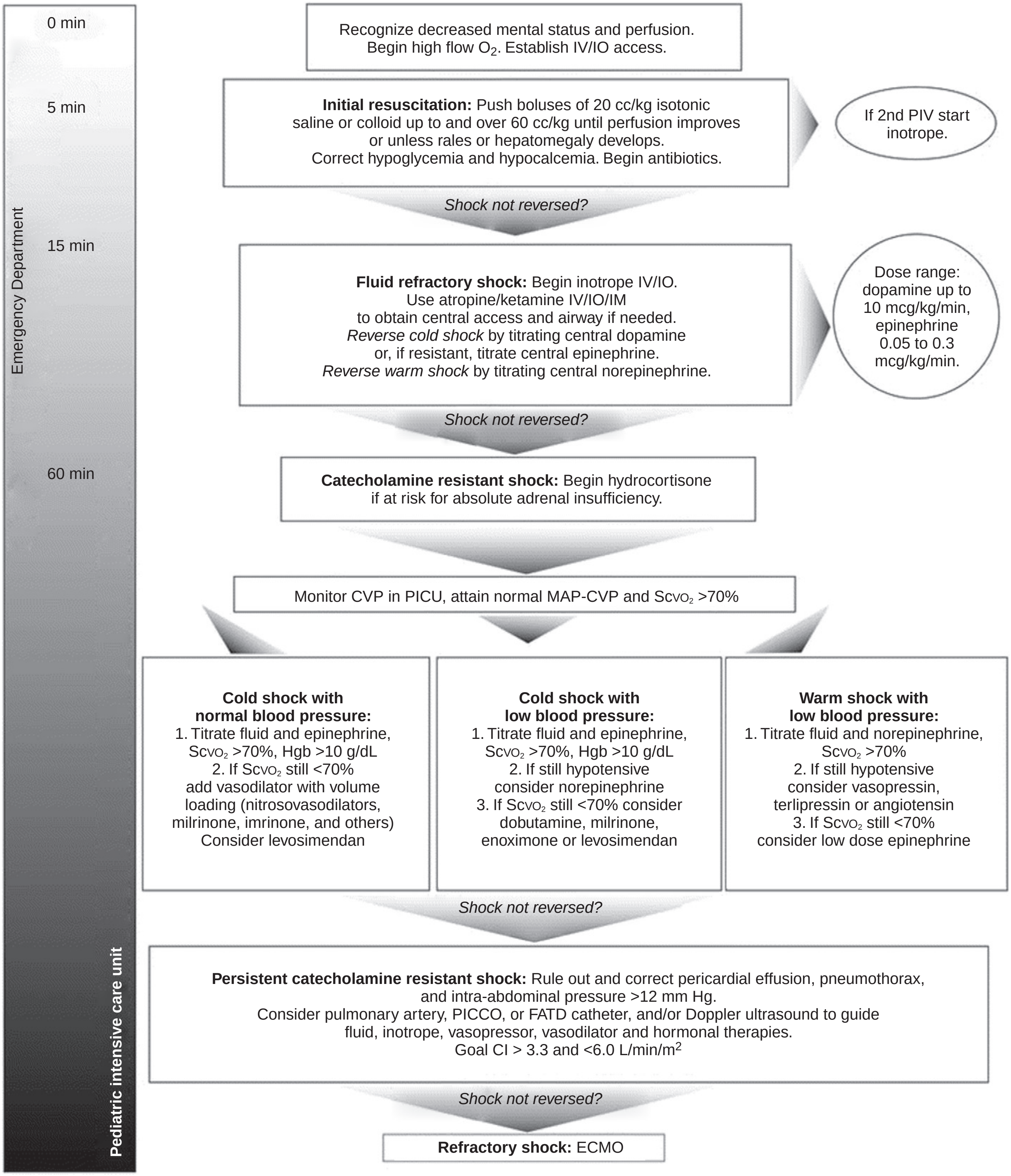


FIGURE 10-4 Algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in infants and children. CI, cardiac index; CVP, central venous pressure; FATD, femoral artery thermodilution; Hgb, hemoglobin; IM, intramuscular; IO, intraosseous; IV, intravenous; MAP, mean arterial pressure; PICCO, pulse index contour cardiac output; PICU, pediatric intensive care unit; PIV, peripheral intravenous (line); $Scvo_2$, central venous oxygen saturation. (Used with permission from Brierley J, Carcillo JA, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 2009;37:666-688.)

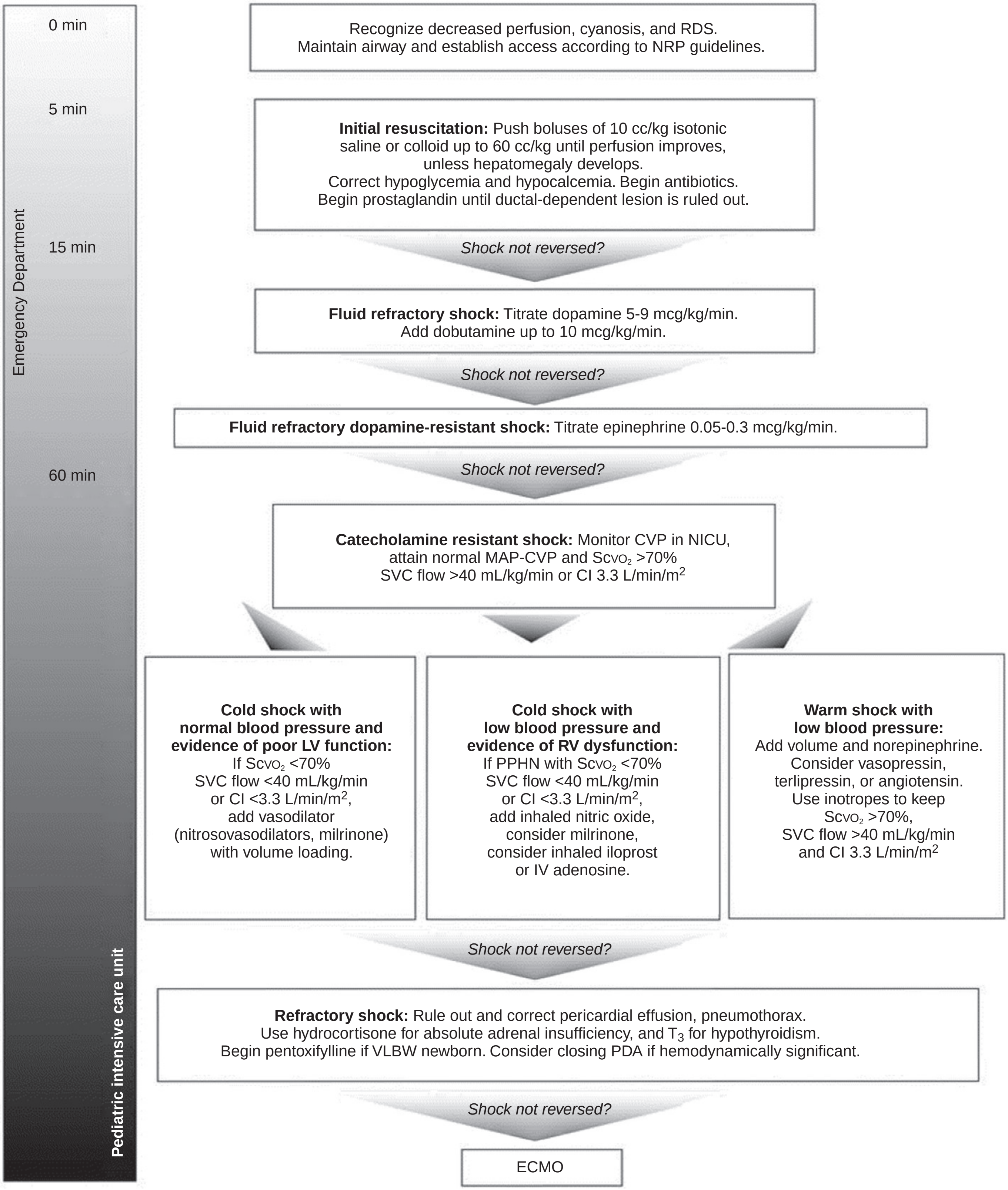


**FIGURE 10-5** Algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in newborns. CI, cardiac index; ECMO, extracorporeal membrane oxygenation; LV, left ventricular; MAP, mean arterial pressure; NICU, neonatal intensive care unit; NRP, Neonatal Resuscitation Program; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension; RDS, respiratory distress syndrome; RV, right ventricular; $ScvO_2$, central venous oxygen saturation; SVC, superior vena cava; $T_3$, triiodothyronine; VLBW, very low birth weight. (Used with permission from Brierley J, Carcillo JA, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 2009;37:666-688.)

can be as much as 200 mL/kg.[119,122,131,135–145] Of note, large volumes of fluid for resuscitation in children have not been shown to increase the incidence of acute respiratory distress syndrome[122,146] or cerebral edema.[122,147] The use of either crystalloid or colloid is acceptable, because three randomized controlled trials have compared the use of colloid versus crystalloid resuscitation in children with dengue shock and found no difference in mortality.[144,145,148]

***Blood Products*** The use of blood transfusion during resuscitation is less well defined. Two small pediatric observational studies have looked at the use of blood to restore intravascular volume; however, no recommendations were made by the investigators.[149,150] A recent randomized controlled trial by Lacroix and colleagues found that a lower transfusion threshold can decrease transfusion requirements without increasing adverse outcomes in stable critically ill children. They demonstrated similar outcomes in 637 pediatric patients managed with a transfusion threshold of hemoglobin (Hb) 7 g/dL versus 9.5 g/dL (38 vs. 39 patients developed new or progressive MODS, and 14 vs. 14 patients died within 28 days).[151] However, these results should be interpreted with caution. Their study population was stable critically ill children defined by mean arterial pressure (MAP) not less than 2 standard deviations (SD) below normal mean for age and no escalation of cardiovascular treatment for at least 2 hours prior to enrollment. Therefore these results may not be applicable to unstable children in septic shock with severe hypoxemia, hemodynamic instability, active blood loss, or cyanotic heart disease.[152] Children in septic shock may benefit from early blood transfusion to restore preload and achieve minimum $Scv_{O_2}$. Although the task force members for the updated ACCM/PALS guidelines report the use of conservative goals for blood transfusion in routine clinical illness (consistent with the randomized controlled trial by Lacroix and colleagues[151]), they suggest that transfusion to a goal Hb greater than 10 g/dL to achieve an $Scv_{O_2}$ greater than 70% is warranted in children with septic shock.[10] They base their recommendation on the previously mentioned report by de Oliveira and colleagues that the use of the 2002 ACCM/PALS guidelines and continuous $Scv_{O_2}$ monitoring improved mortality (11.8% vs. 39.2%) and that the treatment group received more blood transfusions directed toward improving $Scv_{O_2}$ to greater than 70% (45.1% vs. 15.7%).[121]

Fresh frozen plasma (FFP) may be used to correct abnormal prothrombin time and partial thromboplastin time, but should be infused, not pushed as a bolus, because it may produce acute hypotensive effects resulting from vasoactive kinins and high citrate concentration.[10] FFP has been proposed as an adjunctive therapy for septic neonates, especially premature neonates who are deficient in IgG, IgM, IgA, and complement. However, no benefit was found when FFP was administered prophylactically to infants with suspected infection.[153]

***Antibiotics*** Broad-spectrum antibiotics should be administered after appropriate cultures have been obtained during the initial resuscitation period.[8,10] The SSC guidelines recommend that at least two blood cultures be obtained before antibiotics are begun, with at least one drawn percutaneously and one drawn through each vascular access device unless it was inserted recently (<48 hours).[8,154] Cultures of other sites, preferably quantitative, such as urine, cerebrospinal fluid, respiratory secretions, wounds, or other body fluids should also be obtained before antibiotic therapy if not associated with a significant delay in antibiotic administration. Acquiring appropriate cultures prior to antibiotic administration is essential to confirm infection and the responsible pathogens, which will later allow de-escalation of antibiotic therapy after receipt of the susceptibility profile. However, it should not prevent prompt administration of antimicrobial therapy.[8] In the presence of septic shock, each delay of an hour in administering effective antibiotics is associated with a measurable increase in mortality of 7.6%.[155] The SSC guidelines recommend starting IV antibiotics as early as possible, certainly within the first hour of recognition of septic shock and severe sepsis.[8]

It is also imperative that the initial empirical antimicrobial therapy be broad enough to cover all likely pathogens and penetrate in adequate concentrations into the presumed source of sepsis. Failure to initiate appropriate antibiotics against the pathogen that is subsequently identified as the causative organism correlates with increased morbidity and mortality.[156–159] Equally important is the subsequent tailoring of the antibiotic regimen once the causative pathogen and its susceptibilities are identified. This helps to reduce the development of antimicrobial resistance and the likelihood of superinfection with resistant organisms such as *Candida* species, *Clostridium difficile*, or vancomycin-resistant *Enterococcus faecium*.[8]

Selection of appropriate antibiotic therapy is challenging because dynamic epidemiology, multidrug-resistant bacteria, and opportunistic infection make optimal broad-spectrum antimicrobial coverage a moving target. In term and preterm neonates, group B streptococcus and *Escherichia coli* account for most of the bacterial isolates.[160] Although the incidence of coagulase-negative *Staphylococcus aureus* and *Candida* species infections in neonates is rising,[161] historically, the most common organisms identified in adults and older children include *E. coli, Pseudomonas aeruginosa, Klebsiella*, and *Bacteroides* species. However, the epidemiology is constantly changing, now with an increase in gram-positive isolates.[2,162] It is diffcult to define the epidemiology of infective organisms because it changes with time, is unique to each hospital, and varies by patient age.

The RESOLVE trial, a randomized controlled trial that found a lack of proof of efficacy and an increased risk of bleeding of recombinant human activated protein C in pediatric sepsis, may have inadvertently provided some current data on the global bacteriology of pediatric sepsis.[162] The study enrolled 477 patients, aged between 38 weeks corrected gestational age and 17 years, from 104 study sites in 18 countries between November 2002 and April 2005. The most common site of infection was the lung in approximately 37%, followed by the blood in just less than one third of patients. Pure gram-positive infections were more common than pure gram-negative infections, consistent with the data of Martin and colleagues on the rising incidence of gram-positive infections beginning in 1987.[2] The most frequent isolates in lung infections were *Staphylococcus aureus,* followed by *Pseudomonas aeruginosa* and *Candida albicans*. *Neisseria meningitides* and coagulase-negative *Staphylococcus* were the most common cause of bacteremia.

The SSC guidelines recommend empiric antimicrobial therapy for not more than 3 to 5 days, with reduction to the most appropriate single therapy as soon as the susceptibility profile is known. The duration of antibiotics should

**TABLE 10-5**
**Threshold Heart Rates and Perfusion Pressure for Age Groups**

| *Age Group* | *HR (BPM)* | *Perfusion Pressure* (mm Hg)* |
|---|---|---|
| Term newborn | 120-180 | 55 |
| <1 year | 120-180 | 60 |
| <2 years | 120-160 | 65 |
| <7 years | 100-140 | 65 |
| <15 years | 90-140 | 65 |

Modified and used with permission from Brierley J, Carcillo JA, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 2009;37:666-688.
*Perfusion pressure is defined as [mean arterial pressure – central venous pressure] or [mean arterial pressure – intra-abdominal pressure].
BPM, beats per minute; HR, heart rate.

typically be 7 to 10 days unless the patient has an undrainable focus of infection, immunologic deficiency, or a slow clinical response.

***Source Control*** In addition to early broad-spectrum antimicrobial therapy, obtaining emergent source control immediately following initial resuscitation is crucial.[163] Source control includes drainage of abscesses, debridement of infected necrotic tissue, and removal of a potentially infected device after other vascular access has been established.[164] Of course, the selection of optimal source control methods must weigh the benefits and risks of the specific intervention, because it may cause further complications, such as bleeding, fistulas, and inadvertent organ injury. Ideally, source control should be accomplished with the least amount of physiologic disturbance possible.[165]

***Resuscitation Goals*** During resuscitation, several clinical signs and hemodynamic variables can be used to direct treatment to the goal of normal perfusion. Initial fluid resuscitation and inotrope drug therapy are directed toward maintaining threshold HR and perfusion pressure appropriate for age (Table 10-5) and capillary refill less than or equal to 2 seconds. Perfusion pressure is defined as MAP minus central venous pressure (CVP) or MAP minus intra-abdominal pressure (IAP). Subsequent intensive care unit hemodynamic support is directed to goals of $Scvo_2$ greater than 70% and CI 3.3 to 6.0 L/min/$m^2$.[10] Goal urine output is greater than 1 mL/kg/hour in children and greater than 2 mL/kg/hour in neonates. Of note, in VLBW newborns, a MAP of 30 mm Hg is considered the absolute minimum tolerable blood pressure, because a MAP less than 30 mm Hg is associated with poor neurologic outcome and survival in this population.[166] Because blood pressure does not necessarily reflect CO, it is recommended that normal CO and/or SVC flow, measured by Doppler echocardiography, be a primary goal in these extremely premature infants.[167–177]

***Fluid-Refractory Shock*** If shock is not reversed with fluid alone, the algorithm (see Figs. 10-4 and 10-5) proceeds to the treatment of fluid-refractory shock (see Table 10-6 for hemodynamic definitions of shock). Fluid boluses should be continued unless new onset hepatomegaly or rales develop, which suggest fluid overload. Diuretics, peritoneal dialysis, or

**TABLE 10-6**
**The American College of Critical Care Medicine Hemodynamic Definitions of Shock**

**Shock**
Decreased perfusion manifested by altered decreased mental status
Decreased urine output < 1 mL/kg/hr

**Cold Shock**
Shock plus the following:
Capillary refill > 2 seconds
Diminished peripheral pulses
Mottled cool extremities
Low CI with either high SVR and normal BP or low SVR and low BP

**Warm Shock**
Shock plus the following:
Flash capillary refill
Bounding peripheral pulses
High CI with low SVR and low BP

**Fluid-Refractory Shock**
Shock persists despite ≥ 60 mL/kg fluid resuscitation (when appropriate)

**Catecholamine-Resistant Shock**
Shock persists despite use of catecholamines
- Dopamine up to 10 μg/kg/min
- Epinephrine 0.05-0.3 μg/kg/min
- Norepinephrine

**Refractory Shock**
Shock persists despite goal-directed use of inotropic agents, vasopressors, vasodilators, and maintenance of metabolic (glucose and calcium) and hormonal (thyroid, hydrocortisone, insulin) homeostasis

Modified and used with permission from Brierley J, Carcillo JA, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 2009;37:666-688.
BP, blood pressure; CI, cardiac index; SVR, systemic vascular resistance.

continuous renal replacement therapy are indicated for patients who have been adequately fluid resuscitated but cannot maintain subsequent fluid balance by native urine output. No large randomized controlled trial has been performed comparing continuous renal replacement therapy with intermittent dialysis. A retrospective study of 113 critically ill children reported that patients with less fluid overload before continuous venovenous hemofiltration had better survival.[178] Therefore the SSC guidelines recommend instituting continuous venovenous hemofiltration before significant fluid overload occurs. The updated 2007 ACCM/PALS guidelines are consistent with the SSC guidelines and recommend intervention for 10% body-weight fluid overload. Fluid-refractory shock mandates the addition of an inotrope to fluid resuscitation through a second peripheral IV line or through intraosseous (IO) access until central access is obtained. In the case of peripheral infiltration with any catecholamine, its adverse effects may be antagonized by local subcutaneous infiltration of phentolamine (1 to 5 mg diluted in 5 mL of normal saline).[10]

First-line inotrope support in children includes: mid-dose dopamine (5 to 9 μg/kg/minute), dobutamine, or epinephrine (0.05 to 0.3 μg/kg/minute). Dobutamine is preferred when there is low CO with adequate or increased SVR.[132,179–192] This is in contrast to the first-line agent in adults,

norepinephrine, which is used in fluid-refractory vasodilated, and often hypotensive, septic shock.[193–196] Again, the majority of adults with fluid-refractory, dopamine-resistant shock have high CO and low SVR, while children with this condition predominantly have low CO.[10] Dobutamine or mid-dosage dopamine can be used to increase cardiac contractility in patients with impaired contractility on echocardiogram with normal blood pressure.[10] Dobutamine- or dopamine-refractory low CO shock may be reversed with epinephrine infusion.[132,197–200] Epinephrine is more commonly used in children than in adults.

The next step in fluid-refractory shock is the establishment of a definitive airway, if needed, and central vascular access for subsequent inotrope and vasopressor infusion. The work of breathing uses up to 40% of CO. Therefore intubation and mechanical ventilation can help to reverse shock in the pediatric population.[10] The updated 2007 ACCM/PALS guidelines recommend volume loading and peripheral or central, inotropic/vasoactive drug support before and during intubation if there is hypovolemia and cardiac dysfunction. Etomidate is not recommended. The sedative/induction regimen of choice is ketamine, with atropine pretreatment and benzodiazepine postintubation. A short-acting neuromuscular blocker can be used to facilitate intubation as long as airway patency can be maintained.[10] Once the airway and central vascular access are obtained, vasopressors should be initiated. Cold shock (see Table 10-6) is treated with central dopamine, or, if resistant, central epinephrine. Although dopamine remains the first-line vasopressor for fluid-refractory hypotensive shock in the setting of low SVR, it may not work as well in patients less than 6 months old. Dopamine causes vasoconstriction by releasing norepinephrine from sympathetic vesicles as well as acting directly on alpha-adrenergic receptors. Because infants less than 6 months old have immature sympathetic innervation, their releasable stores of norepinephrine are reduced. However, dopamine-resistant shock usually responds to high-dose epinephrine or norepinephrine.[132,201–203] Warm shock (see Table 10-6) is reversed by infusing central norepinephrine. Some committee members who updated the 2007 ACCM/PALS guidelines advocate the use of low-dose norepinephrine as a first-line agent for fluid-refractory hypotensive, hyperdynamic shock. Although the use of norepinephrine as a first-line agent for fluid-refractory shock is more common in adults than in children, there is no level I evidence to recommend one catecholamine versus another.[8] However, most guidelines recommend dopamine and norepinephrine as first-line agents, followed by epinephrine, phenylephrine, or vasopressin.[8]

### Stabilization and Continued Resuscitation

***Catecholamine-Resistant Shock*** If shock is not reversed with fluid and catecholamines, the algorithm (see Figs. 10-4 and 10-5) then proceeds to the treatment of catecholamine-resistant shock (see Table 10-6 for hemodynamic definitions of shock). Care is now directed within the pediatric intensive care unit (PICU) or neonatal intensive care unit (NICU). For those patients at risk for absolute adrenal insufficiency, steroids should be initiated at this time. Management of catecholamine-resistant shock then depends on whether a patient has cold or warm shock and what are his or her specific hemodynamics.

**Steroids** Unlike adults, children are at higher risk for absolute adrenal insufficiency.[10] If a child is at risk of absolute adrenal insufficiency or adrenal pituitary axis failure and remains in shock despite epinephrine or norepinephrine infusion, then hydrocortisone can be administered. High-risk pediatric patients include those with purpura fulminans and Waterhouse-Friederichsen syndrome, congenital adrenal hyperplasia, prior recent steroid use for chronic illness, and children with pituitary or adrenal abnormalities. Hydrocortisone should ideally be administered after obtaining a blood sample for subsequent determination of baseline cortisol concentration. Absolute adrenal insufficiency in children is defined by basal cortisol of less than 18 μg/dL and a peak adrenocorticotropic hormone (ACTH)-stimulated cortisol concentration of less than 18 μg/dL.[10]

There is a lack of data on steroids for septic shock in the pediatric literature. The few studies that have been published demonstrate variable results. In a randomized controlled trial of 98 children with dengue shock, hydrocortisone therapy resulted in improved mortality (18.75% vs. 44%).[204] A second randomized controlled trial of 97 pediatric patients with dengue shock syndrome reported that response to a single IV dose of hydrocortisone (50 mg/kg) as measured by mortality, duration of shock, and amount of replacement fluids required was virtually identical between the two groups.[205] It was concluded that hydrocortisone was of no value in the treatment of dengue shock syndrome. Of note, both studies were underpowered, did not measure cortisol levels in these children, but did match the two cohorts for age, sex, and illness severity. Thus it is difficult to conclude if steroids truly provide a survival benefit. In fact, some investigators have reported that steroid therapy may be harmful for children with sepsis. In a recent retrospective cohort study using the Pediatric Health Information System database, investigators reported that the use of any corticosteroids in children with severe sepsis was associated with increased mortality (30% vs. 18%, odds ratio 1.9, 95% confidence interval 1.7 to 2.2).[206] An important limitation of this study is the lack of illness severity data. Although steroids may have been given preferentially to more severely ill children with a presumed higher probability of mortality, steroid use was an independent predictor of mortality in multivariate analysis.[206] Taking these studies and several case series under consideration, the updated 2007 ACCM/PALS guidelines continue to recommend hydrocortisone only for pediatric patients with absolute adrenal insufficiency, as defined by peak cortisol concentration of less than 18 μg/dL following corticotropin stimulation, or adrenal-pituitary axis failure and catecholamine-resistant shock.[10]

The steroid dose continues to be controversial, but the current recommendation is between 2 mg/kg/day (stress dose) and 50 mg/kg/day (shock dose) of IV hydrocortisone as a continuous infusion or as intermittent boluses, with a plan to wean off as tolerated to minimize potential long-term toxicities such as developmental delay.[10] Although the SSC guidelines now recommend IV hydrocortisone for adult septic shock patients if BP is inadequate with appropriate fluid resuscitation and vasopressor therapy and without cortisol testing, whether this approach should be adopted in pediatric and/or neonatal sepsis without classical adrenal or hypophyseal pituitary axis insufficiency depends on the results of pending prospective randomized clinical trials.[8,10]

**Cold Versus Warm Shock** Management of catecholamine-resistant shock can be divided into three groups: (1) cold shock with low CI, high SVR, and normal BP; (2) cold shock with low CI, low SVR, and low BP; and (3) warm shock with high CI, low SVR, and low BP. The goals for the treatment of catecholamine-resistant shock are the same as mentioned previously: attainment of a normal perfusion pressure (MAP minus CVP) for age, as well as maintenance of $Scvo_2$ greater than 70% and CI 3.3 to 6.0 L/min/$m^2$.

Cold shock with low CI, high SVR, and normal BP is first treated with fluids and epinephrine. Normotensive pediatric patients with a low CO and high SVR require afterload reduction to improve blood flow by increasing ventricular emptying. If $Scvo_2$ remains less than 70%, a short-acting vasodilator should be initiated with volume loading. Sodium nitroprusside or nitroglycerin are first-line vasodilators in patients with epinephrine-resistant septic shock and normal BP, and it may reduce ventricular afterload and result in an improved CO.[207–212] If there is continued low CO, or toxicity develops (e.g., cyanide, isothiocyanate, or methemoglobin toxicity), then a type III phosphodiesterase inhibitor should be used next. Type III phosphodiesterase inhibitors are rarely used in adults with septic shock, because catecholamine-refractory low CO and high SVR is uncommon; however, this hemodynamic state is present in a majority of children with fluid-refractory, dopamine-resistant shock. Therefore use of type III phosphodiesterase inhibitors, such as milrinone and inamrinone (formerly amrinone), is an alternative approach to improve CO and lower SVR in the pediatric population.[213–219] Their mechanism of action is to increase intracellular cyclic adenosine monophosphate (cAMP) by blocking its hydrolysis. This ultimately has the same effect as beta-adrenergic agonists, because they increase intracellular cAMP by stimulating its production. One limitation of type III phosphodiesterase inhibitors is their long half-lives, requiring loading doses with fluid boluses to reach steady state as well as the possibility of slowly reversible toxicities, such as hypotension, tachyarrhythmias, or both, particularly in the setting of abnormal renal (milrinone clearance) or liver (inamrinone clearance) function.[8]

Other vasodilators that have been used in children include prostacyclin, pentoxifylline, dopexamine, and fenoldopam.[220–225] Pentoxifylline, in particular, has been shown to decrease production of TNF and increase survival in murine endotoxin shock,[226] and a randomized controlled trial reported improved outcome with the use of daily 6-hour pentoxifylline infusions in very premature infants with sepsis.[227,228] A Cochrane analysis concurs that this vasodilator and anti-inflammatory agent is a promising therapy deserving evaluation in a multicenter trial.[229] Finally, levosimendan should be considered as a rescue therapy for recalcitrant low CO catecholamine-resistant shock. Levosimendan increases calcium/actin/tropomyosin complex binding sensitivity and has some type III phosphodiesterase inhibitor and adenosine triphosphate-sensitive potassium channel activity. This drug therefore allows improved contractility at a fundamental level, because one of the pathogenic mechanisms of endotoxin-induced heart dysfunction is desensitization of calcium/actin/tropomyosin complex binding.[230–235]

Cold shock with low CI, low SVR, and low BP is also first treated with fluids and epinephrine, but if hypotension persists, norepinephrine should be considered to increase SVR. If $Scvo_2$ is still less than 70%, dobutamine or milrinone should be considered to increase $Scvo_2$ by improving cardiac contractility. Finally, enoximone or levosimendan should be considered as well. Enoximone is a type III phosphodiesterase inhibitor with 10 times more $\beta_1$ than $\beta_2$ cAMP hydrolysis inhibition. Therefore it can increase cardiac contractility with a lower risk of undesired hypotension than milrinone or inamrinone.[236–238] Levosimendan, in the setting of cold shock with low CI, low SVR, and low BP, when added to norepinephrine, will improve CO and $Scvo_2$ as well.

Warm shock with high CI, low SVR, and low BP is treated first with fluids and norepinephrine. Again, some committee members for the updated 2007 ACCM/PALS guidelines advocate the use of low-dose norepinephrine as a first-line agent for fluid-refractory hypotensive (low SVR) hyperdynamic (high CO) shock.[10] If the patient remains hypotensive, the use of vasopressin, terlipressin, or angiotensin can help to restore BP. In patients with vasodilatory septic shock and hyporesponsiveness to catecholamines, vasopressin has been shown to increase MAP, SVR, and urine output.[239–249] Terlipressin, a long-acting form of vasopressin, has demonstrated similar effects with reversal of vasodilated shock as well.[247,250] Angiotensin has been reported to increase BP in patients refractory to norepinephrine, although its clinical role remains to be defined.[251] If $Scvo_2$ remains less than 70%, low-dose epinephrine should be considered to improve cardiac performance as the above potent vasoconstrictors can reduce CO.

***Persistent Catecholamine-Resistant Shock*** If shock is not reversed with fluid, catecholamines, steroids, and other adjunctive therapies the algorithm (see Figs. 10-4 and 10-5) then proceeds to the treatment of persistent catecholamine-resistant shock (see Table 10-6 for hemodynamic definitions of shock). It is important at this point to rule out and correct several potential occult conditions: (1) pericardial effusion requiring pericardiocentesis, (2) pneumothorax requiring thoracentesis or tube thoracostomy, (3) hypothyroidism requiring thyroid hormone replacement therapy, (4) ongoing blood loss requiring hemostasis and/or transfusion, (5) increased intra-abdominal pressure requiring diuretics and/or peritoneal drainage for IAP greater than 12 mm Hg and surgical decompression for greater than 30 mm Hg, (6) necrotic tissue requiring debridement, or (7) excessive immunosuppression or immune compromise mandating a wean of immunosuppressants and restoration of immune function. In addition, therapy can be guided to the goal of CI 3.3 to 6.0 L/min/$m^2$ by the use of pulmonary artery, pulse contour cardiac output, or femoral arterial thermodilution catheters and/or Doppler ultrasonography. Once these feasibly reversible causes are addressed and monitoring has been optimized, if shock persists, the algorithm (see Figs. 10-4 and 10-5) advances to refractory shock and extracorporeal membrane oxygenation (ECMO) as an alternative to consider.[10]

***Refractory Shock*** Extracorporeal membrane oxygenation is a viable therapy for refractory pediatric and neonatal septic shock, although its long-term impact is not known.[8,10] Most centers use refractory shock or $Pao_2$ less than 40 mm Hg after maximal therapy as an indication for ECMO support.[10] Persistent hypotension and/or shock with venovenous ECMO should be treated with dopamine/dobutamine or epinephrine.

Inotrope requirements will usually diminish after venoarterial ECMO. Neonates (80%) and children (50%) have similar survival whether or not the indication for ECMO is refractory respiratory failure or refractory shock from sepsis.[10] Although ECMO survival is similar in pediatric patients with and without sepsis, thrombotic complications can be more common in sepsis.[10]

One U.S. study analyzed 655 patients from a national registry to examine the influence of sepsis on survival from ECMO.[252] The study found that systemic sepsis does not independently influence survival in pediatric ECMO and concluded that although neurologic complications occur more frequently in septic patients on ECMO, this therapy should not be withheld solely because of sepsis. Another study examined the use of ECMO in 12 patients from the United Kingdom and Australia with refractory cardiorespiratory failure resulting from meningococcal disease.[253] The pediatric risk of mortality score ranged from 13 to 40 (median 29, median predicted risk of mortality 72%), and overall, 8 of the 12 patients survived, with six leading functionally normal lives at a median of 1 year (4 months to 4 years) of follow-up. There is a role for ECMO therapy in pediatric and neonatal patients with refractory septic shock, although it remains to be better defined.

## OTHER CONSIDERATIONS

### Intravenous Immunoglobulin

A promising adjuvant therapy in the treatment of sepsis is the administration of polyclonal intravenous immunoglobulin (IV Ig). A recent randomized controlled trial of polyclonal IV Ig in 100 pediatric sepsis syndrome patients aged 1 to 24 months demonstrated a significant reduction in mortality, LOS, and progression to complications such as disseminated intravascular coagulation.[254] The SSC guidelines therefore recommend consideration of IV Ig in pediatric severe sepsis, although more studies may be needed to validate this therapy.

### Recombinant Human Activated Protein C

Recombinant human activated protein C (rhAPC), also known at drotrecogin alfa (activated), or Xigris, is indicated for the reduction of mortality in adult patients with severe sepsis who have a high risk of death (Acute Physiology and Chronic Health Evaluation, or APACHE, II score $\geq 25$) or MODS and no contraindications. rhAPC is contraindicated in clinical situations where bleeding could lead to significant morbidity or death, such as active internal bleeding, recent (<3 months) hemorrhagic stroke, recent (<2 months) intracranial/intraspinal surgery or severe head trauma, trauma with an increased risk of life-threatening bleeding, presence of an epidural catheter, or intracranial neoplasm or mass lesion.[8] The evidence that rhAPC reduces mortality in adult patients with a high risk of death and does not benefit patients at a lower risk of death, but rather increases risk of serious bleeding, is based on the PROWESS[6] (stopped early for efficacy) and ADDRESS[255] (stopped early for futility) randomized clinical trials. An open-label study (EVAO) in children with severe sepsis demonstrated that pharmacokinetics and pharmacodynamics of rhAPC are similar to that in adults.[256] Before EVAO was completed, a global open-label trial in adults and children with severe sepsis (ENHANCE) was initiated to gather additional data for mortality and safety.[257] In the ENHANCE study, the 28-day mortality rate for children was 13.4%, and 5.9% had serious bleeding events during rhAPC infusion, such as central nervous system (CNS) bleed in 2.7% of children.[258] This was followed by the only randomized placebo-controlled trial of rhAPC in children, the RESOLVE (*RE*searching severe *S*epsis and *O*rgan dysfunction in children: a g*L*obal perspecti*VE*) trial, which was stopped early for futility.[162] Because of the low mortality rate of children with sepsis, the primary end point for efficacy in the RESOLVE trial was a reduction in the **c**omposite **T**ime to **C**omplete **O**rgan **F**ailure **R**esolution (CTCOFR) score. The RESOLVE trial showed no significant difference between groups in CTCOFR score or in 28-day mortality. This is quite different from the adult data in the PROWESS trial, which demonstrated a statistically significant reduction in 28-day mortality. It is also important to point out that although there was no difference in the incidence of serious bleeding events between the RESOLVE study groups, more rhAPC patients had CNS bleeding than placebo patients. Furthermore, four of the five patients in the rhAPC group with a CNS bleed were younger than 60 days and weighed less than 4 kg. The SSC guidelines therefore recommend against the use of rhAPC in children because of lack of proof of efficacy and increased risk of bleeding.[8]

## NEONATAL SEPTIC SHOCK

Although the algorithms for time-sensitive, goal-directed stepwise management of hemodynamic support are similar for pediatric patients (see Fig. 10-4) and newborns (see Fig. 10-5) with septic shock, there are several important differences between children and neonates that the clinician should consider.

During the initial resuscitation period, it is crucial to distinguish septic shock from cardiogenic shock resulting from closure of a patent ductus arteriosus in newborns with ductal-dependent complex congenital heart disease. These patients should be started on prostaglandin infusion until an echocardiogram is performed to rule out complex congenital heart disease.

Neonatal septic shock is also complicated by the physiologic transition from fetal to neonatal circulation. In utero, 85% of fetal circulation bypasses the lungs via the ductus arteriosus and foramen ovale. Suprasystemic pulmonary vascular resistance maintains this flow pattern in the antenatal period. However, at birth, inhalation of oxygen results in reduced pulmonary vascular resistance, which allows blood flow through the pulmonary circulation. Closure of the ductus arteriosus and foramen ovale complete this transition.

During sepsis of the newborn, both acidosis and hypoxia can increase pulmonary vascular resistance and arterial pressures, leading to persistent pulmonary hypertension (PPHN). The patency of the ductus arteriosus is maintained, ultimately resulting in persistent fetal circulation. Right ventricular work is increased and can lead to right ventricular failure with right to left shunting at the atrial/ductal levels, manifested by tricuspid regurgitation, hepatomegaly, and cyanosis. Therefore treatment of PPHN requires reduction of pulmonary artery pressures aimed at reversing right ventricular failure. After fluid resuscitation and initiation of catecholamines, if right ventricular dysfunction is present, treatment of PPHN should begin. The patient should be hyperoxygenated

with 100% oxygen, and inhaled NO should be administered as the first treatment when available. Historically, metabolic alkalization (up to pH 7.50) with $NaHCO_3$ or tromethamine was instituted until inhaled NO was available, but this is no longer a common practice. Inhaled NO's greatest effect is typically seen at 20 ppm. Refractory PPHN may be treated with inhaled prostacyclin and/or IV adenosine with variable response.[10]

Key differences in fluid resuscitation between children and neonates include the type of fluid used as well as the rate of infusion. Although crystalloid or colloid can be used to resuscitate children with septic shock and the use of blood transfusion is suggested for Hb less than 10 g/dL to achieve $Scvo_2$ greater than 70% because this is associated with increased survival, the recommendation for neonates is crystalloid for Hb greater than 12 g/dL and packed red blood cells for Hb less than 12 g/dL. Ideally, all packed red blood cells should come from one donor, to limit transfusion reaction risks. Indications for diuretics and complete renal replacement therapy are the same. Furthermore, standard volume resuscitation and vasopressor therapy practices for preterm infants in septic shock use a more cautious, graded approach. This is likely because of anecdotal reports of hemorrhage after rapid shifts in blood pressure in preterm infants at risk for intraventricular hemorrhage (<30 weeks' gestation). Finally, rapid fluid administration can further increase left to right shunting, with ensuing pulmonary edema in the case of VLBW infants who are unable to close their ductus arteriosus because of immature muscle constriction. The majority of these infants are treated medically with indomethacin and the minority with surgical ligation.

Other considerations in neonates include external warming, because their mechanisms of thermogenesis are immature. Also, newborns are at increased risk of hypoglycemia because of reduced glycogen stores and muscle mass for gluconeogenesis; therefore appropriate dextrose infusion should be initiated to maintain serum glucose concentration with frequent monitoring.[10]

Management of pediatric and neonatal sepsis is challenging. It is clear that early diagnosis and time-sensitive, goal-directed therapies are associated with decreased morbidity and mortality in children with sepsis. Emerging novel therapies and improved understanding of existing treatments through both experimental studies and clinical trials will continue to improve current management in an effort to maximize patient survival.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 11

# Surgical Implications of Hematologic Disease

Kelly Walkovich and Raymond J. Hutchinson

Hematologists and pediatric surgeons frequently interact with each other in the comprehensive management of pediatric surgical patients. The evaluation and management of anemia, thrombocytopenia, platelet dysfunction, clotting factor deficiencies, and thrombosis are the common meeting grounds; in addition, maintenance of indwelling central venous lines and the judicious use of transfusion therapy often raise questions of interest to both groups of physicians. The most important considerations in each of these areas are discussed here.

## Anemia

An inadequate mass of red blood cells (RBCs), resulting in insufficient delivery of oxygen to the tissues, can occur for three major pathophysiologic reasons:[1] inadequate production or maturation of RBCs in the bone marrow (e.g., Diamond-Blackfan anemia, transient erythroblastopenia of childhood), loss of red cell mass as a result of bleeding (e.g., gastrointestinal blood loss from Meckel diverticulum) or splenic sequestration (as seen in sickle cell diseases), or (3) RBC destruction (hemolytic disorders).[1] Clearly, a thorough history and physical examination provide invaluable data when planning the workup for a pale child or for the evaluation of a low hematocrit or hemoglobin concentration noted on a complete blood cell count (CBC). In pediatric medicine and surgery, individual and family histories are particularly relevant because of the frequency of congenital and genetic anemias.

In taking the medical history, items of importance include evidence of intrauterine bleeding in the mother or neonatal hemolysis (e.g., from placental abruption or erythroblastosis fetalis, respectively), history of neonatal jaundice or neonatal bleeding, the rate of development of pallor, the presence of scleral icterus, and a history of rectal bleeding. The family history is relevant for identifying other family members with history of anemia or treatment for anemia, splenectomy, or cholecystectomy. A complete physical examination includes assessment for jaundice and degree of pallor, documentation of the size of the spleen and lymph nodes, evaluation for signs of bleeding (including testing the stool for blood), and assessment of cardiovascular stability.

The CBC yields much information regarding the causes of anemia. It provides information regarding two lineages in addition to the red cell lineage: the white cell (myeloid) and the platelet (megakaryocytic). Involvement of more than one hematopoietic lineage often indicates a production problem occurring in the bone marrow; hence, bone marrow aspiration and biopsy are typically done early in the workup of children with multiple cytopenias. The mean corpuscular volume (MCV) allows the classification of anemias into microcytic, normocytic, and macrocytic categories; this can be a useful diagnostic clue and can facilitate a directed workup. Similarly, a mean corpuscular hemoglobin concentration that exceeds 36 is highly suggestive of the presence of a large number of spherocytes, as seen in hereditary spherocytosis.[2] The RBC distribution width index provides information about the size distribution of circulating red cells, allowing the physician to categorize the red cell population as homogeneously small or large or as heterogeneous. This information, when coupled with the MCV, allows a more cost-effective workup. Figure 11-1 provides an algorithm for the workup of a patient with anemia.

### NONHEMOLYTIC ANEMIAS

Underproduction of RBCs because of marrow failure or as a result of deficiency of an essential nutrient, such as iron, is a common mechanism that can lead to severe degrees of anemia. Such severe anemia may present a dilemma when evaluating a patient for a surgical procedure.

#### Marrow Failure

One major clue to the existence of bone marrow failure is the presence of multilineage cytopenias. The concomitant existence of anemia with neutropenia or thrombocytopenia suggests (1) the existence of primary marrow failure resulting from constitutional aplastic anemia (Fanconi anemia) or acquired aplastic anemia or (2) failure of the bone marrow as a result of infiltrative disease, which occurs in cases of acute

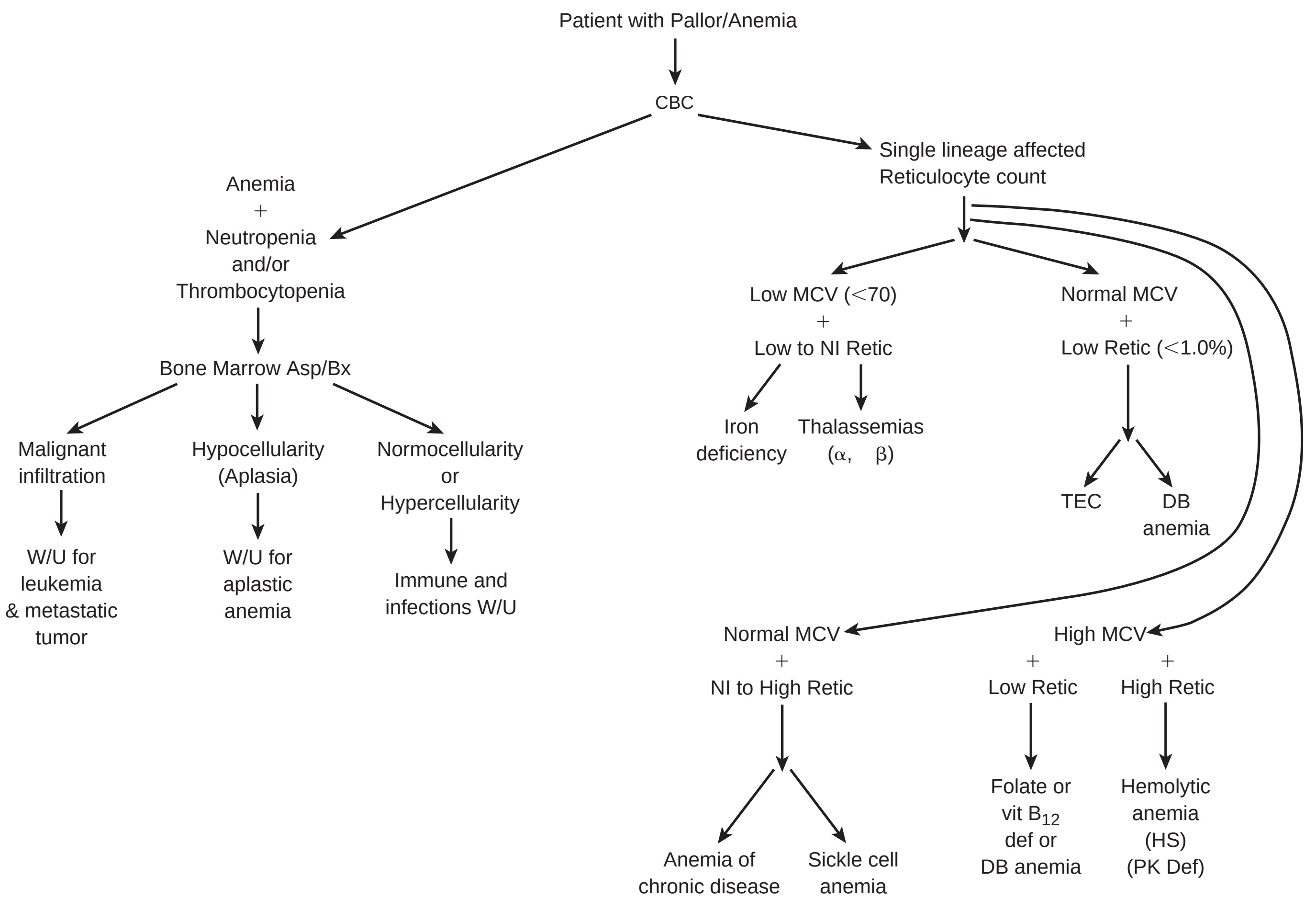


**FIGURE 11-1** Algorithm for the workup of a patient with anemia. Asp/Bx, aspirate/biopsy; CBC, complete blood count; DB, Diamond-Blackfan; Def, deficiency; HS, hereditary spherocytosis, MCV, mean corpuscular volume; Nl, normal; PK def, pyruvate kinase deficiency; Retic, reticulocyte; TEC, transient erythroblastopenia of childhood; W/U, workup.

leukemia or metastatic neuroblastoma. Bone marrow aspiration and biopsy can often quickly resolve uncertainty regarding the diagnosis.

Fanconi anemia is transmitted in an autosomal recessive pattern but affects boys slightly more often than girls (1.2:1).[3] The hematologic presentation is variable, with a single cell lineage often affected early, followed by evolution to multilineage aplastic anemia. The age at presentation ranges from birth to 55 years (median, 6.5 years).[3] Patients affected by Fanconi anemia often exhibit congenital malformations (e.g., cutaneous hyperpigmentation, anomalies of the thumb and radial side of the forearm, microsomy, mental retardation).[4] They are predisposed to malignancies (e.g., leukemia and liver tumors) as a consequence of the associated chromosomal breakage.[5–7] Additional genetic cytopenic syndromes that can progress to multilineage involvement, and thus bear consideration when discussing aplasia, are congenital (CAMT) amegakaryocytic thrombocytopenia, Shwachman-Diamond neutropenia, and dyskeratosis congenita.[3]

Acquired aplastic anemia is idiopathic in at least 50% of cases; commonly observed associations include occurrence after hepatitis B or after the use of drugs such as chloramphenicol, sulfonamides, phenothiazines, and anticonvulsants.[8] Although administration of anabolic steroids (oxymetholone) can lead to improvement in the blood counts of patients with Fanconi anemia,[3] their use is now largely restricted to patients who are not candidates for stem cell transplantation because of concern regarding a negative impact on the outcome of transplantation.[9] Multiagent immunosuppressive therapy with cyclosporine and intravenous antithymocyte globulin, with or without corticosteroids, produces durable responses in approximately 75% of patients with severe acquired aplastic anemia.[10,11] For children with Fanconi anemia or severe acquired aplastic anemia, allogeneic hematopoietic stem cell transplantation offers a potentially curative treatment option.[9,11] Granulocyte colony-stimulating factor (G-CSF) is used in neutropenic patients with Fanconi anemia with benefit,[3] whereas its use in patients with severe acquired aplastic anemia is of uncertain benefit.[12]

Anemia associated with single-lineage erythroid hypoplasia is characterized by normal white blood cell and platelet counts, a low reticulocyte count (<1.0%), and the absence of erythroid precursors on marrow aspirate smears. Two conditions should come to mind when confronted with this clinical picture: Diamond-Blackfan anemia (congenital hypoplastic anemia) and transient erythroblastopenia of childhood (TEC). The former condition is characterized by elements of persistent fetal erythropoiesis, such as a high fetal hemoglobin percentage on hemoglobin electrophoresis, increased erythrocyte adenosine deaminase activity, retained expression of fetal red cell

antigen i, and high MCV of red cells.[13] Patients with TEC usually do not exhibit these features.[14] TEC resolves within 2 to 8 weeks, which is consistent with suppression due to a presumed viral cause.[15–17] Corticosteroids are the mainstay of therapy for Diamond-Blackfan anemia; prednisone 2 mg/kg per day is used initially, followed by tapering to alternate-day dosing or less frequently as the patient's condition allows.[13] Patients with Diamond-Blackfan anemia occasionally become transfusion dependent; in rare cases, patients require allogeneic bone marrow transplantation.[18–20] Although RBC transfusions are occasionally required for patients with TEC, most do not require therapy because recovery is sufficiently rapid.

### Blood Loss

Anemia is an important manifestation of acute and chronic hemorrhage. Significant acute hemorrhage is usually accompanied by signs of cardiovascular stress, consisting of peripheral vasoconstriction, hypotension, tachycardia, and oliguria.[21] If the patient loses more than 30% of the total blood volume, hypovolemic shock often occurs. After acute hemorrhage, it may take several hours before the full effect on the hemoglobin and hematocrit levels can be assessed; a precipitous drop in these values within 1 to 2 hours of the hemorrhage usually indicates blood loss in excess of 20% of the total volume.[22]

Conversely, chronic blood loss resulting from low-grade, slow, or intermittent bleeding is usually not associated with the symptoms of cardiovascular stress. Patients with chronic anemia often exhibit a compensated picture that may not require intervention with transfusion. When transfusion is unavoidable, a judicious approach should be taken because multiple transfusions carry notable risks, including transmission of viral infection[23] and transfusion hemosiderosis.[24]

Sequestration of blood in the spleen is another mechanism of significant blood loss that can lead to anemia.[25] Splenomegaly caused by hemolytic anemias, portal vascular anomalies, or primary pathologic conditions of the liver can lead to sequestration of blood in dilated splenic sinusoids.

The therapeutic approach to the management of patients with anemia resulting from blood loss varies according to the rate at which the anemia developed. To restore blood volume and oxygen carrying capacity to a patient who has lost a large amount of blood, it may be necessary to transfuse a unit of blood quickly. This can usually be accomplished safely, even in young children, over a 15- to 30-minute period, as long as the volume and rate of delivery are adjusted to the child's size and estimated blood loss. Excessive volume expansion can usually be prevented through careful monitoring of the heart rate, arterial blood pressure, venous pressure, and core and peripheral temperatures.[21] Patients with chronic anemia that has gradually reached a level that compromises cardiopulmonary status should receive transfusions of RBCs in amounts that are appropriate to restore cardiopulmonary function to a compensated level. Overtransfusion should be avoided; this is particularly relevant for children with chronic anemia requiring repeated transfusions. For such children, frequent transfusions may result in transfusion hemosiderosis; the greater the number of RBC units transfused, the greater the iron load transfused. After the serum ferritin level exceeds 1000 μg/L, transferrin becomes saturated, and patients are at risk for cardiac and hepatic iron deposition[24]; these patients should be considered for chelation therapy with intravenous or subcutaneous deferoxamine[24] or oral deferasirox (Exjade).[26] Patients in whom moderate anemia develops from blood loss or aggressive hemolysis should undergo slow transfusion back to the baseline level in aliquots of 5 to 10 mL/kg over 2 hours each, with time allowed between aliquots for reequilibration and reassessment of the patient's cardiac status.

### Nutritional Anemias

Iron-deficiency anemia results from inadequate intake of dietary iron, poor absorption, misutilization as a result of defective transport, loss of iron through bleeding, or sequestration of iron in an atypical location (e.g., the lungs in cases of pulmonary hemosiderosis). The age of the patient influences whether he or she will become iron deficient. In infants, who experience rapid expansion of blood volume during growth, 30% of the iron required for hemoglobin production must come from the diet. In adult men, only 5% is derived from the diet,[27] and the remainder is generated by RBC degradation.

The American Academy of Pediatrics[28] recommends dietary iron intake of 1.0 mg/kg per day to a maximum of 15 mg/day for full-term infants, starting by age 3 months. Preterm infants weighing between 1500 and 2500 g require 2 mg/kg per day from dietary and supplemental sources to a maximum of 15 mg/day, starting no later than 2 months of age. Recommendations for very-low-birth-weight infants are even higher: 4 mg/kg per day for those weighing less than 1500 g at birth. In older children and adults, dietary iron requirements vary, depending on growth and gender:

4 to 10 years: 10 mg/day
11 to 16 years: 18 mg/day
Adult men: 10 mg/day
Adult women: 18 mg/day

The peak age range for the development of nutritional iron deficiency is 6 months to 2 years. During this period, children make the transition from being dependent on breast milk or iron-fortified formula to a mixed diet of milk (often cow's milk) and solid foods. Depending on which foods constitute most of the child's diet, dietary iron may be adequate or inadequate. Children who depend heavily on cow's milk, at the expense of solid foods, are especially prone to iron-deficiency anemia. The typical presentation for such children is the gradual development of pallor, a hemoglobin concentration of 3.0 to 6.0 g/dL, and an MCV of 45 to 60 fL. Older individuals are much less likely to experience iron-deficiency anemia, especially from an inadequate diet, unless they participate in fad diets.

Consumption of unprocessed cow's milk by infants, intestinal parasitic infestations, and preexistent iron deficiency may lead to intestinal blood loss. The use of aspirin or aspirin-containing medications may increase intestinal blood loss sufficiently to cause anemia. Other anatomic sources of blood loss and iron deficiency include the following: (1) in the perinatal period–fetal-maternal hemorrhage, placental injury at delivery, and twin-to-twin transfusion through placental communications; (2) in older children—Meckel diverticulum, intestinal duplication, hemorrhagic telangiectasia, and, rarely, bleeding ulcers or gastroesophageal reflux.

The diagnosis of iron deficiency is made by confirming the existence of microcytic, hypochromic anemia in the context of a clinical situation that suggests a possible cause of the deficiency. The low MCV and mean corpuscular hemoglobin concentration should be corroborated with a careful review

of the blood smear. Serum iron studies that measure the serum iron level, total iron-binding capacity, and serum ferritin level finalize the diagnosis. The typical pattern consists of a low serum iron level, high total iron-binding capacity, and low serum ferritin level, consistent with low total-body iron stores. Finally a therapeutic trial of iron should result in an increasing reticulocyte count within 1 week, and the hemoglobin and hematocrit levels should rise soon thereafter.

Treatment consists of the administration of oral iron (ferrous sulfate) at a dose of 6 mg/kg per day of elemental iron. Because ferrous sulfate is only 20% elemental iron, this fact must be taken into consideration when calculating the dose (e.g., a 325-mg tablet of ferrous sulfate contains 65 mg of elemental iron). The iron must be continued for 3 to 4 months. Correction of the anemia, correction of microcytosis, and elevation of the free erythrocyte protoporphyrin level usually occur within that period.[29]

## HEMOLYTIC ANEMIAS

The sickle cell diseases, β-thalassemia, hereditary spherocytosis, and glucose-6-phosphate dehydrogenase and pyruvate kinase deficiencies all have potential ramifications for pediatric surgeons.

### Sickle Cell Diseases

The sickle hemoglobinopathies present early in life with episodes of painful crisis, acute chest syndrome, bacteremia, and splenic sequestration.[30] In a report of the Cooperative Study of Sickle Cell Disease, patients with homozygous sickle cell anemia and those with sickle cell–hemoglobin C disease demonstrated significant incidence rates of painful crisis, acute chest syndrome, and bacteremia; however, all 20 deaths in a cohort of 694 infants followed for 10 years occurred among the patients with homozygous sickle cell anemia.[30] It was also clear from this study that most hand-foot syndromes occurred among the homozygous sickle cell anemia patients in the first 3 years of life.

Several sequelae of the sickle cell disorders are of interest to pediatric surgeons. Painful vasoocclusive crises occasionally masquerade as acute abdominal events that typically require surgical intervention (e.g., appendicitis). Because painful crises are usually accompanied by an elevated leukocyte count, this parameter is not useful in distinguishing appendicitis from a painful crisis. Serial examinations and collaborative evaluation with a hematologist who is skilled in the evaluation of patients with sickle cell diseases reduce the frequency of unnecessary and potentially harmful surgical interventions during painful crises.

Acute chest syndrome can represent a life-threatening situation. Correction of this process requires rapid transfusion to raise the oxygen carrying capacity of the blood and lower the percentage of hemoglobin S to reverse the sickling process; often this is accomplished by exchange transfusion.

For patients with repeated episodes of splenic sequestration, the surgeon may be called on to remove the spleen to reduce the risk of subsequent sequestration, which is characterized by rapid drops in hemoglobin concentration, hematocrit value, and platelet count. At times, progressive sequestration may lead to hypovolemic shock and have life-threatening implications. Historically, splenectomy was justified only after two episodes of sequestration because of concern for splenectomy in young patients (younger than 4 years).[25] However, recent work suggests that splenectomy can safely be performed after one major episode of sequestration.[31] Similarly, the development of symptomatic cholelithiasis usually dictates that cholecystectomy be performed.[32] Patients with sickle cell anemia have a high incidence of perioperative morbidity.[33] Complications that occur at an increased rate in patients with sickle cell disease undergoing surgery include painful crises, acute chest syndromes, and transfusion reactions due to erythrocyte alloimmunization.

Another consideration for pediatric surgeons managing patients with sickle cell diseases is related to the percentage of sickle hemoglobin and the safety of general anesthesia. In the past, RBC transfusion to lower the percentage of sickle hemoglobin to less than 30% was the preferred approach. However, data suggest that patients do just as well with a more conservative approach that aims at achieving a preoperative hemoglobin level of 10 g/dL but does not attempt to lower the hemoglobin S level below an arbitrary cutoff point.[34] Care should be taken to ensure adequate blood oxygenation during a surgical procedure, but excessive transfusion should be avoided.

Further, reducing preoperative transfusions reduces the risk of alloimmunization and transfusion reactions. The development of non-ABO erythrocyte antibodies occurs in 8% to 50% of patients with sickle cell disease, varying with the number of RBC transfusions administered.[35] Clearly, the development of these antibodies adds complexity to surgical procedures and increases the risk of reactions with subsequent transfusions. RBC phenotyping with matching for E, C, and Kell group antigens is recommended because it reduces the risk of alloimmunization.[36,37] Several published studies have questioned the benefit of aggressive preoperative transfusion, suggesting that young patients undergoing low-risk surgery do not require transfusion.[34,38] For others, a conservative transfusion regimen designed to increase the plasma hemoglobin concentration to 10 g/dL offers as much benefit as an aggressive regimen aimed at decreasing the hemoglobin S concentration, with a lower risk of complications.[34]

Postoperative complications of surgery vary, depending on the type of surgical procedure performed, the age of the patient, the status of disease activity and disease-related organ dysfunction, the presence of infection, evidence of chronic lung disease, pregnancy in female patients, and the genetic form of sickle cell disease.[33] Preoperative assessment of lung function with a chest radiograph, oxygen saturation determination, and pulmonary function tests, and of renal function with serum blood urea nitrogen and creatinine measurements, blood pressure measurement, and screening for urinary infection and proteinuria, offer useful strategies for decreasing intraoperative risks.

### β-Thalassemia

β-Thalassemia is characterized by the inability to synthesize normal amounts of β-chain hemoglobin polypeptide,[39] resulting in ineffective erythropoiesis. Patients with homozygous β-thalassemia become dependent on RBC transfusions early in life. As a consequence of extramedullary hematopoiesis, splenomegaly is a frequent finding. Splenic sequestration of RBCs often leads to an enhanced transfusion requirement. When the RBC transfusion requirement exceeds 250 mL/kg per year, splenectomy should be considered because it often reduces the transfusion requirement.[40]

### Hereditary Spherocytosis and Erythrocyte Enzyme Deficiencies

Hereditary spherocytosis and RBC enzyme deficiencies, such as glucose-6-phosphate dehydrogenase and pyruvate kinase deficiencies, result in hemolytic anemia, often associated with gallstone formation. When cholelithiasis is symptomatic, cholecystectomy is necessary. In the case of hereditary spherocytosis, when patients maintain a relatively high reticulocyte count (>10%) in the presence of moderate to severe anemia, splenectomy should be considered when patients reach the age of 5 to 6 years.[41] Splenectomy reduces the risk of the development of gallstones, and it minimizes the chance of a precipitous drop in the hemoglobin concentration when a patient with hereditary spherocytosis experiences a viral infection. Partial splenectomy may offer an alternative in the future, with the definitive risks and benefits yet to be determined, possibly in a randomized clinical trial.[42] The therapeutic value of splenectomy also needs to be considered in patients with other types of hemolytic anemia, such as pyruvate kinase deficiency and refractory autoimmune hemolytic anemia.

# Thrombocytopenia and Disorders of Platelet Function

Bleeding manifestations attributable to platelets can either be the result of quantitatively too few platelets, (i.e. thrombocytopenia), or qualitatively abnormal platelets (i.e. dysfunctional platelets).

Thrombocytopenia is defined as a platelet count less than 150,000/μL, although clinically significant manifestations are generally apparent only at platelet counts less than 100,000/μL. Thrombocytopenia can have either a genetic or an acquired origin.

## GENETIC THROMBOCYTOPENIA

Although rare, several genetic conditions should be considered when thrombocytopenia is diagnosed early in life. Both thrombocytopenia with absent radii (TAR) and CAMT present in the newborn period and are inherited in an autosomal recessive fashion with normal platelet size. As the name implies, TAR is a clinical diagnosis based on variable thrombocytopenia, ranging from 10,000 to 100,000/μL in association with limb abnormalities, most commonly bilateral radius aplasia.[43] No underlying molecular mechanism for TAR has been identified. The thrombocytopenia generally improves over the first year of life, requiring only supportive care with platelet transfusions, and progression to bone marrow failure is rare. Although the thrombocytopenia is expected to resolve within the first year, it should be noted that in the original case series of TAR patients published in 1969, 35% mortality was observed due to intracranial and gastrointestinal bleeds, with the majority of deaths occurring before age 1 year.[44] In addition, many other skeletal abnormalities as well as nonskeletal abnormalities—macrocephaly, short stature, facial dysmorphism, renal malformations, cardiac defects, and capillary hemangiomas—are common in patients with TAR and often require subspecialist care. In contrast, CAMT often presents within the first year of life with more severe thrombocytopenia and elevated serum thrombopoietin levels, and a distinct lack of megakaryocytes in the bone marrow in the absence of other congenital malformations.[43,45] Most patients with CAMT experience bone marrow failure within the first few years of life; patients are also at an increased risk of myelodysplasia and acute leukemia. Bone marrow transplant, preferably with a matched sibling donor, is the only definitive treatment for CAMT. Other bone marrow failure syndromes, in particular Fanconi anemia, can present as isolated thrombocytopenia in infancy before progression to a complete aplastic state. However, the classic physical stigmas of Fanconi anemia (i.e., anomalies of the forearm and thumb, as well as chromosomal breakage analysis with diepoxybutane or mitogen C testing) typically permits distinction between the diagnoses.[3]

In addition, familial thrombocytopenias, including conditions with reduced or increased platelet size, can be appreciated in early childhood. Wiskott-Aldrich syndrome is an X-linked familial microthrombocytopenia due to a defect in the WAS protein, which manifests as thrombocytopenia with small-volume platelets, eczema, and frequent infections due to T-lymphocyte abnormalities and immunoglobulin M deficiency.[46,47] Autoimmune conditions and malignancies, particularly B-cell dyscrasias, are common in patients with Wiskott-Aldrich syndrome.[48] The more rare macrothrombocytopenias can either be related to other disease entities (e.g., velocardiofacial syndrome or pseudo–von Willebrand's disease) or to isolated *MYH-9* macrothrombocytopenia with leukocyte inclusions, hearing loss, or nephritis, or a combination of these conditions.[49]

## ACQUIRED THROMBOCYTOPENIA

Acquired thrombocytopenia can arise from a number of sources, for example, intrauterine exposure to maternal antibodies with antiplatelet surface antigen specificity arising from exposure to certain therapeutic drugs, various viral infections, or the existence of a maternal autoimmune state. Likewise, certain classes of drugs are more likely to induce thrombocytopenia, including antibacterial drugs (e.g., trimethoprim-sulfamethoxazole), anticonvulsant drugs (e.g., phenytoin, carbamazepine), and antipsychotic drugs (e.g., chlorpromazine). Three disorders merit special mention: neonatal alloimmune thrombocytopenia, immune thrombocytopenic purpura, and heparin-induced thrombocytopenia (HIT).

Neonatal alloimmune thrombocytopenia (NAIT) is the most common cause of severe thrombocytopenia in fetuses and newborns.[50] NAIT occurs when an infant's mother becomes sensitized to a foreign paternal platelet antigen inherited by the infant and expressed on platelets during gestation. The mother develops an antiplatelet IgG titer when the maternal-fetal blood barrier breaks down, allowing the infant's platelets to enter the maternal circulation; IgG antibody then crosses back through the placenta to the infant. Platelet counts less than 50,000/μL should prompt consideration for screening for NAIT. The platelet antigen most frequently responsible for this sensitization is PLA1, an antigen for which 98% of the population is positive. Random platelet transfusions generally do not provide a sustained rise in the infant's platelet count, especially when a common antigen, such as PLA1, has led to sensitization; such transfused platelets are rapidly destroyed. Despite their rapid destruction, random

donor platelets may be useful if other treatments are not readily available, especially if the bleeding is life-threatening. As such they are generally the first line of treatment in suspected cases of NAIT. Conversely, the use of maternal platelets (i.e., PLA1 or other specific antigen-negative platelet) typically leads to a sustained rise in the infant's platelet count; when the mother's postpartum condition allows platelet pheresis, this can be a lifesaving intervention. Platelet transfusion is recommended in well, term infants with a platelet count less than 30,000/μL and for premature infants with a platelet count less than 50,000/μL. In infants with intracranial hemorrhage, a platelet count greater than 100,000/μL is the goal. Besides platelet transfusions, intravenous immunoglobulin (IVIG) 1 g/kg per day for 1 to 3 days depending on response, plus/minus intravenous (IV) methylprednisolone 1 mg/kg (maximum 30 mg) every 8 hours, can be administered for marked thrombocytopenia.[51] NAIT usually resolves in 2 to 4 weeks. It should be noted that unlike Rh disease, NAIT can occur with the mother's first pregnancy, and no preventive measures similar to Rh immune globulin (Rhogam) exist. Like Rh disease, however, NAIT is anticipated to be worse with each subsequent pregnancy.[51]

Immune thrombocytopenic purpura occurs in children and adolescents of all ages, but the majority of patients are between 2 and 10 years of age. It often occurs after a viral infection and is believed to be caused by a misdirected antiviral immune response, with antibodies cross-reacting with platelets and leading to splenic consumption.[52] It is a clinical diagnosis based on the acute onset of isolated thrombocytopenia that is frequently concurrent with the abrupt onset of petechiae, bruising, or mucous membrane bleeding, or a combination of these conditions, in an otherwise healthy child. Unlike adults, the majority of children will have spontaneous remission, with at least two thirds of patients having a normal platelet count within 6 months.[53] However, because of the severity of the thrombocytopenia (often <10,000/μL platelets) and the small, less than 1%, associated risk of intracranial hemorrhage,[54] many children are treated with IVIG 0.8 to 1 g/kg IV, anti-D immunoglobulin 75 μg/kg, or oral prednisone.[55] All three treatments can provide a temporary increase in platelet counts. One should note that anti-D immunoglobulin has been reported to cause brisk hemolysis leading to rare renal failure or death, so care should be taken to provide adequate hydration and to monitor for hemoglobinuria.[56] Before prednisone is used, consideration should be given to performing a bone marrow aspiration to rule out leukemia, because leukemia may be partially, but inadequately, treated by prednisone. Platelet transfusions are only clinically indicated in life-threatening bleeding situations and should be used concurrently with IVIG 0.8 to 1 g/kg IV and methylprednisolone 30 mg/kg (maximum 1 g) IV. In children with refractory, symptomatic immune thrombocytopenic purpura, splenectomy or rituximab can be considered.

HIT is an immune-mediated side effect of heparin therapy characterized by thrombocytopenia and paradoxical increased risk for thrombosis. Although previously considered rare in neonates and children, HIT is now recognized to occur in up to 1% to 2% of certain pediatric patient populations, particularly those receiving cardiac surgery or intensive care unit (ICU) care, or both.[57] The thrombocytopenia usually begins 5 to 10 days after the heparin is initiated, although it can occur within the first 48 hours if the patient has previously received heparin.[58] Unlike most other drug-induced thrombocytopenias, which classically lower the platelet count to less than 10,000/μL, HIT typically drops the platelet count by at least 50%, with a resultant platelet count ranging from 20,000 to 150,000/μL, with a median platelet count of 50,000/μL.[59] It should be noted that 10% of patients with HIT have platelet nadirs in the normal range[60]; thus, a normal platelet count does not nullify a diagnosis of HIT. Thrombosis can also precede thrombocytopenia.[60] The risk for HIT is greater with therapeutic rather than prophylactic doses of heparin, for bovine- than for porcine-derived heparin, and for unfractionated as opposed to low-molecular-weight heparin (LMWH).[61]

To make a diagnosis of HIT, both clinical and laboratory features must be present: a triggering agent (i.e., a form of heparin), a significant fall in platelet count with the typical timing, and the identification of heparin-dependent antibodies. A clinical score to assess the pretest probability of HIT has been proposed[62] and is frequently used despite not being validated in a pediatric population. Treatment of HIT requires immediate discontinuation of heparin once HIT is suspected. In addition, because of the risk of significant thrombosis, transition to an alternative anticoagulant is recommended. Warfarin should not be used as a substitute for heparin during an acute HIT episode because it can result in an abrupt decrease in protein C levels, placing the patient at greater risk for thrombotic complications.[63] LMWH to replace unfractionated heparin should also be avoided because of the appreciable cross-reactivity between the two agents. Instead, the alternative agents danaparoid,[64] lepirudin,[57] argatroban[65] or fondaparinux[66] should be considered.

## DISORDERS OF PLATELET FUNCTION

Cutaneous or mucous membrane bleeding despite a normal platelet count suggests the presence of a disorder of platelet function, which may be either acquired or inherited.

Medications are a common cause of acquired platelet function defects. Aspirin, although rarely used in children because of the risk of Reye syndrome, is well documented to inhibit platelet cyclooxygenase irreversibly, resulting in deficiency of thromboxane $A_2$ and inhibition of platelet aggregation.[67] Since platelets are unable to synthesize new proteins, the action of aspirin is permanent and lasts the life of the platelet. Unlike aspirin, ibuprofen is a reversible cyclooxygenase inhibitor, and although data is limited there is some evidence to suggest that platelet function may normalize within 24 hours of cessation of regular ibuprofen use.[68]

Of the inherited platelet dysfunction disorders, von Willebrand disease is the most prevalent.[69] This disorder is characterized by mucosal bleeding caused by abnormal platelet adhesion and aggregation that arises from subnormal levels of factor VIII activity and von Willebrand factor. A number of variants of von Willebrand disease are known to exist; most are transmitted in an autosomal dominant fashion. Recombinant factor VIII/von Willebrand factor concentrate is the treatment of choice to normalize hemostasis. Desmopressin (DDAVP), a synthetic analog of the antidiuretic hormone vasopressin, which transiently increases levels of factor VIII and von Willebrand factor by releasing them from storage pools in the blood can also be used to minimize bleeding. Care should be taken with desmopressin

use because patients are at risk for the development of hyponatremia and seizures. Particular attention should be given to the amount of perioperative fluid the patient receives, and serum sodium levels should be measured during the perioperative period. If factor VIII/von Willebrand factor concentrate is not available, cryoprecipitate can be used. Each unit of cryoprecipitate contains 80 to 100 U of factor VIII and 80 U of von Willebrand factor. A dose of cryoprecipitate providing 10 U of factor VIII/kg of body weight is generally sufficient to achieve adequate hemostasis for surgery. It should be noted that cryoprecipitate is a second-line agent, since during the processing of cryoprecipitate there is no viral inactivation. Failure to correct von Willebrand disease deficiencies before a patient undergoes surgery increases the risk for mucosal bleeding or surface bleeding, or both.

Two other rare inherited platelet dysfunction disorders are Bernard-Soulier syndrome and Glanzmann thrombasthenia.[69] Both conditions are due to a defect in platelet adhesion and can result in severe bleeding. In Bernard-Soulier syndrome the defect is in the GPIb-IX-V platelet surface complex, whereas in Glanzmann thrombasthenia the defect is in the platelet membrane complex GPIIb-IIIa. The two diagnoses can be differentiated by platelet aggregation testing, as Bernard-Soulier syndrome classically demonstrates no agglutination in response to ristocetin but shows otherwise normal agglutination, but Glanzmann thrombasthenia shows a normal ristocetin response despite an absent response to other agents. For bleeding episodes, platelet concentrate transfusion is the appropriate corrective measure. However, patients quickly become resistant to platelet transfusions because of the high risk of alloimmunization.

# Disorders of Coagulation

In evaluating children for bleeding tendencies, the physician should begin with a review of items relevant to a bleeding history. Specifically, this includes inquiring about the occurrence of frequent, large (greater than quarter-sized) bruises in unusual places or after minor trauma, oozing or frank bleeding from the umbilical stump, gum bleeding, epistaxis, hemarthroses, menorrhagia, hematuria, gastrointestinal bleeding, or intracranial bleeding. Moreover, bleeding symptoms from procedures (such as a hematoma with intramuscular injections) and history of bleeding with circumcision, dental extractions, or other surgical procedures should be ascertained. A history of anticoagulation use (i.e., aspirin, heparin, enoxaparin [Lovenox], warfarin) should be obtained. Finally, taking a family history of bleeding tendencies is essential, and that history can either enhance or reduce the probability of diagnosing a bleeding disorder in the patient being evaluated.

The physical examination also provides important information. Bleeding in the skin or mucous membranes (gingival bleeding, petechiae, ecchymoses), soft tissues (hematomas), joints, or on funduscopic examination should be noted.

A good initial laboratory screening panel includes a CBC, prothrombin time (PT), and activated partial thromboplastin time (aPTT) (Table 11-1). Historically, a bleeding time has also proved useful. However, since the bleeding time is subject to considerable variation related to the experience of the person performing the test, the patient's skin temperature, and the length and depth of the incision, the bleeding time is now rarely used. If it is used, the normal range for the bleeding time is 3.5 to 11.5 minutes. Times in the 12- to 15-minute range should be viewed circumspectly, whereas values in excess of 15 minutes are prolonged and abnormal. The CBC is useful to determine the presence of an adequate number of platelets. The PT detects deficiencies of factor VII and factors in the common pathway (Fig. 11-2). The normal range for the PT is 11 to 12 seconds. The most sensitive of the global screening tests is the aPTT. The aPTT detects deficient clotting factors in the intrinsic and common pathways. However, mild deficiencies of factors VIII and IX will not be recognized, and deficiencies of factor VII and factor XIII will not be detected at all by the aPTT.

Specific assays to determine the presence of a single factor deficiency are available. If a satisfactory determination cannot be achieved despite attempts to identify one or more factor deficiencies, a search for a plasma inhibitor should be initiated. This can be accomplished by performing mixing studies with the aPTT or PT, depending on which result is more abnormal. For these studies, normal plasma is mixed with the deficient (patient) plasma in a range of ratios (1:3, 1:1, 3:1). Failure to correct the test completely at the 3:1 (normal patient) mix ratio suggests the presence of an inhibitor. In contrast, factor deficiencies should be totally corrected at the 1:3 mixture and certainly at the 1:1 mixture.

## COAGULATION FACTOR DEFICIENCIES

The most common inherited factor deficiencies include hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency). Hemophilia occurs in approximately 1 in 5000 boys, with hemophilia A accounting for 80% to 85% of the patients and hemophilia B accounting for the remaining 15% to 20%; there are no ethnic predilections.[70] These disorders are inherited as X-linked recessive traits and as such almost exclusively affect boys. Although the majority of patients will have a family history of hemophilia or a bleeding history suggestive of hemophilia, it should be noted that in a third of patients, the diagnosis of hemophilia is the result of a new mutation.[71]

Both factors VIII and IX are critical for thrombin development; thus, deficiency of either leads to bleeding manifestations characterized by oozing or delayed hemorrhage because, although the initial platelet plug is capable of forming, thrombin clot formation is delayed and not robust. Usual bleeding symptoms include bleeding with circumcision, oral bleeding (particularly in infancy from a torn frenulum), easy bruising, hemarthroses, and intramuscular hemorrhage. The frequency and severity of bleeding strongly correlate with the level of active factor. For hemophilia A and B, factor levels of less than 3% are associated with spontaneous hemorrhage into joints and soft tissues. In general factor levels greater than 30% have essentially normal hemostasis. For joint bleeding and bleeding emergencies, such as central nervous system (CNS) bleeding or hemorrhage into the psoas muscle, specific factor recombinant products should be administered rapidly to achieve 100% factor replacement.

The diagnosis of factor VIII deficiency can be made at birth with a prolonged aPTT and a confirmatory low factor VIII level. In the evaluation of factor IX deficiency, however, the physician must consider the physiologic delay in achieving normal levels of the vitamin K–dependent factors (factors II,

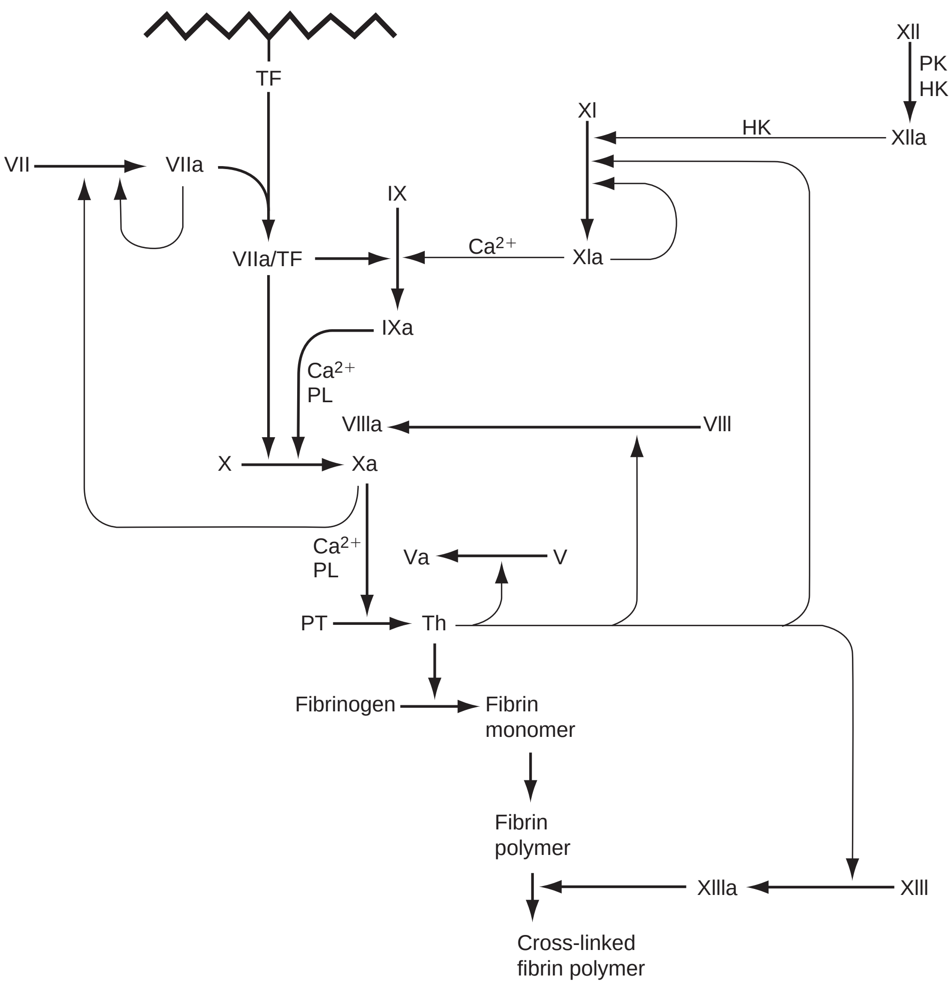


**FIGURE 11-2** Coagulation cascade. HK, high-molecular-weight kininogen; PK, prekallikrein; PL, phospholipid; PT, prothrombin; TF, tissue factor; Th, thrombin. (From Schafer AI: Coagulation cascade: An overview. In Loscalzo J, Schafer AI [eds]: Thrombosis and Hemorrhage. Boston, Blackwell Scientific, 1994.)

VII, IX, and X) in infants. Although confounding the interpretation of the factor IX level in infants, the physiologic delay does not lead to misinterpretation of the near-complete deficiency seen in severe to moderate hemophilia B. A prolonged aPTT with a subsequent factor IX level of less than 10% is consistent with a diagnosis of hemophilia B. Infants with levels in the 10% to 50% range should be retested at 3 to 6 months of age or earlier if clinically significant bleeding occurs. All newborn infants suspected of having hemophilia should have a head ultrasonogram to evaluate for intracranial hemorrhage because 1% to 2% of infants with hemophilia have been reported to have CNS bleeding.[72,73]

Once a diagnosis of hemophilia is made, patients requiring surgery should have a careful presurgical evaluation, including laboratory evaluation for the development of an inhibitor. Specific factor concentrate should be administered before surgery to achieve a level of 100 to 150 U/dL for factor VIII and 80 to 100 U/dL for factor IX, and factor levels should be maintained at 50 to 60 U/dL for 7 to 14 days postoperatively.[70] In trauma scenarios swift action should be taken to provide 100% factor correction before imaging. This is particularly true for head trauma cases because patients with hemophilia experience intracranial hemorrhage 20 to 50 times more frequently than does the general population.[74]

## OTHER FACTOR DEFICIENCIES

Besides the more common factor VIII and IX deficiencies, other factor deficiencies do occur, such as abnormalities in fibrinogen, the soluble precursor of fibrin that is mainly produced in the liver. Dysfibrinogenemias are disorders of fibrinogen function caused by structural defects in the protein; more than 300 abnormal fibrinogens have been described. In contrast, afibrinogenemia is due to a complete absence of fibrinogen.

Afibrinogenemia usually manifests in the neonatal period, with 85% of patients presenting with umbilical cord bleeding,[75] although later age at onset is not unusual. Patients with afibrinogenemia often have mucosal and other bleeding (e.g., bleeding from skin, gastrointestinal tract, and CNS), with intracranial hemorrhage reported as the main cause of death.[76] Hemarthrosis, however, is notably infrequent (particularly compared with patients with severe hemophilia), with joint bleeding observed in 25% of patients.[77] The diagnosis of afibrinogenemia is confirmed by the absence of immunoreactive fibrinogen. The partial thromboplastin time (PTT), PT, and thrombin time (TT) will all be infinitely prolonged because all these tests rely on the formation of fibrin as an end point. Generally fibrinogen levels greater than 50 mg/dL are sufficient

**TABLE 11-1**
**Tests to Detect Bleeding Disorders**

| *Test* | *Parameters Measured* |
|---|---|
| Platelet count | Platelet number |
| Bleeding time | Systemic primary hemostasis<br>Defect of platelet number or function<br>Defect in platelet-vessel wall interaction<br>Primary vascular disorder |
| Prothrombin time (PT) | Extrinsic and common pathways: factors VII, X, V; prothrombin; fibrinogen |
| Activated partial thromboplastin time (APTT) | Intrinsic and common pathways: factors XII, IX, XI, VIII, X, V; prothrombin; fibrinogen; prekallikrein; high-molecular-weight kininogen |
| Thrombin time | Fibrinogen |
| Fibrinogen quantitation | Level of fibrinogen in plasma (mg/dL) |
| Fibrin degradation products | Breakdown products of fibrinogen or fibrin-elevated with increased fibrinolysis or disseminated intravascular coagulation |
| D-dimer assay | Fibrin-specific degradation product; indicator of both thrombin and plasmin generation |
| Euglobulin lysis time | Screening test of fibrinolytic activity |
| Mixing study (using PT or APTT) | Presence of a circulating anticoagulant |
| Antithrombin III (ATIII) activity | Level of the antithrombotic ATIII |
| Protein C, protein S antigen activity | Levels of the antithrombotic proteins C and S |
| Activated protein C resistance assay | Presence of mutant, functionally deficient factor V Leiden (predisposing to thrombosis) |

Data fromSchafer AI: Approach to bleeding. In Loscalzo J, Schafer AI (eds): Thrombosis and Hemorrhage. Boston, Blackwell Scientific, 1994; Comp PC: Approach to thrombosis. In Loscalzo J, Schafer AI (eds): Thrombosis and Hemorrhage. Boston, Blackwell Scientific, 1994; and Santoro SA: Laboratory evaluation of hemostatic disorders. In Hoffman R, et al (eds): Hematology: Basic Principles and Practice. New York, Churchill Livingstone, 1991.

for hemostasis; fibrinogen concentrates, cryoprecipitate, or fresh frozen plasma, or all of these, can be used for fibrinogen replacement as needed.

Unlike afibrinogenemia, which is often diagnosed in childhood, dysfibrinogenemia is often recognized only in adulthood in patients with menorrhagia, prolonged bleeding from trauma or surgery, or abnormal screening laboratory values. The diagnosis of dysfibrinogenemia depends on assays that demonstrate that the functional contribution of fibrinogen to coagulation is abnormal. Most patients with dysfibrinogenemia do not require treatment, but fibrinogen concentrates, cryoprecipitate or fresh frozen plasma, or all of these, can be used for patients with significant bleeding.

Other recognized clotting factor deficiencies and their propensity for associated clinical bleeding are listed in Table 11-2. Deficiencies of prothrombin (factor II), factor V, and factor XI predispose to mild bleeding tendencies, whereas deficiencies of factors VII and X result in variable bleeding tendencies, with some patients demonstrating significant hemorrhagic events. Of note, deficiencies of the contact-activated factors—factor XII (Hageman factor), prekallikrein, and high-molecular-weight kininogen—are not associated with bleeding, and identification of a deficiency should not preclude required surgery.

**TABLE 11-2**
**Clotting Factor Deficiencies**

| *Deficient Factor* | *Clinical Relevance* |
|---|---|
| I | Risk of hemorrhage at levels <50 mg/dL |
| II | Mild bleeding tendency after injuries, dental extractions, surgery |
| V | Mild bleeding tendency (menorrhagia, significant bleeding after injury or surgery) |
| VII | Variable bleeding tendency (intracranial hemorrhage in newborns, menorrhagia) |
| VIII | Moderate to severe bleeding tendency at levels <5% |
| IX | Moderate to severe bleeding tendency at levels <5% |
| X | Variable bleeding tendency (neonatal hemorrhage, bleeding after trauma, menorrhagia) |
| XI | Mild bleeding tendency (menorrhagia, epistaxis, postoperative bleeding) |
| XII | Generally asymptomatic |
| Prekallikrein | Asymptomatic |
| High-molecular-weight kininogen | Asymptomatic |

## ACQUIRED DEFECTS OF COAGULATION

The most common causes of acquired hemorrhagic defects include drug-induced bleeding, disseminated intravascular coagulation (DIC), liver disease, vitamin K deficiency, massive transfusion, and acquired inhibitors to coagulation proteins.[78]

Many drugs have been associated with bleeding, the most obvious of which are the therapeutic anticoagulant medications (i.e., warfarin, heparin, low-molecular-weight heparin) and antiplatelet agents (e.g., aspirin, clopidogrel). Other medication classes, namely β-lactam antibiotics,[79] tricyclic[80] and selective serotonin reuptake inhibitor[81] antidepressants, H2-receptor antagonists,[82] and calcium channel blockers,[83] among others, have been identified as interfering with platelet function, but they rarely result in clinical bleeding. Of note, however, valproic acid, an anticonvulsant agent commonly used to treat pediatric generalized tonic-clonic and absence seizures, has been identified as having several effects on coagulation[84,85] (bone marrow suppression,[86,87] development of antiplatelet antibodies,[88] fibrinogen depletion,[89,90] and induction of factor XIII deficiency[91,92]), and has occasionally been reported to have significant bleeding complications associated with its use.

In patients with clinical bleeding due to drug-induced hemorrhagic defects, the suspected offending agent should be discontinued. Vitamin K and fresh frozen plasma should be considered to reverse warfarin coagulopathy. In addition, platelet transfusions should be used for significant or persistent bleeding, or both.

DIC is an acquired systemic disorder caused by in vivo activation of the coagulation mechanism, resulting in the transformation of fibrinogen to fibrin, which generates thrombi in the microcirculation, with secondary fibrinolysis.[78] The vast majority of DIC cases are due to sepsis from infectious causes, although leukemia and other malignancies, cavernous hemangiomas, acute anaphylaxis, snake bites,

abruptio placentae, and trauma can all be the precipitating cause. The diagnosis of DIC is facilitated by reviewing the peripheral blood smear and identifying schistocytes and thrombocytopenia. Other supporting laboratory tests include prolonged PT/aPTT and decreased fibrinogen with increased D-dimer and fibrin degradation products. A decrease in protein C, protein S, and antithrombin III (ATIII) may also be seen.

Treatment of DIC centers on the correction of the underlying cause and supportive care. Further therapy should be determined by the patient's general condition and the hemorrhagic or thrombotic manifestations. Heparin may be indicated in children with purpura fulminans and signs of thrombosis; however, routine use of heparin, particularly in less severe forms of DIC, is questionable. In the presence of decreased ATIII levels, heparin may not be effective. ATIII concentrate or fresh frozen plasma can be used as supplements. The patient's platelet count and fibrinogen level can be monitored as indices of response to therapy. For patients with primarily hemorrhagic manifestations and little, if any, thrombosis, the administration of platelets and fresh frozen plasma is indicated if bleeding is moderately severe and associated with a decreasing platelet count and prolonged PT/aPTT.

Severe liver disease is often associated with significant clotting factor deficiency. The healthy liver is the site of synthesis of most coagulation factors, including fibrinogen; prothrombin; factors V, VII, IX, X, XI, XII and XIII; prekallikrein; and high-molecular-weight kininogen.[78] In addition, the liver is the source of the natural anticoagulants antithrombin III, protein C, and protein S, as well as inhibitors of fibrinolysis, antiplasmin and alpha-1 antitrypsin. Because the liver is also involved in the clearance of activated clotting factors, liver failure can lead to DIC. However, severe hepatic injury or failure is more typically associated with a hemorrhagic tendency due to the insufficient production of clotting factors. Increased fibrinolysis resulting from decreased hepatic synthesis of inhibitors may also contribute to the hemorrhagic tendency. Measuring factor VIII and factor V levels in a patient can serve as markers of liver function. High factor VIII levels (indicating a lack of liver clearance) and low factor V levels (indicating a lack of liver production) correlate with poor liver function. Treatment of the underlying liver condition and supportive care with fresh frozen plasma or specific factor concentrates, or both, is most useful.

Vitamin K stores are deficient in most normal newborns; this deficiency has the potential to result in a severe bleeding diathesis. Without early supplementation, infants may bruise, have cephalohematomas, and experience gastrointestinal or umbilical hemorrhage, and oozing from puncture sites. Platelet and fibrinogen levels are normal in these infants, but marked prolongation of the PT and aPTT is noted because of the deficiency of vitamin K, thus interfering with the development of essential calcium-binding sites on the vitamin K–dependent coagulation factors,[93] including factors II, VII, IX, and X. Administration of parenteral vitamin K leads to quick cessation of bleeding and correction of the clotting test results. Breast-feeding accentuates the vitamin K deficiency because breast milk contains far less vitamin K (2 to 15 μg/L) than does cow's milk (60 μg/L).[94] Hemorrhagic disease in newborns can be prevented by intramuscular administration of vitamin K shortly after birth. A dose of 0.5 to 1.0 mg of vitamin K1 oxide is recommended; this dose far exceeds the requirement of 25 μg.[78,95]

Although newborns rely on exogenous sources of vitamin K, older infants absorb vitamin K from the colon, and synthesis by bacteria is the primary source. In older children and adults, vitamin K is absorbed from the ileum. The daily requirement of 1 μg/kg is supplied by green leafy vegetables in the diet and is stored in the liver.[96] Thus, malabsorption resulting from cystic fibrosis, biliary atresia, chronic hemolytic anemia with secondary cholelithiasis, and obstructive jaundice, as well as other disorders leading to dysfunction of the upper small intestine, can result in vitamin K deficiency. In addition exogenous medications, namely warfarin, can lead to vitamin K deficiency. Administration of vitamin K intravenously at a dose of 5 to 10 mg leads to clinical improvement within a few hours and correction of the prolonged PT and aPTT within 24 hours.[78]

Massive transfusion therapy, defined as replacing at least one blood volume in 24 hours, can result in significant bleeding resulting from hypothermia, dilutional coagulopathy, platelet dysfunction, fibrinolysis, or hypofibrinogenemia.[97] Agents such as aprotinin, a serine protease inhibitor that modulates the systemic inflammatory response, have been used as effective hemorrhage prophylaxis in cardiac[98] and orthopedic surgeries.[99] In addition activated factor VII has been used as a rescue therapy for life-threatening bleeding.

Several acquired inhibitors to coagulation proteins are known, namely, inhibitors to factors VIII and IX, inhibitors associated with acquired Willebrand syndrome, and lupus anticoagulants (LA). The LAs are the most commonly identified in children and are often recognized after a prolonged aPTT is noted during a routine presurgical evaluation or in association with an infection.[100] The LAs are a group of antibodies against proteins bound to phospholipids; they can be identified by a noncorrecting mixing study. Generally LAs resolve spontaneously within days to weeks and do not require a change in the operative plan.[78]

## THROMBOTIC DISORDERS

The naturally occurring anticoagulants ATIII, protein C, and protein S work to contain excessive in vivo blood coagulation. Thrombosis often results when the activity of one or more of these anticoagulants is deficient.

ATIII is a physiologic inhibitor of thrombin and activated factor V. In addition ATIII is a heparin cofactor that is essential to heparin therapy and is a major inhibitor of blood clotting. This cofactor, which is synthesized in the liver, has a biologic half-life of 2 to 5 days. Congenital ATIII deficiency occurs at a frequency of 1 per 2000 to 5000 individuals.[101] Thrombotic events are often first noted in the second and third decades of life. Surgery, trauma, infection, and pregnancy predispose to thrombotic events. Large amounts of heparin may be required for effective anticoagulation in patients with ATIII deficiency because ATIII is necessary for full heparin activity. Diagnosis is made through a specific assay for ATIII. Oral anticoagulation with warfarin has been the mainstay of therapy. However, purified concentrates of ATIII are available and can be used at a dose of 50 IU/kg for the short term to prevent thrombosis in high-risk situations, such as acute thrombosis, during surgery, or during the third trimester of pregnancy.[102]

Both protein C and protein S are vitamin K–dependent plasma proteins that act in concert to inactivate procoagulants, thereby reducing the risk for thrombosis. Protein C functions

by inactivating factors V and VIII; in its active form, protein C also indirectly facilitates clot lysis.[103] Deficiency of protein C is inherited as an autosomal dominant trait. The homozygous state in infants is characterized by purpura fulminans, retinal thrombotic events with retinal detachment and loss of vision, and other thrombotic events.[104] Heterozygous deficiency of protein C is often asymptomatic during childhood but causes venous thrombosis in adolescents and young adults. Heterozygotes generally have levels of approximately 50%, but these individuals are still at risk for other thrombotic events. Diagnosis is made with a specific assay for protein C. Although it has a role in preventing thrombosis in homozygous individuals who are essentially deficient of protein C, warfarin should be used cautiously, if at all, in heterozygous individuals because their thrombotic tendency can be exacerbated by a further reduction in vitamin K–dependent protein C. In fact, heterozygotes often experience purpuric, thrombotic cutaneous lesions while receiving warfarin, which is a contraindication to its use. Further lowering of the protein C level presumably causes these side effects. Heparin should be used to treat acute venous thrombosis, and protein C concentrates are available to facilitate the management of acute thrombosis in protein C–deficient patients.

Protein S acts as a cofactor for protein C. Deficiency of protein S is associated with recurrent venous thrombosis. Heterozygotes with 35% to 50% of the normal levels of the protein experience recurrent thromboses in adolescence and early adulthood.[105] The same guidelines for use of heparin in treating venous thrombosis apply to patients who are deficient in protein S (as well as those deficient in ATIII and protein C). Caution should be exercised when warfarin is used in protein S–deficient patients.

Besides deficiencies in ATIII, protein C,and protein S, genetic mutations such as factor V Leiden or prothrombin 20210 are associated with an increased risk of venous thromboembolism. Other acquired states, such as increased factor VIII levels with significant infection or inflammatory states, anticoagulation protein deficiencies due to consumption in processes like DIC, and production of parainfectious antiphospholipid antibodies, can all contribute to a prothrombotic state.

One of the largest acquired risk factors for venous thrombosis is the presence of a central venous catheter. More than 50% of deep venous thromboses in children and greater than 80% in neonates are related to indwelling central venous catheters.[105,106] The signs and symptoms of a venous thromboembolism are dependent on the location and chronicity of the clot. For example, acute extremity deep venous thrombosis presents with unilateral limb swelling, whereas acute superior vena cava thrombosis may result in swelling of the face and neck. However, chronic venous thromboembolism may have no signs or symptoms or may have appreciable dilated superficial collateral veins or evidence of venous stasis. Venography is the gold standard for diagnosis of a clot; however, because of the invasive nature of venography, compression ultrasonography with Doppler, computed tomography, and echocardiography are used routinely to diagnosis and follow thrombi. Once a diagnosis of acute venous thromboembolism is identified, initial anticoagulant therapy most frequently relies on unfractionated heparin or LMWH. The latter has become increasingly favored because of its subcutaneous dosing, decreased need for frequent blood monitoring, and decreased risk for the development of HIT. The starting dose of LMWH in nonneonates commonly begins at 1 mg/kg with no bolus given. In full-term infants, the LMWH dose generally is increased to 1.5 mg/kg.[107] The LMWH dose should be titrated to achieve a therapeutic anti-Xa level of 0.5 to 1.0.[78] Unfractionated heparin, however, may be preferred in patients with an increased risk of bleeding or labile clinical status. Nonneonates commonly are loaded with a 50- to 75-U/kg dose of unfractionated heparin, followed by an infusion of 15 to 25 U/kg per hour. Full-term neonates generally require increased doses. The therapeutic anti-Xa range for unfractionated heparin is 0.3 to 0.7.[78] Patients with a known, resolved risk factor generally require treatment for 3 to 6 months; patients with no known clinical risk factor require 6 to 12 months of treatment; and patients with a chronic risk factor or congenital thrombophilia may require indefinite treatment.[78]

## Transfusion Therapy

Greater accessibility to improved blood products has increased the survival of critically ill patients who need enhanced oxygen delivery, intravascular volume expansion, and improved coagulability. The estimated blood volume for infants and young children weighing 10 to 30 kg is approximately 75.4 mL/kg,[108] whereas that for older children and adolescents is 55 to 75 mL/kg.[109] RBC transfusions should be used to correct pathophysiologic events that cause inadequate oxygen delivery and resultant tissue hypoxia. The decision to transfuse RBCs should be based on several factors: signs of tissue hypoxia (tachycardia, tachypnea), extent of blood loss, rate at which anemia has developed, age of the patient, and concomitant or subsequent physiologic stress that the patient may be forced to undergo (e.g., infection, pulmonary compromise, surgery). Transfused RBCs survive for a relatively long time; less than 1% of the number transfused is destroyed daily.[110]

Typically, the number of transfused cells in the recipient's circulation decreases steadily over 110 to 120 days.

Historically, whole blood was the preferred product for transfusion in patients with severe acute blood loss. However, with the increased use of blood fractionation to produce several products from each unit of blood, greater emphasis is now placed on the use of packed RBCs in conjunction with a plasma substitute, if necessary. For hemorrhage of moderate severity, packed RBCs are as effective as citrated whole blood.[108] For severe hemorrhage, plasma substitutes are required when packed RBCs are transfused to prevent an unacceptable increase in hematocrit levels.[110]

To restore blood volume and oxygen carrying capacity to a patient who has lost a large amount of blood, it may be necessary to transfuse a unit of blood quickly. This can usually be accomplished in the same way as discussed previously in the section on blood loss resulting from anemia. When replacement is less urgent, 10 to 15 mL/kg is transfused over 1 to 2 hours. Massive transfusions that involve replacing an amount of blood equal to the patient's blood volume in 24 hours carry the risk of citrate toxicity, electrolyte imbalance, decreased release of oxygen to tissues resulting from diminished RBC 2,3-bisphosphoglycerate content, pulmonary

microembolism, decreased core temperature (if massive amounts of cold blood have been transfused), and thrombocytopenia or DIC. Prevention and successful treatment of the side effects of massive transfusion require careful reassessment of the patient during and after transfusion.

Various plasma substitutes, such as dextran, modified fluid gelatin, and hydroxyethyl starch, have been used to expand plasma volume in hypovolemic patients. However, the possibility of allergic reactions and abnormal bleeding has tempered enthusiasm for their use. Perfluorocarbon compounds, in which oxygen is highly soluble, have been shown to act as effective blood substitutes for oxygen delivery in animals.[111] However, side effects, including lowered platelet count,[112] diminished macrophage function,[113] and activation of complement with resultant pulmonary changes,[114] have severely hampered the use of these compounds; they have undergone evaluation in clinical trials and are currently not recommended for clinical use.[115]

## TRANSFUSION IN PATIENTS WITH CANCER OR IMMUNODEFICIENCIES

The basic principle of transfusing to correct altered hemodynamics and insufficient delivery of oxygen applies when treating immunodeficient patients and those with cancer. No absolute value of peripheral blood hemoglobin concentration or hematocrit below which transfusion is mandated exists. In fact, absolute threshold criteria for transfusion therapy are being abandoned in many centers as a result of concerns about transfusion risks, the high cost of transfusion therapy, and the growing perception that many patients can tolerate lower hemoglobin values than previously believed without adverse physiologic effects. Clearly, the age of the patient, the rate at which hemoglobin or hematocrit values are falling, and concomitant problems influence the decision to transfuse. Children younger than 10 years tolerate hemoglobin values as low as 6 to 7 g/dL without adverse effects. Nevertheless, a rapid decline to this level usually requires RBC transfusion. Similarly, concomitant infection, space-occupying pulmonary disease, pleural effusion, cardiomyopathy, CNS insult, or injury to any major organ may mandate earlier transfusion. The immune state of the patient often warrants special consideration with respect to the type of RBC product chosen and the handling of that product. Many patients with primary immunodeficiency and those with immunodeficiency secondary to therapy should receive blood products that have been irradiated at a level of 2500 to 3000 cGy to prevent graft-versus-host disease.[116] In addition, severely immunocompromised patients, such as bone marrow transplant recipients, who are serologically cytomegalovirus (CMV) negative at the time of transfusion should receive CMV-negative or CMV-safe (leukocyte-reduced) blood products. In fact, many blood banks are releasing only leukocyte-reduced cellular products for all transfusion recipients.

## CHOICE OF RED BLOOD CELL PRODUCT

Fresh whole blood is a suitable choice for use in exchange transfusions when the whole blood being removed from the patient is being replaced (milliliter for milliliter) and when patients with massive blood loss resulting from acute hemorrhage are being treated. For patients in whom excessive increases in intravascular volume may cause problems, other RBC products are preferred.

Packed RBCs are the product of choice for patients with moderate acute blood loss or chronic anemia resulting from underproduction of RBCs or hemolysis. Advantages of packed RBCs include removal of the anticoagulant citrate and 60% to 70% of the plasma.[117] This consideration is particularly important for patients with volume overload or poor cardiac function, or both.

One advantage of washed RBCs is that 85% to 90% of the leukocytes and more than 95% of the plasma have been removed[117]; however, additional expense is incurred for the preparation of this product. Washed RBCs can be used to transfuse patients with a history of nonhemolytic transfusion reactions.

More than 90% of the white blood cells have been removed from frozen deglycerolized RBCs, with retention of minimal plasma (≈0.5% of original plasma).[117] This product is often chosen for patients who require chronic transfusions.

Leukocyte-reduced RBCs are relatively free of leukocytes (≈70% removed)[117] and may be less likely to transmit CMV and other viruses. This product is advantageous for patients with a history of transfusion reactions and for immunodeficient patients at risk for CMV disease.

Each of the products mentioned has a place in transfusion therapy. However, physicians who use these products should bear in mind the appropriate indications for each and the increased cost associated with additional processing of RBCs (e.g., washing, freezing, thawing).

## TRANSFUSION REACTIONS, TOXICITY, AND OTHER COMPLICATIONS

Citrate toxicity resulting from transfusion of the plasma anticoagulant citrate, which binds calcium, may manifest as symptomatic hypocalcemia. Development of this toxicity is the major drawback for using whole blood for rapid RBC and volume replacement.

Transfusion reactions take several forms and usually occur because of patient exposure to proteins from plasma, RBCs, white blood cells, or platelets to which the individual has a natural or an acquired sensitivity. Reactions occur in 2% to 3% of transfusions; of these, 41% are febrile and nonhemolytic, 58% are urticarial, and 1% are delayed hemolytic.[118] For patients with repeated urticaria, the use of washed or frozen RBCs in conjunction with pretreatment of the recipient with an antihistamine or corticosteroid may reduce the incidence of recurrence. Febrile nonhemolytic reactions are usually caused by acquired antibodies to plasma protein or leukocyte alloantigens and occur exclusively in patients with a history of previous transfusion or pregnancy. Pretreatment of the patient with antipyretic agents, antihistamines, or corticosteroids may alleviate symptoms. Because of the sophisticated quality control measures currently in place in modern blood banks, hemolytic reactions are rare. Fever, chills, pain in the abdomen and lower back, tachycardia, hypotension, hemoglobinuria, renal failure, and shock may be manifestations of a hemolytic reaction caused by major blood group incompatibility. When these symptoms are associated with transfusion, the infusion should be stopped, and a sample of the patient's blood should

be sent to the blood bank along with the remainder of the aborted RBC unit. Delayed transfusion reactions occur 3 to 10 days after transfusion, are caused by minor blood group sensitization from previous transfusion, and are usually less severe than reactions due to major blood group incompatibility.

The risk of transfusing infectious agents in blood products has been reemphasized by the acquired immunodeficiency syndrome (AIDS) epidemic. Although less than 5% of AIDS cases have been caused by blood transfusion, fear of acquiring the human immunodeficiency virus (HIV) from transfused blood products remains high because of the associated risk of mortality. Preferential collection of blood products from volunteer donors and HIV screening have reduced the risk for HIV transmission to 1 in 2.3 million units of blood product transfused.[119]

The risk of transmitting certain hepatitis viruses, CMV, and Epstein-Barr virus must also be considered when ordering transfusions. Screening for hepatitis B and hepatitis C has had a positive effect on reducing the risk of acquiring these viruses from transfusions; hepatitis A is not considered to be a risk of transfusion. With the use of volunteer donors and screening for the hepatitis B antigen, the incidence of transfusion-acquired hepatitis B has fallen to 1 in 280,000 transfusions.[120] The use of hepatitis B vaccine for patients who are likely to receive multiple transfusions is a recommended practice. A screening test is now used to detect the hepatitis C virus in the blood of potential donors, and the use of this test has resulted in a risk of 1 in 1.8 million for acquiring this infection through transfusion.[119] CMV is carried in transfused lymphocytes, and infusion of such lymphocytes in immunodeficient individuals can cause serious infection. Use of frozen or washed RBCs, blood products from CMV-negative donors, or leukocyte-reduced RBCs reduces the risk of acquiring CMV-related illness for immunodeficient individuals.[121,122]

Graft-versus-host disease is a potential transfusion-related problem for immunodeficient individuals. This disorder, which is well documented to occur after allogeneic bone marrow transplantation, has been recognized in an increasing number of immunodeficient patients receiving transfusions and in other patients who happen to share an HLA haplotype with the donor. Transfusion-associated graft-versus-host disease (TA-GVHD) has been reported from many countries and centers.[123,124] High fever, scaly maculopapular erythematous rash, diarrhea, hepatocellular damage with morbid elevation of liver enzyme levels, and pancytopenia characterize TA-GVHD. The disorder typically occurs in adults 8 to 12 days after transfusion, whereas in newborns TA-GVHD typically presents as fever on day 28 after transfusion.[123] Overall mortality remains greater than 90%, with most deaths occurring within 1 month of onset.[123,124] Steroids, antithymocyte globulin, cyclophosphamide, and anti–T-cell monoclonal antibodies have been disappointing in the treatment of this disease. TA-GVHD is readily avoided by irradiation of all cellular blood products to be transfused to immunodeficient patients and others at risk of TA-GVHD. Irradiation of cellular products with doses of 2500 to 3000 cGy lethally damages lymphocytes without adversely affecting the function of RBCs, platelets, and neutrophils.[123] The treated blood product is not radioactive and can be handled by hospital personnel in the usual fashion. TA-GVHD has not been demonstrated definitively to occur after transfusion of fresh frozen plasma or frozen RBCs.[124]

Transfusion-related acute lung injury (TRALI) is now the leading cause of transfusion-related morbidity and mortality worldwide,[125,126] given the reductions achieved in infectious risk and hemolytic transfusion reactions. The pathophysiology relates to transfusions of biologically active substances in the blood product; these include donor antibodies that cross-react with leukocyte antigens in the host and lipids and other biologic response modifiers that accumulate in blood during storage.[125] In 2004, the National Heart, Lung, and Blood Institute convened a working group to develop a consensus definition of TRALI.[127] The criteria include

- Satisfying the criteria for acute lung injury (ALI)[128]:
  - Hypoxemia
  - Bilateral infiltrates on chest radiograph
  - Pulmonary artery occlusion pressure less than 18 mm Hg or no clinical evidence of left atrial hypertension
- Onset of signs and symptoms less than 6 hours after transfusion
- No ALI may have been present before transfusion

The patient's clinical course should determine whether the ALI is related to the transfusion. Critically ill patients are those most at risk for TRALI, with the risk factors including septic shock, pulmonary sepsis, aspiration, multiple transfusions, drug overdose in the ICU, long-bone fracture, pulmonary contusion, cardiopulmonary bypass, and burn.[125] Further, there is an independent, dose-dependent relationship between transfusion and the subsequent development of ALI. Mortality rates range from 6% to 15%, with the rate rising to 41% for patients in the ICU.[125,126] The differential diagnosis includes transfusion-associated circulatory overload, an anaphylactoid transfusion reaction, and transfusion of contaminated blood products.[125] Signs and symptoms include severe dyspnea, tachypnea, worsening or new hypoxemia, fever, occasional hypotension, and cyanosis temporarily related to receiving a transfusion.[126] Treatment centers on ventilatory support, fluid management, and reduction in transfusions.[125] If transfusions are necessary, consideration should be given to using washed RBCs and possibly the use of male-only plasma-containing blood products.[125,126] The differentiation of TRALI from transfusion-associated circulatory overload and circulatory overload is accomplished by careful evaluation of clinical signs and symptoms.[129,130]

# Platelet Transfusion

The normal platelet count in children and adults ranges from 150,000/μL to 450,000/μL[131]; levels in newborns are occasionally as low as 100,000/μL.[132] Once released into the bloodstream, platelets circulate for approximately 8 to 10 days. Patients with platelet counts less than 10,000/μL are clearly at risk for hemorrhage,[133,134] whereas individuals with platelet counts less than 50,000/μL carry a risk for bleeding during surgical intervention.[135] Replacing circulating platelets with a transfusion of platelet concentrate reduces the risks for spontaneous bleeding in patients with platelet counts less than 10,000/μL and of intraoperative and postoperative bleeding in individuals with platelet counts less than 50,000/μL.[136]

Random donor concentrates are obtained from whole blood collections through a two-step centrifugation procedure.[137,138] An initial soft spin brings down the RBCs and leaves the platelets suspended in the supernatant plasma. The platelet-rich plasma is then centrifuged at high speeds to pellet the platelets, resulting in a platelet button that is resuspended in 50 mL of plasma. The platelet concentrate is then stored at 20°C to 24°C for up to 5 days. The pH of the concentrate should be maintained at 6.0 or higher.

Single-donor platelets are collected by apheresis techniques; approximately $3 \times 10^{11}$ platelets, which is equal to four to six individual concentrates, are contained in 200 to 3600 mL of plasma.[139] These platelets can be stored for up to 5 days. Single-donor collections are useful for transfusion in patients who have become alloimmunized to random donor concentrates. Identification of compatible single donors through trial and error or by HLA matching prospective donors often results in greater augmentation of the platelet count after transfusion for patients with alloantibodies to platelets. The use of 1-hour posttransfusion platelet counts in patients who are apparently alloimmunized to random donor platelet concentrates is of value in determining the need for single-donor or HLA-matched platelets.[140] If the patient is not septic or sequestering platelets in the spleen, failure to demonstrate an increase in the circulating platelet count 1 hour after transfusion of random donor concentrates usually indicates the existence of platelet alloantibodies. Platelet concentrates are usually used for patients with thrombocytopenia and concomitant bleeding or thrombocytopenia of sufficient magnitude to impart a significant threat of bleeding during surgery or other invasive procedures. When surgery or invasive procedures are required, administration of prophylactic transfusions to thrombocytopenic patients is reasonable for platelet counts less than 50,000/μL.[135] The same threshold for platelet transfusion is reasonable for patients with head trauma and thrombocytopenia. Many oncology centers transfuse patients with cancer in a prophylactic manner, with the threshold for transfusion ranging from 10,000 to 30,000/μL.[134,141,142] Data suggest that minimal risk for bleeding exists when the platelet count is greater than 10,000/μL provided that the patient is afebrile and uninfected. Finally, it is important to consider that platelet concentrates can be used to stop bleeding resulting from impaired platelet function (e.g., Glanzmann thrombasthenia, Bernard-Soulier syndrome) or in acquired platelet functional defects (e.g., aspirin ingestion).

To stop bleeding in a patient with thrombocytopenia, an increase in the platelet count of about 40,000/μL is thought to be necessary.[143] For children, 0.1 U of concentrate per kilogram of body weight usually produces an increment of 40,000 to 50,000/μL; similarly, 4 U/m$^2$ of body surface area accomplishes the same result.[143] In clinical practice, a minimum of 2 U of platelet concentrate is administered, even to infants. This algorithm can be applied to meet the needs of patients with thrombocytopenia undergoing surgery. A platelet count obtained 1 hour after the platelet transfusion usually provides an accurate assessment of the increment achieved; in bleeding patients, cessation of bleeding is the ultimate index. The half-life of transfused platelets averages approximately 4 days; concomitant fever, infection, or conditions favoring platelet consumption decrease platelet survival.[144] The use of ABO-compatible platelets may lengthen survival, although this is controversial.[144,145] Use of single-donor platelets or HLA-matched platelets often lengthens platelet survival in an allosensitized recipient. When a patient demonstrates increments of less than 10,000/μL on two or three successive administrations of random donor platelets, consideration should be given to using single-donor or HLA-matched platelets. However, if a patient with thrombocytopenia is a candidate for bone marrow transplantation from a related donor, use of matched platelets from family members should be avoided to prevent sensitization to minor antigens, because this might increase the potential for graft rejection.

Platelet concentrates are administered through blood filters. The standard 170-μm screen filters remove blood clots and are commonly used to administer platelet concentrates.[146,148] Contemporary microaggregate blood filters remove lymphocytes while allowing platelets to pass through. These filters may reduce the risk for febrile transfusion reactions and may prevent sensitization to HLA antigens through the removal of lymphocytes.[146] However, filters used to prepare leukocyte-reduced RBCs should not be used to transfuse platelet concentrates because they also remove most of the platelets.[147] Irradiation of platelet units to 2500 cGy is appropriate to lower the risk for GVHD in high-risk patients. Platelet function measured by in vitro assays is not altered by this dose of radiation.[148,149]

Small amounts of Rh-positive RBCs in platelet concentrates may be sufficient to stimulate the production of anti-D in Rh-negative individuals.[143,150] Administration of Rh immune globulin may prevent this sensitization in Rh-negative female recipients of platelet concentrates. Transfusion reactions caused by leukoagglutinins that combine with leukocytes and platelets may occur during or shortly after a platelet transfusion.[139,143] Fever and rigor are often associated with reactions to platelet transfusions. Decreasing the rate of infusion may reduce the risk of a febrile reaction. Acetaminophen, intravenous corticosteroids, and parenteral meperidine can be used to ameliorate this type of reaction. Allergic transfusion reactions are characterized by hives and occasional hypotension or bronchospasm.[139,143] Antihistamines and occasionally epinephrine are useful to treat allergic reactions.

A small risk for the transmission of viral infection is associated with the transfusion of platelet concentrate. In addition, because platelets are stored at room temperature, the possibility of bacterial contamination must be considered when patients who have undergone transfusion experience fever, chills, hypotension, or DIC.

*The complete reference list is available online at www.expertconsult.com.*

# CHAPTER 12

# Nutritional Support in the Pediatric Surgical Patient

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The development of modern nutritional support is the result of numerous investigators' contributions during the past 350 years. The first known person to attempt to deliver intravenous nutrition was Sir Christopher Wren, the architect of St. Paul's Cathedral in London, in 1658. Wren used hollow goose quills to infuse wine into dogs. In the 18th century, Claude Bernard, the first modern physiologist, infused numerous substrates into animals. He discovered that intravenously administered sugars could be effectively metabolized only if they were predigested by gastric juices. Thus it was then that the first understanding of the digestion of carbohydrates took hold.[1] In the 1930s, Elman[2] delivered the first successful infusion of protein, as hydrolysates of casein, into patients. In 1949, Rhoads and Vars[3] developed an apparatus for a continuous infusion of intravenous substances into dogs. It was used to definitively show that weight gain could be achieved in puppies by means of intravenous nutrition. Critical refinements in the intravenous solutions, filtration of the infusate, and the use of a central venous catheter allowed Dudrick to infuse concentrated solutions of glucose and amino acids into patients.[4–6] This technique rapidly changed the ability to parenterally nourish adult and pediatric patients. One of the most dramatic cases of the use of parenteral nutrition (PN) was in a newborn with jejunoileal atresia; the infant was maintained by this route for more than 22 months and had weight gain and increased head circumference.[6] Application of this technique in other infants led to dramatic improvements in survival of patients who previously would have died after surgical correction of their congenital anomaly. The past 50 years has led to dramatic developments in both specialized enteral and parenteral products for infants and children.

## Normal Pediatric Growth

Growth and development are unique features to pediatric patients that greatly affect the goals and objectives of nutritional support. The term newborn infant grows at a rate of 25 to 30 g per day during the first 6 months of life, leading to a doubling of the birth weight by 5 months of age.[7] The average infant triples the birth weight by 12 months. By 3 years of age, the weight is 4 times the birth weight, and by completion of the first decade, the weight increases 20-fold. Body length increases by 50% by the end of the first year of life and increases threefold at the end of the first decade of life. The preterm infant's growth pattern is quite distinct from term infants. Most nutrients are accumulated by the fetus in the third trimester of pregnancy. Thus fat accounts for only 1% to 2% of body weight in a 1-kg infant compared with 16% in a term (3.5-kg) infant. An anticipated loss of 15% of a preterm infant's birth weight is usual in the first 7 to 10 days of life, compared with a 7% to 10% weight loss for a term infant, both of which comprise a shedding of excess body water. After this initial period of weight loss, a preterm infant of less than 27 weeks' gestation gains weight at a slower rate of approximately 10 to 20 g per day, because he/she has not yet entered the accelerated weight gain of the third trimester.[8]

## Nutritional Assessment

Nutritional assessment is a critical aspect of the initial evaluation of all surgical patients.[9] The incidence of malnutrition in surgical patients has been well documented in several reviews, and this group comprises 35% to 45% of inpatients.[10] Classical work by Cooper and colleagues[11] showed that 18% to 40% of pediatric surgical patients have malnutrition. This rate of malnutrition has also been shown in other pediatric patients.[12] Aside from surgery, other patients at risk for malnutrition include those with large open wounds with concomitant loss of protein and increased metabolic needs, extensive burns, blunt trauma, and sepsis. An important question is how long the gastrointestinal tract will be dysfunctional after major surgery; this information must be integrated into the nutritional support delivered in the perioperative period. Nutritional assessment can be divided into subjective and objective components. Two basic tools are available: the Mini Nutrition Assessment[13] and the Subjective Global Assessment (SGA). The SGA is performed during the history and physical examination. This should include an evaluation of weight loss

(5% for mild to 10% for moderate to severe malnutrition), anorexia, vomiting, and physical evidence of muscle wasting (indicative of severe malnutrition), and modifications of this have been made for pediatrics, though not as well validated as for adults.[14] SGA has been shown to be an accurate mode of assessing malnutrition for both inpatients as well as non-hospitalized patients. Additionally, although not fully substantiated in young children, both of these nutrition tools have been directly correlated with Acute Physiology and Chronic Health Evaluation (APACHE) II scores and hospital mortality in surgical patients[15,16] The objective portion of the assessment begins with the basic anthropometric measurements of height, weight, and head circumference. Measurements are placed on a standardized growth curve, such as that of the National Center for Health Statistics. From these growth charts, the expected weight for height index can be calculated. As length and head circumference are less affected by excess fat or postoperative fluid fluctuations, length is an excellent indicator of long-term body growth. Acute changes in nutritional status will have a more immediate effect on body weight than length and will decrease the child's weight for height index. Chronic undernutrition, however, will result in a lag in both height and weight. These changes in growth are probably best expressed using a Z-score for weight for length ratios as well as weight, length, and head circumference for age. A number of automated and free software programs are available for such evaluations, such as from the World Health Organization (WHO Anthro [version 3.1, June 2010]). Once patients are more than 2 years of age, this can best be reflected by the child's body mass index (BMI); however, expression of BMI as a Z-score can often add a very useful perspective. Special growth charts are also available for monitoring the growth of children with special health-care needs (e.g., Down syndrome, Prader-Willi syndrome, myelomeningocele, achondroplasia, cerebral palsy). Use of these can give a very important perspective about where a child's growth should lie.[17] An increasingly important group of patients to assess nutrition on are those children with obesity.[18] Assessment of such children requires a high index of suspicion. Although BMI measures weight rather than adiposity, it is still regarded as one of the best tools to perform this assessment, and it is a fairly strong predictive of adult obesity and associated medical complications resulting from an obese state.[19]

### BIOCHEMICAL MEASUREMENTS OF NUTRITIONAL STATUS

Serum albumin level has been used as an indication of chronic nutritional status. However, albumin turnover is slow ($t_{1/2}$ of 20 days). Therefore other plasma proteins, such as prealbumin binding protein ($t_{1/2}$ of 2 days) and retinol-binding protein ($t_{1/2}$ of 12 hours) are indications of a more current nutritional status. There are no established norms for prealbumin or retinol-binding protein in infants and young children.[20] Further, visceral proteins lack specificity under stress and inflammatory conditions, and they are affected by non-nutritional factors. Therefore their levels should be interpreted in the context of nutritional history, underlying diseases, and medication therapy. Ideally, a baseline level is obtained, and then subsequent levels may be used to establish the effects of disease and/or nutritional supplementation. Other parameters that can be useful for measuring nutritional status include bone age and dental status. Malnutrition is a common cause of delayed bone maturation.[21]

### DIRECT MEASUREMENT OF BODY COMPOSITION

Various methods have been created during the past 25 years to more directly measure the body composition of adults and children. Although many of these methods are not readily accessible to most clinicians and, rather, are used for experimental purposes, some, are becoming more commonly used in pediatric clinical settings. Measurement of body water has been done for several years using isotope dilution techniques. This is based on the principle that fat is anhydrous so that most of the isotope is directed into the water compartments of the body.[22] This assumption is not always true; however, such measurements can give an excellent indication of approximate amounts of body fat and water.[23,24] Bioelectrical impedance analysis uses the measurement of the body's impedance to a flow of electrical current as a measure of total body water. Extrapolation of these measurements can allow for the determination of other body compartments, including total body adipose tissue. More recently, dual photon absorptiometry and dual energy x-ray absorptiometry have been used to measure bone mineral content and amounts of fat and body water.[25,26] The accuracy of the instruments is excellent, and because of the low amounts of radiation exposure, dual energy x-ray absorptiometry is becoming the method of choice for measuring pediatric body composition. Standards have only been established down to approximately 6 to 8 years of age[27]; therefore further work is required to understand the use of these measures in small children and infants.

## Nutritional Requirements

### ENERGY REQUIREMENTS

The energy needs of infants and children are unique. Estimates of premature infants show that a 1-kg infant has only a 4-day nutritional reserve, and a full-term infant may live for no more than 1 month without nutrition.[28,29] In children, energy is required for maintenance of body metabolism and growth. A gross estimate of calorie expenditure can be obtained by using the Dietary Reference Intakes (DRIs) for energy requirements, based on the child's age, weight, height, and physical activity, and also based on the Food and Nutrition Board, Institute of Medicine, and National Academy of Sciences guidelines (Dietary Reference Intakes: Recommended Intakes for Individuals in 2006) (http://www.iom.edu/Reports.aspx). Predictive equations (e.g., from the World Health Organization, Schofield equations, and so forth) provide an estimate of the resting energy expenditure (REE), but none are extremely accurate. Other estimates use the amount of calories per length or height for children with chronic health conditions and special health-care needs (e.g., Down syndrome, Prader-Willi syndrome, myelomeningocele, and cerebral palsy; see Table 12-13).

Energy requirements vary depending on age as well as the physiologic status of the child (Table 12-1). Periods of active growth and extreme physical activity will increase energy requirements. The average distribution of kilocalories in

**TABLE 12-1**
**Energy Requirements**

| Daily Energy Requirements (Total kcal/kg) for Pediatric Patients | |
|---|---|
| Preterm neonate | 90-120 |
| <6 months | 85-105 |
| 6-12 months | 80-100 |
| 1-7 years | 75-90 |
| 7-12 years | 50-75 |
| >12-18 years | 30-50 |

Mirtallo J, Canada T, Johnson D: Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr 2004;28:S39-S70.

**TABLE 12-2**
**Daily Fluid Requirements for Pediatric Patients**

| *Body Weight* | *Amount* |
|---|---|
| <1500 g | 130-150 mL/kg |
| 1500-2000 g | 110-130 mL/kg |
| 2-10 kg | 100 mL/kg |
| >10-20 kg | 1000 mL for 10 kg + 50 mL/kg for each kg >10 |
| >20 kg | 1500 mL for 20 kg + 20 mL/kg for each kg >20 |

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a well-balanced diet is as follows: protein, 15%; fat, 35%; and carbohydrate, 50%. Although careful clinical examination is important in making a determination of the child's status, Baker and colleagues[30] showed that the depleted state could not be reliably detected on the basis of the weight-to-height ratio, triceps skinfold, mid–upper arm circumference, hand strength, albumin concentration, total protein level, or creatinine-to-height ratio. Actual measurement or estimation of metabolic rate and energy needs is the best method of following the nutritional status. Commonly used nomograms may significantly underestimate or overestimate energy expenditure.[31–33] One of the most accurate methods of measuring energy expenditure is indirect calorimetry.[34] In indirect calorimetry, carbon dioxide ($CO_2$) production and $O_2$ consumption are measured using a metabolic cart. The sample is best measured in intubated infants, yielding a resting energy expenditure. The energy expenditure or metabolic rate, as measured in cubic centimeters of oxygen per minute, can be converted to calories per hour or per day, if the substrates are known. All measurements are only approximations of caloric needs, for which the surgeon must further adjust according to the clinical course of the patient. Such measurements give an excellent way to monitor patients, particularly those children who are in an intensive care unit setting.[35] In contrast to adults, the rise in REE post-surgery is much less. Mitchell and colleagues[33] found that the REE of postoperative cardiac patients fell to values less than those of normal healthy children who had not undergone surgery. This finding was also confirmed in the study by Letton and colleagues,[36] who examined energy expenditure in young infants in the postoperative period. These studies suggested that reliance on recommended daily allowance (RDA) values may result in overfeeding postoperative children (see the section on complications from overfeeding later). Measurements are critical, because those infants starting with poor nutritional status, or more aggressive surgery (e.g., cardiopulmonary bypass), may have significantly greater energy needs.[37] Indirect calorimetry, however, may be difficult in young infants with uncuffed endotracheal tubes, where an air leak may lead to significant inaccuracies in results. Typically, parenteral energy requirements are lower than enteral or oral requirements because of less thermogenesis with the parenteral route and absence of energy loss in stools.

## WATER

The water content of infants is higher than that of adults (75% of body weight versus 65%) and is proportional to muscle mass. Fluids provide the principal source of water; however, some water is derived by the oxidation of food and body tissues. Requirements for water are related to caloric consumption; so, infants must consume much larger amounts of water per unit of body weight than adults. In general, calorie requirements (kcal/kg/day) are matched to the amount of fluid needs mL/kg/day). The daily consumption of fluid by healthy infants is equivalent to 10% to 15% of their body weight, in contrast to only 2% to 4% by adults. In addition, the normal-content food for infants and children is much higher in water content than that of adults; the fruit and vegetables consumed by infants and children contain about 90% water. Only 0.5% to 3% of fluid intake is retained by infants and children. About 50% is excreted through the kidneys, 3% to 10% is lost through the gastrointestinal tract, and 40% to 50% is insensible loss. Estimation of daily maintenance fluid requirements in infants and children are shown in (Table 12-2).[38]

## PROTEIN

The requirement for protein in infants is based on the combined needs of growth and maintenance (Table 12-3). Two percent of the infant's body weight, compared with 3% of the adult's body weight, consists of nitrogen. The average intake of protein should comprise approximately 15% of total calories administered. Two percent of an infant's body weight, compared with 3% of an adult's body weight, consists of nitrogen. Most of the increase in body nitrogen occurs during the first year of life. The nutritional value of protein is based not only on the amount of nitrogen available but also on the amino acid composition of the protein.[39] Protein provides 4 kcal/g of energy and should be included in estimates of energy (caloric) delivery. Twenty amino acids have been identified, of which eight amino acids (phenylalanine, valine, threonine, tryptophan, isoleucine, methionine, leucine, lysine) are generally considered essential for humans, with an additional four amino acids (cysteine, tyrosine, arginine, histidine)

**TABLE 12-3**
**Daily Protein Requirements (g/kg) for Pediatric Patients***

| | |
|---|---|
| Preterm neonates | 3-4 |
| Infants (1-12 months) | 2-3 |
| Children (>10 kg or 1-10 years) | 1-2 |
| Adolescents (11-17 years) | 0.8-1.5 |

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*Assumes normal age-related organ function.

considered conditionally essential in infants. New tissue cannot be formed unless all of the essential amino acids are present in the diet simultaneously; the absence of only one essential amino acid will result in a negative nitrogen and protein balance. Further, the use of taurine supplementation has been shown to decrease the severity of PN-associated cholestasis.[40] It has also been suggested that proline is essential in preterm infants, although this has yet to be confirmed.[41]

Protein requirements are typically based on age and adjusted based on nutritional status, stress level, severity and type of injury, kidney and liver functions, and other clinical conditions. In general, estimated protein requirements for children based on age are: 0 to 2 years, 2 to 3 g/kg/day; 2 to 13 years, 1.5 to 2 g/kg/day; and 13 to 18 years, 1.5 g/kg/day.[42] Protein requirements are markedly higher in term neonates and infants ranging from 2 to 3 g/kg/day. This estimate is based on several sources. Extrapolation of data on fetal absorption across the placenta during the last trimester indicates protein needs to be 2.2 g/kg/day.[43,44] Delivery of greater amounts of protein to neonates has generally been associated with elevated blood urea nitrogen levels. Protein requirements in premature infants are higher than term infants and range from 3 to 3.5 g/kg/day.[44,45] Such delivery is critical to provide optimal growth and neurodevelopment in infants. In very-low-birth-weight infants, this requirement may approach 3.85 g/kg/day.[46] Such added protein loads must be balanced against the immaturity of the renal system, and the development of uremia should be monitored.[47,48] In particular, taurine is essential for normal neural and retinal development.[49]

Two amino acids that may have significant benefit to the integrity of the gastrointestinal mucosa and the immune status of patients are glutamine and arginine. Although these amino acids are not truly essential, the organism may require additional usage of these during periods of stress. Glutamine has been shown to prevent PN-associated atrophy of the intestine in animals, however, and possibly in humans.[50,51] The efficacy of glutamine in bowel adaptation has been called into question.[52–54] However, a recent meta-analysis of all clinical studies using glutamine showed that glutamine dipeptide significantly reduced the length of hospital stay, and decreased risk of infectious complications rates in surgical patients.[55] Arginine has also been shown to improve nitrogen retention, wound healing, and the immune status.[56,57] However, at least in animal models, early administration of arginine has been shown to worsen the prognosis of animals, because of the activation of nitric oxide within the gastrointestinal tract.[58]

## CARBOHYDRATES

Carbohydrates provide a major and most immediate source of energy through parenteral and enteral routes. Carbohydrates can be provided in one of three ways: monosaccharides (glucose and fructose), disaccharides (lactose, sucrose, and maltose), and complex carbohydrates (starches). Because the body is capable of forming sugars from amino acids, no essential amount of carbohydrate has been defined. However, the addition of small amounts of carbohydrates prevents breakdown of somatic protein sources and thus acts as a protein-sparing substrate.[59] This effect leads to suppression of endogenous glucose production as well as to endogenous glucose oxidation, thereby preventing the oxidation of amino acids that have been derived from skeletal muscles. The body has a limited ability to store glucose, although the substrate is essential and almost continuously needed by the central nervous system. Dextrose is the most common source of carbohydrate, and it yields 3.4 kcal/g. Glucose metabolism may occur aerobically through the tricarboxylic acid cycle, theoretically yielding a maximum of 38 moles of adenosine triphosphatase (ATP)/mole of glucose. Anaerobically, glucose metabolism through the glycolytic cycle yields 2 moles of ATP/mole of glucose, with lactic acid as an end product. Glucose is formed in the liver by means of gluconeogenesis (formation of glucose from noncarbohydrates precursors), which uses alanine and other amino acids from skeletal muscle and lactic acid from the breakdown of glycogen in skeletal muscle through the Cori cycle. Immediately after a meal, glucose absorption contributes to the bulk of circulating glucose. As soon as 4 hours after the meal, these sources are rapidly depleted, and glycogen from the liver becomes a major source of energy for the next 8 to 12 hours. Newborn infants have relatively limited glycogen reserves (34 g), most of which reside in the liver. Thus relatively short periods of fasting can lead to a hypoglycemic state.

The primary enteral carbohydrate delivered to neonates and young infants is lactose.[3] Lactose is broken down into glucose and galactose in the intestines by disaccharidases (e.g., lactase), which are located along the intestinal epithelial border. Because lactose is the predominant carbohydrate of small children, lactase levels remain sufficiently high in most infants until they are at least 2 or 3 years of age. Nonlactose formulas that are soy-based and contain sucrose or corn syrup may provide adequate amounts of carbohydrates (see Enteral Nutrition later). Preterm infants may be unable to digest certain carbohydrates, particularly lactose, because lactase activity in the intestines is inadequate. Thus for premature infants, formulas that have a 50/50 mixture of lactose and glucose polymers are ideal.

Supplementation with inadequate amounts of carbohydrates may lead to a ketotic state, whereby fat and muscles are broken down for gluconeogenesis. Stable infants should receive approximately 40% to 45% of their total caloric intake as carbohydrates. Glucose intolerance does occur and is not only manifested by hyperglycemia but also commonly by hypertriglyceridemia (see the section on hyperglycemia later). Delivery of carbohydrates in amounts greater than the body can use will result in hyperglycemia and lipogenesis (see the section on complications from enteral feeding later).

## FAT

Intravenous lipids have the highest caloric density of the three major nutrients (9 kcal/g). In general, intravenous lipids should comprise between 30% to 50% of all non-nitrogen calories. Lipids have the advantage of being an excellent source of energy and essential fatty acids (EFAs). Linoleic acid is essential for neonates, older children, and adults. Deficiencies of linoleic acid may occur rapidly in neonates. Withholding lipids from the PN of a neonate for as few as 2 to 3 days may lead a biochemical deficiency of fatty acids.[60,61] A deficiency of fatty acids in infants may result when less than 1% of the caloric intake is linoleic acid; in general, 2% to 4% of dietary energy should come from essential fatty acids. Manifestations of fatty acid deficiency include scaly skin, hair loss, diarrhea, thrombocytopenia, and impaired wound

healing.[62] Absence of trace amounts of linolenic acid may also be the cause of visual and behavioral disorders. Fatty acids are an excellent source of energy to all tissues of the body except erythrocytes and the brain. With time, however, the brain can also use fatty acids as an energy source once they are converted to ketones. Fatty acids are carried into the mitochondria for β-oxidation by the carnitine transferase system (see later).

Essentially, two types of fatty acids exist: saturated and unsaturated. Saturated fatty acids lack double carbon bonds and are generally derived from animals. Unsaturated fatty acids have at least one double bond, the position of which is designated by a prefix omega (ω). The two major polyunsaturated fatty acids are linoleic acid, which is an ω-6 fatty acid, and α-linolenic acid, which is an ω-3 fatty acid. Omega-6 fatty acids are usually derived from plants, and ω-3 fatty acids are usually derived from fish oils. Both of these polyunsaturated fats are essential for the development of cell membranes and the central nervous system (CNS), as well as for the synthesis of arachidonic acid and related prostaglandins. Thromboxanes derived from ω-6 fatty acids are potential mediators of platelet aggregation, whereas thromboxanes, derived from ω-3 fatty acids, are potent anticoagulants, as well as docosahexaenoic acid (DHA), which has important roles for CNS development and modulation of inflammatory conditions. Further, ω-6 fatty acids, which form arachidonic acid, also contribute to the formation of prostaglandin (PG) $E_2$, a known immunosuppressant, whereas ω-3 fatty acids contribute to the formation of $PGE_1$ and $PGE_3$, which do not have an immunosuppressive effect. A 1:1 ratio of ω-6 to ω-3 fatty acids seems to be ideal, based on experimental data from animals that survived burns.[63] No data are available on the ideal ratio in neonates or children.

Essential fatty acid deficiency shows an elevated triene-to-tetraene ratio of greater than 0.2, where trienes consist of 5,8,11-eicosatrienoic acid and tetraenes consist of linoleic and arachidonic acids and an eicosatrienoic/arachidonic acid, and low plasma levels of one or more of the essential fatty acids. Overall, any infant not receiving the full amount of lipids should be monitored at least once a month for essential fatty acid deficiency. Absolute values of linoleic and 1-linolenic acid can be ordered, and actually may yield a better perspective for the clinical development of EFA deficiency.

## MINERALS, TRACE ELEMENTS, AND VITAMINS

The normal daily requirement of vitamins has been recently revised by the Food and Drug Administration.[64] Vitamins are essential components or cofactors of various metabolic reactions. Most commercial infant formulas contain adequate amounts of vitamins to meet known daily requirements. Such requirements were established by the American Medical Association (AMA) in the 1970s.[65] Infants who receive other types of formula or human milk may require additional vitamin supplementation.

### Fat-Soluble Vitamins

***Vitamin A*** Vitamin A is principally stored in the liver and is involved in formation of retinoic acid for vision and the coordination of cell cycles. Deficiencies of vitamin A may lead to night blindness, xerophthalmia, poor growth, and impaired resistance to infection. It is also clear, however, that low levels of vitamin A predispose infants to long-term pulmonary disease, and vitamin A levels are low in such infants.[66] In a recent Cochrane review, eight studies were reviewed, and it was found that vitamin A supplementation was associated with a prevention in the development of bronchopulmonary dysplasia (BPD).[67] Neurodevelopment at 18 to 22 months of age was not different between those treated with and without vitamin A. Excessive amounts of vitamin A can be quite deleterious to infants. As little as 6000 μg of retinol daily can produce anorexia, desquamation of the skin, and increased intracranial pressure.[68]

***Vitamin D*** Vitamin D is essential for bone formation and mineral homeostasis. A deficiency may occur with fat malabsorption; however, overuse of vitamin D may lead to hypercalcemia.[69] Most formulas contain adequate amounts of vitamin D (approximately 60 IU/100 kcal). No evidence to support the supplementation of vitamin D to infants for better bone growth beyond that provided by standard formulas exists. During the past decade, a greater appreciation of the link between deficient immune status and low vitamin D levels has been examined in pediatric children. In fact, this association may account for an increased risk of pediatric asthma and food allergies.[70]

***Vitamin E*** Vitamin E seems to have significant antioxidant affects. Vitamin E may prevent the neuropathy seen in infants with biliary atresia as well as muscle weakness in children with cystic fibrosis.[71] The dose of vitamin E required for full-term infants is approximately 0.7 IU/100 kcal of energy intake. Because of its antioxidant action, vitamin E has been used to decrease lung injury in neonates with bronchopulmonary dysplasia. It does appear that usage of vitamin E is beneficial in this regard.[72] It also appears that vitamin E is beneficial in the prevention of retinopathy in premature infants[73]; and it may have a benefit in reducing the incidence of intraventricular hemorrhage.[74]

***Vitamin K*** Vitamin K is required at birth to prevent coagulopathy in newborns and should be administered soon after delivery.[75] Vitamin K is included in most formulas; however, larger amounts may be needed in infants with prolonged episodes of diarrhea. Assessment of deficiencies is most readily done by attaining a prothrombin time.

### Water-Soluble Vitamins

Deficiencies of water-soluble vitamins are rare in formula-fed and breast-fed babies. B vitamins are needed for carbohydrate, protein, and fat metabolism as well as oxidation and reduction reactions. Deficiencies may be seen with short-bowel syndrome and manifest as chelosis and lethargy. Abnormal levels of vitamin $B_1$ (thiamine) are generally the first signs of vitamin B deficiency and can be detected with an erythrocyte transketolase enzyme assay. Vitamin C is required for optimizing several enzyme reactions and has direct antioxidant effects. Excessive amounts of vitamin C may lead to nephrolithiasis and interference with vitamin $B_{12}$ absorption.

**TABLE 12-4**
**Daily Parenteral Trace Element Requirements and Supplementation in Parenteral Nutrition According to the ASPEN Guidelines**

| *Age Group* | *Zinc* | *Copper* | *Manganese* | *Chromium* | *Selenium* |
|---|---|---|---|---|---|
| Adults (mg/day) | 2.5-5 | 0.3-0.5 | 0.06-0.1 | 0.01-0.015 | 0.02-0.06 |
| Adolescents > 40 kg (mg/day) | 2-5 | 0.2-0.5 | 0.04-0.1 | 0.005- 0.015 | 0.04-0.06 |
| Preterm infant < 3 kg (μ/kg/day) | 400 | 20 | 1 | 0.05-0.3 | 1.5-2 |
| Term infant 3-10 kg (μ/kg/day) | 50-250 | 20 | 1 | 0.2 | 2 |
| Children 10-40 kg (μ/kg/day) | 50-125 | 5-20 | 1 | 0.14-0.2 | 1-2 |

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ASPEN, American Society for Parenteral and Enteral Nutrition.

### Trace Elements

Trace elements comprise less than 0.01% of the total body weight in humans.[76] They often function as metalloenzymes, which maximize enzymatic reactions, but may also act as soluble ionic cofactors or nonprotein organic molecules. Without supplementation, specific deficiencies of many of these factors have been manifested clinically in patients maintained on long-term PN as well as those with short-bowel syndrome or malabsorptive conditions. Table 12-4 lists the recommended doses of trace elements.

***Zinc*** Zinc has several biochemical functions, including formation of metalloenzymes, ribonucleic acid (RNA) conformation, and membrane stabilization.[77] In addition, zinc seems to play a critical role in the maintenance of a normal immunologic system. Deficiencies in zinc can arise from various sources that are common in pediatric surgical patients; such sources include the short-bowel syndrome, thermal burns, peritoneal dialysis, inflammatory bowel disease, and other causes of diarrhea. Clinical manifestations of zinc deficiency include growth retardation, alopecia, skin lesions (acrodermatitis enteropathica), impaired lymphocyte function, impaired wound healing, and zinc deficiency can actually lead to diarrhea.[78] Supplementation in infants should be a minimum of 400 μg/kg/day. Because gastrointestinal losses can be higher during episodes of diarrhea and sepsis, higher doses are indicated in these instances. In addition, zinc deficiency may impair recovery of the intestines after massive resection.[79]

***Copper*** Copper is a critical trace element for metalloenzyme function. The main site of copper storage, distribution, and excretion is the liver. Copper deficiency has been reported in patients receiving PN formulas that are not supplemented with copper.[80] Manifestations of copper deficiency include microcytic, hypochromic anemia; neutropenia; hypothermia; mental status changes; and, in children, growth retardation and skeletal demineralization. Removal of copper from infants and children may lead to an aplastic anemic condition, which can be fatal.[81]

***Selenium*** During the past decade, selenium has been acknowledged as an essential trace element. Selenium is a component of a selenoenzyme that helps catalyze glutathione peroxidase, an enzyme system that is necessary to reduce free radicals. The most practical way of measuring selenium levels is by assaying glutathione peroxidase activity in erythrocytes. Selenium levels dramatically decline after as few as 6 weeks of PN.[82] Without the addition of selenium, deficiencies are generally manifested by cardiomyopathy as well as by peripheral myositis with associated muscle tenderness.

***Manganese, Chromium, and Molybdenum*** Although no clear-cut cases of manganese deficiency have been documented in the literature, manganese is an essential element for many organisms and is believed to also be essential for humans. Animals that are deficient in manganese show growth retardation and ataxia in the newborn period.[83] Excess deposition of manganese has been shown to occur in both the liver and brain of infants on prolonged PN, and clinicians should have a very low threshold of eliminating Mn from the trace element package of infants who have developed PN-associated liver disease (PNALD).[84] Chromium seems to have its predominant action as a potentiator of insulin action. Deficiencies of chromium can lead to poor glucose tolerance.[85] Molybdenum is important in the oxidative metabolism of purines and sulfur-containing compounds[86] but is not typically supplemented in PN. Deficiencies of molybdenum are associated with increases in serum uric acid levels.

## Enteral Nutrition

Enteral nutrition (EN) includes oral nutritional supplementation and tube feedings. EN should be the primary source of nutrients if the gastrointestinal tract is functional. Even when full feedings are not tolerated enterally, the provision of small volumes of "trophic" feedings may prevent further deterioration of intestinal function.

### INDICATIONS

Infants in a state of good health before surgery or trauma can sustain 5 to 7 days without significant energy intake and without serious systemic consequences, provided that adequate nutritional support is initiated thereafter. Premature infants less than 32 to 34 weeks' gestation do not generally have a maturely coordinated suck and swallow. Feedings must therefore be provided enterally either by bolus every 2 to 3 hours or by continuous feedings. The overall growth patterns are exceedingly poor for premature infants. In addition, the younger an infant's gestational age, the greater the percentage who are discharged with growth restriction. In fact, almost 100% of infants born at 24 weeks' gestational age will be discharged with a diagnosis of growth restriction. Therefore aggressive feeding even within the first 24 hours of life is generally considered advisable. Enteral feedings are begun after the resolution of the postoperative ileus. There are many high-calorie formulas available to address variable needs (Tables 12-5 (infant) and 12-6 (pediatric). Children who have specific

**TABLE 12-5**
**Infant Formulas**

| *Formula* | *kcal/mL* | *Protein (g/L)* | *Protein (% kcal)* | *Protein Source* | *Carbohydrate Source* | *Carbohydrate (% kcal)* | *Fat Source* | *Fat (% kcal)* | *Indications* |
|---|---|---|---|---|---|---|---|---|---|
| Similac Special Care (Ross) | 0.81 | 24 | 12 | Nonfat milk, whey | Lactose, corn syrup solids | 41 | MCT oil, soy oil, coconut oil | 47 | Prematurity |
| Neosure (Ross) | 0.73 | 21 | 11 | Nonfat milk, whey | Lactose, corn syrup solids | 42 | MCT oil, soy oil, coconut oil | 48 | Prematurity, discharge formula |
| Enfamil (Mead Johnson) | 0.67 | 14 | 8.5 | Whey, nonfat milk | Lactose | 43.5 | Palm olein, soy oil, coconut oil, sunflower oil | 48 | Standard |
| Similac (Ross) | 0.67 | 14 | 8 | Nonfat milk, whey | Lactose | 43 | Soy oil, coconut oil, safflower oil | 49 | Standard |
| | 0.81 | 17 | 8 | Nonfat milk, whey | Lactose | 43 | Soy oil, coconut oil, safflower oil | 49 | |
| Prosobee (Mead Johnson) | 0.67 | 17 | 10 | Soy isolate, methionine | Corn syrup solids | 42 | Palm olein, soy oil, coconut oil, sun oil | 48 | Lactose intolerance, galactosemia |
| Isomil (Ross) | 0.67 | 17 | 10 | Soy isolate, methionine | Corn syrup, sucrose | 41 | Soy oil, coconut oil, safflower oil | 49 | Lactose, malabsorption, galactosemia |
| Nutramigen (Mead Johnson) | 0.67 | 19 | 11 | Casein hydrolysate, cystine, tyrosine, tryptophan | Corn syrup solids, modified cornstarch | 41 | Palm olein, soy oil, coconut oil, sun oil | 48 | Protein intolerance |
| Pregestimil (Mead Johnson) | 0.67 | 19 | 11 | Casein hydrolysate, cystine, tyrosine, tryptophan | Corn syrup solids, modified cornstarch, dextrose | 41 | MCT oil, Corn oil, Soy oil, safflower oil | 48 | Protein intolerance, cystic fibrosis, neonatal cholestasis, short-bowel syndrome |
| Alimentum (Ross) | 0.67 | 19 | 11 | Casein hydrolysate, cystine, tyrosine, tryptophan | Sucrose, modified tapioca, starch | 41 | MCT oil, safflower oil, soy oil | 48 | Protein intolerance, neonatal cholestasis |
| Neocate (Scientific Hospital Supplies) | 0.67 | 21 | 12 | Free amino acids | Corn syrup solids | 47 | MCT oil, safflower oil, corn oil, soy oil, sun oil | 41 | Food allergy, protein intolerance, short-bowel syndrome |
| Enfaport Lipil (Mead Johnson) | 1 | 35 | 14 | Calcium caseinate, Sodium caseinate | Corn syrup solids | 41 | MCT oil (84%), soy oil | 45 | Chylothorax, LCHAD deficiency |

LCHAD, long-chain hydroxyacyl-CoA dehydrogenase deficiency; MCT; medium-chain triglyceride.

Composition of infant and pediatric formulas is summarized in Tables 12-5 and 12-6, respectively. Enfamil (Mead Johnson) and Similac (Ross, Columbus, Ohio) both have milk-based proteins and contain lactose as the carbohydrate source. There are only limited reasons to use soy formulas. The soy-based products include Prosobee (Mead Johnson) and Isomil (Ross). Both contain corn syrup solids as a carbohydrate source. Isomil also contains sucrose. Soy formulas are indicated to manage galactosemia and primary or secondary lactase deficiency. Soy formulas should not be used in patients with a documented allergy or intolerance to milk protein, because one third of infants who have an allergen-induced reaction to cow's milk are also intolerant of soy. Therefore a protein hydrolysate or elemental formula is recommended in infants who have milk-protein intolerance. Protein hydrolysates include Nutramigen (Mead Johnson), Alimentum (Ross), and Pregestimil (Mead Johnson). Alimentum and Pregestamil also provide 50% to 55% of fat as medium-chain triglycerides (MCT). If infants have continued symptoms of protein intolerance when ingesting a protein hydrolysate, then an amino acid–based formula may be provided. For the infant population, Neocate (Scientific Hospital Supplies, Gaithersburg, Md.) is the only amino acid–based formula available. Children older than 12 months of age who continue to be intolerant of milk protein may respond well to Peptamen, Jr (Clintec, Chicago, Ill.), which is a whey protein hydrolysate. If an amino acid–based formula is needed in children older than 12 months of age, options include Neocate 1+ (Scientific Hospital Supplies), L-emental (Gala/Gen/Nutrition Medical, Arden Hills, Minn.), and Elecare (Ross). Neocate 1+ and Elecare both have long-chain triglycerides. Sixty-eight percent of the fat in L-emental is derived from MCT. The authors thank Megan Perkowski, RD, for her contribution and editing of this table.

**TABLE 12-6**
**Pediatric Formulas**

| *Formula* | *kcal/mL* | *Protein (g/L)* | *Protein (% kcal)* | *Protein Source* | *Carbohydrate Source* | *Carbohydrate (% kcal)* | *Fat Source* | *Fat (% kcal)* | *Indications* |
|---|---|---|---|---|---|---|---|---|---|
| Pediasure (Ross) | 1.0 | 30 | 12 | Milk protein concentrate, whey protein, soy isolate | Corn maltodextrin, sucrose | 53 | Safflower oil, soy oil, MCT oil | 35 | Standard, oral feeds, tube feeds |
| Boost (Mead Johnson) | 1 | 42 | 17 | Milk | Corn syrup, sucrose | 68 | Canola oil, corn oil, sunflower oil | 15 | Standard, oral feeds, tube feeds |
| Peptamen, Jr (Clintec) | 1.0 | 30 | 12 | Hydrolyzed whey | Maltodextrin | 55 | MCT, soy oil, canola oil | 33 | Short-bowel syndrome, cholestasis, pancreatitis |
| L-emental (GalaGen/ Nutrition Medical ) | 0.8 | 40 | 16 | L-Amino acids | Maltodextrin, modified starch | 82 | Safflower oil | 2 | Short-bowel syndrome, IBD, pancreatitis |
| Elecare (Ross) | 0.67 | 21 | 15 | L-Amino acids | Corn syrup solids | 43 | MCT, safflower oil, soy oil | 42 | Malabsorption, food allergies |
| Suplena (Ross) | 1.8 | 45 | 10 | Sodium caseinate, milk protein isolate | Corn maltodextrin, sucrose | 51 | Safflower oil, soy oil, canola oil | 48 | Renal failure |

IBD, inflammatory bowel disease; MCT, medium-chain triglyceride.
The authors thank Megan Perkowski, RD, for her contribution and editing of this table.

underlying diseases associated with malabsorption may benefit from specialized formulas. Once oral feeds are clinically possible they should begin. Delay in initiating oral nutrient swallowing will result in long-term oral aversion.

## DELIVERY MODALITIES

Aside from oral intake, a number of modalities are available for enteral delivery. These include nasogastric and nasojejunal feedings. Children receiving gastric feedings tolerate a higher osmolarity and volume than those being fed into the small bowel. Furthermore, gastric acid may benefit digestion, has a bactericidal effect, and is associated with less-frequent gastrointestinal complications.[7] Auscultation of air insufflated into the tube is inadequate. Confirmation must be obtained by aspiration of gastrointestinal contents or radiographic confirmation.[87] For patients requiring feedings for more than 8 weeks, a more permanent feeding access (e.g., gastrostomy tube) should be considered. The preoperative assessment usually consists of an upper gastrointestinal series followed by a 24-hour pH probe study if the results of the upper gastrointestinal study are abnormal. If either of these studies reveals reflux, a fundoplication should be done at the time the gastrostomy tube is placed. Assessment of gastric emptying should also be done before surgery, with a nuclear gastric-emptying study.[88,89] The most common procedure for gastrostomy placement is a percutaneous endoscopic gastrostomy (PEG) tube.[90] An improvement in gastrostomy tubes is the gastrostomy "button." The button is made of nonreactive Silastic components. It has a valve placed into a low-profile device that lies almost flush with the abdominal wall, and it can be capped between uses.[91] These buttons may now be placed at the same time as the percutaneous endoscopic procedure.[92] It has been reported that the incidence of complications is less with a PEG technique compared with other approaches; however, several complications have been described, including improper placement (i.e., close to the pylorus), inadvertent placement through an adjacent loop of bowel, necrosis of the tract of the gastrostomy tube, and technical failures that require laparotomy.[93]

Use of jejunal tubes is plagued with problems, including involuntary dislodgement of transpylorically placed tubes and catheter obstruction because of inspissation of feedings or instillation of medications. Short-term complications of surgically-placed J-tubes include intra-abdominal abscess and volvulus with bowel infarction. Long-term complications include intestinal obstruction and peritonitis. When using tubes passed distal to the pylorus, continuous drip feedings are recommended to prevent the development of diarrhea and other symptoms of dumping. Verification of the location of the tube is mandatory before beginning enteral tube feedings. This requires either aspiration of enteric contents or radiologic confirmation.

## ENTERAL FORMULAS

The choice of formula depends on the age of the patient and the condition of the gastrointestinal tract. In general, term infants should be maintained on human milk (see later) or a standard 20 kcal/oz formula (see Tables 12-5 and 12-6). Cow milk–based formulas for term infants contain nutrients that closely approximate the nutritional profile of human milk. Some formulas have added arachidonic acid (ARA) and docosahexaenoic acid (DHA), the two fatty acids that are found in human milk and believed to be essential for brain and eye development; however, no strong evidence-based literature supports the need for this. A lactose-based formula is generally the first choice, because it is the most physiologically

**TABLE 12-7**

**Enteral Nutrition Administration to Preterm Infants**

| *Birth Weight (g)* | *≤1000* | *>1000 to <1250* | *1250 to 1500* | *>1500 to 2000* | *>2000 to 2500* |
|---|---|---|---|---|---|
| Volume of first feeding<br>Schedule of feeding | 10-20 mL/kg/day | 10-20 mL/kg/day | 20 mL/kg/day | 20 mL/kg/day | 5 mL every 3 hours |
| Volume rate of feeding advances | 10-20 mL/kg/day | 10-20 mL/kg/day | 20 mL/kg/day | 20 mL/kg/day, may advance as tolerated | 5 mL every other feed as tolerated |

Btaiche I, Khalidi N, Kovacevich D (eds): The Parenteral and Enteral Nutrition Manual, ed 9. Ann Arbor, Mich, 2010, University of Michigan, University of Michigan Hospitals and Health Centers.

similar to human milk and is the least expensive. Soy formulas are indicated to manage galactosemia and primary or secondary lactase deficiency. Soy formulas should not be used in patients with a documented allergy or intolerance to milk protein, because one third of infants who have an allergen-induced reaction to cow's milk are also intolerant of soy. Therefore a protein hydrolysate or elemental formula is recommended in infants who have milk-protein intolerance. Further, soy formulas are not recommended for premature infants, because of their high aluminum content, which may contribute to osteopenia.

Calories from enteral nutrition can be added by increasing the volume delivered, increasing the concentration of the formula, or by supplementing the feedings. Formula concentrations may be increased to 30 kcal/oz; however, highly concentrated formulas may be difficult for some infants to digest, because they have a higher renal solute load and it may take time for them to build up tolerance. Higher concentrations have also been associated with a necrotizing enterocolitis–type process.[94] Formula supplementation can be done by the addition of a glucose polymer or fats (as medium-chain triglycerides or vegetable oil). Each 0.5 g of glucose polymer added to an ounce of standard formula increases calories by 0.06 kcal/mL, therefore creating a total caloric delivery of 0.73 kcal/mL. The addition of 0.5 g of oil to formula increases calories by 0.13 kcal/mL or a total of 0.8 kcal/mL. Caution must be taken when supplementing calories in this fashion, because it may compromise the ability of the infant to consume sufficient amounts of protein or minerals if the amount of formula is limited. However, up to 2 g of glucose polymer or 1 g of oil per ounce of formula can be added safely.

Standard premature infant formulas are milk-based formulas that provide 22 to 24 calories/ounce, and are optimized for required vitamins, minerals, and trace element needs. A portion of fat is provided as medium-chain triglycerides (MCT) to compensate for the limited bile salt pool in young infants. MCTs can be absorbed directly through the basolateral surface of the epithelial cell without the need for bile salts. MCTs, however, cannot be used to prevent essential fatty acid deficiency (all of which are long-chain triglycerides). The carbohydrate is composed of glucose polymers, as well as lactose, to optimize carbohydrate absorption in the presence of limited lactase activity. Premature infants are at increased risk for necrotizing enterocolitis. This risk is not increased with gastrointestinal (GI) priming feeds; however, excessive advancements in the rates of these feedings have been shown to put neonates at increased risk. In general, feeding advancements should not exceed 20 mL/kg/day.[61] Whether feedings are given through a bolus or continuous methods does not appear to influence hospital outcomes or days to reach full feeding.[95,96]

### Administration of Enteral Nutrition

For preterm infants, a feeding protocol is typically followed to maintain consistency of practice and reduce the incidence of necrotizing enterocolitis, and these guidelines are now well established.[97,98] For term infants, intermittent enteral feeding can be initiated at 2 to 5 mL/kg every 3 to 4 hours. Feeding is advanced in increments of 2 to 5 mL/kg every two feedings to a goal rate as tolerated. Guidelines have been revamped for safe delivery of enteral nutrition, and are given in Table 12-7 for term and premature infants. Feeding residuals are checked before each intermittent feeding, and enteral nutrition is held if the residual volume is greater than twice the administered volume.

## HUMAN MILK

Human milk has a variety of advantages compared with commercial formulas. The American Academy of Pediatrics advocates nursing until 1 year of age; yet, the majority of mothers in the United States stop nursing by the infant's second month of life.[99] Breast-feeding provides both nutrition as well as passive immunologic protection to the neonate. Breast milk contains 87% water and provides 0.64 to 0.67 kcal/mL. The fat content of breast milk is fairly high, at 3.4 g/dL. The protein content of human milk (0.9%) is lower than that of bovine milk or commercial formulas but appears much better absorbed because of the higher amounts of whey content. Casein, which predominates in bovine milk, is a complex of protein and calcium. The whey fraction contains primarily lactalbumin and, as well, lactoferrin, an iron-binding protein that is bacteriostatic to *Staphylococcus aureus* and *Escherichia coli* by restricting iron availability.[100] Additionally, ingestion of human milk allows for the acquisition of passive immunity by the transfer of both immunoglobulins and lymphocytes from the mother.[101] Breast milk also contains elevated levels of cysteine, which is potentially essential for a neonate, and taurine, which is needed for bile salt excretion and neurologic and retinal development. Despite similar amounts of trace elements, human milk allows for a more efficient absorption of these elements compared with commercial formulas. The immunologic advantages of breast milk include the transmission of both humoral as well as cellular factors to the neonate.[101] Although human milk has many advantages, high demands for calcium, phosphorus, electrolytes, vitamins, and trace elements cannot be achieved with human milk alone. Because of this, human milk fortifiers (one pack per ounce) should be added to breast milk fed to preterm infants. Supplementation should continue until the child achieves the weight of a term infant. When human milk fortifier is added to human milk, the hang time of the final reconstituted formula is 2 hours. Because of reports of vitamin D

deficiency and rickets in breast-fed infants, the American Academy of Pediatrics recommends beginning, within the first few days of life, a daily supplementation of vitamin D 400 IU to all breast-fed and non–breast-fed infants who do not receive at least 1000 mL of daily vitamin D-fortified formula or milk.[102]

## COMPLICATIONS OF ENTERAL FEEDING

The gastrointestinal tract generally tolerates feedings quite well once the postoperative ileus has resolved. Not uncommonly, the critically ill child will sustain a loss of a significant portion of the absorptive function, often because of a lactase deficiency. Symptoms are generally manifested by cramping, diarrhea, or emesis. Symptoms will often improve with the initiation of a lactose-free diet. Enteral nutrition is the preferred route of feeding when oral nutrition is not possible or adequate. In the critically ill child, frequent interruptions of enteral feeding for procedures, feeding intolerances, fluid restriction, or gastrointestinal dysmotility result in suboptimal enteral nutrition delivery.[103,104] The gastrointestinal tract generally tolerates increased volume more readily than increased osmolarity. Therefore in situations of gastrointestinal dysfunction, such adverse symptoms can be avoided by initiating ¼-strength formula and slowly advancing the formula concentration. Second, administration of formula by continuous drip may be better tolerated than bolus feedings. The risk of gastroesophageal reflux and dumping symptoms are thereby greatly reduced. Aspiration is a major risk of enteral feedings. Rapid-bolus nasogastric feedings may lead to a high incidence of reflux. Complications can be decreased with the use of a slow, continuous infusion or, preferably, with jejunal feedings.[105] However, this latter method has become controversial. Although patients with delayed gastric emptying (e.g., infants with sepsis, recent trauma, electrolyte imbalance, or receipt of opiates) or those who are comatose may be at risk for aspiration; in stable patients, a continuous infusion through a nasogastric tube is associated with no higher incidence of aspiration than is infusion through a nasoduodenal tube.[106] When the patient's clinical condition allows, raising the backrest or the head of the bed to 30 to 45 degrees during continuous feeding decreases the risk of aspiration.[107] Third, care must be taken to ensure that the enteral formula does not become contaminated, either during preparation or at the bedside. Expiration times should be observed. Finally, pectin, Metamucil, Lomotil, paregoric, or Imodium may be required for those who have lost a significant amount of their bowel length (see Short-Bowel Syndrome section). Assessment of adequate absorption can be carried out most readily by the testing of the stool for the absorption of carbohydrates, by measuring stool pH, and detecting for reducing substances. The presence of a stool pH less than 5.5 or a reducing substance of greater than one-half percent indicates the passage of unabsorbed carbohydrates into the stool, and once detected, should lead to a decrease in the formula concentration of carbohydrate.

# Parenteral Nutrition

Parenteral nutrition (PN) is the intravenous administration of balanced and complete nutrition to support anabolism, prevent weight loss, or promote weight gain. Because acute illness causes mobilization of energy and protein stores, appropriate and timely nutrition should be provided to prevent malnutrition and promote speedy recovery.[108] PN is indicated when oral or enteral feeding is not possible, or as a supplemental nutrition when enteral feeding fails to meet nutritional needs. PN should be used for the shortest time possible, and oral or enteral feeding should be initiated as soon as clinically feasible. Although enteral feeding can prevent gut atrophy and reduce the risk of PN-associated hepatobiliary complications,[109–111] a recent meta-analysis showed that the incidence of complications resulting from enteral and parenteral nutrition are essentially the same.[112]

## INDICATIONS FOR PARENTERAL NUTRITION

Parenteral nutrition is ideal for maintaining nutrition in infants and children who are unable to tolerate enteral feedings. Clinical conditions in children likely requiring PN include gastrointestinal disorders (short-bowel syndrome, malabsorption, intractable diarrhea, bowel obstruction, protracted vomiting, inflammatory bowel disease, enterocutaneous fistulas), congenital anomalies (gastroschisis, bowel atresia, volvulus, meconium ileus), radiation therapy to the gastrointestinal tract, chemotherapy resulting in gastrointestinal dysfunction, and severe respiratory distress syndrome in premature infants. Very-low-birth-weight infants are generally intolerant of enteral feeding and require PN during the first 24 hours following birth. Signs of starvation may be seen in underfed premature infants in as soon as 1 to 2 days. Although older children and adults generally do not require PN unless periods of starvation extend beyond 7 to 10 days, young infants require PN if periods of starvation extend beyond 4 to 5 days.

Protein and calories are essential for growth but must be provided in appropriate proportions for their optimal utilization. Very-low-birth-weight infants are born with limited nutritional reserves, loose protein in desquamated epidermal cells and urine, and quickly use their somatic protein reserves for energy if inadequate nutrition is provided early after birth. Providing early nutrition within 24 hours after birth is essential for the transition from fetal to extrauterine life to prevent growth failure and neurodevelopmental delays. Therefore prompt initiation of PN within a few hours after birth is essential. Further, because very-low-birth-weight infants have shown decreased plasma amino acid levels following birth, protein intake at about 3.8 to 4.0 g/kg/day improves nitrogen retention and stimulates weight gain.[113,114]

## VENOUS ACCESS

The type of venous access varies depending on the nutritional needs of the patient. Although peripheral PN may be used for a limited number of days, the high risk of using peripheral veins is extravasation of the solution with a subsequent inflammatory response and potential skin necrosis. Since the mid-1990s, a percutaneous intravenous catheter (or PIC-line) has been used. These catheters are relatively small in diameter (2-Fr or 22-gauge). They are placed through the child's peripheral veins, in the upper or lower limbs, and passed into the central venous system. These catheters are extremely well tolerated in adults and children; they can often be maintained for several weeks with reasonably low infection rates.[115,116] Unlike the placement of a Broviac-type catheter, which

requires local or general anesthesia, PIC-lines can generally be placed in the neonatal intensive care unit (NICU) with minimal sedation. Another advantage of these catheters is avoidance of pneumothorax, because access is through the extremities rather than the chest. The cost of the peripheral access devices is considerably less than that of Broviac-type catheters; however, PIC-lines have similar or higher incidences of venous thrombosis, and comparable rates of infection and complications.[117]

For infants and children who require longer durations of infusion, central venous PN may be administered through a tunneled Silastic catheter (e.g., Broviac, 2.7- or 4.0-Fr). Such a catheter often has a woven Dacron cuff. Although the tunneling of the catheter and cuff has not been shown to reduce catheter sepsis, the use of a cuff can prevent accidental dislodgement.[118] The catheter may be placed into the superior or inferior vena cava. The ideal position for the tip of the catheter is the junction of the right atrium and the superior vena cava. The child's facial, external jugular, subclavian, or saphenous veins are ideal locations for access. In children who weigh less than 750 g, the internal jugular or femoral vein may need to be used because of the small caliber of other vessels.

## PARENTERAL NUTRITION: COMPOSITION AND REQUIREMENTS

Parenteral nutrition is a source of macronutrients (amino acids, dextrose, lipid emulsions), micronutrients (multivitamins, trace minerals), fluids, and electrolytes.

### Amino Acids

Pediatric parenteral crystalline amino acid formulas provide essential and nonessential amino acids specifically balanced to meet the needs of the developing child. Neonatal-specific amino acid formulas are formulated to closely reproduce the plasma amino acid profile of breast-fed infants. These formulas have led to greater weight gain and improved nitrogen balance in infants compared with standard amino acid formulas.[119] Some amino acids, such as cysteine, tyrosine, glycine, and taurine, are considered conditionally essential for the child. Taurine supplementation for premature infants is essential to promote bile acid conjugation and to improve bile flow[120] and has been shown to decrease the degree of PN-associated cholestasis.[40] Premature infants are at risk for taurine deficiency as a result of elevated renal taurine losses and their low capacity for taurine synthesis resulting from low cystathionase enzyme activity.[49,121] Amino acids are a source of energy (4 kcal/g) and nitrogen for protein synthesis. Parenteral amino acids should provide approximately 10% to 15% of total calories. Amino acids are started at 1 g/kg/day and advanced to goal over 2 to 3 days. To simulate intrauterine protein accretion rates, low-birth-weight infants may need up to 3.85 g/kg/day of amino acids.[46,122] Amino acid requirements are 2.5 to 3 g/kg/day in term infants, 1.5 to 2 g/kg/day in older children, and 1 to 1.5 g/kg/day in adolescents. Amino acid doses should be adjusted based on the patient's clinical condition and nutritional status. For example, higher amino acid doses are required for wound healing. Patients with liver failure and hyperammonemia require lower amino acid doses. Higher amino acid doses are required in patients treated with dialysis or continuous renal replacement therapies to make up for losses through the dialysis membrane and filter.[123,124]

### Dextrose

Hydrous dextrose is the major source of energy and provides carbon skeletons for tissue accretion. Dextrose also acts as a protein-sparing substrate by preventing breakdown of somatic protein stores by suppression of gluconeogenesis.[125] In most children and adolescents receiving PN, parenteral dextrose usually provides 50% to 60% of total calories. The caloric value of hydrous dextrose is 3.4 kcal/g. In infants, PN should be initiated at a dextrose infusion rate of 4 to 8 mg/kg/min to maintain adequate serum glucose concentrations. Lower amounts of glucose in a young neonate will lead to hypoglycemia because of inadequate hepatic production of glucose. Dextrose infusion is thereafter advanced at a daily rate of 2 mg/kg/min until the nutritional goal is achieved. The maximum dextrose infusion rate should not exceed 10 to 14 mg/kg/min, which can usually be achieved when PN is administered through a central venous catheter.[126,127] Premature infants with hypoglycemia or failure to thrive may require higher dextrose infusion rates up to 20 mg/kg/min to maintain euglycemia and promote adequate growth.

### Lipid Emulsions

Intravenous lipid emulsions are a condensed source of energy and essential fatty acids, providing 9 kcal/g of energy. The caloric value of lipid emulsions varies with the lipid emulsion concentration. Lipid emulsions at 10%, 20%, and 30% concentrations yield 1.1 kcal/mL, 2 kcal/mL, and 3 kcal/mL, respectively. Currently marketed intravenous lipid emulsions in the United States are made of long-chain triglycerides (LCT). Lipids usually provide 30% to 50% of the non-nitrogen caloric needs or about 20% to 30% of total calories. Typically, lipid emulsions in infants and children are initiated at a dose of 1 g/kg/day and advanced by 1 g/kg/day to a maximum of 3 g/kg/day. Gradually increasing the daily lipid intake (0.5 or 1 g/kg/day) does not seem to improve lipid clearance. However, the lipid emulsion is cleared better[128,129] and lipid utilization is improved[130] when lipid is infused continuously over 24 hours rather than intermittently or for part of the day. Keeping the intravenous lipid infusion rate below 0.12 g/kg/hour improves lipid clearance.

There are also differences between the clearances of lipid emulsions. The 20% lipid emulsion is favored rather than the 10% emulsion because of its better clearance as a result of its lower phospholipid content.[131,132] Because lipid emulsions are derived from vegetable oils, they are also a natural source of variable amounts of vitamin K[133] and vitamin E isomers.[134,135]

### Multivitamins

Pediatric parenteral multivitamins contain a combination of water-soluble and fat-soluble vitamins that are added to the daily PN (Table 12-8). Several pediatric multivitamin formulas are available in the United States. No parenteral multivitamin products are currently available to specifically meet the needs of premature infants. Pediatric parenteral multivitamins provide low vitamin A and high water-soluble vitamins to premature infants. Higher vitamin A intake may be essential in

**TABLE 12-8**
**Pediatric Intravenous Multivitamin Formulation and Requirements for Infants and Children Up to 11 Years of Age**

| *Vitamin* | *Composition (per 5 mL)* |
|---|---|
| **Fat-Soluble Vitamins** | |
| Vitamin A | 2300 IU |
| Vitamin D | 400 IU |
| Vitamin E | 7 IU |
| Vitamin K | 200 μ |
| **Water-Soluble Vitamins** | |
| Thiamine ($B_1$) | 1.2 mg |
| Riboflavin ($B_2$) | 1.4 mg |
| Niacin ($B_3$) | 17 mg |
| Pantothenic acid ($B_5$) | 5 mg |
| Pyridoxine ($B_6$) | 1 mg |
| Cyanocobalamin ($B_{12}$) | 1 μ |
| Biotin (H) | 20 μ |
| Folate | 140 μ |
| Ascorbic acid (C) | 80 mg |
| Dose | <1 kg: 1.5 mL/day; 1 to <3 kg: 3.25 mL/day; >3 kg: 5 mL/day |

Mirtallo J, Canada T, Johnson D: Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr 2004;28:S39-S70.

**TABLE 12-9**
**Daily Electrolyte and Mineral Requirements for Pediatric Patients***

| *Electrolyte* | *Preterm Neonates* | *Infants/ Children* | *Adolescents and Children >50 kg* |
|---|---|---|---|
| Sodium | 2-5 mEq/kg | 2-5 mEq/kg | 1-2 mEq/kg |
| Potassium | 2-4 mEq/kg | 2-4 mEq/kg | 1-2 mEq/kg |
| Calcium | 2-4 mEq/kg | 0.5-4 mEq/kg | 10-20 mEq |
| Phosphorus | 1-2 mmol/kg | 0.5-2 mmol/kg | 10-40 mmol |
| Magnesium | 0.3-0.5 mEq/kg | 0.3-0.5 mEq/kg | 10-30 mEq |
| Acetate | As needed to maintain acid-base balance | | |
| Chloride | As needed to maintain acid-base balance | | |

*Assumes normal age-related organ function and normal losses.
Mirtallo J, Canada T, Johnson D: Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr 2004;28:S39-S70.

low-birth-weight infants who are at increased risk for lung disease.[136] Depletion of water-soluble vitamins occurs rapidly under stressful conditions. Thiamine is a cofactor for normal dextrose metabolism. Dextrose is normally metabolized to pyruvate, which is then converted to acetyl coenzyme A, which undergoes oxidation through the citric acid cycle. If thiamine deficiency occurs, pyruvate is instead converted to lactate, which can result in lactic acidosis.[137] Lactic acidosis has been reported in patients who received dextrose infusions without thiamine supplementation,[138,139] and fatalities from lactic acidosis resulting from thiamine deficiency were also reported during periodic multivitamin shortages in the United States.

## Trace Elements

Standard pediatric trace mineral formulas contain zinc, copper, manganese, and chromium, and some formulas have added selenium. Trace element formulas are designed to meet the recommendations of the American Gastroenterological Association (AGA)-AMA and the Society of Clinical Nutrition for daily intravenous supplements of trace minerals in the absence of deficiencies.[65] The Safe Practice Guidelines by the American Society for Parenteral and Enteral Nutrition (ASPEN) recently issued different guidelines with lower daily parenteral trace element requirements and supplementation (see Table 12-4).[140] Trace element status varies with the patient's underlying clinical conditions, and are mentioned in a preceding section of this chapter. Whenever trace elements are restricted or supplemental doses are given, blood trace element concentrations should be periodically measured to avoid deficiencies or toxicities.

## Fluids and Electrolytes

A parenteral nutrition solution should be not be used to manage acute fluid and electrolyte losses. Instead, patients should receive a separate intravenous solution for fluid and electrolyte supplementation (Table 12-9). In the home setting, fluid and electrolyte requirements are incorporated into the PN admixture for convenience of administration. Maintenance fluid and electrolyte requirements in children are shown in the respective chapters. Electrolyte adjustments in PN are based on serum electrolyte concentrations. Adjustments should account for all electrolyte sources and losses, acid-base status, clinical conditions, and medications that affect electrolyte balance.

***Sodium*** Sodium can be provided in PN solutions in the form of chloride, acetate, or phosphate salts. Neonates and especially premature infants develop a natruresis during the first 1 to 2 weeks following birth, resulting from their immature kidney function. Because adequate sodium intake is essential for protein synthesis and tissue development, adequate sodium supplementation is necessary and is guided by serum and urine sodium levels.[141] Premature infants may require as much as 8 mEq/kg/day of sodium, and this decreases with age such that in older children needs range from 1 to 2 mEq/kg/day. Maximum sodium concentration in PN solutions should not exceed normal saline solution equivalent (154 mEq of sodium/L).

***Potassium*** Potassium can be provided in PN solutions in the form of chloride, acetate, or phosphate salts. Higher potassium requirements are needed during anabolism[142] and to correct any gastrointestinal or renal potassium losses. Potassium concentrations in the PN solution should not exceed 120 mEq/L, and potassium infusion rates in infants and children should not exceed 0.5 mEq/kg/hour[143]; in adolescents dosage should be at 0.7 mEq/kg/hour. With higher potassium infusion rates, the patient should be placed in the intensive care unit on a cardiac monitor.

***Chloride and Acetate*** The chloride to acetate ratio in the PN solution can be adjusted based on the patient's acid-base status. Acetate is converted in vivo to bicarbonate at a 1:1 molar ratio. A high acetate-to-low chloride ratio is indicated to help correct the metabolic acidosis, such as resulting from lower intestinal bicarbonate losses. High acetate may also be used to help a child compensate for a respiratory acidosis. Premature infants are

especially at risk for acid-base changes because of their inadequate response resulting from inefficient hydrogen ion excretion and bicarbonate reabsorption by the kidneys.[141,144] A low acetate-to-high chloride ratio minimizes the bicarbonate load in patients with metabolic alkalosis such as resulting from excessive gastric fluid and electrolyte losses. Great caution should be used when adjusting the chloride-to-acetate ratio because dramatic acid-base changes may rapidly occur.

***Calcium and Phosphate*** Calcium and phosphate requirements in infants and children are greater compared with adults because of increased demands for growth. Corticosteroids and loop diuretics that are commonly used in neonatal and pediatric intensive care patients can further increase calcium requirements by increasing calcium losses. Following birth, hypophosphatemia is commonly observed in premature infants, resulting from high urinary phosphate excretion.[145] Because phosphates dissociate into monobasic and dibasic forms, depending on solution pH, they should be dosed in millimoles (mmol) instead of mEq to avoid dosing errors. Calcium and phosphate should be provided in adequate ratio and amounts to optimize bone mineralization and prevent metabolic bone disease.[146] Bone mineralization is optimized at an intake ratio of 2.6 mEq of calcium:1 mmol of phosphorus (1.7 mg calcium:1 mg phosphorus).[147] Inadequate calcium and phosphorus supplementation is problematic because of a solubility limitation. As such, enteral calcium and phosphorus supplementation may be required. Also, cysteine hydrochloride, an acidic compound that can be added to the PN solution, can be used to lower the solution pH and allow higher calcium and phosphate amounts in PN. An acidic medium favors the formation of monovalent phosphates instead of the divalent phosphates that otherwise would bind to calcium. Cysteine hydrochloride is added to the neonatal PN solution at a dose of 40 mg/g of amino acids.[148] Calcium and phosphorus can safely be added to PN when the concentrations provided satisfy the following equation:

$$\text{Calcium (mEq)} + \text{Phosphorus (mmol)} < 30 \text{ (per 1000 mL of PN)}$$

Because of these solubility issues, the full needs for optimal tissue and bone growth may not be met unless calcium and phosphorus are also provided enterally.

## ADDITIVES TO PARENTERAL NUTRITION

### Heparin

The addition of heparin to the PN solution at a concentration of 0.5 to 1 units/mL[149] maintains the patency of the venous catheter,[150] and reduces vein irritation.[151] Further, heparin is a cofactor of lipoprotein lipase, an enzyme released from the vascular endothelium, which enhances the clearance of lipid particles and thus enhances lipid clearance.[152] Heparin should not be used in patients with bleeding or at risk for bleeding, or in patients with thrombocytopenia.

### Histamine-2 Receptor Antagonists

Histamine-2 receptor antagonists, such as ranitidine, famotidine, and cimetidine, are compatible with PN and may be added to the PN solution for stress ulcer prophylaxis or to decrease gastric secretions.

### Regular Insulin

Regular insulin is compatible with the PN solution. However, insulin therapy is difficult to regulate in infants, and intravenous insulin should be administered as a separate intravenous infusion to allow safe titration of the insulin dose.

### Iron Dextran

Iron deficiency anemia may occur in PN-dependent patients. Iron is not routinely added to PN. Iron dextran is the most common parenteral iron available for use when oral iron absorption is unreliable or results in gastrointestinal intolerance and is the only parenteral iron formulation that can be added to PN solutions. Because iron can be used as a substrate for bacterial proliferation, iron dextran should be avoided in infected patients. Because severe anaphylactic side effects may occur with iron dextran, an intravenous test dose must be first administered before the total dose is given. Although not recommend by manufacturers, its use during the first 4 months of life has been safely done by many qualified groups. Daily iron dextran doses up to 1 mg/kg have been added to neonatal PN to prevent iron deficiency anemia. Iron replacement calculations can be found in Table 12-10. The estimated total iron dextran dose can be equally divided into incremental doses and added to the daily supply of non–lipid-containing PN solution until the total replacement dosage is given. Iron dextran at therapeutic doses is incompatible with lipid emulsions.[153] Other potentially safer intravenous iron preparations are iron sucrose and sodium ferric gluconate; however, a test dose of these other iron preparations must also be given to determine the potential for an adverse reaction. Their use has been predominately in renal failure patients but also appears effective in children.[154]

### Carnitine

Carnitine is a quaternary amine required for the transport of long-chain fatty acids into the mitochondria, where they undergo oxidation.[155] Premature infants are at risk for carnitine deficiency because of their limited carnitine reserves and reduced ability for carnitine synthesis.[156] Reduced fatty acid oxidation and elevated serum triglyceride concentrations have been correlated with low plasma carnitine concentrations.[157] Although many enteral formulations contain carnitine, PN solutions are carnitine-free. Supplementation of L-carnitine to PN normalized plasma carnitine concentrations[158] and improved fatty acid oxidation. Premature infants who develop

**TABLE 12-10**

| Intravenous Iron Replacement Therapy |
|---|
| **Calculation for Total Iron Replacement Dose** |
| mL of iron dextran = 0.0476 × weight (kg) × ($Hb_n - Hb_o$) + 1 mL per 5 kg of body weight (up to a maximum of 14 mL) |
| 1 mL of iron dextran = 50 mg of elemental iron |
| $Hb_n$ = desired hemoglobin (g/dL). The desired hemoglobin is 12 if patient weighs < 15 kg or 14.8 if patient weighs > 15 kg.<br>$Hb_o$ = measured hemoglobin (g/dL) |
| **Maximal Daily Iron Replacement Dose** |
| Infants weighing < 5 kg: 25 mg |
| Children weighing 5-10 kg: 50 mg |
| Children > 10 kg: 100 mg |

unexplained hypertriglyceridemia during lipid infusion may benefit from L-carnitine supplementation at a dose of about 10 mg/kg/day.[159] In neonates, L-carnitine 20 mg/kg/day for 8 weeks resulted in higher-than-normal plasma total carnitine concentrations. Doses of L-carnitine exceeding 20 mg/kg/day in infants are unlikely of clinical benefit. Larger oral L-carnitine doses have caused seizures, diarrhea, nausea, abdominal cramps, and may negatively affect growth by possibly increasing the infant's metabolic rate. Parenteral L-carnitine doses of 48 mg/kg/day in low-birth-weight infants increased protein oxidation, decreased nitrogen balance, and increased the time to regain birth weight.[160]

## COMPLICATIONS OF PARENTERAL NUTRITION

Despite more than 40 years of experience with PN, complications continue to be a major obstacle in the care of pediatric patients. Complications of PN can be classified into metabolic, respiratory, hepatobiliary, and infectious.

### Metabolic Complications

***Hyperglycemia*** Hyperglycemia in patients receiving PN is primarily the result of excessive dextrose infusion. Factors that exacerbate glucose intolerance include sepsis, surgery, diabetes, pancreatitis, prematurity, and corticosteroid therapy. Elevated blood glucose may coincide with PN initiation, but endogenous insulin secretion usually adjusts within 48 to 72 hours. Untreated hyperglycemia causes osmotic diuresis that can lead to hyperosmolar, hyperglycemic, nonketotic dehydration with electrolyte disturbances,[127] impaired phagocytosis,[161] and liver steatosis.[162] Intensive insulin therapy to maintain tight glucose control in critically ill patients has variably affected patient outcomes and was associated with increased incidence of hypoglycemia. Although an earlier study in critically ill surgical adult patients showed decreased patient morbidity and mortality with continuous insulin infusion to maintain blood glucose levels between 80 to 110 mg/dL,[163] a recent large multicenter study reported that a more permissive glycemic target range of 140 to 180 mg/dL is desirable, because tight glycemic control was associated with increased patient mortality.[164] Data in pediatric intensive care unit patients showed that intensive insulin therapy targeting age-adjusted blood glucose levels was associated with decreased inflammatory response, reduced secondary infections, a shorter length of intensive care unit stay, and increased incidence of hypoglycemia.[165] Although uncontrolled hyperglycemia is unacceptable, there is disparity in practice of glycemic control in pediatric intensive care units, and the long-term outcomes and optimal blood glucose targets in these children remain unknown.[166]

The first attempt in managing hyperglycemia is to decrease the dextrose load or reduce the infusion rate. However, this may compromise nutritional intake, because dextrose is the major source of calories in PN. If reducing dextrose does not improve hyperglycemia, insulin therapy is then indicated. Because infants have a variable response to insulin therapy,[167] adding insulin to the PN solution should be avoided. Instead, a regular insulin drip should be initiated and titrated based on serial glucose checks.

***Hypoglycemia*** Hypoglycemia with PN is usually the result of a sudden reduction of the PN infusion rate. In patients who receive PN during a portion of the day ("cycled"), hypoglycemia may be avoided by gradually reducing the rate during the 1 to 2 hours prior to discontinuation. Capillary glucose levels (chemsticks) should be monitored 15 to 60 minutes (typically 30 minutes) after PN is discontinued to check for any reactive hypoglycemia. Premature infants are at very increased risk for hypoglycemia because of their underdeveloped metabolic response[168]; cycling of PN in this group of patients is typically not safely performed until the child is more mature. If PN is unavoidably to be discontinued, intravenous administration of 10% dextrose in water, following PN discontinuation, will prevent symptomatic hypoglycemia.[9] Iatrogenic hypoglycemia can result from insulin therapy. If insulin is added in PN, adjustments to the insulin dose, guided by regular capillary glucose level checks, are necessary when metabolic stress decreases, pancreatitis resolves, or when corticosteroid therapy is tapered or discontinued.

***Hypertriglyceridemia*** High dextrose infusion is the primary cause of hypertriglyceridemia in PN patients. Excessive carbohydrate intake enhances hepatic and adipose tissue lipogenesis.[169] Other factors that predispose to hypertriglyceridemia in pediatric patients receiving PN include prematurity,[170] lipid overfeeding,[171,172] critical illness, and sepsis.[173] Although the tendency would be to reduce lipid infusion, a reduction in dextrose would be far more effective. However, the dextrose infusion rate should not be decreased to less than 4 mg/kg/minute in infants, a minimum rate required for protein-sparing effect. If hypertriglyceridemia persists despite reducing glucose intake, the lipid emulsion dose and rate should be decreased to keep triglyceride levels less than 275 mg/dL. A lipid dose of 0.5 to 1 g/kg/day in children would prevent essential fatty acid deficiency. If the 10% lipid emulsion is used, switching to the 20% lipid emulsion is recommended because of its better clearance.[174] Carnitine deficiency should be ruled out, especially in premature infants and those with renal insufficiency, because it may also be a cause of hypertriglyceridemia (see previous).

***Metabolic Acidosis*** Metabolic acidosis may result from excessive chloride (hyperchloremic acidosis may occur with serum chloride levels >130 mEq/L) or high amino acid load in PN. The addition of cysteine hydrochloride to the PN solution to improve calcium and phosphate solubility may also cause acidemia,[48] which may also lead to just the opposite effect—a leaching of calcium from the infant's bones. Premature infants and patients with liver or renal disease are at increased risk for metabolic acidosis and should be closely monitored for acid-base changes.

***Electrolyte Disturbances*** Hypokalemia, hypomagnesemia, and hypophosphatemia may result from increased requirements during anabolism and protein synthesis (refeeding syndrome), which is particularly common in the severely malnourished patient. Slow advancement of feeding with electrolyte repletion is recommended.[142] Phosphate is required intracellularly for generation of high-energy phosphate bonds and bone formation, and intracellular shift of phosphate occurs with carbohydrate infusion.[175] Severe hypophosphatemia may lead to hypoventilation, neurologic and cardiac

disturbances, and coma.[176] Apparent hypocalcemia in malnourished patients is often secondary to a reduced serum albumin concentration with proportionally low total serum calcium. Hyperkalemia, hypermagnesemia, and hyperphosphatemia may result from increased intake in combination with decreased renal function and hypercatabolism.

***Metabolic Bone Disease*** Metabolic bone disease, including osteopenia, osteomalacia, and rickets, is a complication in PN-dependent patients. Diagnosis is often difficult and may not be evident until a pathologic fracture is observed. Biochemical markers may reveal elevated serum alkaline phosphatase concentrations, hypercalciuria, low to normal plasma parathyroid hormone (PTH), and low 1,25 dihydroxyvitamin D.[177,178] Several factors predispose to PN-associated metabolic bone disease, including calcium and phosphorus deficiency, excessive losses of calcium resulting from diuretics, excessive vitamin D intake,[179] and aluminum toxicity.[180] Maximizing calcium and phosphorus intake is most important to improve bone mineralization. Calcium deficit is the result of limitations on the amount of calcium supplementation and the resultant hypercalciuria from amino acids,[181] with secondary metabolic acidosis.[182] Aluminum, a contaminant of the PN solution, is another possible cause of metabolic bone disease. Aluminum causes bone remodeling by impairing calcium fixation in bones,[183] impairing PTH secretion, or reducing the formation of active vitamin D.[184] Premature infants and patients with renal failure are at highest risk for aluminum toxicity resulting from their reduced ability for aluminum elimination. Additional vitamin D administration may actually be dangerous, because vitamin D may also play a role in the pathogenesis of metabolic bone disease; however, the exact mechanism is unknown. Withdrawing vitamin D from these patients leads to improvement in bone demineralization, resolution of bone pain, positive calcium balance,[179] and normalization of plasma active vitamin D and PTH concentrations.[185]

### Hepatobiliary Complications

Hepatobiliary complications associated with PN include cholestasis, steatosis, and cholelithiasis. Multiple factors may predispose to PN-associated hepatobiliary complications, including prematurity, overfeeding, PN dependence, absence of enteral stimulation for gall bladder contraction, short-bowel syndrome, and recurrent sepsis.[186,187] Cholestasis is the most common hepatobiliary complication in children receiving PN. Jaundice may occur as early as 2 to 3 weeks after PN initiation. A serum conjugated bilirubin concentration greater than or equal to 2 mg/dL is commonly used as a biochemical marker of cholestasis.[187] A rapid rise in direct bilirubin is a strong predictor of impending hepatic failure. Use of a taurine-supplemented PN solution has been shown to decrease the degree of cholestasis in premature infants and those with necrotizing enterocolitis.[40] In infants with short-bowel syndrome, a direct bilirubin greater than 2.5 mg/dL for more than 4 months was associated with an 80% mortality[189] and suggests a potential criteria for referring patients for transplant evaluation.[190] Strategies to prevent or reduce PN-associated liver disease (PNALD) include initiation of enteral feeding, weaning PN, avoiding overfeeding,[191] balancing calories,[192] "cycling" PN,[193,194] and avoiding and promptly treating sepsis.[192] Pharmacologic interventions include improving bile flow with the administration of bile acids or use of cholecystokinin, both have been studied in controlled prospective trials without any proven benefit.[195,196] Oral antibiotics, such as oral gentamicin and metronidazole have been used to decrease intestinal bacterial overgrowth and reduce bacterial translocation.[197] During the past decade, it has become apparent that soybean-based intravenous fat emulsions are a causative agent of PNALD. Strategies to either reduce the amount of these fats[198] or replace them with a fish-oil–based intravenous fat[199–201] have proven successful in reversing PNALD, thus making soybean fats a potential contributing factor to this disease process.

### Infectious Complications

Sepsis is one of the most frequent and serious complications of centrally infused PN in infants and children.[202] Fever and sudden glucose intolerance are suggestive of sepsis. Persistent hyperglycemia has been shown to increase infection rates, and intensive control is recommended.[203] Microbial culturing of PN should be performed if PN is suspected as a source of microbial contamination, though this is a rare occurrence with the use of strict sterile compounding techniques. Catheter-related infections remain the main cause of sepsis in patients receiving PN. Although not specific for children, guidelines for the diagnosis and treatment of central venous access infections have recently been established by the Infectious Disease Society of America[204] and the European Society of Parenteral and Enteral Nutrition.[205] Microorganisms may enter the bloodstream (1) along the catheter tract, starting at the skin exit site; (2) through a contaminated intravenous solution; (3) by breaks in sterility at the catheter hub–blood drawing or cleaning intravenous tubing; or (4) from a distant septic site or the GI tract. The catheter in this case, acts as a foreign body focus for bacterial growth. The most important factors in reducing the incidence of septic complications are placement of catheters under strict aseptic conditions and meticulous care of the catheter sites. Factors that correlate with catheter-related infections include prolonged catheterization, use of the catheter for multiple purposes, manipulation of the catheter hub, and chronic PN therapy. Most series report an incidence of 0.5 to 2.0 infections per 1000 catheters-days for a nonimmunosuppressed patient with a central venous catheter.[206,207] For immunosuppressed patients (e.g., hematology or oncology patients), a rate of 2 to 3 infections per 1000 catheter-days is generally reported.[208,209] A considerably higher rate of infection is found in children with the short-bowel syndrome; this rate ranges from 7 to 9 infections per 1000 catheter-days.[210–213] Several measures have proven effective in preventing catheter-related infections, including the use of sterile barriers and topical disinfectants during catheter insertion, use of antimicrobial-coated catheters, and regular catheter flushing. Although some individual studies have shown benefit with chlorhexidine-impregnated catheters, a recent review found no benefit but did suggest beneficial reduction of infections when catheters were either heparin-coated or antibiotic-impregnated.[214] Use of chlorhexidine-impregnated dressings has been shown to reduce pediatric catheter infections.[215] Guidelines for the prevention and management of catheter-related infections have been published elsewhere.[216,217] In general, nonpermanent polyvinyl chloride lines should be removed with catheter sepsis; however, more than 80% of patients with a Silastic catheter (e.g., Broviac or Hickman) will be able to have the infection cleared with intravenous antibiotics. Another technique to treat such

infections is the antibiotic-lock technique. This technique allows delivery of markedly higher doses of antibiotics into the catheter with allowance of the antibiotic to remain in the lumen while it is not in use.[218,219] This allows use of antibiotics that would normally have such high minimal inhibitory concentrations (MIC) that systemic use would result in renal failure (e.g., nafcillin for a staphylococcal line infection). Antibiotic lock methods are used routinely in some centers but are probably most useful in patients who may not tolerate an aminoglycoside or vancomycin. Because of this problem, as well as the risk of developing resistant organisms in the patient, ethanol-lock therapy has become commonly used to both treat as well as prevent the development of pediatric central venous-line infections.[220–222] Overall, the use of ethanol lock can reduce infections by almost 10-fold. However, complications may occur because of the risk of precipitation of heparin or citrate with ethanol, which requires that these two agents *not* be used when patients are receiving ethanol lock.[221] Additionally, ethanol may weaken plastics in the catheter and should *not* be used if the device is composed of polyurethane.[223] Because of the high failure rate of antibiotics, most patients with a *track* infection should have the line removed. Most children with fungal infections should also have the catheter removed, because of reports of fatalities and high failure rates with attempts at trying to salvage the line with antifungal therapy.[224] Attempting to maintain a catheter with a *Candida* infection is associated with a mortality of up to 25% and the low chance of clearing the infection with the line in place (13%).[225] Only a relatively short course of antifungal agents needs to be given after the catheter is removed (7 to 14 days); however, the results of blood cultures must be negative.[226] For unusual cases in which central venous access has been lost because of previous placement of several catheters, a trial of antifungal agents with the line in place may be attempted. An uncommon fungal organism associated with PN is *Malassezia furfur.* This organism thrives in a lipid-rich environment, but as long as lipids are withheld, it generally responds to antifungal treatment without catheter removal.

### Complications from Overfeeding

Overfeeding can lead to a number of adverse consequences. The administration of excessive dextrose may lead to osmotic diuresis and subsequent dehydration resulting from serum glucose levels exceeding renal tubular reabsorption threshold. Immunologic suppression has also been associated with overfeeding and is believed to be due to an inactivation of the complement system, as well as a depression of natural killer activation (see previous section on hyperglycemia). Overfeeding may also adversely affect the liver, because excessive glucose, which is not oxidized, is converted into fat (lipogenesis). These changes may lead to elevated serum triglyceride levels and hepatic steatosis that may be injurious to the liver. Additionally, overfeeding from carbohydrates associated with lipogenesis will lead to high carbon dioxide production, as reflected by an elevated respiratory quotient (RQ).[227] A RQ value exceeding 1 may represent overfeeding, and this high level may exacerbate ventilatory impairment in a critically ill child, because it represents excessive carbon dioxide production. Overfeeding should be avoided and caloric needs are best assessed in the critically ill child using indirect calorimetry. Overfeeding critically ill patients may also lead to fluid retention that may further compromise respiratory function.

### Technical Complications

In recent years, the incidence of technical complications caused by the placement of central venous lines in infants and children has been greatly reduced by careful attention to technique and by radiologic confirmation of catheter position. The incidence of cardiac arrhythmias caused by catheter irritation has been greatly reduced by placing the tip of the catheter at the junction of the superior vena cava and right atrium. Another important point is to ensure that a subclavian catheter is not inserted too medially, because this could lead to a pinching of the catheter between the first rib and clavicle, with the potential shearing off of the distal catheter into the heart.[228] Even with the proper positioning of a silicone catheter, thrombosis of the vein in which the catheter resides can occur, especially in the critically ill patient with sepsis and reduced circulation. Thrombosis of the great vessels will require anticoagulation and catheter removal. Pulmonary embolism and infection of these thrombi have been reported in infants and small children.[229] Thrombolytic therapy has proven effective in clearing the catheter of clots and avoiding the need for catheter replacement.[230] This procedure may be repeated at least twice to ensure removal of thrombus. Patients with long-term indwelling lines may have occlusion from either lipids or calcium deposits. These patients should also receive a trial of ethanol and dilute hydrochloric acid.[231] Since 1996, use of percutaneous intravenous central catheters (PICCs) has become the dominant mode of PN delivery in the United States.[232] This mode of insertion has the advantage of avoiding many of the complications associated with central venous catheters and can be often easily inserted on the floor with little or no sedation[233,234]; however, thrombotic events are more frequent than with centrally placed catheters. A reduction in these thrombotic events is seen if the catheters are placed in a central position, rather than in the juncture of the periphery and central venous system.

## ADMINISTRATION OF PARENTERAL NUTRITION

Neonates are generally started on PN within the first 12 hours after birth; and many centers now stock a pre-made 10% dextrose (D10%) solution for such use in their units. Neonates tend to be somewhat intolerant of large amounts of dextrose or amino acids for the first 2 to 3 days of life. Dextrose solution concentrations are generally initiated at 10% to 12.5%, and the concentration is slowly increased on a daily basis to between 20% and 25%. Monitoring of the patient's glucose levels and electrolyte balance and checking for glucosuria will confirm whether the child can tolerate this level of dextrose administration. PN may be administered through a peripheral or central venous catheter. The risk of developing phlebitis in peripheral veins is greater when the PN solution osmolarity exceeds 600 to 900 mOsm/L.[235] Intravenous solutions with higher osmolarities must be infused through a central vein. The maximum dextrose concentration in peripherally infused solutions in infants and children is 12.5%. Because lipid emulsions are isotonic solutions, coinfusion of lipids with peripheral PN protects the veins and prolongs the viability of peripheral intravenous catheters.[236] Because calcium phosphate precipitates are potentially life threatening in PN solutions, the Food and Drug Administration has recommended

that PN solutions be infused through an inline filter. A 0.22-μ filter is used for non–lipid-containing PN solutions, whereas a 1.2-μ filter is used for total nutrient admixtures to allow lipid particles (0.5μ in diameter) to pass through the filter. PN should be initiated as a continuous infusion spanning 24 hours. For patients receiving long-term PN, delivery may be given spanning a shortened period of time (e.g., 16 hours). Importantly, to avoid hypoglycemia or hyperglycemia, the rate of infusion needs to be reduced by half for 1 to 2 hours before terminating or starting up infusion each day. Additionally, neonates, particularly premature infants, have limited glycogen reserves and generally do not tolerate cycling of PN. A suggested guideline for writing orders for neonatal PN is given in Figure 12-1. Adequate maintenance of catheters and

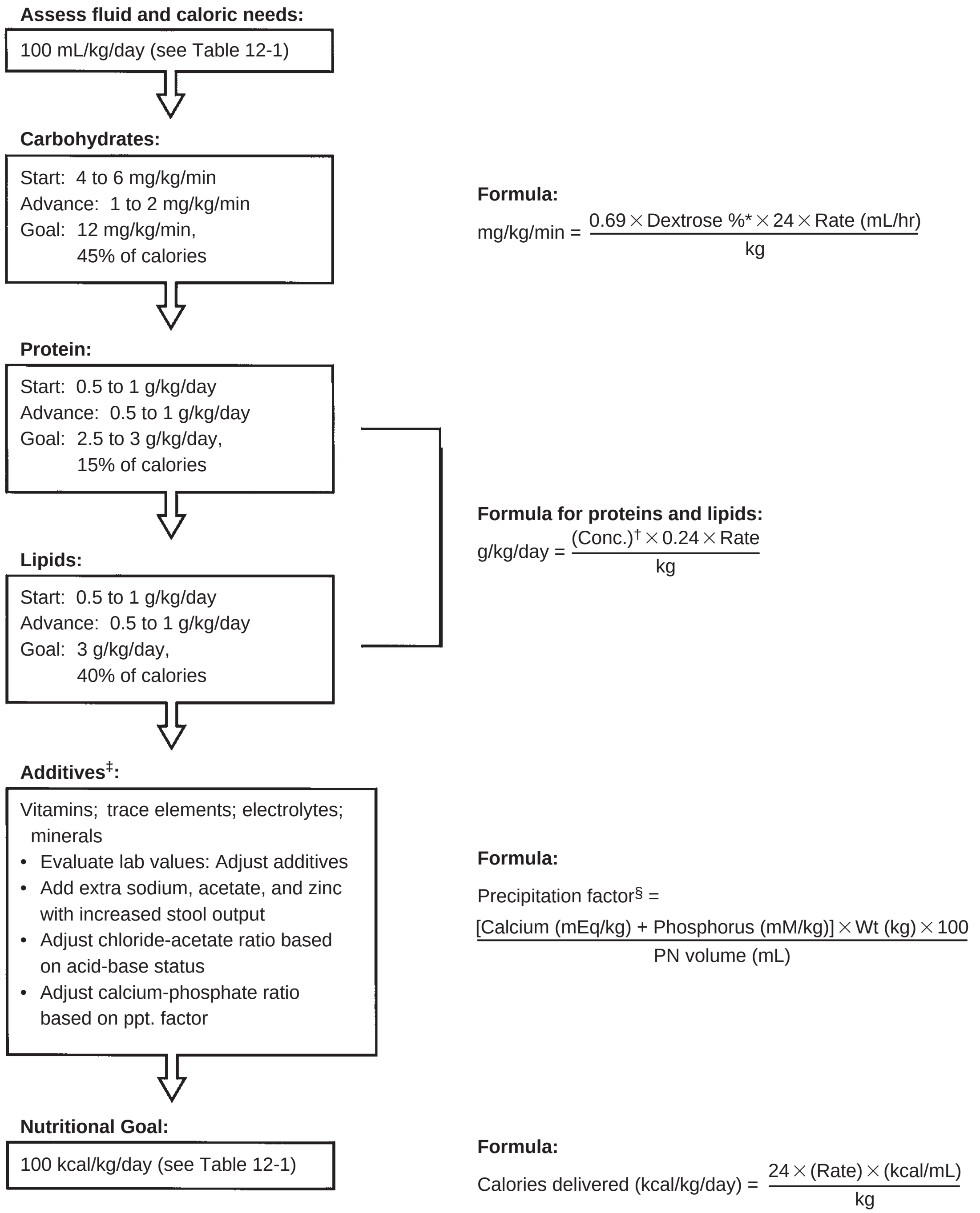


**FIGURE 12-1** Schematic diagram of how to begin to approach writing parenteral nutrition orders for a neonate or young infant. Fluids should be adjusted based on the infant's gestation age and body weight.

*Dextrose concentration should be used as the percent number (i.e., 20 for 20%). Conc, concentration; PN, parenteral nutrition; ppt, precipitation.

†The concentration in this formula should be written as the percent number (i.e., 4.25 for 4.25%).

‡See relevant tables for each of these additives.

§If the amino acid concentration is greater than 1.5%, the precipitation factor should be less than 3. If the final amino acid concentration is greater than 1% and less than 1.5%, a precipitation factor should be less than 2. Also, for an amino acid concentration less than 1%, calcium and phosphate should not be added. Adjustments to this formulation need to be done if additives (e.g., cysteine) are placed in the parenteral nutrition.

prevention of infection demands meticulous care, because catheters are a common source of sepsis in neonates.[211] Maintenance of all of these catheters requires that the skin site be cleansed with an antiseptic solution and dressed in a dry fashion every other day.[237] Tubing and infusion bags are changed every 72 hours, along with a new inline filter. Tubing used to deliver lipids must be changed every 24 hours.

### Monitoring of Laboratory Values

Monitoring of laboratory values is essential, because aberrations in these values are common in pediatric patients, particularly at the initiation of PN. Table 12-11 gives a suggested guide for such monitoring. A complete blood count, glucose, blood urea nitrogen, creatinine, and electrolytes (sodium, potassium, chloride, carbon dioxide) levels should be measured at initiation and on a biweekly basis. Liver function tests (alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, and total direct bilirubin) should be done, and magnesium, albumin, calcium, and phosphorus levels should be checked at initiation and weekly. Triglyceride levels should be maintained until the desired level of fat intake is reached.

**TABLE 12-11**
**Guidelines for Blood Laboratory Monitoring of Nutrition Support in Parenteral Nutrition–Dependent Pediatric Patients**

| | *Initial* | *Daily* | *2 to 3 Times/ Week* | *Weekly* | *As Indicated* |
|---|---|---|---|---|---|
| Glucose | X | X | X | | |
| BUN, creatinine | X | X | X | | |
| Sodium, potassium, chloride, carbon dioxide | X | X | X | | |
| AST, ALT, LDH, alkaline phosphatase, total and direct bilirubin, GGTP | X | | | X | |
| Magnesium, calcium, phosphorus | X | | X | | |
| Albumin, total protein | X | | | X | |
| Triglycerides | X* | | | X | |
| Hb, Hct, CBC, platelets, PT | X | | | | X |
| Copper, zinc, selenium, chromium, manganese, iron | | | | | X |
| TIBC, ferritin | | | | | X |
| Vitamin concentrations | | | | | X |
| Chemsticks | | | | | X |
| Ammonia | | | | | X |
| Blood cultures | | | | | X |

*Measured once goal lipid infusion reached.
ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CBC, complete blood count; GGTP, gamma-glutamyl transpeptidase; Hb, hemoglobin; Hct, hematocrit; LDH, lactate dehydrogenase; PT, prothrombin time; TIBC, total iron-binding capacity.

# Special Problems in the Nutritional Support of the Pediatric Surgical Patient

## NUTRITION IN THE PEDIATRIC SURGICAL PATIENT

The surgical patient responds to the stress of surgery quite differently than older children or adults.[238] The metabolism of children is markedly affected by operative stress. The time period of increased energy expenditure, however, is much shorter than in adults.[239] Induction of anesthesia has profound effects on body metabolism, with agents such as fentanyl having a beneficial effect in reducing the catabolic effect.[240] Moreover, protein turnover and catabolism seems not to be affected by major operative procedures in neonates. PN, however, in surgical neonates is associated with increased production of oxygen-free radicals, and this may contribute to suppression of the immune status. Thus utilization must be tempered with any potential benefit. A discussion of the use of nutrition support both preoperatively and postoperatively follows.

## INDICATIONS FOR PREOPERATIVE NUTRITION

In malnourished adults, provision of enteral feedings preoperatively for 2 to 3 weeks may reduce postoperative wound infections, anastomotic leakage, hepatic and renal failure, and length of hospital stay.[241,242] Data for PN support are less clear. A meta-analysis demonstrated only a marginal benefit of preoperative PN. Little benefit, and possible increase in complications, was noted in mildly or moderately malnourished patients.[243] The most significant benefit has been documented in severely malnourished patients who have developed fewer noninfectious complications if receiving perioperative PN (PN presurgery for 7 to 15 days, and postsurgery for 3 days).[244] However, PN patients were noted to have an increased infection rate that could not totally be explained by the use of central venous catheters. This suggests that the use of PN may actually predispose patients to increased infectious complications. Thus unless there are clear indications of severe malnutrition (see Subjective Global Assessment in the previous section on nutritional assessment), a delay in operative management in order to provide preoperative PN is *not* indicated.[9] An extrapolation of these findings to neonatal patients is difficult because of their limited nutritional stores. However, because of similarities in the metabolic response to surgery, it seems reasonable to apply these same conclusions to the pediatric population.

## INDICATIONS FOR POSTOPERATIVE NUTRITION

Use of aggressive postoperative nutritional support is even more controversial. In critically ill adult patients, early enteral nutrition within 24 to 48 hours of admission to the intensive care unit has been shown to reduce infectious complications.[245,246] However, gastrointestinal complications and feeding intolerance can be a considerable limitation to the adequate delivery of enteral nutrition.[247] These data suggest that, when used, postoperative nutrition should be started

early, using a combination of PN and EN until the gastrointestinal tract fully recovers. A recent controlled study examining the effect of postoperative PN in children demonstrated a positive effect on nitrogen balance and levels of insulin growth factor-1 (IGF-I); however, no clinical benefit was noted.[248] The effect of PN on postoperative healing has been negligible. In the postoperative period, there are higher infection rates in patients on PN. Meta-analysis studies show that there is an actual adverse effect to postoperative PN.[243] Although prolonged starvation postoperatively places patients at adverse risk,[249] postoperative PN should be restricted to infants who will not tolerate even a short period of starvation or to older children who will probably not start enteral nutrition for at least 5 to 7 days. In well-nourished adolescents, this period of time should increase to 7 to 10 days.[9]

## NUTRITIONAL SUPPORT IN THE CRITICALLY ILL SURGICAL PATIENT

Nutritional care of the critically ill or septic postoperative patient represents a much greater challenge. Clinically, a critically ill child manifests poor enteral feeding, anorexia, and often a paralytic ileus. Insulin resistance results in hyperglycemia and hypertriglyceridemia. Control of this hyperglycemia has been shown to have a significantly beneficial effect in preventing sepsis.[203] Visceral protein stores become progressively reduced with time. Although measurements of albumin may change slowly because of its long half-life ($t_{1/2} > 18$ days), other measures of visceral protein status, such as prealbumin levels ($t_{1/2} = 2$ days), will better reflect these metabolic derangements. Estimates of energy needs during this time are important. Energy needs of postoperative or septic critically ill infants have not uncommonly been overestimated. Almost one third of an infant's energy needs is provided to support growth (30 to 35 kcal/kg/day). Because a cessation of growth occurs during periods of sepsis and critical illness, a marked decrease in energy needs may ensue. In a study of critically ill, postoperative infants, the mean measured basal energy expenditure was only 43 kcal/kg/day.[36] However, results are extraordinarily variable, further emphasizing the utility of performing indirect calorimetry. The use of indirect calorimetry can also yield information on the respiratory quotient (see previous) and aid in the prevention of overfeeding. Combined enteral and PN feedings in critically ill adult patients on ventilator support is controversial and may not be recommended.[250] Although not as well studied in neonates, data from meta-analyses in adult patients suggest that PN has little proven benefit to most critically ill surgical patients, and thus supplementation should be used sparingly in the initial few days of support until it is determined that the length of starvation will exceed 5 to 7 days.[251]

## BILIARY ATRESIA

The infant with biliary atresia, even after a clinically successful hepatic portoenterostomy, will typically have lower than normal amounts of bile flow into the intestine. This subsequently leads to a profound defect in fat digestion and absorption. Such a deficit may leave the infant with an essential fatty acid deficiency and inadequate absorption of fat-soluble vitamins.[252] Consequently, this will lead to a lack of bone mineralization as well as failure to thrive. The essential goals for such an infant are to provide adequate calories using a formula that maximizes fat intake. A commonly used formula in these patients is Pregestimil (Mead Johnson & Company, Evansville, Ind.). This formula has a large amount of medium-chain triglycerides and sufficient linoleic acid to prevent fatty acid deficiency in the face of decreased absorption. Use of this formula has been shown to increase growth in such patients.[253] Portagen (Mead Johnson & Company) should not be used in cholestatic infants, because it does not provide sufficient essential fatty acids to prevent deficiency. When PN is needed, a standard crystalline amino acid solution should be used; there is no proven benefit to hepatic formulas. Breastfeeding, although generally ideal in infancy, should be used cautiously in patients with biliary atresia. Breast milk has a much higher fat content than commercially available formulas and may not be well tolerated in these children. Vitamin supplementation is critical in patients with biliary atresia (Table 12-12). Unfortunately, supplemental vitamins are rarely covered by medical insurance payers despite the fact that they are medically necessary. Frequent monitoring of vitamin levels is essential to ensure sufficient supplementation is being achieved. The addition of water-soluble vitamins to levels greater than those provided in standard infant formulas should be carried out by the administration of a multivitamin preparation. Iron, zinc, and calcium deficiencies should be ruled out. From a practical perspective, it may be difficult and expensive to administer so many vitamins to a small infant. Many have used a combination form of fat-soluble vitamins (vitamins A, D, E, and K [ADEK] 0.5 mL/kg); however, vitamin K may be inadequate in this formulation, and additional supplementation (2.5 mg/day) should be given. Vitamin levels should be followed and deficiencies corrected with individual vitamins. Protein metabolism is impaired in children with biliary atresia, increasing from 4% to 9% of energy expenditure in healthy infants to 17% in patients with biliary atresia.[254] Pierro and colleagues[255] have shown that resting energy expenditure was about 29% higher than expected in infants with biliary atresia and that only 35% of the metabolizable energy intake was retained for growth in these children. Optimal growth and nutrition in infants with biliary atresia has recently been associated with improved outcomes and should be a major goal for pediatric surgeons.[256]

**TABLE 12-12**
**Vitamin Therapy in Cholestasis**

| *Name* | *Dose* | *Supplied As* |
|---|---|---|
| Vitamin A | 10,000-15,000 IU/day | 3-mg tablets |
| (Aquasol A; Centeon) | (50,000 IU = 15 mg) | 3-mg, 7.5-mg, or 15-mg capsules |
| | | 50,000 IU/mL drops |
| Vitamin D: 1,25(OH)$_2$D$_3$ | 0.01-0.05 μg/kg/day | 0.25 and 0.5 μg capsules |
| (Rolcaltrol; Roche Laboratories) | | 0.1 μg/mL/liquid |
| Vitamin E TPGS | 25 IU/kg/day | 26.7 IU/mL liquid |
| (Liqui-E; Twinlab) | | |
| Vitamin K | 2.5-5 mg/day | 5-mg tablets |

## SHORT-BOWEL SYNDROME

The nutritional support of a child with the short-bowel syndrome (SBS) is complex and requires a multidisciplinary approach with the pediatric surgeon, pediatric gastroenterologist, pharmacist, and dietitian working together. Although initially the child's main or sole caloric source will be through PN, enteral feedings should be initiated as soon as possible after the onset of the short-bowel syndrome. Enteral feedings will both stimulate small-bowel adaptation and prevent the development of PN-associated cholestasis. The ideal enteral solution should be isotonic. The protein source should be predominately elemental. Dipeptides and tripeptides have often been advocated, because this source of protein is most easily and efficiently absorbed.[257] Although data are limited, others have found better feeding tolerance with the use of an elemental (pure amino acid) enteral nutrition formula.[258] The formula should have at least 50% of medium-chain triglycerides because this type of fat is well absorbed through the basolateral wall of the intestinal enterocytes and into the portal venous circulation. However, medium-chain triglycerides contain no essential fatty acids; thus these fats cannot be the sole source of lipids in these patients, and supplemental long-chain triglycerides should be provided to prevent essential fatty acid deficiency. Tables 12-5 and 12-6 give recommended formulas for children of different ages. Despite the use of these elemental formulas early in the initiation of feedings, more complex diets, particularly human milk, appear to have the greatest benefit in achieving intestinal adaptation, and a modified regular diet should eventually be initiated.[259]

High stool output is associated with excessive losses of zinc, magnesium, sodium, bicarbonate, and potassium.[260] These losses must be monitored. Total-body sodium depletion has been shown to be associated with failure to thrive, despite the administration of adequate amounts of calories.[261] A simple way to detect such a deficit is to measure a spot urine sodium. A urine sodium of less than 10 mEq/L may well indicate total-body sodium depletion, and supplementation (sodium chloride or sodium bicarbonate, as indicated) by the oral route should be given on a daily basis.[262] A major obstacle to feeding advances may be high stool output. The etiology of this high output may include infections, malabsorption, rapid transit, as well as bile acid irritation of the colonic epithelium.[263] The child's stool should intermittently be assessed for infections. Additionally, measurement of stool pH, reducing substances, and qualitative fecal fats should be checked. Stool pH less than 5.5 and an elevated reducing substance level (greater than 0.5%) indicate carbohydrate malabsorption. Formulas with sucrose as the carbohydrate will not yield a positive reducing substance test despite carbohydrate malabsorption. Elevation in fecal fats will suggest fat malabsorption, which may require modification of the child's enteral diet (i.e., increase the percentage of medium-chain triglycerides). An increase in stool alpha-1 antitrypsin would indicate a protein malabsorption, although much less commonly encountered. Use of a resin binder (e.g., cholestyramine) will markedly reduce bile acid irritation and has proven extremely effective in many infants who have their small bowel in continuity with a portion of the colon. However, excessive use of bile acid binders, such as cholestyramine, may result in depletion of the circulating bile acid pool and thereby further limit fatty acid absorption. Because many infants with short-bowel syndrome have dysmotility, it is only after all other etiologies have been eliminated (i.e., infectious, bacterial overgrowth, bile acid irritation, and potentially correctable malabsorption) that an agent to reduce motility (e.g., Imodium) should be considered.

## OBESITY

Obesity has become a worldwide issue, with a striking increase in obesity rates being reported in North America as well as Europe and Asia.[264,265] Rates in the United States demonstrate a greater than threefold increase in obesity during the past 30 years. The implications of this rise in obesity are dramatic. First, more than 50% of children who are diagnosed with obesity will carry this excess weight into adulthood. Second, a number of secondary complications have been manifested in these children, including the prediabetic condition of syndrome X, type 2 diabetes mellitus, coronary artery disease, and obstructive sleep apnea.[266,267] Additional problems include bone and joint disease and cholelithiasis. The difficulty in the diagnosis of obesity has hampered the identification and treatment of many of these children. Although a National Institutes of Health (NIH) consensus has established a BMI of greater than 40 as morbid obesity,[268] BMIs change dramatically during adolescence and do not follow a linear curve. A more consistent diagnosis is based on the number of standard deviations from the mean using Centers for Disease Controls (CDC) standardized growth curves.[269] In this regard, at risk for overweight is defined as being at the 85th percentile, and overweight is defined as being at the 95th percentile.[264] Factors influencing the development of obesity are environmental as well as genetic.[270] The risk of obesity increases to 80% if one parent is also obese.[271]

Treatment of this condition is complex, and no ideal approach has been advanced. For the pediatric surgeon, use of surgery may be appropriate; however, it is essential that a team approach be applied to these children.[272] This approach includes pediatricians, nurses, nutritionists, psychiatric support, as well as the surgeon. The key issues when contemplating surgical intervention for obese adolescents include a careful patient evaluation and selection based on sufficient maturity to understand the implications of this lifelong decision, as well as the willingness to participate in follow-up for the rest of their lives. Vitamin and nutrient deficiencies are very common in such patients and require monitoring on an every-6-month basis.[273] Levels that are commonly deficient include protein, vitamin $B_{12}$, folate, iron, calcium, vitamin D, and thiamine.

## FAILURE TO THRIVE

Malnutrition in childhood is associated with poor growth and development. The diagnosis of failure to thrive is based on a weight more than two standard deviations less than the mean weight percentile (Z score of 2.0) resulting in a child falling at 2.1%.[274] Failure to thrive is symmetric, in which height, length, and development of other body organs fall below the fifth percentile, or asymmetric, in which the weight is below the fifth percentile but length and head circumference are within normal limits. In general, patients with symmetric failure to thrive have more profound malnutrition and suffer from greater neurologic underdevelopment than those with asymmetric failure to thrive; the latter patients have relatively

normal cognitive development. Recent investigations have shown that abnormal cognitive development in patients with failure to thrive probably results from a poor social environment and is often reversible.[275,276]

The approach to feeding a patient with failure to thrive should include a multidisciplinary assessment of medical, social, and psychological factors. A systematic evaluation to rule out neurologic pathology, swallowing disorders, feeding aversion, malabsorption, and metabolic disorders should be done. A trial of feeding the child in a hospital setting can often identify a problem with the child's home and social environment. Nutritional support for an infant should begin at approximately 50 kcal/kg/day and be increased by 20 to 25 kcal/kg/day as long as gastrointestinal tolerance to the feeding is adequate. Stool weight should be less than 150 g/day in young infants. Feedings may increase to 150 to 240 kcal/kg/day to achieve adequate catch-up growth,[277] but overshooting is not uncommon, and such high energy delivery states demands close clinical observation.

Supplementing the formula with additional potassium (up to 5 mEq/kg/day) may also be required during the first week of nutritional rehabilitation. Levels of potassium, magnesium, and phosphate need to be closely monitored, because they often drop rapidly after the initiation of feedings. One simple method to calculate caloric needs is that for each gram of weight gain desired per day, 5 additional calories should be provided.

## CHILDREN WITH SPECIAL CARE NEEDS

Between 10% and 20% of children in the United States have special health care needs because of chronic illness and developmental disorders.[278] For several of these disorders, pediatric surgeons take an active part in the nutritional care of the patients. Some of the disorders include several neurologic impairments; developmental delay; cerebral palsy; and such genetic syndromes as trisomies 13, 18, and 21 and Cornelia de Lange and Rett syndromes. Pediatric surgeons are often responsible for providing nutritional access in many of these patients as well as for maintaining nutritional care before and after surgery. Potential factors that may contribute to poor nutrition in these patients include feeding disorders, uncoordinated tongue movements, poorly coordinated swallowing reflexes, gastroesophageal reflux with associated nutrient loss, and increased energy expenditure caused by muscle spasticity or athetosis (a mixed pattern of too much and too little muscle tone). Because measuring energy expenditure in these children may be impractical, estimates of energy needs can be based on previous studies of resting energy expenditure. Children with spastic-type (hypertonia) cerebral palsy may have lower energy needs than normal; adolescents require a total of approximately 1200 to 1300 kcal/day.[279,280] Children with athetosis may require a higher-than-normal calorie intake, sometimes more than twice the RDA. Children with myelomeningocele are far less active than their peers; for that reason, their energy needs are approximately only 50% to 60% that of normal children (Table 12-13).

**TABLE 12-13**
**Guidelines for Estimating Caloric Requirements Based on Height in Children with Developmental Disabilities**

| *Condition* | *Caloric Recommendation* |
|---|---|
| Ambulatory, ages 5 to 12 years | 13.9 kcal/cm height |
| Nonambulatory, ages 5 to 12 years | 11.1 kcal/cm height |
| Cerebral palsy with severely restricted activity | 10 kcal/cm height |
| Cerebral palsy with mild to moderate activity | 15 kcal/cm height |
| Athetoid cerebral palsy, adolescence | Up to 6000 kcal/day |
| Down syndrome, boys, ages 1 to 14 years | 16.1 kcal/cm height |
| Down syndrome, girls, ages 1 to 14 years | 14.3 kcal/cm height |
| Myelomeningocele | Approximately 50% of RDA for age after infancy; may need as little as 7 kcal/cm height to maintain normal weight |
| Prader-Willi syndrome | 10-11 kcal/cm height (maintenance)<br>9 kcal/cm height (to promote weight loss) |

RDA, recommended daily allowance.
From Nelson JK, Moxness KE, Jensen MD, Gastineau CF: *Mayo Clinic Diet Manual*, ed 7, St Louis, 1994, Mosby-Year Book. Used with permission.

If the child's body habitus is markedly abnormal, a more appropriate estimate of energy needs should be based on surface area rather than weight. Repeated assessments of the child's growth during nutritional supplementation are essential, because obesity in these children is common. Obesity can cause a considerable burden on the family and caregivers because of the increased difficulty in moving an overweight child.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 13

# Pediatric Anesthesia

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Dr. Marc Rowe, a leader in pediatric surgery, noted, "no matter how skilled and experienced the pediatric surgeon, safe conduct of the newborn patients through the perioperative period requires an equally competent pediatric anesthesiologist."[1] Anesthetic management of both neonates and older children must take into account the process of rapid growth and development. The child's variable anatomic, physiologic, pharmacologic, and psychological characteristics, as well as the magnitude of the surgical problem, influence anesthetic care. This chapter provides an overview of important issues in pediatric anesthesia and pain management that are directly related to clinical management.

## Physiologic Considerations

During the first 3 months of life, circulatory and ventilatory adaptation is completed, thermoregulation processes change, the sizes of body fluid compartments shift toward adult values, skeletal muscle mass increases, and hepatic enzyme systems and renal function mature. Over the next 2 years, the child approaches adult physiologic but not psychological maturity. Between the ages of 18 months and 5 years, children demonstrate sufficient awareness of their surroundings so that psychological aspects of care become an issue. Anxiolytic agents may be useful in the child's preoperative preparation. Healthy preschool-aged children (2 to 6 years) present relatively few technical problems to the anesthesiologist, but the child's fear, apprehension, and lack of cooperation are of concern. Anxiety treatment before surgery in school-aged children (6 to 18 years) may also be necessary.

Newborns can feel acute pain and process established pain (postoperative pain). At birth peripheral nociceptors function similarly to mature receptors.[2] However, the nerves responsible for transmitting the immediate chemical, thermal, and mechanical painful stimuli to the central nervous system (CNS) are not fully mature, nor are the inhibitory pathways from the CNS mature.[3] In the past, because of their inconsistent response to pain, neonates did not receive adequate analgesia for procedures known to cause pain in adults.[4–6] However, neonates of various gestational ages clearly respond to painful stimuli by measurable physiologic, metabolic, and clinical changes, and analgesia and anesthesia attenuate these changes.[7]

Neonates are sensitive to anesthetic agents and have inefficient mechanisms of drug metabolism and elimination.[8] Until infants are 1 month old, there is a marked interpatient difference in the volume of distribution, sensitivity of the CNS, and quality and quantity of transport proteins such as albumin and $\alpha_1$-acid glycoprotein. These interpatient differences contribute to neonates' varied and often unpredictable responses to anesthetic agents.

After the first several weeks of life, drug metabolism gradually becomes so efficient that many of the opioid agents, such as fentanyl and morphine, have a shorter half-life in infants and young children than in older children and adults. The doses per body weight of intravenous (IV) anesthetic agents (e.g., thiopental and propofol) are higher in the first 6 months of life than during any other period (Fig. 13-1).[9] During the first year of life, the concentration of inhalation agent needed to maintain anesthesia is greater than during any other period (Table 13-1 and Fig. 13-2). However, the infant's heart is more sensitive to these higher concentrations.

## Anesthetic Risk and Common Complications

Recent animal studies have stimulated debate and concern that anesthetic gases and drugs may be toxic to the immature developing brain.[10,11] Jevtovic-Todorovic and associates[10] began this recent controversy after publishing the results from a study in which 7-day-old rats were exposed to commonly used anesthetics for a total of 6 hours. The authors found that these rats exhibited learning/memory deficits, and histologic specimens of the brain revealed widespread apoptotic neurodegeneration and deficits in hippocampal synaptic function. The results of this study caused concern throughout the pediatric anesthesia community and was the subject of a Federal Drug Administration (FDA) advisory committee meeting.[12–15]

The FDA committee found that at present practice changes would be ill advised. On the one hand there is no doubt that animals varying from rats to primates have exhibited signs of neurotoxicity when exposed to higher levels of anesthetic

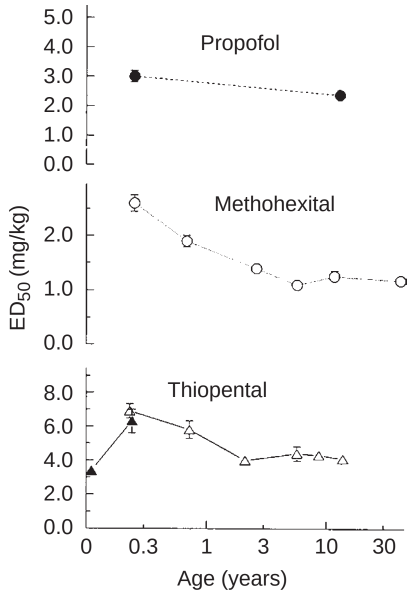


**FIGURE 13-1** Estimated $ED_{50}$ (dose of a drug that will induce anesthesia in 50% of patients) plus or minus the standard error in various age groups. Methohexital is indicated by open circles, thiopental by open or filled triangles, and propofol by filled circles. The vertical scales were adapted to yield the same height at $ED_{50}$ for children 7 to 16 years of age. (From University and University Hospital of Lund: Intravenous Induction of Anesthesia in Infants and Children. Lund, Sweden, Studentlitteratur, 1991.)

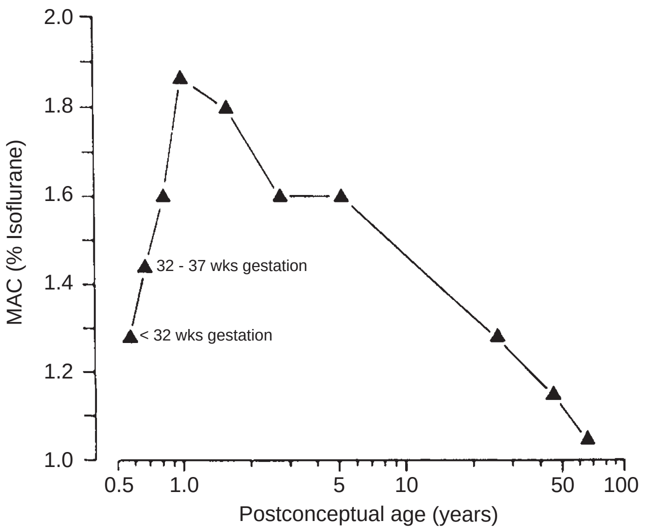


**FIGURE 13-2** Minimum alveolar concentration (MAC) of isoflurane according to gestational age. (From LeDez KM, Lerman J: The minimum alveolar concentration [MAC] of isoflurane in premature neonates. Anesthesiology 1987;67:301.)

**TABLE 13-1**

**Age Versus Mean Minimum Alveolar Concentration of Inhaled Anesthetics in Children**

| *Age (mo)* | *Halothane*[*] | *Isoflurane* | *Desflurane*[‡] | *Sevoflurane*[§†] |
|---|---|---|---|---|
| 1 | 0.87 | 1.6 | 9.16 | 3.2-3.3 |
| 2 | 1.08 | 1.9 | 9.4 | 3.2-3.3 |
| 14 | 0.97 | 1.8 | 8.72 | 2.5 |
| 44 | 0.91 | 1.6 | 8.54 | 2.5 |
| 480 | 0.76 | 1.2 | 7.5 | 2.5 |

*Data from Cook DR, Marcy JH: Pediatric anesthetic pharmacology. In Cook DR, Marcy JH (eds): Neonatal Anesthesia. Pasadena, CA, Appleton Davies, 1988.
†Data from Cameron CB, Robinson S, Gregory GA: The minimum anesthetic concentration of isoflurane in children. Anesth Analg 1984;63:418.
‡Data from Taylor RH, Lerman J: Minimum alveolar concentration of desflurane and hemodynamic responses in neonates, infants, and children. Anesthesiology 1991;75:975.
§Data from Lerman J, et al: The pharmacology of sevoflurane in infants and children. Anesthesiology 1994;80:814.

agent than is normally experienced by human infants and children. On the other hand 4 million children are exposed to anesthesia, and predictable patterns of brain injury have yet to be identified.[14] More animal studies are needed with doses and duration of exposure that reflect human exposure to these agents.[16] More important, clinical studies evaluating neurodevelopment in children exposed to anesthetic drugs are critical to better understand the effect of general anesthesia on neurologic development. Two multicenter clinical protocols for studying these issues have been developed and implemented.[11,13]

The American Society of Anesthesiologists (ASA) risk classification system is used by anesthesiologists to estimate the severity of their patients' medical conditions and to determine the relative risk for morbidity and mortality secondary to the anesthetic agent, not the surgery.[17,18] The ASA classification system does not predict surgical risk, because the type of operative procedure is not taken into consideration.[19] The ASA classification allows the anesthesiologist to tailor the plan for anesthesia based on the patient's underlying condition. The six ASA classes are as follows:

ASA 1: normal healthy patient
ASA 2: patient with mild systemic disease
ASA 3: patient with severe systemic disease
ASA 4: patient with severe systemic disease that is a constant threat to life
ASA 5: moribund patient who is not expected to survive without the operation
ASA 6: A declared brain-dead patient whose organs are removed for donor purposes
E: Any patient in whom an emergency operation is required

Because of their medical complexity, patients in ASA classifications 3 and 4 should have a consultation with an anesthesiologist before the day of surgery. The Vanderbilt Children's Hospital recommendations for preoperative visit are shown in Table 13-2.

Death caused by anesthesia alone is uncommon. Mortality related to anesthesia varies from 1 in several hundreds of thousands for healthy children undergoing routine procedures to greater than 1:10,000 in neonates and infants with congenital or neurologic diseases.[20,21] Keenan and colleagues suggested that the use of pediatric anesthesiologists for all infants younger than 1 year might decrease anesthetic morbidity in this group.[23] Auroy and associates observed that a minimum of 200 pediatric cases per year per pediatric anesthesiologist is necessary to reduce the incidence of complications and improve the safety in pediatric practice.[24]

**TABLE 13-2**
**Summary of Fasting Recommendations to Reduce the Risk of Pulmonary Aspiration***

| *Ingested Material* | *Minimum Fasting Period (hr)*† |
|---|---|
| Clear liquids‡ | 2 |
| Breast milk | 4 |
| Infant formula | 6 |
| Nonhuman milk§ | 6 |
| Light meal¶ | 6 |

*These recommendations apply to healthy patients who are undergoing elective procedures. They are not intended for women in labor. Following these guidelines does not guarantee that complete gastric emptying has occurred.
†Fasting periods apply to all ages.
‡Examples of clear liquids are water, fruit juices without pulp, carbonated beverages, clear tea, and black coffee.
§Because nonhuman milk is similar to solids in terms of gastric emptying time, the amount ingested must be considered when determining an appropriate fasting period.
¶A light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time. Both the amount and the type of food ingested must be considered when determining an appropriate fasting period.
Data from ASA Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures, A Report by the American Society of Anesthesiologists. 1999.

The Pediatric Perioperative Cardiac Arrest Registry (POCA) was created in 1994 in an attempt to determine the clinical factors and outcomes associated with cardiac arrest in anesthetized children.[25] Through this registry, it was determined that anesthesia-related cardiac arrest occurred most often in patients younger than 1 year and in patients with severe underlying disease. Cardiac arrest during emergency surgery, especially in children with severe underlying disease, was associated with increased mortality. In this study, medication-related problems accounted for 37% of all cardiac arrests and 64% of arrests in ASA 1 and ASA 2 patients. A POCA update published in 2007 revealed that the decreased use of halothane (a potent cardiac depressant) in favor of sevoflurane decreased the number of cardiac arrests due to medications from 37% to 15%.[26] The most common causes of cardiac arrest in the POCA update were hypovolemia from blood loss and metabolic complications from blood transfusion.

## LARYNGOSPASM

Laryngospasm is a common complication of inhalation anesthesia in children. Laryngospasm is defined as glottic closure caused by reflex constriction of the intrinsic laryngeal muscles.[27] If not treated quickly laryngospasm makes ventilation of a patient's lungs difficult and can lead to hypercarbia, hypoxia, cardiac collapse, and death. Although the majority of laryngospasm episodes are self-limited or responsive to conservative maneuvers, the anesthesiologist must be prepared to treat laryngospasm to restore normal ventilation.

The incidence of laryngospasm is higher in children than in adults. Olsson and Hallen studied the incidence of laryngospasm in 136,929 patients of all ages over an 11-year period (1967 to 1978) and found an incidence of 8.7 per 1000 patients.[28] They reported that the laryngospasm incidence during general anesthesia correlated inversely with age, with higher rates in children between birth and 9 years (17.4 per 1000 patients) and the highest incidence in infants between birth and 3 months (28.2 per 1000 patients). In adolescent patients, a significantly higher laryngospasm incidence was found in boys than in girls (12.1 versus 7.2 per 1000 patients). The study also showed that children with upper respiratory infections or bronchial asthma had a very high laryngospasm rate (95.8 per 1000 patients).

Treatment of incomplete airway obstruction includes removing the irritating surgical stimulus, removing debris from the larynx, and deepening anesthesia. Lung ventilation is facilitated by applying gentle continuous positive airway pressure as 100% oxygen is administered through a tight-fitting facemask. If airway maneuvers do not improve ventilation, a muscle relaxant is required. Intramuscular (IM) or IV succinylcholine will relax the vocal cords, allowing adequate lung ventilation.[29]

## POSTOPERATIVE APNEA

Former preterm infants receiving general anesthesia are at risk for postoperative apnea. Regardless of whether they have a history of apnea, premature infants and full-term infants less than 44 weeks' postconceptual age may develop apnea in the postoperative period.[30–32] Postoperative apnea is defined as cessation of breathing or no detectable air flow for 15 seconds or longer, or less than 15 seconds with bradycardia. The cause of this phenomenon is unknown. Recovery from general anesthesia may unmask immature central respiratory regulation or decrease upper airway tone; both factors are believed to be responsible for postoperative apnea.[33] Although postoperative apnea usually develops in the first 2 hours after the anesthesia, it may present as long as 12 hours after anesthesia.

Several investigators have tried to establish a postconceptual age after which healthy premature infants with no history of neonatal apnea can be discharged on the day of surgery. Unfortunately, the recommendations vary from 44 weeks to 60 weeks.[32,34–36] The variance of recommendations are based in part on the sophistication of monitoring. The more sophisticated the monitoring, the higher the rate of identified apneic spells. Because considerable controversy exists, each hospital must develop its own policy. It is reasonable to monitor former premature infants for 24 hours if their postconceptual age is 55 weeks or less. Obviously, children with serious medical or neurologic problems or a history of significant and recurrent neonatal apnea are exceptions to this recommendation.

So far, anemia is the only independent risk factor identified that increases the likelihood of postoperative apnea in this at-risk population.[33,37] It has been recommended that anemic preterm infants with hematocrit values less than 30% have elective surgery delayed and receive iron supplementation until the hematocrit is greater than 30%. If surgery cannot be deferred, anemic infants must be observed and monitored very carefully for postoperative apnea.

## OBSTRUCTIVE SLEEP APNEA SYNDROME

Obstructive sleep apnea syndrome (OSAS) is a disorder of breathing during sleep that is characterized by prolonged partial upper airway obstruction (obstructive hypopnea) or intermittent complete obstruction (obstructive sleep apnea, OSA)

with or without snoring. OSAS is also associated with moderate to severe oxygen desaturation that disrupts normal sleep-time breathing and normal sleep patterns.[38] The most common cause of OSAS among children is upper airway narrowing with adenotonsillar hypertrophy. OSAS also occurs in infants and children with upper airway narrowing due to craniofacial anomalies and in those with neuromuscular diseases, including cerebral palsy and muscular dystrophy.[39,40]

In recent years, the epidemic increase in the prevalence of obesity during childhood seems to be contributing to substantial changes in the cross-sectional demographic and anthropometric characteristics of the children being referred for evaluation of OSAS. Although less than 15% of all symptomatic habitually snoring children were obese (i.e., >95% for age and gender) in the early 1990s, more than 50% fulfilled the criteria for obesity among all referrals to a Kentucky sleep center.[40,41]

Symptoms of OSAS include nocturnal snoring, breathing pauses, gasping, use of accessory muscles of respiration, enuresis, and excessive sweating.[42] In addition, children with OSAS have a host of sequelae, which are usually reversible after adenotonsillectomy but can lead to perioperative complications during and after surgery. Children with OSAS have a higher incidence of postoperative respiratory complications, including prolonged oxygen requirements, airway obstruction requiring a nasal airway, and major respiratory compromise requiring airway instrumentation.[43]

To date, the subpopulation of children with OSAS that must be monitored in the hospital is still unknown. Children who are most likely to experience postoperative respiratory complications and have a higher postoperative respiratory disturbance index on their postoperative polysomnogram include children younger than 3 years of age, children with severe OSAS diagnosed by preoperative polysomnography, and those with associated medical conditions such as hypotonia, morbid obesity, failure to thrive, or severe structural airway abnormalities.[44,45] These children are not candidates for outpatient surgery and should receive medical care in centers with pediatric inpatient facilities and pediatric intensive care unit support. High-risk patients should be monitored overnight with continuous pulse oximetry because standard apnea monitoring is unable to detect obstructive apnea and hypopnea. Patients can be discharged when significant oxygen desaturation during sleep has resolved.

# Preanesthesia Evaluation and Preparation

The primary purpose of a preoperative visit is to obtain information about the surgical problem and medical history and to assess the child's ability to tolerate anesthesia. The preoperative evaluation permits the identification of abnormalities that should be corrected before administration of an anesthetic; these disorders include severe anemia, sickle cell abnormalities, acute systemic infections, and active lower respiratory processes such as asthma, bronchopulmonary dysplasia, and cystic fibrosis.

In addition, the preoperative visit should be used to address the child's and parent's anxiety about the scheduled surgery and anesthesia. Preoperative behavioral evaluation programs are common in major pediatric hospitals. These preparation programs may provide narrative information, hospital tours, role rehearsal, and child life counseling.[46,47] Outpatient surgery programs may minimize a young child's separation anxiety. Ordinarily, a simple explanation of what the patient can expect before induction of anesthesia reduces the element of surprise and can be used to reinforce preoperative teaching materials. In older children, the preoperative visit allows the anesthesiologist to establish rapport, which fosters trust and may enhance cooperation. In some clinics, parents actively participate in the anesthesia induction process.[47,48] For some but not all parents and preschool-aged children, this joint experience minimizes fear and anxiety.

## PREOPERATIVE FASTING

The patient's stomach must be empty to prevent aspiration of stomach contents into the lungs during anesthesia induction. However, the patient should also be optimally hydrated. These two goals are compatible and are not difficult to achieve. Patients who are fed at the usual mealtimes and sleep through the night present no particular problems if procedures are scheduled for the early morning hours.

Numerous studies have failed to document an increased pulmonary aspiration risk when fasting guidelines are relaxed.[49,50] The perioperative fasting guidelines developed by the ASA are listed in Table 13-2.[51] These guidelines allow children to ingest clear liquids up to 2 hours before scheduled surgery. Infants and toddlers can be fed breast milk up until 4 hours before surgery, and infants and young children can be fed formula up until 6 hours before surgery.

If these details are not clearly stated in an itemized fashion with specific times, fluids may inadvertently be withheld from some children, particularly infants, for excessively long periods. Procedures should be scheduled according to age, with the youngest patient being the first on the operating schedule. Both the surgeon and the anesthesiologist must be alert to delays and ensure that the infant's fluid restriction is revised accordingly.

## PREANESTHESIA MEDICATIONS

Various drugs and routes of administration have been described as parts of premedication regimens. In the past, many anesthesiology departments created their own unique mixtures of sedative-hypnotic, narcotic, and antisialagogue medications, which were usually administered by the IM route. The goal of this premedication was to allay anxiety, provide analgesia, decrease autonomic (vagal) reflexes, decrease airway secretions, and reduce the volume and acidity of gastric fluid. The oral or nasal route is now preferred.

Premedication should provide a rapid level of short-term sedation that allows easy separation of the child from the parents and a smooth induction of anesthesia. Because children are usually not in pain before elective surgery, the use of opioids as part of standard premedication is not required. Antisialagogues were useful when diethyl ether and cyclopropane were the commonly used inhalation anesthetics. The newer inhalation agents do not significantly increase the quantity of oral secretions, thereby eliminating the need for anticholinergic premedication.

Midazolam is a popular, short-acting benzodiazepine that is now used frequently for preoperative sedation. It is an anxiolytic, hypnotic, and anticonvulsant agent, with antegrade but not retrograde amnestic properties.[52,53] At physiologic pH, midazolam becomes lipophilic, allowing quick absorption by the gastrointestinal tract and rapid entry into the CNS.[52] Sedative doses of IV midazolam can depress the hypoxic ventilatory drive and attenuate reflex cardiorespiratory responses to hypoxemia.[54] When combined with opioids, IV midazolam is likely to place unmonitored patients at significant risk for apnea and hypoxemia.[55]

In children, sedation with midazolam can be delivered by the intranasal, oral, rectal, IV, or IM route. The bioavailability of intranasal midazolam is 51% of the IV dose, and the speed of onset is 45% faster than with the rectal route.[56] Wilton and colleagues reported that intranasal midazolam given to children between 18 months and 5 years of age at a dose of 0.2 mg/kg calmed the patient within 5 to 10 minutes of administration.[57] Davis et al. found that intranasal midazolam at a dose of 0.2 to 0.3 mg/kg produced excellent sedation without prolonging recovery from anesthesia or time to hospital discharge in infants and small children undergoing very short ambulatory surgical procedures.[58] Cardiorespiratory depression has not been encountered when recommended doses of intranasal midazolam (0.2 to 0.3 mg/kg) or oral midazolam (0.5 to 0.75 mg/kg) are administered to otherwise healthy children for preoperative sedation.[57,59] Commercially prepared oral midazolam produces satisfactory sedation and anxiolysis within 10 to 20 minutes of consumption.[60] Oral midazolam prepared from the IV product has an onset time between 20 and 30 minutes.

Intranasal midazolam can cause mild, transient burning of the nasal mucosa, and amounts greater than 1 mL of a 0.5% solution (5 mg/mL) may produce choking and coughing. If more than 1 mL of 0.5% midazolam is necessary, the oral route is usually better tolerated. Oral midazolam prepared from the IV product should be flavored with sweetened clear liquids or syrup to mask the bitter taste. It has been demonstrated that commercially prepared oral midazolam has a more consistent bioavailability and pH characteristics. This stability allows doses as low as 0.25 mg/kg while still producing adequate sedation.[60]

Preoperative medication given to increase the pH of gastric fluid or to promote gastric emptying is not needed in healthy children, because pediatric pulmonary aspiration is rare.[61,62] Clear liquids administered to infants, children, and adults up to 2 hours before surgery do not alter residual gastric volume.[63] In fact, some children who have consumed liquids have a lower residual gastric volume and a higher gastric pH than controls who have had nothing by mouth (NPO).

# Fluid Requirements

## MAINTENANCE FLUID REQUIREMENTS

Various calculations involving body weight, surface area, and calorie expenditure have been used to determine fluid therapy for full-term infants and children.[64–66] Body weight and calorie expenditure, as well as estimates of insensible water loss, renal water requirement, stool water loss, and water needed for growth, determine the amount of fluid needed for maintenance. Calorie expenditure is related to size: infants weighing 1 to 10 kg require 100 calories/kg; small children weighing 10 to 20 kg require 1000 calories/day plus 50 calories/day for each kilogram greater than 10 kg; older children weighing more than 20 kg require 1500 calories/day plus 25 calories/day for each kilogram greater than 20 kg. For every 100 calories that the patient consumes, 67 mL of water is required for solute excretion; an additional 50 mL per 100 calories is associated with insensible loss, but 17 mL per 100 calories is produced by oxidation. Thus, infants and children need 100 mL of water for each 100 calories expended. Assuming that there are 25 hours in a day, a simple formula can be used to calculate the hourly maintenance fluid needed by healthy full-term infants and children. For children weighing 1 to 10 kg, the hourly maintenance fluid requirement (MFR) is 4 mL/kg per hour. For patients weighing 10 to 20 kg, the hourly MFR is 4 mL/kg per hour for the first 10 kg, plus 2 mL/kg per hour for each kilogram between 10 and 20 kg. For patients weighing more than 20 kg, the MFR is calculated as 4 mL/kg per hour for the first 10 kg, plus 2 mL/kg per hour for the next 10 kg, plus 1 mL/kg per hour for each additional kilogram greater than 20 kg. For example, a 28-kg child requires 68 mL of maintenance fluid per hour.

For every 100 mL of water given to an infant or child, 3 mEq $Na^+$, 2 mEq $K^+$, 2 mEq $Cl^-$, and 5 g glucose (to prevent ketosis) are required. It is more convenient to equalize the sodium and chloride requirements at 3 mEq. For routine IV fluid therapy, 5% dextrose in 0.25% normal saline meets these requirements. However, this is not an ideal fluid for intraoperative use, as noted later.

### Premature or Critically Ill Infants

Many factors influence water and electrolyte balance in premature or critically ill infants. The infant's gestational age, postnatal age, weight, renal solute load, and maximum renal concentrating ability are variables. Tissue destruction and catabolism that result from disease, stress, infection, reduced bowel activity, phototherapy, and gastric or intestinal drainage affect fluid therapy. These issues are reviewed by Bell,[65] Rowe,[67] and Hammarlund.[68]

## INTRAOPERATIVE FLUID REPLACEMENT

Intraoperative fluid replacement involves the initiation of fluid management or, alternatively, a continuation of ongoing therapy. Fluid replacement can simply consist of replacing the deficit from preoperative fasting and providing maintenance fluids. Fluid therapy can also be complex when preoperative deficits, translocated fluids, and variable blood loss are part of the equation.

### Estimated Fluid Deficit

The fluid deficit incurred during fasting should be replaced during anesthesia. Assuming a child is healthy at the time of fasting, the fluid deficit is estimated by multiplying the hourly MFR by the number of hours the patient has had nothing by mouth. This deficit can be replaced during surgery and if necessary in the recovery room. Maintenance fluids should continue in conjunction with replacement fluids.

### Role of Glucose

Surgery may cause the release of stress hormones that decrease insulin sensitivity, so serum glucose levels are usually elevated during surgery. If serum glucose concentrations become too

high, glycosuria and osmotic diuresis ensue. Hyperglycemia may contribute to neurologic damage subsequent to episodes of severe ischemia and hypoxia.[69–71] Several studies have shown that healthy infants and children remain euglycemic for up to 17 hours after the start of a fast. These studies suggest that healthy infants and children do not require glucose-containing solutions during surgery.[72,73] Frequent monitoring of blood sugar should accompany fluid and glucose therapy in patients who are at high risk for hypoglycemia (e.g., premature infants and those who are small for gestational age, children on total parenteral nutrition, and patients with diabetes).

### Choice of Intraoperative Fluid

For most patients, lactated Ringer solution can be used to provide maintenance and replacement fluids for intraoperative losses. The electrolyte composition of lactated Ringer is similar to that of serum. Hyponatremia with associated neurologic complications can occur if hypotonic solutions are used for fluid maintenance and replacement of third space fluid losses.

Surgical trauma is associated with isotonic transfer of fluids from the extracellular fluid compartment to the interstitial compartment.[74] This acute sequestration of edematous fluid to the interstitial compartment is called third-space loss. The greater the third-space volume losses, the greater the loss of intravascular volume. The magnitude of third-space loss varies with the surgical procedure and is usually highest in infants having intraabdominal surgery. In pediatric patients, estimated third-space loss is 6 to 10 mL/kg per hour during intraabdominal surgery, 4 to 7 mL/kg per hour during intrathoracic surgery, and 1 to 2 mL/kg per hour during superficial surgery or neurosurgery. Generally, lactated Ringer solution is used to restore third-space losses. In cases of massive volume replacement, some advocate using 5% albumin to restore one third to one fourth of the loss. The end point of third-space replacement therapy is maintenance of adequate blood pressure, tissue perfusion, and urine output.

## BLOOD REPLACEMENT

Blood replacement depends on the patient's needs, and clear communication between the surgeon and the anesthesiologist is crucial. Accurately measuring blood loss and assessing the limit of safe blood loss in infants are vital parts of any replacement regimen. Weighing sponges and using calibrated miniaturized suction bottles and visual estimates define the magnitude of blood loss. Allowable blood loss is determined by calculating the starting blood volume and measuring the hemoglobin or hematocrit of the patient.[75,76] Other factors used to determine allowable blood loss include the patient's age, cardiopulmonary status, and general medical condition. These factors are also used to determine the risk versus benefit of blood transfusion.

### Estimating Allowable Blood Loss

Several methods have been proposed for estimating allowable blood loss. The formulas range from simple to complex, but all involve an estimate of blood volume. Allowable blood loss can be calculated using the following equation:

$$\text{ABL} = \text{Weight (kg)} \times \text{EBV} \times [\text{Ho} - \text{Hl}]/\text{H},$$

where ABL is allowable blood loss, EBV is estimated blood volume, Ho is the original hematocrit, Hl is the lowest acceptable hematocrit, and H is the average hematocrit ([Ho + Hl] / 2).

This equation assumes that blood loss and replacement are gradual and exponential. Estimated blood volume is approximately 90 mL/kg for neonates, 80 mL/kg for infants and children, and 65 to 78 mL/kg for adolescents. This equation has general applicability for all age groups.

The ideal fluid to replace blood loss until the lowest acceptable hematocrit value is reached is a matter of controversy.[77–79] Generally, lactated Ringer solution is given in an amount equal to 2 to 3 times the estimated amount of lost blood except in situations of massive transfusion when massive transfusion protocols are followed (see later).

### Blood Products

Blood component therapy depends on the clinical setting and the availability of various blood products. Fresh whole blood (i.e., blood that was obtained less than 4 hours previously) has limited availability. Thus treatment with component therapy rather than fresh whole blood is the rule rather than the exception.[80,81] Packed red blood cells (RBCs) have a hematocrit value between 55% and 75% and are relatively hyperkalemic (K ± 15 to 20 mEq/L) and acidotic (pH <7.0). The estimated rise in hematocrit for every 10 mL/kg of packed RBCs (assuming a hematocrit of 70%) depends on the patient's age, size, and estimated blood volume (Table 13-3).

The need for platelets during surgery can be predicted from the preoperative platelet count. Platelets are mobilized from the spleen and bone marrow as bleeding occurs. An infant with a high preoperative platelet count (>250,000/mm$^3$) may not need a platelet transfusion until two to three blood volumes are lost, whereas an infant who has a low count (<150,000/mm$^3$) may need platelets after only one blood volume is lost. Two platelet packs/10 kg increases the platelet count by 50,000 to 100,000/mm$^3$.

Fresh frozen plasma (FFP) is indicated for emergency reversal of warfarin, for correction of microvascular bleeding in the presence of elevated prothrombin time and partial thromboplastin time, and as part of a massive transfusion protocol.[81] Ten to 20 ml/kg of FFP usually raises the level of coagulation factors by 20%. FFP contains the highest concentration of citrate per unit volume of any blood product; thus rapid FFP

**TABLE 13-3**
**Estimated Rise in Hematocrit with Increasing Blood Volume**

| | *Blood Volume (mL/kg)* | *Estimated Rise Age in Hematocrit** |
|---|---|---|
| Premature | 100 | 6.30 |
| Infants | | |
| Term infants | 90 | 7.00 |
| Preschool-aged children | 80 | 7.7 |
| School-aged children | 75 | 8.2 |
| Adults | 65 | 9.3 |

*The estimated rise in hematocrit for every 10 mL/kg of packed red blood cells (RBCs) (assuming a hematocrit of 70%) depends on the patient's age, size, and estimated blood volume.

causes the greatest change in ionized calcium. Under most circumstances, mobilization of calcium and hepatic metabolism of citrate are sufficiently rapid to prevent precipitous decreases in ionized calcium. However, because infants' calcium stores are small, rapid infusion of FFP can acutely decrease ionized calcium and cause significant decreases in arterial blood pressure.[82] Treatment of acute hypocalcemia includes IV calcium chloride (10 mg/kg) or calcium gluconate (30 to 60 mg/kg), which effectively increases ionized calcium and ameliorates hemodynamic changes.

When blood loss approaches one blood volume many centers have established massive transfusion protocols.[83] These protocols help prevent the acidosis, hypothermia, and coagulopathy seen when only packed RBCs are infused during massive hemorrhage.[79] The goals of these protocols are to improve communication between the surgeon, anesthesiologist, and blood bank to expedite delivery of appropriate quantities of blood products to the patient care team. Although the transfusion and coagulation management in children experiencing severe hemorrhage is not well studied, it is prudent to develop a massive transfusion protocol. The goal of transfusion is to deliver blood products that resemble whole blood. Current data support the use of plasma-to-RBC-to-platelet at 1:1:1.[84,85]

# Inhalation Anesthetic Agents

Several inhalation agents are available for induction and maintenance of anesthesia. The choice of agent depends on the age of the child and the disease process. Each agent has general and specific advantages and disadvantages (Table 13-4). None ensures hemodynamic stability. In patients with significant cardiac depression or hemodynamic instability, inhalation agents are generally avoided or used in markedly reduced concentrations. In healthy children, most inhalation agents can be used safely and successfully regardless of age.

To spare children an awake placement of an IV catheter, anesthesia is often induced by inhalation. However, inhalation anesthesia in children has some risk and is associated with an increased incidence of bradycardia, hypotension, and even cardiac arrest.[25,86] These risks have been reduced with the use of sevoflurane rather than halothane.[26] In premature or critically ill infants, the incidence of untoward effects from potent inhalation agents is attributed to age-related differences in uptake, anesthesia requirements, and cardiovascular system sensitivity. The uptake of inhalation anesthetics is more rapid in infants and small children than in adults because of major differences in blood-gas solubility coefficients,

**TABLE 13-4**
**Inhalation Anesthetics**

| *Agent* | *Advantages* | *Disadvantages and Precautions* |
|---|---|---|
| Nitrous oxide | Inexpensive<br>Odorless | Should be used as a supplement to other inhalation or intravenous anesthetics to provide complete general anesthesia |
| | Rapid onset and recovery of clinical effects | In critically ill patients, can be a potent vasodilator |
| | When combined with potent inhalation anesthetics, side effects of potent agents are reduced | Expands gas-containing spaces, such as the intestines or middle ear; increases the expansion of pneumothorax and pneumocephalus |
| | Activates the sympathetic nervous system, which attenuates cardiac depression or vasodilatation caused by potent inhalation agents | Exposure to operating room atmosphere contamination may cause neuropathies |
| Halothane | Nonpungent odor<br>Effective inhalation induction agent | Causes cardiac depression manifested as bradycardia and decreased myocardial contractility |
| | Bronchodilator (like all potent inhalation agents) | Causes halothane-associated hepatitis (rare in children) |
| | | Sensitizes the myocardium to the arrhythmogenic properties of epinephrine; however, infants and children require higher doses of epinephrine to stimulate ventricular arrhythmias than do adolescents and adults |
| Isoflurane | Maintains myocardial contractility and heart rate | Pungent odor |
| | Minimal sensitization of the myocardium to the arrhythmogenic properties of epinephrine | Not an effective inhalation induction agent |
| | | Can cause bradycardia in neonates and young infants |
| | | May cause hypotension by decreasing systemic vascular resistance |
| Sevoflurane | Nonpungent odor | More expensive than halothane |
| | Effective inhalation induction agent<br>Low blood-gas coefficient | Metabolized by liver, releasing free fluoride ions; theoretical risk for renal diabetes insipidus |
| | Maintains myocardial contractility and heart rate | Degradation in Baralyme and soda lime, forming potentially toxic metabolites |
| | Minimal sensitization of the myocardium to the arrhythmogenic properties of epinephrine | Increased incidence of postanesthesia delirium |
| Desflurane | Low blood-gas coefficient | Pungent odor |
| | Maintains myocardial contractility and heart rate | Poor inhalation induction agent |
| | Minimal sensitization of the myocardium to the arrhythmogenic properties of epinephrine | High incidence of laryngospasm |
| | | Expensive |
| | | Increased incidence of postanesthesia delirium |

blood-tissue solubility coefficients, body composition, ratio of alveolar ventilation to functional residual capacity, and distribution of cardiac output.[87–89] Thus, early in the course of anesthesia induction, infants have higher tissue concentrations of the drug in the brain, heart, and muscle than do adults.

## MINIMUM ALVEOLAR CONCENTRATION

The minimum alveolar concentration (MAC) is the minimum concentration of an inhaled anesthetic at 1 atm of pressure that prevents skeletal muscle movement in response to a surgical incision in 50% of patients. The MAC of a volatile anesthetic changes with the patient's age (see Table 13-1). LeDez and Lerman[91] showed that premature infants younger than 32 weeks' gestation have a lower MAC for isoflurane than do neonates of longer gestation. For all anesthetic agents, the MAC is highest at 6 to 12 months of age. The increased MAC requirement in conjunction with the rapid uptake of anesthetic makes infants and children very susceptible to anesthetic overdose.[92,93]

## NITROUS OXIDE

Because nitrous oxide is a nonpotent inhalation agent with a MAC of 105%, it is usually used as an adjunct to the more potent inhalation agents. Nitrous oxide reduces the side effects of these agents by reducing the amount required for effective analgesia. During the induction phase of anesthesia, nitrous oxide hastens the uptake of potent inhalation agents. Eger and Saidman[93a] noted that nitrous oxide is more soluble than nitrogen in blood and thus distends any air-containing space, such as the intestines, to which it is carried. As a result, nitrous oxide is usually avoided in patients with closed pneumothorax, intestinal obstruction, or air in the cerebral ventricles. Nitrous oxide has been implicated in lymphocyte depression, testicular damage, birth defects, and miscarriages with chronic exposure, so it is important to adequately scavenge this gas in the operating suite.

## HALOTHANE

Halothane was once the most commonly administered anesthetic agent in children because it was less likely than isoflurane and desflurane to cause airway irritability. However, halothane was not an ideal induction agent because of its potential to cause bradycardia, hypotension, and ventricular ectopy secondary to induced sensitivity to catecholamines. In the United States, sevoflurane (because of its cardiovascular safety profile) has replaced halothane as the induction agent of choice.[94]

## ISOFLURANE

Isoflurane has a lower solubility coefficient than that of halothane, so induction and recovery with isoflurane is faster than with halothane. However, isoflurane causes moderate to severe airway irritability if used as an induction agent.

The cardiovascular effects of isoflurane in children are well documented. Unlike adults, unpremedicated infants 5 to 26 weeks of age who were anesthetized with isoflurane showed a decrease in heart rate similar to that seen with halothane and a decrease in blood pressure half that seen with halothane.[95] In children older than 2 years who did not receive atropine, isoflurane preserved heart rate and cardiac function better than did halothane.[96] Halothane and isoflurane both reduced blood pressure. Isoflurane reduced peripheral vascular resistance but preserved cardiac output. Gallagher and colleagues[97] compared the anesthetic effects of halothane and isoflurane on cardiac function in 15 older children using pulsed Doppler echocardiography.[97] Cardiac output, heart rate, and myocardial contractility were preserved with isoflurane, but contractility was decreased with halothane. Kotrly and associates[98] found that isoflurane preserved the baroreceptor response in adults more than halothane did.

## DESFLURANE

Desflurane is a potent inhalation agent. The blood-gas solubility is low and similar to nitrous oxide.[99] Because it is a pungent airway irritant, desflurane results in an unacceptably high incidence of laryngospasm, coughing, and hypoxia when used as an induction agent in children.[100–102] Patients anesthetized with desflurane have a faster emergence from general anesthesia.

The cardiovascular profile of desflurane is age dependent.[100] When desflurane was given at a MAC of 1 before incision, the arterial blood pressure decreased approximately 30% compared with awake values, and the heart rate decreased significantly or remained the same. Thus at a MAC of 1, desflurane, like isoflurane and halothane, seems to attenuate the baroreceptor response in children. Weiskopf and colleagues[103] also demonstrated that in adults, rapid increases in desflurane from a MAC of 0.55 to 1.66 can transiently increase arterial blood pressure and heart rate; this excitation is associated with an increase in sympathetic and renin-angiotensin system activity.

## SEVOFLURANE

Sevoflurane is a potent inhalation agent with a low blood-gas solubility coefficient. It does not have a pungent odor and has replaced halothane as the inhalation anesthetic of choice for infants and children.[104,105] Clinical studies with sevoflurane inpediatric patients have found shorter times to emergence than with halothane.[94] This may be related to the low blood-gas solubility. Sevoflurane has fewer cardiovascular side effects than halothane.[94,108–112] Wodey and colleagues[111] compared cardiovascular changes at equipotent concentrations of sevoflurane and halothane in infants. They concluded that in infants, sevoflurane decreases cardiac output less than does halothane, and a minor decrease in contractibility is compensated by a greater decrease in systemic vascular resistance (SVR) without a change in heart rate.[111] Unlike halothane, sevoflurane does not increase the sensitivity of the myocardium to the arrhythmogenic effects of epinephrine.[113] Sevoflurane causes a significant decrease in respiratory resistance, and it is an effective bronchodilating agent.[114]

One theoretical concern surrounding the use of sevoflurane is that it is metabolized in the liver by the cytochrome system, with the subsequent release of fluoride and the potential for renal diabetes insipidus. However, renal concentrating ability and normal creatinine clearance have been demonstrated in adult volunteers subjected to prolonged sevoflurane exposure. In addition to in vivo metabolism, sevoflurane

undergoes degradation by soda lime and barium hydroxide lime (Baralyme) to produce two potentially toxic olefins, compound A and compound B. Although human exposure to sevoflurane administered by circle absorption systems has not demonstrated toxicity, animal studies have yielded conflicting histologic evidence of chemical-induced toxicity.[97,115,116] Frink and associates[117] concluded that the concentrations of compound A measured in pediatric patients during sevoflurane anesthesia using a 2-L flow circle system were low, and there was no evidence of abnormal renal or hepatic function up to 24 hours after anesthesia.

## Emergence Delirium

The advent of the use of volatile anesthetics in children brought with it the new entity of emergence delirium (ED). ED is a dissociated state of consciousness in which children are inconsolable, irritable, uncompromising, or uncooperative, or a combination of these behaviors.[118] It occurs in 2% to 80% of children, depending on the age of the patients, anesthetics used, and the type of surgery. It usually occurs within 30 minutes after the conclusion of the anesthesia procedure and is typically self-resolving within 30 minutes.[119] Children experiencing ED are disruptive to the postanesthesia care unit (PACU) and increase the risk of injury to themselves and others; ED is also associated with parent dissatisfaction with the hospital care. The current theories on the causes of ED involve the direct interaction of volatile agents on neurons. The two most prominent theories are an uneven susceptibility of neurons to volatile anesthetics or direct, low-level activation of excitatory neurons by volatile anesthetics.[120,121]

The main risk factors are age, perioperative anxiety, and the anesthetics used, with volatile agents causing the most ED.[119] Preventive measures include preoperative anxiolysis, avoidance of volatile anesthetics, and preemptive treatment. Multiple agents have been used for preemptive treatment, and most are given 10 minutes before the patient wakes up. They include fentanyl, propofol, ketamine, nalbuphine, and dexmedetomidine. Once a child is in ED, fentanyl, midazolam, propofol, or dexmedetomidine can be used for treatment.

Dexmedetomidine, a highly specific and selective $\alpha_2$-adrenergic agonist, is becoming an important drug in the treatment of ED. It can be given either preoperatively as an anxiolytic agent, intraoperatively for ED avoidance, or postoperatively for the treatment of ED. Currently, there are six prospective clinical trials that have shown that dexmedetomidine significantly reduces the incidence of ED when given to children before recovery from volatile anesthetics.[122] Doses range from 0.15 to 1 μg/kg given either as a bolus or infusion before completion of surgery. Once a child is in ED, a single bolus dose of 0.5 μg/kg can be used as treatment. Side effects are minimal and usually consist of bradycardia with a concomitant decrease in blood pressure.

## Neuromuscular Blocking Agents

Neuromuscular blocking agents (i.e., muscle relaxants) are used to facilitate endotracheal intubation, to provide surgical relaxation, and to facilitate controlled mechanical ventilation. This is accomplished through blockade of the nicotinic acetylcholine receptor site on the neuromuscular junction. The use of neuromuscular blocking agents reduces the need for potent inhaled anesthetics or IV sedative-hypnotics. Throughout infancy, the neuromuscular junction matures physically and biochemically. The contractile properties of skeletal muscle change, and the amount of muscle in proportion to body weight increases. As a result, the neuromuscular junction is variably sensitive to relaxants.[123] In addition, age-related changes in the volume of distribution of relaxants, their redistribution and clearance, and possibly their rate of metabolism occur. These factors influence the dose-response relationships of relaxants and the duration of neuromuscular blockade.[124–126]

When allowances are made for differences in the volume of distribution and for the type and concentration of anesthetic, infants seem to be relatively resistant to succinylcholine and relatively sensitive to nondepolarizing relaxants (Table 13-5). The degree of neuromuscular blockade should be monitored with a nerve stimulator during the course of the operation, and the patient should be treated with a dose of the selected agent sufficient to achieve the desired degree of block. The paralysis caused by nondepolarizing relaxants should be reversed at the end of each operation unless postoperative mechanical ventilation is planned. Anticholinesterase drugs, such as neostigmine and edrophonium, combined with anticholinergics are given to prevent muscarinic side effects. The effectiveness of reversal is judged by muscle strength, adequacy of ventilation, and response to nerve stimulation. Minimum criteria for withdrawing assisted ventilation should include good muscle tone, flexing of the arms and legs, and adequate respiratory effort.

Neuromuscular blocking agents have no sedative, hypnotic, or analgesic effects, but they may indirectly decrease metabolic demand, prevent shivering, decrease nonsynchronous ventilation, decrease intracranial pressure, and improve chest wall compliance. Major organ failure, up-regulation of acetylcholine receptors, malnutrition, electrolyte and acid-base abnormalities, drug interactions, and muscle atrophy can also have a profound influence on the kinetics and dynamics of relaxants. In addition, repeated doses of relaxants over relatively long periods without monitoring of neuromuscular transmission may lead to prolonged muscle weakness despite discontinuation of therapy. Knowledge of neuromuscular pharmacology and its modification by age, concurrent medications, and concurrent disease processes permits a more rational use of neuromuscular blocking agents in patients in intensive care.

### COMPLICATING CONDITIONS OF DEPOLARIZING BLOCKING AGENTS

The use of succinylcholine for elective pediatric procedures has been abandoned secondary to multiple case reports of cardiac arrest from hyperkalemia due to undiagnosed muscular dystrophy. Life-threatening hyperkalemia can also be caused by succinylcholine in all of the following situations: burns on greater than 8% of the body, upper motor neuron lesions, lower motor neuron lesions, crush injuries, neuromuscular diseases, and chronic ongoing sepsis. It is also a known triggering agent of malignant hyperthermia (MH). The FDA issued the following "Black Box" warning in 1993 because of previous listed potential complications:

> Since there may be no signs or symptoms to alert the practitioner to which patients are at risk, it is recommended that the use of succinylcholine should be reserved for emergency intubation or

**TABLE 13-5**
**Muscle Relaxants**

| *Agent* | *Type* | *Dose* | *Metabolism and Excretion* | *Advantages* | *Disadvantages and Precautions* |
|---|---|---|---|---|---|
| Succinylcholine | Short acting; depolarizing | IV: 1.0-2.0 mg/kg IM: younger than 6 mo, 4.0-5.0 mg/kg; older than 6 mo, 3.0-4.0 mg/kg | Pseudocholinesterase | Rapid onset; rapid recovery; may be delivered through intravascular or intramuscular routes | Masseter muscle spasm; trigger for malignant hyperthermia; bradycardia; hyperkalemia leading to life-threatening arrhythmias; myoglobinemia (muscle injury); muscle fasciculations; increased intraocular pressure; prolonged neuromuscular blockade with pseudocholinesterase deficiency<br>Avoid in patients with muscular dystrophy; multiple trauma >24 hr; burns >24 hr; spinal cord injury >24 hr; malignant hyperthermia–susceptible |
| Mivacurium | Short acting; nondepolarizing | Intubation: 0.2 mg/kg Maintenance: 0.1 mg/kg | Plasma cholinesterase | Recovery time 10 min; infusion possible | Histamine release; unpredictable intubating conditions |
| Atracurium | Intermediate acting; nondepolarizing | Intubation: 0.5 mg/kg Maintenance: 0.15 mg/kg | Ester hydrolysis; Hoffman degradation | Recovery time 30 min regardless of age; can be used in renal and kidney disease; infusion possible | Histamine release; (metabolite of Hoffman degradation); epileptogenic in high doses |
| Cisatracurium | Intermediate acting; nondepolarizing | Intubation: 0.1 mg/kg Maintenance: 0.03 mg/kg or 1-2 mcg/kg/min continuous | Ester hydrolysis; Hoffman degradation | Recovery time 30 min; no cardiovascular effects; infusion possible | |
| Rocuronium | Intermediate acting; nondepolarizing | Intubation: 0.6 mg/kg (onset 50-80 sec) or 1.2 mg/kg (onset 30 sec) Maintenance: 0.1 mg/kg | Liver and renal | Recovery time 15-40 min (dose dependent); can be used for rapid-sequence intubation; infusion possible | Slight vagolytic effect |
| Vecuronium | Intermediate acting; nondepolarizing | Intubation: 0.1 mg/kg Maintenance: 0.02 mg/kg | Kidney and liver | Recovery time approx 30 min in children; no histamine release at up to 0.4 mg/kg; no effect on cardiovascular system | Long-acting muscle relaxant in infants; recovery time approx 70 min. |
| Pancuronium | Long acting; nondepolarizing | Intubation: 0.1 mg/kg Relaxation: 0.02 mg/kg | Kidney and liver | Recovery time approximately 50 min; inexpensive | Vagolytic effect; tachycardia; hypertension; histamine release |

IV, intravenous.

in instances where immediate securing of the airway is necessary (e.g., laryngospasm, difficult airway, full stomach, or for IM route when a suitable vein is inaccessible).

Succinylcholine is broken down by plasma cholinesterase and is the reason for the short period of paralyzation (3 to 5 minutes). However, 1 in 3000 to 1 in 10,000 patients may be homozygous for an alternative version of the plasma cholinesterase enzyme. This enzyme has limited ability to bind and break down succinylcholine. In this patient population, muscle paralysis from succinylcholine can last up to 8 hours.[127]

## Malignant Hyperthermia

MH is a life-threatening condition characterized by hyperthermia, hypermetabolism, and muscle injury that occurs in response to a triggering agent. Potent inhalation agents (not nitrous oxide) and the depolarizing muscle relaxant succinylcholine are two potent triggers in children. Triggers that stimulate MH cause excessive release of $Ca^{2+}$ from the sarcoplasmic reticulum of skeletal muscle into the myoplasm, resulting in a chain of metabolic events that culminates in heat production, cell injury, hyperkalemia, and myoglobinemia.[128] The mortality rate for untreated MH is greater than 60%; rapid treatment with dantrolene reduces mortality to almost zero.

The incidence of fulminant MH is approximately 1 in 50,000 to 1 in 100,000 in adults and 1 in 3,000 to 1 in 15,000 in children. Most cases of MH occur in patients thought to be healthy. Predisposition to MH is a familial condition of multigenetic inheritance. First-degree relatives are at high risk; second-degree relatives have a lower but significant risk of MH developing in response to the appropriate triggering agents. Patients with Duchenne muscular dystrophy are thought to be at high risk for the development of MH. Other

diseases associated with the development of MH are central core disease and King-Denborough syndrome.

The classic signs of MH include tachycardia, ventricular dysrhythmias, tachypnea, a rapid increase in temperature to greater than 39.5° C, rigidity of the jaw or generalized rigidity, metabolic and respiratory acidosis, and decreased mixed venous oxygen saturation. Associated laboratory values include hyperkalemia, hypercarbia, respiratory and metabolic acidosis, increased creatine phosphokinase and lactate levels, blood clotting abnormalities, and myoglobinuria.

The clinical diagnosis of MH should be considered before signs of hypermetabolism and elevated temperature reach extremes. The early signs of the disorder include tachypnea, tachycardia, increased end tidal carbon dioxide ($ET_{CO_2}$), and ventricular dysrhythmias. These signs must be evaluated quickly because they can have many causes, such as iatrogenic hyperthermia, sepsis, pheochromocytoma, hyperthyroidism, ventilator valve malfunction with rebreathing of carbon dioxide, inadequate levels of anesthesia, and faulty temperature and $ET_{CO_2}$ monitors.

Management of an acute episode of MH is outlined in Table 13-6. The cornerstone of treatment is IV dantrolene, which must be diluted with sterile, preservative-free, distilled water. The initial IV dose is 2.5 mg/kg, although much higher doses may be required. The usual dose limit of 10 mg/kg may be exceeded if necessary.[129] Dosing of dantrolene should be guided by clinical and laboratory signs and carried out every 5 minutes until metabolic acidosis has resolved. Dantrolene decreases the release of calcium from the sarcoplasmic reticulum by decreasing the mobility of calcium ions or the protein that transports calcium across membranes and is specific for skeletal muscle.[130,131] Dantrolene attenuates muscle hypermetabolism, reducing muscle rigidity and restoring normal muscle function. As skeletal muscle function normalizes, serum potassium levels decrease and abnormal lactic acid production slows.[132] Patients respond to dantrolene within 20 minutes. The $ET_{CO_2}$ begins to decrease in 6 minutes, and arterial blood gas analysis demonstrates significant resolution of metabolic and respiratory acidosis within 20 minutes.[132] By 45 minutes, metabolic and respiratory acidosis and hyperthermia should be resolved. Dantrolene treatment at higher doses is necessary if metabolic dysfunction persists.[129]

Parents of an affected child may wish to have a muscle biopsy and contracture testing because negative findings mean that other relatives have no increased risk of MH.

In patients with a personal history or a strong family history of MH, surgery can be safely performed under regional or local anesthesia. General anesthesia with nontriggering agents can also be used. All nondepolarizing muscle relaxants and IV anesthetic agents are safe to use in patients who are susceptible to MH. Monitoring for the early signs of MH and initiating quick treatment are the most important aspects of caring for these patients.

**TABLE 13-6**

**Management of Acute Episodes of Malignant Hyperthermia**

| |
|---|
| Stop inhalation anesthetics immediately |
| Cancel or conclude surgery as soon as possible |
| Hyperventilate with high-flow 100% oxygen |
| Administer IV dantrolene (2.5 mg/kg) and repeat as needed |
| Give more dantrolene if signs of the condition reappear |
| Initiate cooling with hypothermia blanket, IV cold saline solution (15 mL/kg for 10 min), ice packs in the axillary region and groin, and lavage of body cavities with cold saline solution if core temperature is >37° C. Stop cooling when core temperature falls to 38° C |
| Correct metabolic acidosis with 1.0 to 2.0 mEq/kg sodium bicarbonate as an initial dose |
| Administer calcium (10 mg/kg calcium chloride) or insulin (0.2 U/kg) in 50% dextrose in water (1 mg/kg) to treat the effects of hyperkalemia |
| Administer lidocaine (1 mg/kg) to treat ventricular arrhythmias |
| Maintain urine output at 2 mL/kg/hr with furosemide (1 mg/kg) and additional mannitol if needed. |
| Insert arterial and central venous catheters |
| Repeat venous blood gas and electrolyte analysis every 15 min until signs of the disorder resolve and vital signs normalize |

# Intravenous Anesthetic Agents

## PROPOFOL

Propofol is a sedative-hypnotic, lipophilic IV agent used for induction and maintenance of anesthesia. It has become the IV agent of choice because of its favorable pharmacokinetic profile. The pharmacokinetics of propofol are characterized by rapid distribution, metabolism, and clearance. After termination of an infusion, redistribution to the peripheral tissues results in a prompt decrease in plasma concentration. Propofol is eliminated by hepatic conjugation to inactive metabolites, and excretion is by the renal route.[133]

Multiple studies have shown that the dose of propofol needed for induction is indirectly related to age. A typical induction dose is between 2.5 and 3.5 mg/kg.[134–137] Although the mechanisms that contribute to different dose requirements in younger children compared with older children have not been delineated, Westrin[137] hypothesized that because infants have a greater cardiac output in relation to body weight and a larger vessel-rich component, arterial peak concentration reaching the brain may be lower than that achieved in adults.

Propofol can induce hypotension, but the mechanism through which this occurs has not been clearly established.[135,138,139] Aun and associates[138] compared the hemodynamic responses to an induction dose of thiopental (5 mg/kg) or propofol (2.5 mg/kg) in 41 healthy children aged 8 months to 12 years. Heart rate, blood pressure, and velocity of flow were measured. The 28% to 31% reduction in mean arterial pressure after propofol administration was significantly greater than that after thiopental administration (14% and 21%, respectively). The 10% to 15% reduction in cardiac index was similar for both drugs. The children studied tolerated the hypotensive episodes without requiring pharmacologic intervention. Hannallah and associates[135] noted that like adults, children anesthetized with propofol have a slower heart rate than those given a volatile agent. Atropine may be useful to attenuate the bradycardia that can develop in young children when propofol and an IV opioid are used to maintain anesthesia. Keyl and colleagues[140] concluded that the vagally mediated heart rate response to cyclic peripheral baroreflex stimulation was markedly depressed during propofol anesthesia; there was also an impaired blood pressure response to cyclic baroreceptor stimulation.

Pain at the site of injection occurs in up to 50% of patients receiving propofol through a vein in the dorsum of the hand.[141] Pain on injection of propofol can be attenuated or eliminated by injection through a large antecubital vein or by adding 0.1 mg/kg of lidocaine to every 2 to 3 mg/kg of propofol drawn into the syringe.[142]

Long-term sedation with propofol in the pediatric population is not recommended. Five deaths of infants and children (4 weeks to 6 years old) involving propofol infusions were reported in 1992.[143] These deaths involved lipemia, metabolic acidosis, hyperkalemia, and rhabdomyolysis. Further case reports have delineated what is now called propofol infusion syndrome (PIS). Risk factors for PIS include young age and propofol infusion rates of 70 μg/kg/min or greater for longer than 48 hours. However, there are reports of PIS in cases in which infusions were continued for less than 48 hours at lower levels.[144]

## THIOPENTAL

Thiopental is a barbiturate induction agent that can be administered by the IV or rectal route. The dose required for IV induction varies with age. Several studies[145,146] confirmed previous findings by Cote and colleagues[147] and Brett and Fisher,[148] who showed that thiopental requirements are higher in children (Fig. 13-3). Barbiturates decrease cerebral blood flow and intracranial pressure. The direct myocardial depression and venodilatation caused by thiopental are well tolerated by healthy children.[145] In patients who are hemodynamically compromised, however, these cardiovascular effects can result in significant hypotension. Thiopental should be avoided in children who are dehydrated, have heart failure, or have lost a significant amount of blood. Side effects seen with an induction dose of thiopental include hiccups, cough, and laryngospasm. Valtonen and associates[149] reported these side effects in 20% of children aged 1 to 6 years. Extravasation can cause tissue injury caused by thiopental's alkalinity. Barbiturates also cause histamine release, which is why they are often avoided in patients with a history of asthma.[150,151]

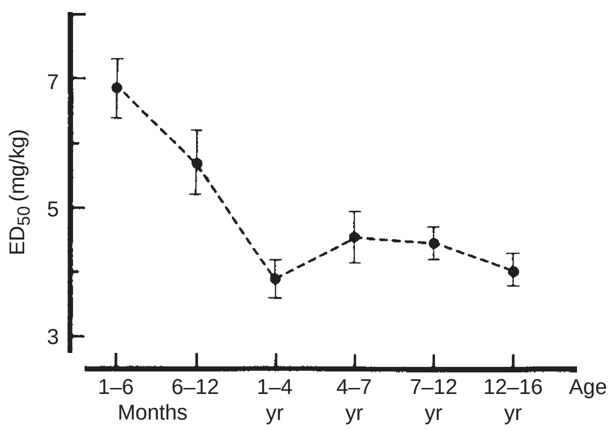


**FIGURE 13-3** Estimated $ED_{50}$ (the dose of a drug that will induce anesthesia in 50% of patients) plus or minus the standard error for thiopental in various age groups. (From Jonmarker C, Westrin P, Larsson S, Werner O. Thiopental requirements for induction of anesthesia in children. Anesthesiology 1987;67:104.)

## KETAMINE

Ketamine is a derivative of phencyclidine that antagonizes *N*-methyl-D-aspartate (NMDA) receptors. It causes a central dissociation of the cerebral cortex along with causing cerebral excitation. It is an excellent analgesic and amnestic, with recommended doses of 1 to 3 mg/kg IV, 5 to 10 mg/kg IM, or 5 to 10 mg/kg PO. The IV dose has a duration of 5 to 8 minutes. Glycopyrrolate or similar antisialagogue should be given for the copious secretions associated with ketamine use.

Ketamine increases heart rate, cardiac index, and systemic blood pressure. It also causes bronchodilation with minimal effects on respiration.[152,153] There is no direct effect on pediatric pulmonary artery pressure as long as ventilation is controlled. Its systemic effects are sympathetically mediated. However, ketamine will cause bradycardia and a decrease in systemic vascular resistance in patients who are depleted of catecholamine. Also, it is the only IV anesthetic to increase both intracranial pressure and intraocular pressure. Therefore, it is relatively contraindicated in patients in whom these increases could be detrimental.

## ETOMIDATE

Etomidate is a steroid-based hypnotic that has minimal effects on the hemodynamics or cardiac function of a patient at clinical doses. It also has minimal effects on respiratory parameters. Therefore, it is useful in pediatric patients with known or anticipated hemodynamic instability. The main drawbacks to its routine use are pain with injection and adrenal suppression even after one dose. Typical dosages for induction are 0.2 to 0.3 mg/kg IV.

# Monitoring

## NONINVASIVE MONITORING

The ASA has established standards for basic anesthesia monitoring, which include continuous evaluation of the patient's oxygenation, ventilation, circulation, and temperature during the use of all anesthetics. Delivery of an adequate oxygen concentration is ensured by measuring the inspired concentration of oxygen in the patient's breathing system using an oxygen analyzer on the anesthesia machine. Blood oxygenation is measured by pulse oximetry. Ventilation is ensured by qualitative clinical signs such as chest excursion, observation of the reservoir breathing bag, and auscultation of breath sounds as well as continual monitoring for the presence of end-tidal carbon dioxide. When ventilation is controlled by a mechanical ventilator, a continuous device that is capable of detecting the disconnection of system components is used. Circulation is monitored by a continuously displayed electrocardiogram, arterial blood pressure reading, and heart rate, which is determined and evaluated at least every 5 minutes. In addition, adequate circulation is ensured by auscultation of heart sounds, palpation of a pulse, monitoring of a tracing of intraarterial pressure, ultrasonographic pulse monitoring, or pulse plethysmography or oximetry. Temperature monitoring is required to aid in the maintenance of appropriate body temperature during all anesthesia.[154]

### Temperature Monitoring

The oral or nasal cavity is the most common site for temperature measurement in the pediatric population. Midesophageal or nasopharyngeal temperature better reflects core temperature compared with rectal or tympanic measurements. However, tympanic temperature theoretically provides ideal information because it most closely reflects the temperature of the brain. Rectal temperature is also a common site for temperature measurement, despite the following disadvantages: (1) potential for perforation of the bowel wall with a stiff thermistor probe wire, (2) potential dislodging of the probe, and (3) excessive warming of the thin tissues of the perianal and coccygeal area by the circulating warm water mattress. A more fundamental objection is that rectal temperatures, in general, do not promptly track rapid temperature changes, such as those that occur during deliberate hypothermia or rewarming.

### Pulse Oximetry

Continuous, noninvasive monitoring of arterial oxygen saturation ($Sao_2$) can be accomplished by pulse oximetry. The oximeter is usually placed on a finger or toe, but any site is acceptable as long as a pulsating vascular bed can be interposed between the two elements. Two wavelengths of light chosen for their relative reflectance with oxygenated versus deoxygenated hemoglobin illuminate the tissue under the probe. Through expansion and relaxation, the pulsating vascular bed changes the length of the light path, thereby modifying the amount of light detected. The result is a characteristic plethysmographic waveform, and artifacts from blood, skin, connective tissue, or bone are eliminated. This technique is accurate with oxygen saturation values from 70% to 100%. Reduction in vascular pulsation—for example, with hypothermia, hypotension, or the use of vasoconstrictive drugs—diminishes the instrument's ability to calculate saturation. In addition to a continuous indication of $Sao_2$, the pulse oximeter usually provides a continuous readout of pulse rate and amplitude.

### Capnography

The presence of end tidal $CO_2$ ($ETco_2$) is the gold standard in confirming proper endotracheal tube placement and measuring the adequacy of ventilation. Plotting $ETco_2$ versus time produces the classic time-capnograph curve. In Figure 13-4, *A,* the curve represents an ideal time-capnograph tracing during quiet respiration with no rebreathing of exhaled gas. The maximum value of $ETco_2$ at number 4 represents alveolar gas, which is in equilibrium with arterial $CO_2$ ($Paco_2$). In the absence of any ventilation-perfusion (V/Q) mismatch, the value at 4 should be within 2 to 4 mm Hg of $Paco_2$. Any discrepancy that is larger points to an increase in V/Q mismatch due to larger dead-space ventilation.

An ideal capnographic tracing cannot always be obtained, but the abnormal curve may be diagnostic or highly suggestive of certain types of problems involving the patient, the anesthesia circuit, or the ventilation technique. In Figure 13-4, B, several capnographic tracings are presented that represent changes or pathologic features in ventilation. In all of these, the maximum obtained $ETco_2$ is no longer indicative of $Paco_2$.

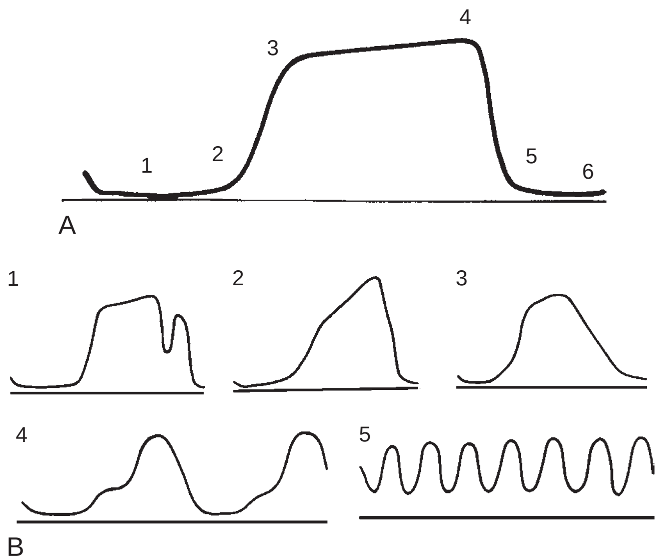


**FIGURE 13-4** **A,** Ideal capnographic tracing. Exhalation begins *(1)*. Anatomic dead space is cleared *(1-2)*. Dead-space air mixes with alveolar gas *(2-3)*. Alveolar plateau *(3-4)*. End-tidal maximum value; inspiration begins *(4)*. Dead-space air is cleared *(4-5)*. Inspiratory gas is devoid of carbon dioxide *(5-6)*. **B,** Types of capnographic tracings: Efforts at spontaneous breathing with incomplete neuromuscular blockade *(1)*. Respiratory obstruction *(2)*. Lack of sustained pressure resulting from a large leak in the breathing system *(3)*. In the Mapleson D system, when large amounts of fresh gas flow at small tidal volumes, the expired carbon dioxide is diluted and achievement of a stable alveolar plateau is prevented *(4)*. The effect of partial rebreathing of carbon dioxide from the expiratory limb of the Mapleson D system, when fresh gas flows at small amounts, is excessively rapid ventilation and small tidal breaths *(5)*.

### Monitoring Neuromuscular Function

The only satisfactory method of monitoring neuromuscular function is stimulation of an accessible peripheral motor nerve and observation or measurement of the response of the skeletal muscle supplied by this nerve. Various nerve stimulators are commercially available. Usually, the ulnar nerve is stimulated at the wrist with surface electrodes, and the response of the adductor pollicis brevis is noted. Supramaximal electrical stimuli are necessary to ensure full activation of the nerve. The evoked response to single repeated nerve stimuli at 0.1 Hz or train-of-four stimulation at a low frequency (2 Hz for 2 seconds) allows continuous monitoring of neuromuscular transmission after the administration of muscle relaxants. Tetanic rates of stimulation (50 Hz), train-of-four ratios, or double-burst stimulation allow the assessment of neurotransmission after reversal.

In adults clinical signs of adequate neuromuscular transmission include the ability to sustain a head lift for 5 seconds in conjunction with a vital capacity of at least 15 to 20 mL/kg or a negative inspiratory force of 30 cm $H_2O$. Because an infant cannot lift the head for 5 seconds, the ability to flex its arms or legs is a reliable sign of adequate neuromuscular transmission. Because vital capacity cannot easily be determined in infants, inspiratory force is measured instead. The ability to sustain tetany of 30 to 50 Hz for 5 seconds or a near-normal train-of-four ratio (>0.7) is also a reliable sign of adequate neuromuscular transmission.

### INVASIVE MONITORING

The availability of sophisticated noninvasive monitoring devices has reduced the need for invasive monitoring. The need for invasive monitoring is driven more by patient condition than by surgical procedure.[155] Intraarterial and, to a lesser degree, central venous and pulmonary artery catheters are required for the continuous measurement of pulse, intravascular pressures, and serial arterial blood gas concentrations, blood chemistry values, and coagulation abnormalities intraoperatively and postoperatively for extended periods in critically ill patients.

The most desirable site for arterial sampling is the right radial artery, where the concentration of oxygen tension most closely resembles that of the carotid artery. Postductal arteries have lower oxygen tension in the presence of right-to-left shunting and may become occluded during procedures such as repair of coarctation of the aorta. When the radial artery is not available, the femoral, dorsalis pedis, or posterior tibial artery may be used. In infants, the brachial and axillary arteries are generally avoided because of the risk of loss of the limb. Femoral artery catheterization may be complicated by joint injury, and cannulation of the superficial temporal artery is associated with a risk of temporal lobe infarction resulting from retrograde perfusion of the vessel during flushing. Despite their accessibility during the first 10 days of life, umbilical arteries are a limited option because the incidence of infection is high. In addition, because of the risk for thrombosis and embolism, the catheter tip must be carefully positioned above the diaphragm or below the third or fourth lumbar vertebra away from the origins of the celiac, mesenteric, and renal arteries. Also, when blood is sampled from below a patent ductus arteriosus in a patient with right-to-left shunting, oxygen saturation in the umbilical arteries may be less than that of the carotid or right radial artery and thus lead to the administration of dangerously high oxygen concentrations.

The indications for central venous catheterization, and especially for flow-directed pulmonary artery (Swan-Ganz) catheters, are limited in infants and children. The procedure is probably indicated more often for patients in the intensive care unit than for those in the operating room. Central venous catheterization is indicated for patients having operations involving major blood loss, shock, and low-flow states. The preferred route of access for either catheter is the internal jugular vein, although the subclavian and femoral veins are alternatives. Placing the catheter and monitoring the pressure in a major vein returning blood to the heart allows proper maintenance or adjustment of the patient's circulating blood volume.[155] Possible complications include atrial or ventricular arrhythmias, thromboembolic phenomena, hemothorax, pneumothorax, and infection.

## Pain Management

Children of all ages feel pain. Although progress remains to be made, recent interest in and awareness of pain in pediatric patients, along with philosophical shifts and technical advances, have markedly improved pain management for children.[156,157]

Appropriate care of pediatric surgical patients entails pain management tailored to each child's age, emotional and developmental maturity, and surgical procedure. Children's ability to both experience pain and to tolerate potent analgesia has been questioned.[158,159] Many pediatric patients undergo surgery without adequate pain management. Historically, up to 40% of children undergoing surgical procedures have reported moderate to severe pain on the first postoperative day.[160] Although many children continue to receive inadequate perioperative analgesia, the evolution of integrated, multidisciplinary approaches has dramatically improved treatment strategies for pediatric surgical patients.[161] Preoperative, intraoperative, and postoperative strategies for minimizing pain should be based on the planned surgical procedure, anticipated severity of postoperative pain, anesthesia technique, and expected course of recovery.[162] Children must be reassessed at frequent intervals, with analgesic regimens modified accordingly.

Acute pain is a physiologic response to actual or impending tissue damage and may provide helpful information regarding the location and nature of injury or illness. Accordingly, there is often reluctance to provide potent analgesia to patients who will potentially undergo surgical procedures before obtaining a definitive diagnosis. It is now increasingly recognized that this dramatically undertreats pain in such patients, particularly children.[163] Appropriately titrated analgesia not only relieves pain and reduces distress but also often allows a more thorough and accurate evaluation, particularly in frightened or uncooperative pediatric patients. IV morphine, for example, provides significant analgesia to children with acute abdominal pain without masking focal tenderness or impairing the clinical diagnosis of appendicitis.[164] The traditional teaching that potent analgesia must be withheld from patients, including children, who may potentially have diagnoses requiring surgery is invalid and should be abandoned.

### PERIOPERATIVE PLANNING AND GENERAL APPROACH

The goal of perioperative pain management is to maximize patient comfort while minimizing side effects such as excessive sedation or respiratory depression. Multiple techniques are available and are chosen and titrated to effect based on each child's particular needs. Planning begins with the preoperative anesthesia evaluation and continues throughout the surgical procedure and postoperative period.

Nonpharmacologic techniques, such as distraction and guided imagery, may augment analgesia, enhance patient cooperation, and minimize pharmacologic therapy.[165] Nonopioid analgesics most commonly include acetaminophen, nonsteroidal antiinflammatory agents, and ketamine. Oral opioids are often adequate for the treatment of mild to moderate pain, whereas IV opioids are the mainstay of therapy for moderate to severe pain. Persistent requirement for IV opioids can be managed with continuous infusion or patient-controlled analgesia (PCA) modalities. Regional anesthesia may also be used as part of a comprehensive analgesia regimen. A useful paradigm that can be applied to pediatric pain management is the World Health Organization's analgesic ladder (Fig. 13-5).[166]

### DEVELOPMENT AND PHYSIOLOGY

Children of all ages feel pain, but the type and intensity may vary dramatically. Although peripheral nociceptors are fully functional at birth,[167–170] central modulation and pain

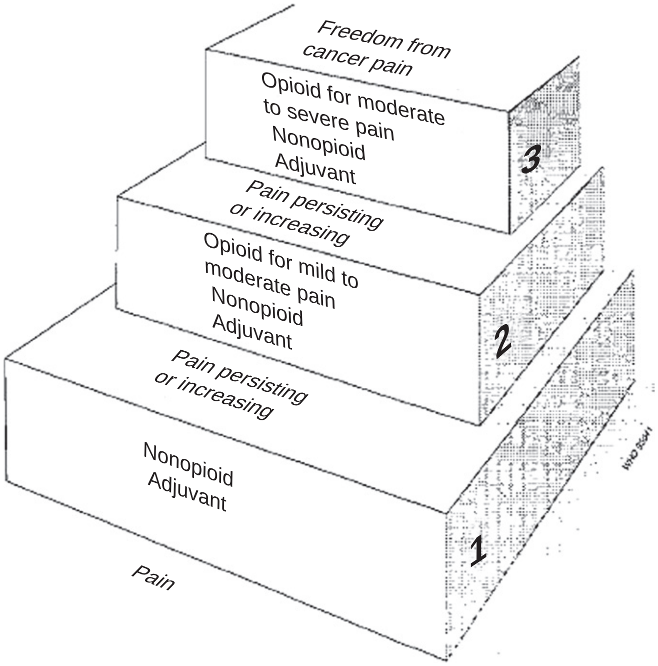


**FIGURE 13-5** First proposed in 1986 as a protocol for managing cancer pain, the analgesic ladder has become a popular and effective model for pain management in a variety of settings and can be applied to pediatric surgical patients. (From World Health Organization: Cancer Pain Relief: With a Guide to Opioid Availability, ed 2. Geneva, World Health Organization, 1996, p 15.)

perception in children are not well understood. Further, many reflex pathways allowing the expression of nociception are structurally and functionally immature in neonates and young infants.[171] Thus, although peripheral nociceptors register painful stimuli, central processing of pain in these young patients is more variable, and their ability to indicate pain perception is more limited. The response of infants and young children to pain is therefore unpredictable, particularly in premature neonates,[170] which often leads to inadequate pain management.

## HYPERSENSITIZATION AND PREEMPTIVE ANALGESIA

Acute pain is a physiologic response to actual or impending tissue damage. Untreated, persistent, or severe pain, however, may contribute to potentially detrimental pathophysiologic processes.[170,172] Tissue injury and inflammation enhance peripheral nociceptor activity, resulting in hypersensitivity to mechanical and chemical stimuli. In animal models, dorsal horn neurons respond to sustained afferent stimulation with neurophysiologic and morphologic changes consistent with increased excitability. The development of peripheral and central hypersensitization may alter normal sensory perception (dysesthesia), accentuate pain due to noxious stimuli (hyperalgesia), and produce pain in response to normally innocuous processes (allodynia), suggesting that hypersensitization at the cellular and neurophysiologic level correlates with clinical hypersensitivity to pain.

Preemptive analgesia before tissue injury may inhibit stimulation of nociceptive pathways, blunting the neuroendocrine stress response and preventing the development of peripheral and central hypersensitivity.[173] General anesthesia alone is ineffective for such purposes; nonsteroidal antiinflammatory drugs (NSAIDs), opioids, and a variety of local anesthesia techniques have been studied in animal models, with variable results.[173–175] Animal models generally suggest that preemptive analgesia, before noxious stimuli decreases dorsal horn neuron hyperexcitability, blunts observed pain behaviors and lowers clinical analgesic requirements. Human studies, however, have yielded conflicting and frequently negative results, particularly in children.[176–182] Subjective pain scores, objective assessments, and analgesic requirements are not dramatically affected in most patients by varying the timing of the analgesic technique before or after surgery. Preemptive analgesia as a strategy for blunting hypersensitization and reducing perioperative pain remains a subject of ongoing investigation and controversy.[183–187]

## PAIN ASSESSMENT

Pain assessment in pediatric patients can be challenging. Preverbal or developmentally delayed children may be unable to convey the severity or even the presence of pain to caregivers. In patients of any age, it may be difficult to distinguish pain from agitation. Nonetheless, pain in children should be recognized, assessed, and treated promptly.

Numerous tools have been developed and prospectively validated to allow ongoing quantitative assessment of pain in children of all ages and developmental skills.[188,189] In preverbal, young, or developmentally delayed patients, numerous tools allow the quantitative assessment of pain intensity by generating a pain score derived from the objective assessment of various pain-associated behaviors. The recently developed neonatal pain, agitation, and sedation scale (N-PASS) is a useful tool to assess pain in neonates 0 to 100 days of age and may also be applied to intubated or extremely premature children.[190–192] The face, legs, activity, cry, and consolability (FLACC) scoring system is valid and reliable for pain assessment in patients 5 to 16 years of age. Analog scales, useful for school-aged patients, use drawings or photographs of faces in varying degrees of distress, with colors, arrows, lines, or numbers (usually 0 to 10) for patients to indicate their level of pain.[193] Subjective, self-reported analog pain scores and objective, behavioral assessment pain scores in children are often discordant,[194] likely reflecting difficulties in distinguishing pain, agitation, and other causes of distress. The particular pain assessment tool chosen is less important than application of the tool to the appropriate population and consistent use of the tool in each patient over time.

## NONOPIOID ANALGESICS

Often overlooked, nonopioid analgesics are important adjunctive agents in pediatric pain management. They are often adequate for mild to moderate pain and may reduce opioid requirement in cases of moderate to severe pain.[195] Unlike opioids, nonopioid analgesics generally demonstrate a ceiling effect: exceeding recommended doses does not significantly improve analgesia but does increase the risk of side effects and toxicity.[196] Common nonopioid analgesics for children include acetaminophen, various NSAIDs, and in appropriate settings ketamine (Table 13-7).

**TABLE 13-7**
**Common Nonopioid Analgesics for Children**

| *Drug* | *Dose* | *Comments* |
|---|---|---|
| Acetaminophen | 20 mg/kg PO load (max 1000 mg), then<br>15 mg/kg PO (max 1000 mg) q4h<br>40 mg/kg PR load (max 1300 mg), then<br>20 mg/kg PR (max 1300 mg) q4h<br>Max 4 g/24 hr PO or PR | Good antipyretic<br>Hepatic toxicity with overdose |
| Selected nonsteroidal anti-inflammatory drugs (NSAIDs) | | |
| Choline magnesium trisalicylate | 10 mg/kg PO or PR (max 1000 mg) q6h<br>Max 4 g/24 hr | Good antipyretic<br>Only NSAID without platelet dysfunction<br>No association with Reye syndrome |
| Ibuprofen | 10 mg/kg PO or PR (max 800 mg) q6h<br>Max 4 g/24 hr | Good antipyretic |
| Ketorolac | 0.5 mg/kg IM or IV (max 30 mg) q6h<br>Total duration must be <5 days | Poor antipyretic<br>Potentially significant platelet dysfunction |
| Ketamine (requires appropriate personnel and monitoring) | 4.0-10.0 mg/kg PO (adult dose, 300-500 mg) | Anticholinergic agent; reduces sialorrhea |
| | 3.0-5.0 mg/kg IM (adult dose, 150-300 mg) | Benzodiazepine; may prevent agitation |
| | 0.5-1.0 mg/kg IV (adult dose, 50-100 mg) | Increases intracranial pressure; may precipitate seizures |

IM, intramuscular; PO, orally; IV, intravenous.

## Acetaminophen

Acetaminophen remains popular for the management of mild to moderate pain in children and as an antipyretic. Acetaminophen is a potent inhibitor of cyclooxygenase but has virtually no antiinflammatory activity and therefore few gastrointestinal, renal, or hematologic complications. The primary toxicity of acetaminophen is hepatic injury, seen with acute and chronic overdose. Acetaminophen may provide complete analgesia for mild to moderate pain and reduces opioid requirements in the treatment of moderate to severe pain, particularly when given on a scheduled basis. Procedural and perioperative analgesia with acetaminophen is enhanced by NSAIDs.[197]

Acetaminophen is available in a variety of oral and rectal preparations in the United States (see Table 13-7); IV preparations are available in other countries. The total dose should not exceed 4 g/day.

Rectal absorption of acetaminophen is slower and bioavailability is more variable than with oral administration, requiring higher doses for equivalent analgesia.[198] Although rectal acetaminophen has been shown to reduce pain scores and lower opioid requirements after surgical procedures, including myringotomy tube placement and inguinal hernia repair,[199] at least 40 mg/kg must be given.[200]

## Nonsteroidal Antiinflammatory Drugs

Like acetaminophen, NSAIDs may provide adequate analgesia for mild to moderate pain and are useful in conjunction with opioids in the management of moderate to severe pain.[202,201] NSAIDs are particularly effective for musculoskeletal pain. Unlike acetaminophen, NSAIDs have significant antiinflammatory activity. NSAIDs reduce mesenteric and renal perfusion and impair platelet function, potentially causing gastrointestinal ischemia, renal insufficiency, and bleeding. Risk is higher with elevated doses or prolonged administration.

Choline magnesium trisalicylate is the only NSAID that does not cause significant platelet dysfunction and may be useful in patients with coagulopathy or those who are at risk for bleeding during surgery. Pediatric aspirin use has declined dramatically since the described association with Reye syndrome in children with primary varicella.[196] Although choline magnesium trisalicylate is an aspirin derivative, it has no known association with Reye syndrome; nonetheless, it may be prudent to limit its use in children to patients who have previously had primary varicella or received varicella immunization. Choline magnesium trisalicylate is available in liquid and tablet preparations; the liquid preparation can be given rectally at the same dose to patients unwilling or unable to tolerate oral administration (see Table 13-7). The total dose should not exceed 4 g/day.

The most widely used oral NSAID in children in the United States is ibuprofen, available in a variety of liquid, tablet, and capsule preparations (see Table 13-7). An IV formulation is now available but is licensed only for medical closure of patent ductus arteriosus in infants. Ibuprofen is a moderate-potency analgesic and an excellent antipyretic with an impressive pediatric safety record, but it is still underused for procedural and perioperative pain management in children.[201] The liquid preparation can be given rectally at the same dose as choline magnesium trisalicylate. The total dose should not exceed 4 g/day.

Ketorolac is the only NSAID available for IV use as an analgesic (see Table 13-7). Indomethacin may be given IV but is approved only for medical closure of patent ductus arteriosus in infants. Ketorolac is a high-potency NSAID with an analgesic efficacy similar to that of many opioids and provides superior perioperative analgesia compared with other NSAIDs or acetaminophen.[203] Ketorolac may be particularly useful in patients who are intolerant of opioids, or in procedures that involve a high risk of postoperative nausea and emesis. Initially approved only for IM administration, ketorolac is safe and effective when given IV.[204] Oral ketorolac administration is approved for adults but not for children.

The volume of distribution and plasma clearance rate of ketorolac in children are roughly twice those in adults, but

the overall elimination half-life is similar.[205] As the most potent NSAID, ketorolac also has the highest incidence of side effects; total duration of therapy must not exceed 5 days to avoid potentially serious gastrointestinal and renal complications. Given its ability to compromise mesenteric perfusion, ketorolac should probably be avoided in infants at risk for necrotizing enterocolitis.

Significant platelet dysfunction may develop after a single dose of ketorolac, and its use in patients at high risk for bleeding is controversial. Initial experience indicated greater intraoperative blood loss during tonsillectomy in children receiving perioperative ketorolac,[198] and retrospective studies reported higher rates of postoperative hemorrhage.[206,207] Other retrospective studies suggested otherwise,[208] and prospective, randomized trials have shown only statistically insignificant trends toward increased bleeding.[209] The product literature warns against using ketorolac in patients at high risk of bleeding; it is probably prudent to avoid administering ketorolac to such patients until more definitive information is available.

### Ketamine

Ketamine can be used as an adjuvant analgesic in perioperative pain management. More recently, ketamine has been recommended for procedural analgesia and sedation in children in a variety of settings[210,211] and has become particularly popular in pediatric emergency departments, given its favorable safety profile.[212,213] Concomitant administration of anticholinergic agents to prevent sialorrhea, and benzodiazepines to decrease the likelihood of hallucinations and delirium, has traditionally been recommended. Recent data suggest these practices are of limited efficacy.[214] Adequate monitoring and immediate availability of appropriate resuscitation equipment and personnel are mandatory for children receiving Oketamine.[215]

## OPIOID ANALGESICS

Reluctance to use opioids in children is a common excuse for inadequate pain management in the pediatric population. Opioids are the mainstay of pharmacologic therapy for moderate to severe pain, however, and have established roles in procedural and perioperative pain management for children.[216] Acting on various subtypes of opioid receptors throughout the CNS, opioids cause dose-dependent pain relief and respiratory depression; other side effects include somnolence, miosis, decreased gastrointestinal motility, nausea, and urinary retention. Many opioids induce histamine release, causing urticaria, pruritus, nausea, bronchospasm, and occasionally hypotension. Pruritus is more common, and typically more intense, with neuraxial administration, likely owing to the CNS opioid effect rather than histamine release. Opioid side effects can be managed with a variety of agents (Table 13-8).

The opioid receptor antagonist naloxone rapidly reverses opioid effects. Mild respiratory depression or somnolence can be treated with IV naloxone 1.0 μg/kg titrated every 1 to 2 minutes as needed; doses of 10 to 100 μg/kg should be reserved for apnea or coma secondary to opioid overdose. Higher or repeated doses may be necessary. Naloxone may precipitate withdrawal in opioid-dependent patients, and pulmonary edema has been reported with higher doses. A low-dose naloxone infusion (0.25 μg/kg/min) may reduce the incidence of unwanted opioid side effects without significantly affecting analgesia for patients on patient-controlled opioid analgesic regimens.[217] Opioid analgesics do not generally have maximum effective doses. Recommended doses are for initial administration in opioid-naive patients; titration to clinical effect is required, and higher doses may be necessary. Increased dosage requirements (tolerance, tachyphylaxis) are often observed with prolonged administration or persistent pain. Opioid therapy longer than 7 to 10 days may result

**TABLE 13-8**
**Agents for Management of Opioid Side Effects**

| *Side Effect* | *Agent* | *Dose* | *Comments* |
|---|---|---|---|
| Apnea, coma | Naloxone | 10-100 μg/kg IV or IM q1-2 min PRN<br>Usual initial max: 400 μg<br>Higher or repeated doses may be required | Resedation may occur<br>Withdrawal in opioid-dependent patients<br>Higher doses may cause pulmonary edema |
| Mild respiratory depression, mild sedation | Naloxone | 1.0 μg/kg IV or IM q1-2 min PRN<br>Usual initial max: 400 μg<br>Higher or repeated doses may be required | Resedation may occur |
| Constipation | Docusate | 5.0 mg/kg PO (max 100 mg) bid | Stool softener |
| Nausea | Metoclopramide | 0.1 mg/kg IV (max 10 mg) q6h PRN | Extrapyramidal side effects |
| | Ondansetron | 0.1 mg/kg IV (max 4.0 mg) q6h PRN | Expensive |
| | Promethazine | 0.25-0.5 mg/kg PO, PR, or IV (max 25 mg) q6h PRN | May cause somnolence |
| Pruritus | Diphenhydramine | 0.5-1.0 mg/kg PO or IV (max 50 mg) q6h PRN | May cause somnolence |
| | Hydroxyzine | 0.5-1.0 mg/kg PO or IV (max 50 mg) q6h PRN | May cause somnolence |
| | Nalbuphine | 0.05 μg/kg IV (max 5.0 mg) q4h PRN | For pruritus from neuraxial opioid |
| | Naloxone | 1.0 μg/kg/hr IV infusion | For pruritus from neuraxial opioid |

IM, intramuscular; IV, intravenous; PO, orally; PRN, as needed;

in physical dependence, requiring weaning before discontinuation to avoid withdrawal.[218] Tolerance and dependence may occur independently. Addiction, a psychopathologic condition of volitional drug-seeking behavior, rarely develops in children receiving appropriately dosed opioids for analgesia and is not a valid reason to withhold therapy.[216] Opioids are commonly administered in conjunction with sedative-hypnotic agents, particularly benzodiazepines, increasing the risk of respiratory depression and desaturation.[219–221] Careful titration of doses, appropriate monitoring, and full capability to manage complications, including respiratory depression and apnea, are essential. Appropriate reversal agents should be available.

Opioid use in neonates and young infants has been the subject of much investigation and controversy. Historical studies in rats and humans suggested increased permeability of the neonatal blood-brain barrier to opioids, particularly morphine, and greater clinical respiratory depression.[222,223] It has more recently and more accurately been realized that the pharmacologic properties and clinical effects of morphine,[224–228] fentanyl,[229] and indeed all opioids in human neonates are subject to great individual variability. In general, opioid clearance is decreased and elimination is more prolonged in neonates than in older children, with values approaching adult levels by several months of age. There is no intrinsic reason to withhold opioid therapy from children of any age provided that doses are individualized to each patient and titrated to clinical effect.

## Oral Opioids

When pain needs allow and gastrointestinal function permits, oral opioids offer freedom from parenteral therapy. Onset of action is relatively slow, rendering oral opioid therapy unsuitable for the acute management of severe pain. Several lower-potency oral opioids are used commonly in children (Table 13-9), providing adequate analgesia for mild to moderate pain.

Codeine, available in liquid and tablet preparations, is commonly used in combination with acetaminophen. Codeine has a high rate of gastrointestinal upset. Hydrocodone, available in liquid and tablet preparations, is also usually used in combination with acetaminophen or an NSAID. Hydrocodone tends to cause less gastrointestinal upset than does codeine. Oxycodone is available in tablet preparations containing only oxycodone or in combination with acetaminophen or an NSAID; liquid preparations contain only oxycodone. This analgesic causes little gastrointestinal upset and is generally well tolerated. Sustained-release oxycodone is available for chronic therapy.

Although often given IV, higher-potency opioids may also be given orally (Table 13-10). The histamine release induced by morphine may cause urticaria, pruritus, bronchospasm, and even hypotension at higher doses, although these are less common with oral administration. Sustained-release oral morphine is available for chronic therapy. Hydromorphone causes less histamine release than does morphine. Methadone is particularly useful for chronic therapy in opioid-dependent patients.[230] Treatment of psychopathologic opioid addiction with methadone may be undertaken only in federally licensed facilities.

Oral transmucosal fentanyl citrate (OTFC) is a formulation of fentanyl in a lozenge attached to a stick. Oral transmucosal fentanyl citrate may provide effective preanesthetic sedation in children,[231,232] as well as analgesia and sedation for painful procedures,[233] although nausea and emesis are common. Appropriate monitoring is required.

**TABLE 13-9**
**Lower-Potency Oral Opioids for Children**

| *Drug* | *Dose* | *Comments* |
|---|---|---|
| Codeine | 1.0 mg/kg PO q4h (adult dose, 30-60 mg) | Tablet and liquid preparations |
| | | Usually in combination products with acetaminophen |
| | | High rate of GI side effects |
| Hydrocodone | 0.2 mg/kg PO q4h (adult dose, 10-15 mg) | Tablet and liquid preparations |
| | | Usually in combination products with acetaminophen or NSAID |
| | | Moderate rate of GI side effects |
| Oxycodone | 0.1 mg/kg PO q4h (adult dose, 5-10 mg) | Tablet preparations as oxycodone or in combination products with acetaminophen or NSAID |
| | | Liquid preparation as oxycodone |
| | | Low rate of GI side effects |
| | | Sustained-release product available for chronic therapy |

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PO, orally.

## Intravenous Opioids

IV opioids are the mainstay of therapy for moderate to severe pain (see Table 13-10). Subcutaneous or IM administration, although pharmacologically reliable, causes additional pain and distress, particularly in children, and should be avoided.[234–236] Side effects are more common and potentially more serious with IV opioids, mandating appropriate monitoring and prompt management of complications. Neonates and young infants receiving IV opioids should be monitored particularly closely, and doses should be reduced by 25% to 50%. Equipotent doses of opioids entail a similar risk of side effects.[216]

Morphine is the traditional IV opioid analgesic but hydromorphone causes less histamine release. Although historically popular, meperidine offers no significant advantages over other opioids and causes no less hepatobiliary spasm at equipotent doses. Meperidine is useful at lower doses for the treatment of shivering but is no longer recommended as a primary analgesic.[216,218,237,238] A benefit of IV methadone is its longer duration of action with dosing regimens suggested at 6 to 12 hours. Pediatric surgical patients receiving intraoperative methadone require less subsequent analgesia than those receiving intraoperative morphine.[235] The risk of respiratory depression and other opioid side effects is also prolonged with methadone.

Fentanyl is commonly used for procedural and perioperative pain management in children because of its rapid onset and short duration of action. Fentanyl is highly lipophilic; high-dose, repeated, or sustained administration results in

**TABLE 13-10**
**Higher-Potency Opioids for Children**

| *Drug* | *Dose** | *Comments* |
|---|---|---|
| Fentanyl | 5-15 μg/kg PO (adult dose, 400 μg)<br>0.5-1.0 μg/kg IV (adult dose, 50-100 μg) q1h<br>Infusion: 0.5-1.0 μg/kg/hr (adult dose, 50-100 μg/hr)<br>Patch: 25 μg = 1 mg/hr IV morphine | Oral preparation for single-dose use<br>Rapid infusion may cause chest wall rigidity in infants<br>Transdermal patch not for acute management |
| Hydromorphone | 20-40 μg/kg PO (adult dose, 2.0-4.0 mg) q3h<br>10-20 μg/kg IM, IV, or SC (adult dose 1.0-2.0 mg) q3h<br>Infusion: 4 μg/kg/hr (adult dose, 0.2-0.3 mg/hr) | Less histamine release than morphine |
| Meperidine | 1.0 mg/kg PO, IM, IV, or SC (adult dose, 50-100 mg) q3h<br>Infusion: not recommended | Neurotoxic metabolite may cause seizures; higher risk with renal disease<br>No hepatobiliary advantages |
| Methadone | 0.1 mg/kg PO (adult dose, 5-10 mg) q6-12h<br>0.05 mg/kg IV (adult dose, 2.5-5.0 mg) q6-12h<br>Infusion: not generally used | Useful for long-term therapy, including palliative care<br>Treatment of opioid addiction must be in a federally licensed facility |
| Morphine | 0.3 mg/kg PO (adult dose, 15-30 mg) q3h<br>0.1 mg/kg IM, IV, or SC (adult dose, 5-10 mg) q3h<br>Infusion: 0.02 mg/kg/hr (adult dose, 1.0-1.5 mg/hr) | Histamine release may cause urticaria, pruritus, bronchospasm, hypotension<br>High dose and rapid administration increase histamine release<br>Sustained-release oral preparation available for chronic therapy |

*Recommended doses are for initial administration in opioid-naive patients; titration to clinical effect is required, and higher doses may be necessary. Doses should be reduced 25% to 50% in neonates and young infants.
IM, intramuscular; IV, intravenous; PO, orally; SC, subcutaneous.

significant tissue accumulation and a markedly prolonged duration of effect.[239] Fentanyl is also available as a transdermal patch that provides continuous transcutaneous absorption, mimicking IV infusion; one 25-μg fentanyl patch is roughly equivalent to 1.0 mg/hour IV morphine. Onset is slow, and absorption is somewhat variable. Although useful in some settings for the management of chronic pain, transdermal fentanyl is not indicated for acute pain management.[216,240]

Continuous infusion is an effective means of providing analgesia to infants and children requiring more than occasional doses of IV opioids. Respiratory depression is uncommon in healthy patients at suggested doses, which neither prevent spontaneous ventilation nor hamper weaning from mechanical ventilatory support.[241] Methadone infusion is generally neither necessary nor helpful in most children because of the drug's long half-life. Adequacy of analgesia, level of sedation, and degree of respiratory depression should be followed closely, and the infusion titrated as required. All patients receiving continuous opioid infusions should probably receive continuous pulse oximetry, with cardiorespiratory monitoring for neonates and young infants. Doses in opioid-naive neonates and young infants should generally be reduced by 25% to 50%.[242,243]

## Patient-Controlled Analgesia

Historically, it has been all too common to provide opioids only after patients feel pain. This can lead to a vicious circle of symptomatic pain followed by frequently delayed administration of medication, with the resultant risk of persistent pain or excessive sedation (Fig. 13-6).[244] This pattern exposes patients to potentially significant opioid side effects while providing only intermittent analgesia. Optimally, opioid levels should be maintained above the threshold for analgesia but below that for obtundation or apnea, preserving a balance between desired efficacy and undesired toxicity (Fig. 13-7).[245] Intermittent bolus dosing of opioids at appropriate intervals

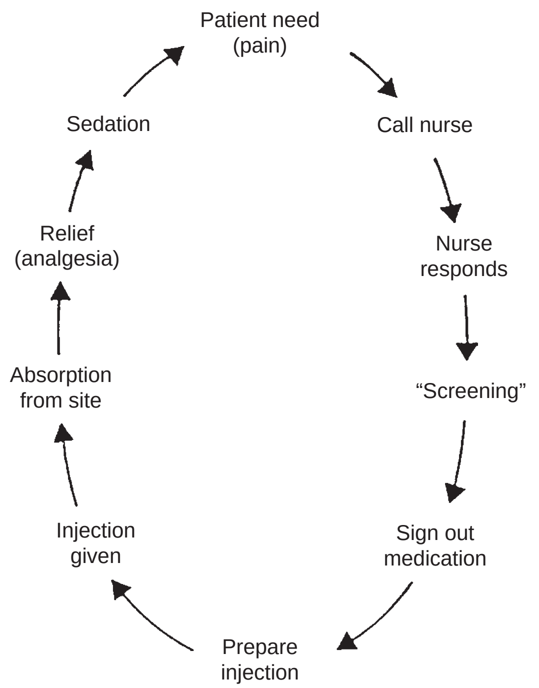


**FIGURE 13-6** Vicious circle of conventional opioid therapy. (From Graves DA, Foster TS, Batenhorst RL, et al: Patient-controlled analgesia. Ann Intern Med 1983;99:360-366.)

before patients experience pain may maintain opioid levels within this analgesic window, but this is time-consuming for staff and entails the risk of drug accumulation. Continuous opioid infusion eventually establishes a pharmacologic steady state but lacks easy short-term adjustment. A safe, effective, and readily titratable modality for IV opioid administration in children is PCA.[200,244,246]

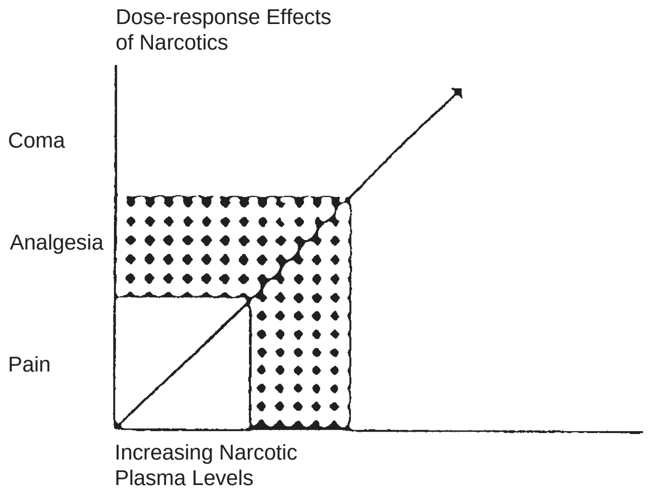


FIGURE 13-7 Analgesic window of opioid therapy. Idealized dose-response curve shows the continuum from pain to analgesia to coma associated with increasing plasma opioid levels. The shaded area depicts the analgesic window between inadequate pain relief and excessive sedation. (From Berde CB: Pediatric postoperative pain management. Pediatr Clin North Am 1989;36:921-940.)

**TABLE 13-11**
**Patient-Controlled Analgesia Regimens for Children**

| *Drug* | *Demand Dose** | *Basal Infusion (if used)* |
|---|---|---|
| Fentanyl | 0.5-1.0 μg/kg IV (adult dose, 50-100 μg) | 0.5-1.0 μg/kg/hr IV (adult dose, 50-100 μg/hr) |
| Hydromorphone | 4 μg/kg IV (adult dose, 0.2-0.3 mg) | 4 μg/kg/hr IV (adult dose, 0.2-0.3 mg/hr) |
| Meperidine | Not recommended | |
| Methadone | Not generally used | |
| Morphine | 0.02 mg/kg IV (adult dose, 1.0-1.5 mg) | 0.02 mg/kg/hr IV (adult dose, 1.0-1.5 mg/hr) |

*Generally every 8-10 min for patient-controlled analgesia; every 15-60 min for nurse- or parent-controlled analgesia. Recommended opioid doses are for initial administration in opioid-naive patients; titration to clinical effect is required, and higher doses may be necessary. Doses should be reduced 25% to 50% in neonates and young infants.
IV, intravenous.

With PCA, opioid delivery is controlled by a device that allows administration of small doses of drug in response to patient request, usually by pressing a button; an appropriate lockout interval is programmed to prevent excessive administration. Analgesia is excellent, and with appropriate doses, serious complications are rare.[235] With proper instruction, most school-aged children can safely and effectively use PCA for opioid delivery.[235,247] Nurse- or parent-controlled analgesia can be used for children unable or unwilling to control their own pumps,[249,250] although the risk of respiratory depression increases if dosing intervals are not adequately adjusted, particularly in combination with basal infusions.[251] Overall risk of complications with so-called PCA by proxy in children is not elevated compared with the PCA, although risk of serious complications requiring intervention may be somewhat increased.[252] Morphine is the most common choice for PCA, but hydromorphone or fentanyl can be used (Table 13-11). Meperidine PCA is not recommended because of the increased risk of toxicity with sustained administration. Methadone PCA has been described in pediatric cancer patients with significant opioid requirements and tolerance to other agents,[253] but it is neither necessary nor helpful in most children because of the drug's long half-life. Routine PCA regimens provide a specified dose every 8 to 10 minutes for patient-controlled administration or every 15 to 60 minutes for nurse- or parent-controlled administration. Longer dosing intervals may be safer in younger or more medically fragile patients. Concomitant basal infusion to ensure ongoing analgesia and sustain drug levels during sleep has been advocated[254] but has not been shown to improve analgesia significantly.[255,256] PCA basal infusions in adults have been shown to increase the risk of respiratory complications,[257,258] but this has not been observed in children. PCA basal infusions in pediatric patients, although safe, appear to offer little analgesic benefit except in the setting of significant opioid tolerance. Patients receiving PCA should be assessed frequently, and doses and intervals should be adjusted appropriately. Continuous pulse oximetry is recommended for children receiving any opioid infusion. Cardiorespiratory monitoring may be appropriate in very young or medically fragile patients. Instruction of patients, families, and caregivers regarding appropriate PCA use is essential.

## Regional Anesthesia

Regional anesthesia with a local anesthetic can be provided by topical application or direct infiltration at desired sites or by myriad peripheral nerve, plexus, or neuraxial blocks. An advantage of regional anesthesia is that pain relief is often provided without reliance on opioids or other systemic agents, although these may be needed in some children despite apparently successful block.[259] Greater apprehension and variability in developmental and emotional maturity in pediatric patients may explain this unpredictable requirement for supplemental analgesia. Regional anesthesia in children entails a lower risk of adverse effects, including nausea, sedation, and respiratory depression, than does systemic opioid therapy.[245,259,260,261] Regional anesthesia may be particularly advantageous in patients with potentially increased sensitivity to opioids, including neonates and children with chronic respiratory disease. In some settings, regional anesthesia in children has been shown to improve surgical outcomes.[255] Topical anesthesia can be applied to children without sedation or anesthesia. Infiltration anesthesia can be accomplished in cooperative or older children, or it can be performed during surgical procedures. In contrast to adult practice, peripheral nerve, plexus, and neuraxial blocks in children are most commonly performed after induction of general anesthesia.[263,264] Theoretically, this prevents the detection of complications, including paresthesias, failed block, or injection into undesired sites or structures; fortunately, serious complications of regional techniques in anesthetized children are rare.[234,265,266] Performance of regional anesthesia after induction but before surgical incision offers the advantages of lighter intraoperative anesthesia and more rapid emergence and recovery.[267] The use of ultrasonographic imaging to visualize anatomic structures and facilitate placement of peripheral and neuraxial blocks has grown in popularity over the past few years.

**TABLE 13-12**
**Maximum Recommended Doses of Local Anesthetics**

| Local Anesthetic | Maximum Recommended Dose (mg/kg)* |
|---|---|
| Bupivacaine | 3.0 |
| Levobupivacaine | 3.0 |
| Lidocaine | 5.0 |
| Prilocaine | 7.0 |
| Ropivacaine | 4.0 |

*Addition of a vasoconstrictor such as epinephrine or phenylephrine to local anesthetic solutions may prolong absorption and modestly increase the maximum recommended dose, but this is not reliable.

Ultrasonographically guided blocks may decrease the overall local anesthetic requirement, and thereby toxicity, by providing real-time data regarding spread of the injected solution in proximity to the targeted structure. This imaging modality is also likely to decrease risk of complications such as inadvertent intrathecal, intravascular, intrapleural, or intraperitoneal injection. Although small-scale studies suggest improvement in outcome, larger-scale studies are currently under way regarding the improved safety and efficacy of ultrasonographic guidance over conventional methods of nerve blockade.[268–271] Lidocaine provides dense analgesia but has a relatively short duration of action and often induces motor block. In topical preparations, lidocaine is commonly combined with prilocaine, which may cause methemoglobinemia, particularly in large doses or in small patients. Bupivacaine is widely used in children because of its longer duration of action and relative selectivity for sensory over motor block. It is highly cardiotoxic, however, and thresholds for cardiac and neurologic toxicity are similar; dysrhythmias may occur before obtundation or seizures are noted. Ropivacaine has moderately greater selectivity for sensory over motor block than does bupivacaine, with a relatively higher threshold for cardiac toxicity, but widespread use is limited primarily by cost. Adherence to maximum recommended doses (Table 13-12) reduces the risk of toxicity.

## TOPICAL ANESTHESIA

Numerous formulations of local anesthetics provide cutaneous analgesia without the need for injection (Table 13-13), potentially reducing or eliminating the need for systemic analgesia and sedation.

Eutectic mixture of local anesthetics (EMLA) cream is a combination of 2.5% lidocaine and 2.5% prilocaine. Applied in a thick layer and covered with an occlusive dressing for at least 60 minutes, EMLA provides effective cutaneous analgesia for minor procedures, including circumcision and even chest tube removal.[188,272–275] Analgesia increases with application up to 4 hours.[276] EMLA cream is easy to apply; patients and families can do so at home. Side effects include erythema, blanching, and rash. The prilocaine component has caused concern about the risk of methemoglobinemia, particularly with generous application or in infants, but this is rare when the product is used appropriately.

Several other preparations of topical anesthetics are available. ELA-Max is an over-the-counter preparation of 4% or 5% liposomal lidocaine.[277] Numby Stuff is a unique system of topical anesthesia using mild electrical current to promote rapid iontophoretic intradermal transport of a solution of 2% lidocaine and 1:100,000 epinephrine.[278,279] TAC (tetracaine, adrenaline, cocaine) is available in a variety of preparations and provides effective cutaneous analgesia for the repair of superficial lacerations in children.[280–283]

**TABLE 13-13**
**Topical Anesthetic Formulations**

| *Product* | *Ingredients* | *Comments* |
|---|---|---|
| ELA-Max | Liposomal lidocaine 4% or 5% | Apply for 30 min<br>No dressing required<br>Nonprescription |
| EMLA | Lidocaine 2.5% + prilocaine 2.5% | Apply for 1-4 hr<br>Requires occlusive dressing<br>Prilocaine may cause methemoglobinemia |
| Numby Stuff | Iontocaine (lidocaine 2% + epinephrine 1:100,000) | Apply for 10 min<br>Requires specialized electrodes, generator<br>Tingling sensation may frighten some children |
| TAC | Cocaine 4%-11.8% + tetracaine 0.5%-1% + epinephrine 1:2000-4000 | Apply for 20 min<br>Avoid mucous membranes<br>Avoid terminally perfused areas<br>Potential cocaine toxicity |

## INFILTRATION ANESTHESIA

Infiltration with local anesthetic provides effective analgesia for minor procedures and can be performed in cooperative or older patients without sedation or anesthesia. Any appropriate solution may be used. The acid pH of many local anesthetic solutions enhances solubility and prolongs shelf life but is responsible for much of the pain associated with injection. Buffering pH helps reduce pain in awake patients and may increase efficacy. Addition of 1.0 mEq sodium bicarbonate to 10 mL local anesthetic significantly reduces pain during injection without precipitation of the solution.[284] The bicarbonate is added immediately before use. Infiltration anesthesia provides adequate analgesia after minor, but not major, surgical procedures.[285] The technique is straightforward, and the risk of local anesthetic toxicity is low if maximum recommended doses are not exceeded. Wound infiltration during inguinal hernia repair in children provides analgesia similar to that afforded by ilioinguinal-iliohypogastric nerve block [286,287] or caudal block [288] for 2 to 4 hours after the procedure. Longer-term analgesia is inferior, however.[289]

## PERIPHERAL NERVE AND PLEXUS BLOCKS

Successful block of virtually any peripheral nerve or plexus is possible with appropriate equipment and sufficient practitioner interest.[289,290] Regional anesthesia has been advocated for potentially optimizing analgesia, minimizing opioid

requirements, and improving pulmonary function.[291] Peripheral nerve blocks are readily performed in children; several are particularly applicable to pediatric surgical patients. Plexus blocks are performed less frequently in children than in adults, often secondary to practitioner inexperience but also because of logistic challenges in the application of adult techniques to pediatric practice. IV regional anesthesia of the extremity, or Bier block, has been described in children,[292] but its application may be limited by the risk of local anesthetic toxicity. Performance of peripheral nerve and plexus blocks before surgical incision offers the theoretical advantages of preemptive analgesia and lessened overall pain experience, but this has not been reliably demonstrated in clinical practice, particularly in children.[176,177,182] Timing appears to be less important than the regional block's performance.

## RECTUS SHEATH BLOCK

Recent interest in umbilical surgery in children, particularly the application of laparoscopic techniques, has prompted research on the use of regional anesthesia for such procedures. Terminal cutaneous branches of the lower thoracic intercostal nerves supply the skin of the anterior abdominal midline. Although infiltration anesthesia is readily accomplished in this area, specific nerve block offers the advantage of prolonged analgesia. Rectus sheath block for repair of umbilical and paraumbilical hernias in children has been described[293] and with minor modifications has been described as paraumbilical block.[294] Injection is made halfway between the umbilicus and the lateral linea alba (Fig. 13-8).[294] A blunt-bevel needle is introduced through the skin with slight medial angulation until a pronounced give or "pop" is felt as the needle pierces the external rectus sheath. After negative aspiration for blood and a negative test dose to reduce the likelihood of intravascular injection, 0.25 to 0.5 mL/kg of local anesthetic is deposited; little or no resistance should be felt. The needle may be withdrawn and a subcutaneous weal made toward the umbilicus for improved coverage of distal cutaneous braches. Injection is then repeated on the contralateral side. Rectus sheath block can be used at other dermatomal levels for the repair of midline ventral hernias above or below the umbilicus.[290]

## ILIOINGUINAL-ILIOHYPOGASTRIC BLOCK

The ilioinguinal and iliohypogastric nerves are terminal cutaneous branches of the lumbar plexus. The ilioinguinal nerve arises from the first lumbar spinal nerve roots and supplies much of the external genitals and part of the proximal thigh; the iliohypogastric nerve arises from the 12th thoracic and 1st lumbar spinal nerve roots to innervate the skin of the anterior abdominal wall above the inguinal ligament. The two nerves are usually blocked in conjunction, providing analgesia for procedures on the ipsilateral groin, including inguinal hernia repair and orchiopexy.[295]

Injection is made 1 to 2 cm medial and 1 to 2 cm superior to the anterior superior iliac spine (Fig. 13-9).[267] A blunt-bevel needle is introduced perpendicular to the skin until a distinct give or "pop" is felt as the needle pierces the Scarpa fascia, adherent to the aponeurosis of the external oblique muscle. After negative aspiration for blood and a negative test

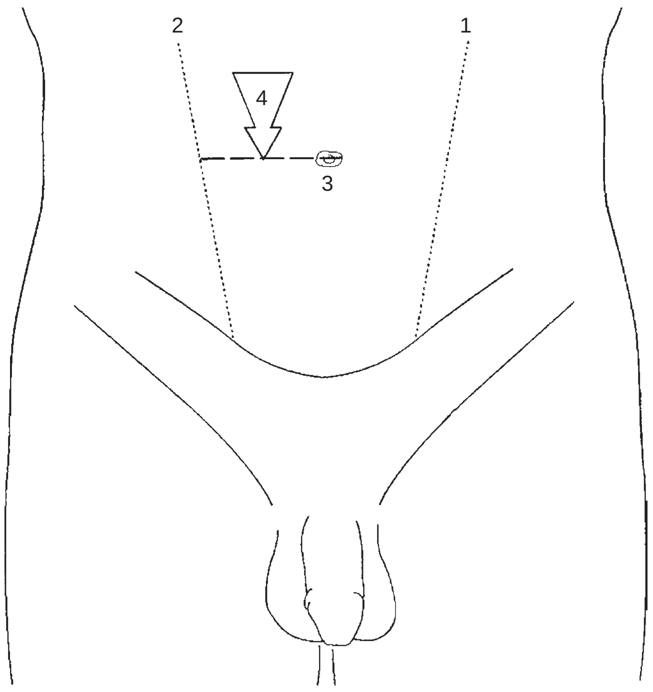


**FIGURE 13-8** Landmarks for rectus block at the umbilicus. Injection is made halfway between the umbilicus and the lateral linea alba. Left and right lateral lineae albae *(1* and *2)*. Umbilicus *(3)*. Right-sided injection site *(4)*. The left-sided injection site is symmetrically located. (From Courreges P, Poddevin F, Lecoutre D: Para-umbilical block: A new concept for regional anaesthesia in children. Paediatr Anaesth 1997;7:211-214.)

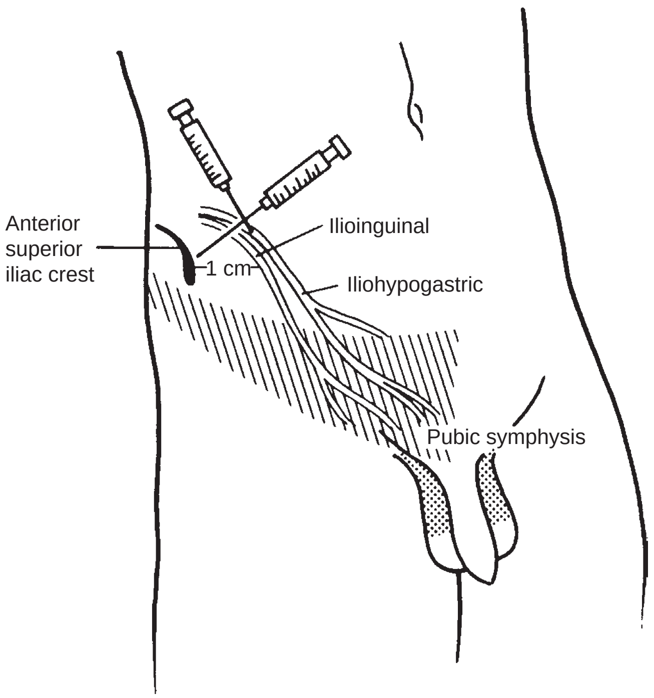


**FIGURE 13-9** Landmarks for ilioinguinal-iliohypogastric block. Injection is made 1 to 2 cm medial and 1 to 2 cm superior to the anterior superior iliac spine. Cutaneous innervation of the ilioinguinal nerve includes much of the external genitals and part of the proximal thigh; cutaneous innervation of the iliohypogastric nerve includes the skin of the anterior abdominal wall above the inguinal ligament. (From Yaster M, Maxwell LG: Pediatric regional anesthesia. Anesthesiology 1989;70:324-338.)

dose to reduce the likelihood of intravascular injection, 0.5 to 1.0 mL/kg of local anesthetic is deposited. Total volume of local anesthetic required for adequate blockade may be reduced with ultrasonographic guidance.[296] The needle may be withdrawn and a subcutaneous weal made toward the umbilicus for improved coverage of distal cutaneous branches of the iliohypogastric nerve. Ilioinguinal-iliohypogastric block provides only cutaneous analgesia; supplemental anesthesia is required for visceral manipulation. Because of this lack of visceral coverage, ilioinguinal-iliohypogastric block is inferior to caudal block at blunting the neuroendocrine stress response to orchiopexy.[297] The ilioinguinal-iliohypogastric block may also be paired with a caudal block for superior analgesia.[298] Bilateral block can be performed, but application may be limited in small children by the dose of local anesthetic required.

## FASCIA ILIACA BLOCK

The femur and anterior thigh receive innervation from the femoral nerve; the medial and lateral proximal thigh are supplied by the obturator and lateral femoral cutaneous nerves, respectively. Simultaneous block of all three nerves can be accomplished by various techniques, including fascia iliaca block, with resultant analgesia of the proximal leg, although sparing the posterior thigh. This block is appropriate for procedures involving the bony femur or soft tissues of the proximal thigh and may be particularly useful in children undergoing quadriceps muscle biopsy for evaluation of myopathy, in whom volatile anesthetic agents are best avoided. Fascia iliaca block is increasingly common in pediatric practice[290,299] and ultrasonographic guidance appears to result in a technically superior block.[300] Injection is made 1 to 2 cm medial and 1 to 2 cm inferior to the anterior superior iliac spine, just inferior to the junction of the middle and lateral thirds of the inguinal ligament (Fig. 13-10).[289] A blunt-bevel needle is introduced with slight inferior and lateral angulation, perpendicular to the iliac wing, until two distinct gives or "pops" are felt as the needle pierces first the fascia lata and then the fascia iliaca; the former is usually more pronounced than the latter. Alternatively, the needle may be advanced until encountering the iliac wing and then withdrawn slightly. After negative aspiration for blood and a negative test dose to reduce the likelihood of intravascular injection, 0.5 to 1.0 mL/kg of local anesthetic is deposited; little or no resistance should be felt. Continuous fascia iliac block in children has been described.[301] Bilateral block can be performed, but application may be limited in small children by the dose of local anesthetic required.

## PENILE BLOCK

Penile block provides analgesia for circumcision and other distal penile procedures, including simple hypospadias repair; caudal block is preferred for more proximal procedures, such as repair of complex hypospadias.[302–305] In general, penile

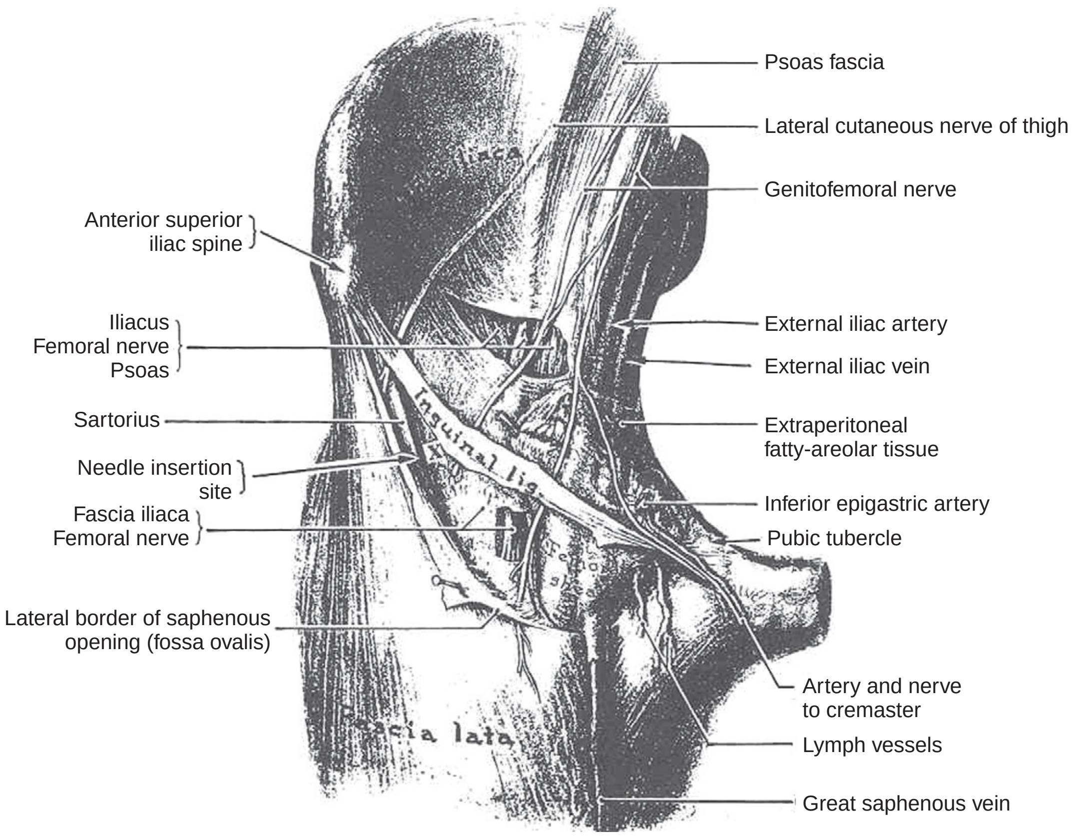


**FIGURE 13-10** Landmarks for fascia iliaca block. Injection is made 1 to 2 cm medial and 1 to 2 cm inferior to the anterior superior iliac spine, just inferior to the junction of the middle and lateral thirds of the inguinal ligament. (From Sethna NF, Berde CB: Pediatric regional anesthesia. In Gregory GA [ed]: Pediatric Anesthesia, ed 3. New York, Churchill Livingstone, 1994, pp 281-318.)

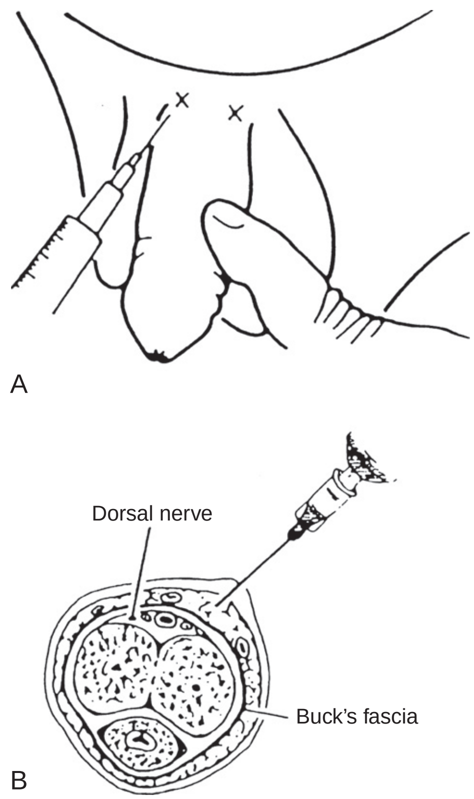


**FIGURE 13-11** Landmarks for penile block. **A,** Injection is made at the base of the penis lateral to the midline at approximately the 10 and 2 o'clock positions. **B,** The dorsal vein, two dorsal arteries, two dorsal nerves, and three corpora of the penis lie beneath the Buck fascia. **(A** From Yaster M, Maxwell LG: Pediatric regional anesthesia. Anesthesiology 1989;70:324-338. **B** From Rice LJ, Hannallah RS: Local and regional anesthesia. In Motoyama EK, Davis PJ [eds]: Smith's Anesthesia for Infants and Children, 5th ed. St Louis, CV Mosby, 1990, pp 393-426.)

block has fewer complications than does caudal block, in particular a lower incidence of motor block, but caudal block has a higher success rate and provides more prolonged analgesia. Penile block is not free of risk; puncture of dorsal penile vessels may lead to hematoma,[306] and gangrene of the glans penis has been reported. Local anesthetic solutions for penile block should not contain epinephrine or other vasoconstrictors. Injection is made at the base of the penis lateral to the midline at approximately the 10 and 2 o'clock positions (Fig. 13-11).[267,309] Alternatively, a single injection can be made in the midline. A blunt-bevel needle is introduced perpendicular to the skin until a distinct give or "pop" is felt as the needle pierces the Buck fascia. After negative aspiration for blood and a negative test dose to reduce the likelihood of intravascular injection, 0.5 to 1.0 mL/kg of local anesthetic, up to 10 mL, is deposited; little or no resistance should be felt. The process is then repeated on the contralateral side. Ring block at the base of the penis superficial to the Buck fascia provides equivalent analgesia and may reduce the risk of hematoma.[306]

## NEURAXIAL BLOCK

Neuraxial block involves either spinal or epidural techniques. Spinal block, with injection of anesthetic directly into the cerebrospinal fluid of the spinal subarachnoid space, is performed almost exclusively for procedures in infants at high risk of apnea after general anesthesia, although continuous spinal techniques are occasionally used for palliative analgesia. Epidural block, with injection of anesthetic into the potential space between the ligamentum flavum and the dura mater, is a far more common technique for procedural and perioperative pain management in children. Anesthetic can be administered as a single injection or by repeated injections or continuous infusion through an indwelling catheter. Contraindications to neuraxial block include patient or parent refusal, coagulopathy predisposing to neuraxial hematoma, local or systemic infection carrying the risk of neuraxial abscess or meningitis, increased intracranial pressure, and anatomic deformity. Most contraindications are relative; risks and benefits must be weighed in each patient.

## CAUDAL BLOCK

The most common neuraxial block in children is caudal block,[267] in which the epidural space is accessed via the sacral hiatus created by the failure of fusion of the spinous process of the fifth sacral vertebra. The technique is relatively straightforward, the success rate is high, and the complication rate is low.[310,311]

Injection is made between and slightly inferior to the sacral cornua (Fig. 13-12).[267] A blunt-bevel needle is introduced with approximately 45 degrees of cephalad angulation until a distinct give or "pop" is felt as the needle pierces the sacrococcygeal ligament, the most inferior aspect of the ligamentum flavum. If bone is encountered, usually representing the posterior aspect of anterior sacral elements, the needle is withdrawn slightly and redirected more parallel to the skin. Correct positioning of the needle tip within the epidural space is confirmed by loss of resistance to injection. After negative aspiration for blood and a negative test dose to reduce the likelihood of intravascular injection, the full dose of anesthetic is injected. Serious complications associated with caudal block include intravascular or intraosseous injection, inadvertent dural puncture with resultant spinal anesthesia, injury to pelvic contents, and hematoma; these complications are rare.[312] Caudal block is most commonly performed as a single injection of anesthetic providing reliable analgesia below the umbilicus in patients weighing less than approximately 30 kg. Perhaps because of their lower overall sympathetic tone, infants and children do not generally demonstrate hemodynamic instability after neuraxial block. Caudal block in pediatric patients induces significant changes in regional

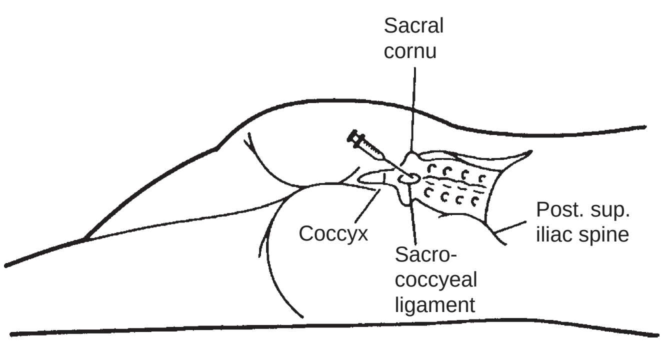


**FIGURE 13-12** Landmarks for caudal block. Injection is made between and slightly inferior to the sacral cornua. (From Yaster M, Maxwell LG: Pediatric regional anesthesia. Anesthesiology 1989;70:324-338.)

blood flow but does not significantly alter heart rate or blood pressure.[313] The agents administered determine the duration of analgesia after caudal block. Local anesthetic may provide analgesia for several hours and does not cause urinary retention at usual doses.[314] Bupivacaine 0.0625% to 0.25% is used most commonly. The addition of an opioid prolongs analgesia but increases the risk of side effects, particularly respiratory depression. Duration of analgesia and risk of side effects are greater with increasing opioid hydrophilicity, which promotes uptake into the cerebrospinal fluid and enhances distal spread. Caudal fentanyl, a highly lipophilic opioid, can be used for outpatient and ambulatory surgery in children. Caudal morphine, a highly hydrophilic opioid, provides analgesia for more than 12 hours but entails a significant risk of side effects, including pruritus and respiratory depression, for up to 24 hours.[315,316] Neuraxial morphine should not be used for outpatient analgesia. Caudal hydromorphone provides more prolonged analgesia than does caudal fentanyl, with less risk of respiratory depression than does caudal morphine. Caudal administration of clonidine[317,318] and ketamine[319] has been described and may be particularly advantageous in patients with potentially increased sensitivity to opioids, including neonates and children with chronic respiratory disease.

**TABLE 13-14**
**Agents for Epidural Infusion in Children***

| ***Local Anesthetic***† | ***Opioid***†,‡ |
|---|---|
| Bupivacaine 0.0625%-0.1% (max dose 0.4 mg/kg/hr) | Fentanyl 0.5-1.0 μg/kg/hr (adult dose, 50-100 μg/hr) |
| OR | OR |
| Levobupivacaine 0.0625%-0.1% (max dose 0.4 mg/kg/hr) | Hydromorphone 2.0-4.0 μg/kg/hr (adult dose, 150-300 μg/hr) |
| OR | OR |
| Lidocaine 0.1%-0.5% (max dose 3 mg/kg/hr) | Morphine 3.0-6.0 μg/kg/hr (adult dose, 250-500 μg/hr) |
| OR | AND/OR |
| Ropivacaine 0.1%-0.2% (max dose 0.5 mg/kg/hr) | Clonidine 0.25-0.5 μg/kg/hr (adult dose, 25-50 μg/hr) |

*Thoracic catheters commonly deliver 0.2-0.3 mL/kg/hr (max 5-10 mL/hr); lumbar catheters, 0.3-0.4 mL/kg/hr (max 10-15 mL/hr); and caudal catheters, 0.4-0.5 mL/kg/hr (max 15-20 mL/hr).
†Recommended local anesthetic and opioid doses should be reduced 25% to 50% in neonates and young infants.
‡Recommended opioid doses are for initial administration in opioid-naive patients; titration to clinical effect is required, and higher doses may be necessary.

## CONTINUOUS TECHNIQUES

Single-injection caudal block works well for pain anticipated to last less than 24 hours; even caudal morphine does not provide reliable analgesia beyond this time frame. For pain of longer duration, continuous techniques are preferred. Excellent analgesia can be provided by repeated injection or continuous infusion of anesthetic through indwelling epidural catheters, which can be placed via caudal, lumbar, or thoracic approaches to the epidural space in children.[320–322] Cervical epidural catheters for palliative care in children have been reported,[323,324] and tunneled catheters for prolonged analgesia have been described.[325] Epidural catheters are commonly placed directly at the desired vertebral level in patients weighing more than 5 to 10 kg. Once the epidural space is reached, the epidural catheter is advanced through the needle. Threading more than 3 cm beyond the needle often causes catheter coiling at the level of insertion.[326] The risk of spinal cord damage when placing thoracic or lumbar epidural catheters is always a concern, especially in the anesthetized or heavily sedated patient; these fears are largely theoretical, although neurologic complications have been reported.[327] Inserting the epidural catheter in the low lumbar or caudal space (after termination of the spinal cord) and threading a styletted catheter cephalad to the desired level may decrease the risk of direct spinal cord injury with high rates of success, particularly in neonates and young infants in whom the epidural fat is more gelatinous and the epidural space is largely free of fibrous septa.[263] This technique is often paired with conventional radiography, fluoroscopy, nerve stimulation, or electrocardiographic guidance to confirm correct catheter placement.[328–331] Ultrasonographic imaging of the spine may allow calculation of the skin-to-epidural space distance, localization of important bony and soft tissue landmarks, and even direct visualization of the epidural catheter in certain cases.[332–334]

Skin preparation with chlorhexidine rather than iodine-containing solutions confers a lower risk of subsequent catheter colonization.[335] The agent selected for epidural infusion depends on the dermatomal position of the catheter tip relative to the site of pain as well as on the distribution and intensity of analgesia desired. Numerous combinations of local anesthetic and opioid are commonly used in the United States (Table 13-14); other agents are used in other countries.[336,337] Concomitant administration of local anesthetic and opioid is synergistic and enables dose reductions of both agents, minimizing motor block and decreasing the risk of opioid side effects.[245,338] If the epidural catheter tip has been appropriately positioned in close dermatomal proximity to the site of pain, diluted local anesthetic with a lipophilic opioid such as fentanyl may be sufficient. If the epidural catheter tip is at a dermatomal level distant from the painful area, or if this area covers multiple dermatomes, addition of an increasingly hydrophilic opioid such as hydromorphone or morphine may be necessary. Epidural opioids provide excellent analgesia but are associated with side effects, including pruritus, nausea, urinary retention, and respiratory depression; risk of side effects increases with increasing opioid hydrophilicity. Opioid side effects can be managed with a variety of agents (see Table 13-8). Clonidine can be used to reduce or eliminate opioids in an epidural infusion, providing similar analgesia but avoiding opioid side effects.[339,340] This may be particularly advantageous in patients with potentially increased sensitivity to opioids, including neonates and children with chronic respiratory disease.

Close observation of patients receiving epidural infusions is essential. Continuous pulse oximetry and cardiorespiratory monitoring have been recommended for any child receiving an epidural opioid.[338] Alternatively, all patients receiving epidural infusions may be provided continuous pulse oximetry, with cardiorespiratory monitoring reserved for patients at increased risk of respiratory depression. Neonates and young infants, children with neurologic or pulmonary disease, and patients receiving a hydrophilic opioid such as morphine may merit more intensive monitoring.[234] Level of consciousness, adequacy of analgesia, degree of motor and sensory block, and presence of side effects should be assessed regularly and frequently for all patients receiving epidural

infusions. Continuous neuraxial techniques require significant caregiver diligence and expertise but provide superb analgesia for children with severe pain.

## COMMENTS

Appropriate pain management in children requires an understanding of developmental and physiologic issues unique to pediatric patients. A coherent plan encompassing the entire perioperative course should be developed, providing analgesia in proportion to pain and preempting pain whenever possible. Numerous tools are available to perform ongoing quantitative assessment of pain in all children.

Nonpharmacologic techniques may reduce the need for pharmacologic agents, and nonopioid analgesics may reduce the need for opioids. Opioids, however, remain the mainstay of therapy for moderate to severe pain and in appropriate doses can be used in patients of any age. Regional anesthesia with local anesthetic optimizes analgesia and reduces the need for systemic agents. Topical and infiltration anesthesia may be provided or specific peripheral nerve, plexus, or neuraxial blocks may be performed. Pain management is individualized, pain relief is assessed regularly, and regimens are modified as needed to optimize analgesia, minimize side effects, and facilitate recovery.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 14

# Clinical Outcomes Evaluation and Quality Improvement

Tamara N. Fitzgerald and R. Lawrence Moss

Decades of increasing resources for medical research and the explosion of information technology have created an enormous increase in the body of information available to practicing surgeons. In pediatric surgery, as in all disciplines, clinicians strive to offer their patients the benefit of all available data to provide the best care. Evidence-based medicine (EBM) is the practice of identifying the best available scientific evidence and applying this evidence to the medical care of patients. Sackett defined EBM as "the integration of best research evidence with clinical expertise and patient values."[1] EBM exists in two forms: the application of data to the care of individual patients and the development of evidence-based guidelines to guide the care of groups of patients within an institution or health system.

Actual medical decision making is best accomplished through a process by which the physician and patient (or family in the case of children) come to a health care decision based on the best available evidence, thoughtful application of the evidence to the patient, and personal factors such as quality-of-life and social or religious preferences. The development of clinical guidelines is a collaborative process by which relevant and knowledgeable practitioners critically review existing data and develop a plan of care for a set of patients with a particular disease process.[2] Patients treated by these guidelines are then followed prospectively to ensure that the anticipated improved outcome is realized. Guidelines are continually modified in an iterative process so that they can be refined, updated, and improved.

Several sources provide an extensive review of the principles of EBM and can provide the pediatric surgeon with a more detailed description than space allows here.[1,3–5] In this chapter, we provide an overview of the concepts that we believe are essential to the practicing pediatric surgeon who wishes to use most effectively the ever-growing body of information to provide the most rational, scientifically based, and current care to his or her patients. The first section discusses the concepts of study design and the second section focuses on the interpretation of data from clinical studies. The third section reviews the concepts of quality and outcomes assessment of one's own practice or institution in comparison to a standard.

## Study Design and Sources of Evidence

A basic understanding of the types of evidence that exist and the advantages and limitations of each study design is essential for the modern clinician. Varying levels of evidence are available for almost any imaginable clinical problem. The ability to understand which type of evidence a given study provides is critical to being able to determine the relevance of the study's findings to a particular patient or clinical situation. The spectrum ranges from personal anecdotal experience to large, multicenter clinical trials that examine specific questions in a rigorous but perhaps tangentially relevant manner. There is a hierarchy in study design, and the rating system used to evaluate diagnostic tests and therapies is described in Table 14-1. Studies are discussed in the following sections in order of increasing scientific rigor and reliability: case reports, case series, cross-sectional studies, case-control studies, retrospective cohort, prospective cohort, and randomized clinical trials.

### CASE REPORTS

Often when a clinician encounters a rare or interesting problem, it becomes the topic for a case report. In surgery, case reports are often used to introduce a novel procedure or technique. They are anecdotal in nature and represent the experience of just one or a few cases. Although they provide very little objective data, they serve to identify new disease processes or unexpected responses to treatment. They may also provide information and motivation for more rigorous clinical investigation. Case reports are particularly useful in the field of pediatric surgery in which the clinician frequently encounters rare or "never seen before" anomalies and responses to treatment. They can help the clinician realize possibilities beyond those discussed in a standard text and can allow the field to learn more collectively about rare conditions than would ever

**TABLE 14-1**
**Rating System Used to Evaluate Diagnostic Tests and Therapies**

| | |
|---|---|
| **Evidence Rating in Support of a Diagnostic Test** | |
| Class I | Evidence obtained from a blinded prospective study<br>Patient population represents a broad spectrum of persons with disease |
| Class II | Evidence provided by a blinded prospective study<br>Patient population may be a narrow spectrum of persons with disease |
| Class III | Evidence provided by a retrospective study<br>Patient population may be a narrow spectrum<br>Test is applied in a blinded evaluation |
| Class IV | Any design in which test is not applied in blinded evaluation<br>Evidence may be provided by expert opinion alone<br>May be a descriptive case series (without controls) |
| **Evidence Rating in Support of a Therapy** | |
| Class I | Prospective RCT<br>Masked outcome assessment in a representative population<br>Meets the following criteria:<br>a. Primary outcome is clearly defined<br>b. Exclusion/inclusion criteria are clearly defined<br>c. Adequate accounting for dropouts and crossovers<br>d. Relevant baseline characteristics are presented and equivalent |
| Class II | Prospective matched group cohort study with masked outcome assessment<br>RCT that lacks one criteria listed in a-d above |
| Class III | Other controlled trials in which outcome assessment is independent of treatment |
| Class IV | Evidence from uncontrolled studies, case series, or case reports |

RCT, randomized controlled trial.

be possible in a single practice or institution. However, the data in a case report are anecdotal and the application of any anecdotal data to one's own patient is quite limited.

## CASE SERIES

A case series is the observational experience of a surgeon or group of surgeons and reports on a series of patients with a particular disease or treatment. As such, there is usually no comparison between groups or any information about the outcome of a different treatment. Furthermore, the patient population usually represents a select group that has been referred to that surgeon or center for a particular reason, and the surgeon has often selected patients who are thought to be likely to do well with the procedure. This phenomenon is often referred to as "cherry picking." Data on patients at the same center who did not receive the operation being studied or data comparing the institution's patients with the disease to broader populations of patients are usually not provided. This markedly limits the reader's ability to determine the relevance of the results to his or her patients.

In case series, it is difficult for the authors to maintain objectivity. Investigators are often introducing a procedure or treatment that they truly believe "works" and they are motivated to demonstrate their success. Therefore, adverse events may be underreported and outcomes exaggerated. This bias is usually introduced subconsciously even with the best of intentions. In comparing one case series to another case series, there may also be variations in disease severity, comorbid conditions, operative technique, and postoperative care that are not addressed. Therefore, one cannot reliably make decisions about which treatment is superior based on case series data. In pediatric surgery, case series compose the vast majority of the clinical evidence.[6]

Consider the treatment for necrotizing enterocolitis (NEC). For years there were multiple case series that presented conflicting data as to whether laparotomy or peritoneal drainage was superior in the management of intestinal perforation. Proponents of laparotomy claimed superior results, whereas those in favor of peritoneal drainage reported data supporting a less invasive approach. Not until clinical trials were performed was it determined that the type of operation performed does not influence survival or other clinically pertinent early outcomes.[7–9]

The limitations of case series can also be seen in the history of in utero tracheal occlusion for congenital diaphragmatic hernia (CDH). In animal models, tracheal occlusion was shown to induce lung growth and respiratory maturation. Case series data were then published that showed tracheal occlusion improved lung function.[10] However, when a prospective randomized trial was conducted, the outcomes for infants treated with in utero tracheal occlusion were no better than those treated with standard postnatal care. In this randomized trial, survival in the control group was much higher than anticipated. Tracheal occlusion did not improve survival or morbidity rates.[11,12]

## CROSS-SECTIONAL STUDIES

Cross-sectional studies are useful for characterizing the prevalence of a condition or risk factor in a particular population. Measurements are made at a specified time in a population, one patient at a time. There is no longitudinal component of the investigation. For example, all children in the emergency room during a certain month may have their blood drawn once to determine the incidence of antibodies indicating prior exposure to a particular virus. These studies can be inexpensive and easy to conduct.

However, cross-sectional studies may not detect certain data depending on the timing and method of data collection. A good example is the hidden mortality of CDH. In Norway mortality from CDH was thought to be 30%, as reported from hospital records. However, on a more comprehensive survey of neonatal deaths it was found that many infants died soon after birth from CDH and never presented to a major referral center. The true incidence of CDH was at least 1 in every 5000 live births and the actual mortality from CDH was closer to 66%.

Cross-sectional studies have other limitations. Although they are useful for characterizing the prevalence of a condition or a risk factor in a study population, their inability to demonstrate a temporal relationship limits the ability to infer causation. However, these studies do provide preliminary data to justify further epidemiologic investigation.

## CASE-CONTROL STUDY

The case-control study begins with choosing an outcome of interest, with a goal to evaluate for exposures that are associated with this outcome. By design, these studies are retrospective.

Patients with a particular diagnosis (cases) are compared with similar individuals who are otherwise healthy (controls). For example, an investigator wishes to determine what factors are associated with the development of NEC in the newborn intensive care unit (NICU). Newborns with NEC are identified and comprise the case group. A second set of newborns would then be chosen from the NICU who do not have NEC (controls), but are "similar" in every other way to the case group. "Similar" is subject to interpretation and choosing the two groups appropriately is the key to success in this study.

A case-control study compares the relative prevalence of factors that might be associated with the outcome in the case and control groups. Using the example of patients with NEC, one might find that the incidence of a particular type of feeding was twice as prevalent in the group of newborns with NEC (cases) than other babies (controls). The study identifies the association but tells the investigator nothing definitive about the cause of NEC. It is entirely possible that the mode of feeding had nothing to do with the cause of NEC. Perhaps newborns fed the particular type of feeding were more likely to be small for gestational age or perhaps they were likely to come from a particular socioeconomic group with a high incidence of NEC. The case-control study can provide interesting hypotheses for further study but is only able to identify the odds of an association between a risk factor and outcome and *not* the relative risk of the outcome given the risk factor. This is a nuanced but critical difference.

It is also important that case controls studies "match" for the prevalence of certain characteristics that are known to affect the outcome so that the characteristics are found at the same prevalence in each group (e.g., gestational age). Ideally this requires that the investigators know in advance what all the factors are. This is, of course, not possible. If this was known, the study would be unnecessary.

This study design is easy to perform with relatively little expense. It is an efficient means to study rare conditions and infrequent outcomes, and several exposure variables can be studied simultaneously. Therefore this study design lends itself well to logistic regression models, which help elucidate the manner in which one factor is associated with another and to clarify the relationship of each individual factor to the outcome.

Disadvantages of case-control design include the tendency for bias and the fact that identifying all important potential confounding factors is almost impossible. Recall bias and survivorship bias are two notable problems. Recall bias stems from the phenomenon that those affected by a disease are more likely to remember potential risk factors than those not affected. For example, in neonates born with birth defects, mothers may be more likely to remember potential teratogenic exposures compared with those mothers with healthy newborns. Survivorship bias occurs when data from survivors are included and data from deceased patients are either excluded or cannot be obtained. This type of bias may also result when patients with poor outcomes are lost to follow-up.

A recent study regarding perforated appendicitis provides a good example of case-control design.[13] In this multi-institutional study, children with perforated appendicitis in whom postoperative abscess developed made up the case group, whereas those who did not develop an abscess comprised the control group. Multivariate analysis with logistic regression was used to determine the factors that were independently associated with postoperative abscess development. A sample population consisting of 75% of the data was used to create the model, and then the model was tested on the remaining 25% of the data. The results showed that several factors were independently associated with abscess formation. Although this design was not able to show that these factors were causative of abscess formation, this information could be used to develop treatment guidelines that could then be evaluated prospectively.

## RETROSPECTIVE COHORT

A retrospective cohort study is designed to compare the outcomes of two groups of patients after an exposure. In surgical studies, the exposure is typically the operation. The study is conceptualized and the hypothesis is created after the patients have been treated and the outcome has occurred. This creates important limitations. For example, suppose that an investigator wished to determine if laparoscopic fundoplication reduces the length of hospital stay. He or she must first define a set of criteria that determines the cohorts: for example patients younger than 15 years of age with reflux confirmed by pH probe who underwent fundoplication. Patients are then identified who meet these criteria and assigned to one of two cohorts based on whether their operation was open or laparoscopic.

Several limitations are immediately apparent. One could ask why some patients in the study underwent laparoscopic fundoplication while others had an open procedure. Certainly, there was no effort to have any similarity between the two study groups because the study was not conceived when the treatment was done. It is very likely that there are large differences in patient characteristics and in the characteristics of the surgeons performing the procedure. It is also likely that the criteria for operation versus medical therapy were different in the two cohorts. Although it is important for investigators to report on covariates (factors that may affect outcome, such as age, neurologic status, and length of medical treatment) it is impossible to ensure that they will be equal between the cohorts or to make appropriate statistical adjustments when they are not. Further, it is not even possible for the investigators to know what covariates might be important or to what degree. A further limitation is the subjectivity of the outcome variables. Outcomes like death are objective, but the timing of when a surgeon chooses to discharge a patient is subjective.

Data in a retrospective cohort study must be retrieved from the medical record. The record is frequently incomplete or inaccurate.[14] The record was created before the study was designed and solely to meet the clinical needs at the time. Therefore it is almost inconceivable that all or even most of what the investigator wishes to find will be present or available in a consistent manner.

A retrospective cohort study can use either concurrent or historical controls. Concurrent controls were treated during the same period as the study patients. Remember that just because they are treated during the same period does not mean that they have the same characteristics, but at least this design does not have the additional limitations seen in studies using historical controls.

Historical controls were treated during different periods. Factors that can change over time include but are not limited to referral patterns, operating surgeons, indications and

contraindications for operation, availability and quality of nonoperative treatments, accuracy of tests to measure the disease or outcome, prevailing practice patterns, and even the natural history of disease. Returning to our example of laparoscopic versus open fundoplication, many of these factors have changed over the past decade.[15,16] Medical therapy for reflux has evolved considerably.[17] Our ability to define severity of reflux objectively through pH and impedance measurements has improved.[18] The subset of patients with reflux who are referred for operation has changed considerably over time.[19]

## PROSPECTIVE COHORT

A prospective cohort study is designed to compare the outcomes of two groups of patients after an exposure. The study is planned and inclusion and exclusion criteria are created before the patients are enrolled and data collected. The resulting data are more complete than a retrospective study because the investigators can observe and record the appropriate findings as they occur. Various outcome measures can be prespecified and recorded, such as length of stay, disease recurrence, or side effects. Patients are followed until a set end point is reached. For example, intestinal failure has been studied in neonates with NEC. All neonates with suspected or confirmed NEC, as defined by preset entry criteria, were enrolled. Study end points were defined as the development of intestinal failure or the achievement of full enteral feeds. Risk factors such as birth weight, antibiotic use, requirement for mechanical ventilation, exposure to enteral feeding, and small-bowel resection at surgery were monitored and recorded.[20]

The strength of this study design is a predetermined set of criteria to assess outcomes. This protects against "data mining," a phenomenon in which one may find a statistically significant difference in outcomes between groups if multiple outcomes are investigated. For example, an investigator may perform a study to investigate whether birth weight, race, or sex are associated with the development of esophageal reflux. If the study is completed and none of the factors investigated was found to be related to reflux, the investigator may be disappointed and want to search other factors. He may then look back into the medical record for the presence of asthma, mechanical ventilation, or obesity. If the investigator continues to expand the number of outcomes investigated, he or she will eventually find an association, most likely based on chance and not a true relationship. Therefore predetermined outcomes in the prospective cohort study protect against "data mining."

Several limitations are inherent to this study design. Foremost, there is no randomization. To return to our previous example of neonates with NEC,[20] these babies may receive surgery or drain placement in the instance of a bowel perforation. However, the decision for operation was made by individual surgeon preference, not a randomization process. The choice of intervention (drain placement versus laparotomy) could influence the length of mechanical ventilation or time to enteral feeds. The extent of small-bowel resection was also determined at operation, and different surgeons are likely to have different thresholds for bowel that should be removed. However, the length of bowel remaining will certainly be a factor in how the infant will tolerate enteral feeds.

Although this study design is inferior to a randomized clinical trial, it is sometimes the only appropriate study that can be performed.[21] Prospective cohort studies can provide valuable information on outcomes and are less expensive to perform than are randomized trials. They can be used to generate data so that randomized trials can then be performed.

Prospective observational studies can raise ethical concerns. Ethicists and other members of the research community have questioned whether investigators have an obligation to address the underlying needs of special populations and not just exploit their condition for the purposes of research. This is of particular interest in disadvantaged communities and developing countries.[22]

The degree of study validity lies in the similarity and selection of groups and in the definition of the cohort. Statistical methods can be used to take into account inequalities in the cohort, but when possible, covariates that are likely to affect outcomes between groups must be matched. If highly selective inclusion criteria are used, this may limit the general applicability of the results. Because patients are not randomized, bias may select patients into treatment groups. Also, investigator bias may alter outcomes. For example, investigators have studied long-term pulmonary function after extracorporeal membrane oxygenation (ECMO).[23] Cohorts consisted of infants with meconium aspiration syndrome, CDH, sepsis, or persistent pulmonary hypertension. Because of the invasive nature of ECMO, it would have been unethical to subject patients with these diseases to ECMO if it was not necessary. However, these cohorts represent infants with very different disease processes, and the disparity of disease states may explain the difference in their lung function, which may or may not be related to ECMO. They were also compared with healthy infants who never received ECMO. Therefore bias is difficult to remove from this study design, and it is difficult to ascertain from this study the role that ECMO has in preserving lung function.

An additional challenge in the pediatric population is that disease states tend to be rare and a multicenter approach may be needed to gain enough patients. For this reason, these studies can often be expensive. However, they are useful to characterize the natural history of a disease and relative risks. Prospective cohort studies can also be used to develop multi-institutional prospective databases, which can be used to study multiple risk factors and outcomes simultaneously. One such example is the database generated by the National Institute of Child Health and Human Development Neonatal Research Network, a consortium of 16 tertiary neonatal centers within the United States. Among other studies, this database has been used to examine the incidence and morbidity of short-bowel syndrome.[24]

## PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

The randomized controlled trial (RCT) is the gold standard to compare treatment outcomes and acquire necessary data.[25] The first RCT in health care was reported in the 1940s.[26] To illustrate the importance of rigorous scientific inquiry, Sacks and associates compared RCT and historical control

trials (HCT) by searching the literature for therapies studied by both methods. Seventy-nine percent of HCTs found the therapy better than the control regimen, but only 20% of RCTs agreed. Biases in patient selection may weight the outcome of HCTs in favor of new therapies.[27] Unfortunately, information gained from nonrandomized studies continues to guide many of our treatment decisions because of the lack of RCTs.[28] In 2001, there were only 134 RCTs in pediatric surgery, accounting for 0.17% of the articles published in 33 years.[29]

In RCTs the study population and the disease of interest are clearly defined, and patients are randomized into two treatment groups but are otherwise treated identically. It is essential that the only variable that differs between the two groups is the one that is being studied. Theoretically the randomized design ensures that any observed differences should be due to the treatment and not to other factors. By randomly assigning patients into two groups, there is a built-in control for unknown clinical parameters that may influence treatment response. Thus the randomization process should eliminate confounding covariates. The RCT is the gold standard of clinical evidence and is the most powerful study design. In addition to research benefits, patients may also benefit from participation in trials because participating centers may focus increased attention and resources on these patients and their disease processes. Participating patients have been shown to have improved outcomes regardless of assignment.[30]

The main weaknesses of the RCT are that they are time intensive and expensive to conduct. It is not unusual for a trial to cost upward of $5000 per patient.[31] Additional staff may be required to conduct surveys, obtain informed consent, record results, analyze data, and organize protocol requirements. For surgeons participating in the study, there is an increase in paperwork and administrative oversight.[32] As previously noted, pediatric disease states are rare and therefore an appropriately powered study will require the participation of several institutions and surgeons. This can significantly increase the complexity of data acquisition and maintenance of study uniformity.[33]

The RCT should include a broad patient population. If the inclusion criteria are too narrow, the results may not be applicable to a larger patient population.[34] For example, if an investigator wishes to study the routine use of a nasogastric tube after laparotomy in children, but then excludes all emergency cases and children with developmental delays, the results of the study are applicable only to elective cases in developmentally normal children. Likewise, if a trial is conducted in a geographic region that is racially homogeneous, the results of the study may not apply to children of other racial backgrounds.[35]

In addition, the ability of a randomized trial to control chance is limited by sample size. Therefore the RCT must be appropriately powered to yield accurate results. In many RCTs, the sample size calculation is not reported, is frequently incorrect, and is based on erroneous assumptions.[36] The CONSORT group is an international consortium that has issued guidelines for conducting and reporting results of RCTs.[37] It provides a minimum set of recommendations for reporting RCTs. In this way, authors can report trial findings in a complete and transparent fashion, thereby facilitating critical interpretation of the results. The CONSORT statement comprises a 25-item checklist.[38] According to this statement, calculation of sample size must be reported and justified. The CONSORT statement has been adopted by several journals, including the *Journal of Pediatric Surgery*.[39,40]

Conducting a surgical RCT poses several challenges. If the condition under investigation is rare, or if there is difficulty enrolling patients, the RCT may take years to conduct and there is a chance that the therapy may be obsolete before the trial has been completed. Surgical techniques may evolve over the course of the study. Skill level is variable between surgeons and therefore the outcome is operator dependant. It is difficult to standardize an operation, as surgeons have different techniques, operating facilities, and learning curves.[41] Most pediatric surgery RCTs require a multicenter study, which increases the variability in clinical care and makes consistency across patients difficult.

One such example is the Necrotizing Enterocolitis Trial (NET). This RCT has enrolled patients from neonatal surgical units in Europe, Asia, Australia, and Africa. In this study, infants were randomized to peritoneal drainage or laparotomy. The results indicated that peritoneal drainage does not immediately improve clinical status and that the evidence does not support using peritoneal drainage as a temporizing measure.[8] Similarly, a second study conducted in the United States and Canada showed that the choice of operation did not influence survival or other short-term clinical outcomes.[9] To accomplish statistical power in both of these trials, patients from a large geographic region were enrolled. These examples illustrate that enacting study protocols, standardizing the care of patients, and collecting data is more complex when multiple institutions must coordinate efforts.

True blinding of the investigators in a surgical RCT is difficult. In RCT involving medication, it is relatively simple to give one group of patients the therapeutic drug and the control group a placebo. However, if one group of patients receives laparoscopic surgery and the control group receives the traditional open procedure, both surgeon and patient will know which operation was performed. Some investigators have chosen to openly discuss the operation with patients and families and not attempt a blinded approach. This approach has been applied to open versus laparoscopic pyloromyotomy for pyloric stenosis. In the seminal study performed by St. Peter and colleagues, patients were randomly assigned to open or laparoscopic pyloromyotomy, but both the surgeon and the guardians knew the procedure to be performed. Postoperative pain management, feeding schedule, and discharge criteria were standardized for both groups. The laparoscopic technique was found to be superior to the open method in several outcomes.[42] However, one could argue that the surgeon's operating time or the perception of postoperative pain could be influenced by the knowledge of which technique was performed.

Investigators have attempted multiple blinding strategies in these situations. For example, while the patient is still under anesthesia, the surgeon may place identical wound dressings for both the laparoscopic and open operations.[43] When it is not possible to blind the investigators performing the procedures, it may be possible to blind the investigators evaluating the outcome. For example, a common scenario occurs in trials involving carotid endarterectomy versus stenting. In this situation, the patient and surgeon know the procedure performed, but a blinded practitioner such as a neurologist can assess for postoperative stroke symptoms and neurologic deficits.[44] When the outcome is soft (such as length of stay or pain), blinding is more difficult. Hard outcomes such as death or postoperative laboratory values are affected less by the blinding process.

In addition to study blinding, randomization may also pose a problem in surgical RCT. Patients may initially agree to be randomized but may change their minds after learning to which treatment group they have been randomized. For example, in a RCT comparing best medical therapy with surgery, patients may agree to be randomized, but after being placed in the best medical therapy group may decide that they would really like to receive surgical therapy or vice versa. In this scenario, investigators often address the problem with the "intention to treat" approach, whereby all patients are included in the analysis despite which treatment they did or did not receive. This analysis should be adequately performed and described in the data reporting.[45]

## SUMMARIES OF EVIDENCE

To make evidence-based decisions for a particular patient or group of patients, data from multiple sources must be combined. No single data source, not even a well-conducted RCT, can provide all the evidence that a practitioner needs to choose the appropriate course of therapy for a patient. The medical literature is full of papers that combine evidence, and three examples are discussed here: review articles, meta-analysis, and systematic reviews.

### Review Articles

Reading a review article on a disease process or treatment of interest can be an excellent first step toward familiarization with the current literature. It is a compilation of the existing literature and evidence deemed important or relevant by the author. However, the quality of the review is largely dependent on the author. The referenced articles are typically chosen by the author and the comments regarding the validity of these articles or their relevance to patient care are usually the author's opinion. In many cases the review may not be comprehensive because conflicting evidence is omitted.

For example, there may be an author who has written extensively about the repair of abdominal wall defects. This author is asked to write a review article on the topic by a respected journal. Imagine that this author is a long-standing advocate of early cesarean section and delivery. The author may be more likely to reference articles from institutions that share this view. He or she may be more familiar with the theoretical physiologic benefit of this approach and perhaps more likely to reference experimental studies with this perspective versus opposing views. Consider that the author is very experienced with this disorder and has a large referral base. She is likely to include excellent outcomes from her own institution in the review. These excellent outcomes could be due to myriad ways that her institution provides quality care that might have nothing to do with the fact that the treated babies were delivered by early cesarean section. The result is an article that provides important information on the topic but is decidedly slanted toward one viewpoint.

The author is probably a highly ethical and well-intentioned individual who truly believes in the superiority of her approach. Nevertheless, the structure of a review article and the lack of rigorous constraints on selection of articles and methods of review are likely to produce a result that strongly reflects the author's views. This is not necessarily negative, as viewpoints of experts can be of great value. However, it is crucial that the reader of a review article understand its inherent limitations and is able to place its conclusions in the broader perspective of other types of evidence. We would go so far as to suggest that even this chapter on EBM reflects our own biases and viewpoints and should be considered in the context of other information written by those with a different outlook.

### Meta-analysis

When there are data from several sources, a meta-analysis can be performed by combining the results of multiple clinical studies into aggregate data (Fig. 14-1). True meta-analysis is the analysis and compilation of data from randomized trials, but in the absence of RCTs, other data types are sometimes combined as well. It is assumed that the quality of studies is comparable and that the patient populations are equivalent. It also assumes that measurement techniques and factors examined are similar. The quality of the meta-analysis is therefore directly related to whether these assumptions are true and also to the quality of the original data.

In pediatric surgery, meta-analysis has been limited by the small number of RCTs and prospective cohort data. For example, meta-analysis was performed to evaluate laparoscopic versus open appendectomy in the pediatric population.[46] At the time of this analysis, only 30 studies had been performed over a 10-year period that matched the inclusion criteria. Of these studies, 12 were retrospective, 11 were prospective, and only 7 were randomized. Only 14 of the studies contained at least 50 patients in each group (laparoscopic or open). Therefore, meta-analysis is an important tool to gain a big-picture approach to a particular treatment and to incorporate data from multiple sources, but it is ultimately limited by the quality of the original data.

### Systematic Reviews

Systematic reviews use algorithms to search, analyze, and combine the existing literature. Often both published and unpublished results are included in the search. The rigorous search algorithm minimizes bias, and these reviews provide a highly accessible source of quality information. Unfortunately in pediatric surgery, there are limited topics on which systematic reviews have been performed because of the lack of primary data.

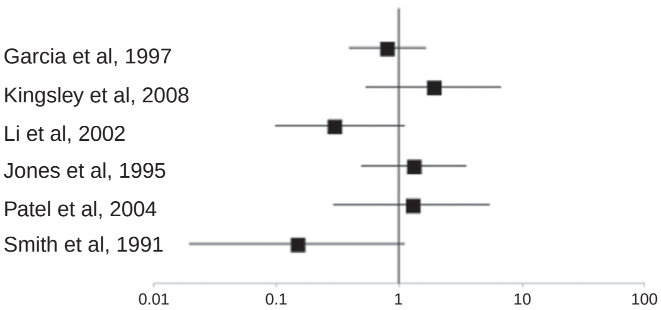


**FIGURE 14-1** A forest plot illustrates the relative strength of treatment effects in multiple RCTs contributing to a meta-analysis. The relative risk of a treatment in a single RCT is represented by a square, and the CI is represented by the extent of the horizontal line. The area of each square is proportional to the study's weight in the meta-analysis. When multiple studies fall either to the left or the right of the central axis (relative risk = 1), this indicates a strong treatment effect. When studies are scattered to the left and right of the central axis, this indicates a weak treatment effect.

An excellent source of systematic reviews is the Cochrane Collaboration and Best Evidence. The Cochrane Collaboration is an international consortium of physicians, statisticians, and epidemiologists. It is the first, largest, and most successful group, and they have provided a model for consortiums that have followed. The mission of the group is to review the scope of the world's literature, primarily through RCTs. Only treatments are included. Usually, diagnostic tests or risk factors are not reviewed. The resulting reviews can be found in the Cochran Collaboration database[47] and PubMed.

Best Evidence is another review that is edited by experts in EBM and tends to be highly clinical in nature. Unlike the Cochran Collaboration, Best Evidence also includes analyses on therapy, diagnosis, cost effectiveness, and complications.

## Application of Clinical Evidence

### HYPOTHESIS TESTING

When reviewing a study, one must have a basic understanding of the statistical methods and pitfalls that can result in erroneous conclusions. The discipline of statistics is dependent on the notion of chance, that there is a random nature to all outcomes. When two groups are compared (treatment versus no treatment), the null hypothesis is that there is no difference between the groups. The *P* value is the probability that the observed difference is due to chance alone. Results are commonly considered statistically significant when $P < 0.05$ (there is less than a 5% chance that the difference observed was by chance). If multiple outcomes are examined, at $P = 0.05$, 1/20 of these outcomes will occur by chance alone. Therefore it is easy to see how multiple hypothesis testing can result in erroneous conclusions. This is often referred to as "data mining" or "sifting the data." The most simple statistical method to correct for multiple comparisons is to define significance as the desired *P* value (usually $P < 0.05$) divided by the number of comparisons. This is called the Bonferroni correction. The confidence interval (CI) is the probability that the same difference would occur if the study were repeated an infinite number of times. Therefore, a CI of 95% means that a difference would be seen in 95% of the repetitions of the study. There are many tests available to calculate *P* and CI. The correct test is dependent on the number of observations, number of groups compared, whether the data is continuous versus categorical, and if risk adjustment is required.

### SUBJECTIVE VERSUS OBJECTIVE DATA AND RISK

Many kinds of outcomes can be studied, and data can be either objective (such as laboratory values or vital signs) or subjective (pain scales or physical examination). Objective data are more easily analyzed with statistical methods, and the results are often more straightforward to interpret. However, subjective data can be validated by using multiple observers. For example, if one outcome of a study is a radiographic finding, this type of data may vary depending on the radiologist examining the case. If multiple radiologists report their findings on the radiograph and are blinded to the opinions of their peers, a measurement of interobserver variability can be obtained. The measurement is known as the kappa value, for which a value of one indicates complete agreement between observers and a value of zero indicates no agreement.

Event rates and risk are important concepts to understand when deciding how a study result should impact the current standard of care. The event rate (ER) is the probability that an outcome will occur in a defined population. The control event rate is the probability that an outcome will occur with standard therapy, and the experimental event rate is the probability of the outcome with experimental therapy. Relative risk reduction and absolute risk reduction are the proportional and absolute risk values reduced by the experimental treatment, respectively. Number needed to treat (NNT) is the number of patients who need to be treated to prevent one adverse event. Therefore the impact of therapy depends on the event rate in the population, and the magnitude of risk reduction is greater for common events.

### ERROR

All diagnostic tests and clinical studies contain errors. A type I error is rejecting the null hypothesis when it is true. This is also referred to as the false-alarm rate or the false-positive rate. In other words, a difference is observed when there is none. Alpha is the probability of a type I error, and when alpha is low, the specificity of a study is high.

The type II error is failing to reject the null hypothesis when it is false (the study does not find a difference when one exists). When the type II error is small, the sensitivity is high. Usually this type of error occurs because the sample size was too small. Beta is the probability of a type II error and can be minimized by performing power calculations during the planning of the study to ensure an adequate sample size. The study's statistical power should be stated in the results section of the manuscript. Unfortunately, no amount of statistical prowess can compensate for insufficient power. Therefore, for the results of a study to be reliable, type I and II errors must be minimized.

### IDENTIFYING BIAS AND DETERMINING VALIDITY

Many types of bias exist and can be pervasive and difficult to recognize. Selection bias refers to an imperfection in the selection process. This can result in subjects who are not typical of the target population or subjects who are more likely to have the outcome of interest. For example, a study may conclude that laparoscopic colon resection is superior to the open technique. However, a bias may exist if patients who presented with nonemergent conditions were offered the laparoscopic procedure, whereas patients who presented with an acute abdominal process were treated with the open procedure.

Information bias can be introduced by the way data is obtained. Patients who are interviewed may recall different events than patients filling out a survey. However, patients completing an anonymous survey may be more likely to give truthful responses than those being interviewed. Recall bias refers to a selective memory of past events. For example, parents of children with digestive disorders or food allergies may be more likely to remember what the child ate in previous days than families with healthy children.

Before data from a study can be used in clinical decision making, the clinician must ask about the applicability and validity of the study. The characteristics of the patients in the study should be similar to the patient who will be treated. The clinician must ask, “Are the patients in the study similar to my patient?” and “Does the sensitivity analysis include values that my patient would use?” Also, the validity of the study must be examined. The evidence needs to meet minimum criteria and the conclusions must be logical and complete.[25] If there are “soft spots” in the evidence, these should be dealt with appropriately. If possible, the analysis should be validated in a prospective study.

## GUIDELINES AND PATHWAYS

Once several valid studies have been performed and there exists a body of clinical evidence, guidelines and pathways can be constructed. Health care entities are increasingly relying on clinical guidelines, which typically focus on managing a particular type of patient. Guidelines are useful for cost savings, outcomes improvement, and error reduction. The difference between algorithms, guidelines, and pathways is an important distinction. An algorithm is a checklist or detailed list of instructions to carry out a specific task. A guideline is a standardized set of recommendations for a specific problem. A pathway combines several practice guidelines into a set of recommendations and may track a patient through diagnosis, management, rehabilitation, and follow-up.

Guidelines can be created to improve outcomes, to minimize variation in practice between physicians, or to contain excessive costs. To create a guideline, practitioners agree on a standard of care based on the available evidence. If the evidence is inadequate, that step is either decided on by consensus or left to the discretion of the physician. It is important that key members of the community “buy in” to the guidelines for implementation to run smoothly. Outcomes should be measured before and after implementation for validation purposes. However, it has been shown that implementing guidelines improves patient outcomes.[48] This is due in part to the observation that obtaining consistency may be more important than finding the “best” guideline.

Advantages of guidelines include reduction in errors of omission (forgetting an order) and reduction in errors of commission (e.g., drug dosage errors). There is an increase in efficiency and a potential cost savings, and guidelines often minimize confusion among staff. Hospital lengths of stay are decreased and patients have better outcomes. Potential disadvantages include loss of physician autonomy and potential dissonance if not all providers agree with the guidelines, as there is a recommended acceptance of the value judgments inherent in the guideline. It may become cumbersome if different entities (e.g., Medicare and the American Heart Association) promote different guidelines. If guidelines do not account for individual variation between patients, harm can result. There is a potential for legal liability if an undesirable outcome results despite proper adherence. For this reason, clinicians are ultimately responsible for deciding if a guideline is valid and whether or not it is applicable to their patient.

In summary, before applying current evidence to patient care, the clinician must carefully analyze the available data. This includes understanding the benefits and limitations of the study design, as well as the statistical analysis and significance of the data. The clinician must determine if a study result is applicable to a particular patient. Over time, applying this information to patient care can improve the quality of care. Introducing guidelines and pathways is one way to improve patient outcomes, and must be validated. Therefore clinicians should have a basic understanding of quality assessment.

# Outcomes and Measuring Quality of Care

## QUALITY OF CARE ASSESSMENT

There is growing recognition that there is great variation in surgical care between institutions and practitioners. Patients and families want to make informed decisions and are asking for more data regarding their health care choices. In addition, clinical leaders want to improve the quality of care. Therefore there is a need to assess performance and patient outcomes. A good performance measure will guide patients toward hospitals and clinicians with better results. Performance analysis can include structural, process, and outcome measures. Transparency of performance measures leads all institutions to take steps to improve results and elevates the overall level of medical care.

### Specific Measurements

There are three widely used measures to determine healthcare “quality”: structure, process, and outcome. Health care structure consists of elements that are fixed characteristics of the system that will not vary between individual providers. Examples of structural measures include nurse/patient ratios and whether or not there is a dedicated intensive care team. Measures of health care structure are expedient and inexpensive because the data are generally obtained from preexisting administrative records. Measures tend to be efficiently analyzed; a single measure may be compared to several outcomes. Unfortunately the number of measurements is limited and measures do not reflect individual performance, which many clinicians find unfair. An example of comparing structural measures would be evaluating the inpatient mortality rates of teaching versus nonteaching hospitals. One may find that mortality is higher in teaching facilities. Although the correlation may be strong, the analysis reveals little about the causative relationship between the variables. It is possible that quality of care is worse in teaching hospitals. It is also possible that teaching hospitals have more complex or high-risk cases. The ability to perform accurate risk adjustment is relevant here as it is to both process and outcome measures as well.

A second way to measure health care quality is to evaluate processes of care. These are services provided, medications prescribed, and other interventions applied to the care of patients. Process measures reflect care that patients actually receive and are directly actionable for quality improvement. An example of a process measure would be determining how many patients are asked to rate their level of pain as part of routine vital signs or whether patients receive the appropriate antibiotics before surgical incision. One benefit of process measures is that risk adjustment is often unnecessary. For example, it is well established that all patients receiving

surgery should receive an antiseptic skin preparation before incision. Therefore it is unnecessary to collect data regarding illness severity for the purposes of risk adjustment. Process measures are designed to determine how closely the care actually delivered resembles the care that the facility intended to deliver.

Because process measures are easy to implement and enforce, they are often the focus of regulatory agencies. The Surgical Care Improvement Project (SCIP) is a national partnership that was formed to improve patient safety by decreasing postoperative complications.[49] SCIP focuses on antibiotic prophylaxis, perioperative glucose control, appropriate preoperative hair removal, postoperative normothermia, perioperative beta blockade, and venous thromboembolism prophylaxis. For example, the SCIP guidelines suggest that antibiotics should be received within 1 hour before surgical incision, should be appropriately selected for the procedure to be performed, and should be discontinued within 24 hours of surgery. Compliance with these types of guidelines can be easily monitored and publically reported.

Unfortunately, studies have shown that institutions that score high on process measures do not necessarily have better outcomes. For example, a recent study compared the rate at which facilities provided timely and appropriate preoperative antibiotics to actual wound infection rates. Many of the centers with the highest rate of compliance with antibiotic use unexpectedly had the highest rate of wound infections.[50] In addition, hospitals that scored high on performance measures for the treatment of heart failure did not show any difference in patient outcomes within 1 year of discharge.[51] An additional limitation is that there is currently a lack of reliable data infrastructure. Many databases contain information on outcomes, and lack information on process of care. Therefore, measures may be difficult to define with existing databases, and the link between the measure and important patient outcomes is variable.

The third type of measurement is outcome data, which is the measurement most familiar to clinicians. End points can include variables such as mortality, complications, length of hospital stay, patient satisfaction, and readmission. Direct outcome measurements are appealing because they have inherent face validity and directly address variables that are most clinically important. Outcome measures are easily accepted by clinicians and hospitals. For example, ability to compare morbidity and mortality between centers in the Veterans Administration (VA) Hospitals through the National Surgical Quality Improvement Program (NSQIP) allowed improvements to be instituted that improved patient outcomes.[52] Collection of accurate outcome data requires a highly skilled data collection team and is time and resource intensive. Comparative outcome data between centers is of limited value without adequate risk adjustment. For example, hospitals and physicians who avoid high-risk patients or complicated procedures may appear to have better outcomes if a thorough risk adjustment is not performed. The most robust and accurate models for risk adjustment in surgical patients have been developed by the American College of Surgeons' NSQIP.[53,54]

## Improving Performance

Several organizations use performance measures to make recommendations regarding guidelines and to focus efforts to improve outcomes. The National Quality Forum (NQF), Joint Commission of Accreditation of Healthcare Organizations (JCAHO), and the Center for Medicare and Medicaid Services (CMS) have focused mainly on process measures and hospital-based care. The LeapFrog Group is a consortium of employers and health care payers who developed an extensive set of quality measures for value-based purchasing assessment.[55]

## Databases and Networks

Several collaborative efforts have been undertaken to create databases for quality improvement and outcomes research. The most well known is NSQIP, which was developed to improve the quality of surgical care on a national level. The American College of Surgeons (ACS) adopted this system after it was successfully implemented in the VA system. NSQIP provides reliable and risk-adjusted outcomes data. Because of the national scope of the project, surgical quality can be compared between hundreds of institutions. A rigorously trained clinical nurse reviewer collects information from the medical record. Data are collected prospectively and reported as the observed/expected ratio for mortality and numerous specific morbidities. Since the implementation of NSQIP in the VA system, 30-day mortality and morbidity were reduced by 45% and 27%, respectively (Fig. 14-2).[52] This translates to tens of thousands of lives saved.

The most important strength of NSQIP is that risk adjustment is done effectively and in a manner that is widely accepted as valid. Also, participating institutions can access

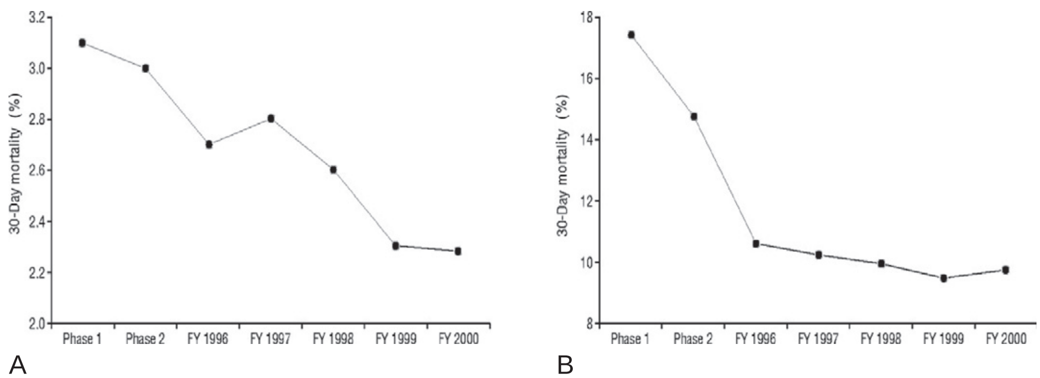


**FIGURE 14-2** Thirty-day postoperative mortality **(A)** and morbidity **(B)** for all major operations performed in the Veterans Affairs hospitals throughout the NSQIP data collection process. A 27% and 45% decrease in mortality and morbidity, respectively, were observed.[60] FY = fiscal year.

their own outcomes and compare their results against others. The program is expensive to implement, as it requires an annual fee as well as the salary of a dedicated nurse. It is not yet designed for assessing procedure-specific performance. At this juncture NSQIP provides informative data regarding general and vascular surgery in adults. The program is evolving to provide procedure- and specialty-specific outcomes in many disciplines. A separate pediatric program is under development.[56]

The Children's Oncology Group provides a wonderful success story of how large cooperative trials and evidence-based practice were used to decrease mortality for children with cancer. Through modification of therapeutic regimens based on multicenter RCTs, this group was able to decrease mortality from acute lymphocytic leukemia by 70%, without the development of any new drugs.[57,58] More recently, the American Pediatric Surgical Association (APSA) Outcomes and Clinical Trials Center was established in 2000. The objective of the center is to promote evidence-based guidelines through research efforts and outcomes analysis. Capabilities of the center include project coordination, database management, and data analysis.[59] These research efforts will no doubt be instrumental in providing new outcomes data, which will then be used to determine clinical guidelines.

## Conclusions

With the numerous sources of data available to surgeons, the application of EBM to patient care has become a complex and rewarding endeavor. Study design in many ways determines the strength of the data and to which patients the results can be applied. Therefore it is essential that pediatric surgeons understand the strengths and limitations of clinical studies and basic principles of statistics when evaluating clinical evidence. In addition, outcomes research and quality of care measurement is in a state of evolution and is already influencing the practice of surgery. Therefore clinicians should continue to carefully evaluate clinical evidence, as well as their own outcomes, so that we can constantly improve the health of our patients.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 15

# Ethical Considerations

Benedict C. Nwomeh and Donna A. Caniano

Ethics is concerned with questions of right and wrong. Medical ethics, also known as bioethics, outlines the standards, principles, and rules of conduct that govern physician behavior, the practice of medicine, and the conduct of biomedical research and training. However, although the core principles of medical ethics are immutable, our notion of what constitutes ethical practice is constantly challenged by evolving cultural norms, particularly within the milieu of an increasingly multicultural society and the rapid pace of technologic advancement. Furthermore, there are significant overlaps between the distinct disciplines of law and medical ethics, such that evolving standards of one affects the other.[1] Thus a new statute or court ruling sets a standard of conduct that often compels adjustment in the rules of ethical conduct. Conversely, the pronouncement of new ethical guidelines by professional medical organizations frequently influences the work of legislatures and the courts. Ethics tells us what we ought to do but the law stipulates what we must do. Together, law and ethics define the rules of conduct within which medicine is practiced, but like medicine itself, both are dynamic disciplines that undergo constant adjustment.

Beauchamp and Childress have articulated certain *prima facie* principles that define the most fundamental foundations of medical ethics.[2] The tetrad of principles includes beneficence, nonmaleficence, autonomy, and justice. The first two of these principles, beneficence and nonmaleficence, are derived from the Hippocratic obligations to "act in the best interests of the patient" and to "do no harm." The other two principles, based on relatively recent concepts, are (1) autonomy, which respects the right of competent persons to give informed consent for medical treatment and to have control over their bodies and (2) justice, which involves the fair and equitable distribution of the benefits (and risks) of medical care to all persons.

Although principle-based and duty-based ethics tend to be given the most attention, some ethicists make a strong case for virtue-based ethics and contend that virtue is derivable from the nature of medicine as a human activity and is an irreducible element in medical ethics.[3] Ethical principles, per se, focus on the action or actions that give rise to dilemmas, such as withdrawing life-sustaining treatment from a terminally ill patient. In contrast, virtue ethics emphasizes the agents (physicians) and the recipients (patients) of principle-based actions and decisions. Pellegrino and Thomasma cite the relevance of virtues such as trust, compassion, prudence, justice, courage, phronesis or common sense, fortitude, integrity, honesty, and self-effacement in confronting practical problems such as care of the poor, research with human subjects, and the conduct of the healing relationship.[3] In practice, physicians' ethical behavior is shaped as much by the core ethical principles as by the special bond that sickness and the response to it creates between healer and patient. In addition, pediatric surgeons are challenged by issues that are distinctive to the profession of surgery and other factors that are unique to the care of infants and children.

In this chapter we review some of the basic ethical concepts and responsibilities pertinent to pediatric surgery and explore thorny issues related to the extremes of prenatal care and the end of life. We address common surgical and ethical dilemmas in operative management, such as in adolescent bariatric surgery. We also highlight new areas of ethical concerns such as surgical error, and aspects of professionalism in the relationships between physicians and industry. Finally, we discuss the ethical imperatives of multiculturalism and why the prevailing ethical landscape should not deter much needed research and innovation in pediatric surgery.

## Resolution of Ethical Dilemmas

The essence of pediatric surgery was underscored by Potts in his classic monograph *The Surgeon and the Child*, in which he noted that "the satisfaction of correcting a deformity in a newborn infant lies in the fact that all his life lies before him. Parents hope for miracles, but are grateful for the best that can be given by a mere human being."[4]

This profound statement is applicable, whether the pediatric surgeon is repairing a major congenital anomaly, treating a devastating traumatic injury, or resecting a malignancy. However, in the course of providing the best possible care to children and their families, the pediatric surgeon will occasionally encounter ethical and moral issues.

A classic moral dilemma arises when two or more conflicting ethical principles support mutually inconsistent actions. A common situation is when there is a conflict between the

principles of autonomy and beneficence—when parents desire a course of treatment for their child that does not align with the opinion of the pediatric surgeon. The pediatric surgeon may also encounter moral dilemmas in the form of moral uncertainty and moral distress when the prognosis is unclear for a given condition, when two or more equally valid treatment options are available, or when parents disagree with each other, or the surgical recommendations, or both. Therefore the need often arises to resolve the moral basis by which decisions should be made, who should make those decisions, and how decisions should be implemented.

Little[5] has identified five pillars that mark the moral domain of the surgeon-patient relationship: rescue, proximity, ordeal, aftermath, and presence. These factors may be present in other therapeutic relationships as well, but they have a special intensity in surgery. The term *rescue* acknowledges the elements of surrender and dependency that patients and their families experience when they have little control over the proposed surgical remedy. This situation can be mitigated if the pediatric surgeon confronts and negotiates the patient's (and family's) surrender and dependency within the context of the surgeon's power. *Proximity* refers to surgeons' acknowledgment of the close, intimate interactions they have with their patient, who must forgo their autonomy, acknowledge dependency, face risk, and yet place trust in the surgeon. *Presence* is both a virtue and a duty for surgeons, to be a visible and engaged presence throughout the entire surgical experience. In pediatric surgery, this professional obligation extends to the long-term follow-up of patients, often into young adulthood.

The foregoing ethical and moral principles and virtues are brought to bear in the ordinary course of a pediatric surgeon's daily work, in which ethical dilemmas are frequently encountered. Resolution of ethical problems in a given pediatric surgical patient requires a patient-centered approach that uses all members of the health care team working together in a manner that promotes respect for all parties and all views.

As we and others have noted, successful outcomes require that the team (1) develop common moral language for the discussion of moral issues, (2) have training in how to articulate their views about issues, (3) have common experiences on which to base recommendations, and (4) agree on a moral decision-making method for all to use in the course of their deliberations.

Bayliss and Caniano previously outlined the following set of guidelines to provide a framework for the effective resolution of difficult moral problems[6]:

1. Identify the decision makers. For most cases in pediatric surgery, the decision makers will be the parents, unless the patient is a mature minor.
2. Ascertain "value data" from the parents and other relevant family members. These may include their views on the sanctity of life, spirituality and religious beliefs, cultural norms, and community values.
3. Collect all relevant medical information, including the prognosis. Clarify the areas of uncertainty and identify whether additional diagnostic testing would be of value in the decision making process.
4. Define all treatment options, including their benefits, risks, and chances of achieving the desired outcomes.
5. Provide the parents with a professional recommendation for the best treatment option.
6. Seek a consensus resolution that can be accepted by all participants.

In order for the above paradigm to be successful, the health care team must accept that rational people of good will may hold divergent views that are irreconcilable, even after extended discussions. The goal of reaching a consensus decision should be viewed as a successful outcome for all participants.

# Informed Consent and Assent

The doctrine of informed consent is based primarily on the ethical principle of respect for individual autonomy, but also on beneficence and justice. These three pillars, established in the Belmont Report[7] to guide human subjects' research, have become the basis for ethical and legal requirements for informed consent for research as well as clinical care. Respect for patients' *autonomy* recognizes the right of each person to make their own decisions. The principle of *beneficence* requires physicians to propose only those interventions intended to promote the well being of the patient, and *justice* requires that the patient be treated in the same manner as any other individual under similar circumstances.

In pediatric surgery, fulfillment of a child's autonomy typically requires surrogate decision makers (in most cases, the parents) to speak, understand, and consent on behalf of infants, children, and adolescents. In some cases, court-appointed guardians or other spokespersons may fulfill this role, depending on applicable laws. In some jurisdictions, and in certain specific circumstances, adolescent patients may be granted authority to make their own decisions about the health care they receive. This situation is particularly applicable to adolescents with chronic illnesses, such as sickle cell disease, cystic fibrosis, and advanced malignancies. However, when an adolescent's consent to or refusal of surgery is in direct opposition to parental wishes, the assistance of social services and legal counsel may be required.

Recognition of children as "persons" with inherent rights underscores the necessity for their participation in the decision-making process.[8] Therefore, the traditional emphasis on the child's "best interests" may be insufficient to address the child's "rights," and although the *informed permission* given by parents may be sufficient for ethical purposes and is required for legal purposes, it does not satisfy the strict moral standards of the doctrine of informed consent. Therefore, a specific role has been advocated for children in their own decision making, particularly for older children and adolescents. This concept of pediatric *assent* was articulated by William Bartholome when he wrote, in 1982, that "assent of the child is indeed an idea before its time. It is a fragile idea that can easily be crushed amidst the boulders of consent, autonomy, rights, and competence. It's an idea that is so foreign to adult reality that its central thrust is missed even by astute minds."[9]

Several decision-making models have been proposed as a template for pediatric assent, but they differ primarily on the relative roles assigned to the child and the parents and whether they should be guided by the principle of autonomy or follow a best-interests design.[10] Nevertheless there is broad agreement that, depending on the circumstances, the *assent* of the pediatric patient should be sought as appropriate to their development, age, and understanding in conjunction with informed permission from the parent or legal guardian. Every state has enacted minor consent statutes that seek to

determine instances in which children can give their informed consent, as highlighted in a policy statement by the American Academy of Pediatrics (Table 15-1).[11] However, in most instances parent/guardian consent is required by law. Pediatric surgeons have an ethical duty to familiarize themselves with their own institutional guidelines and appropriate local statutes.

For surgical procedures, the essential components of the informed consent process include (1) a surgeon who provides adequate information to facilitate decision making and (2) a competent patient or legal proxy who indicates full understanding of the intervention, including the indications, risks, and possible alternatives, and who voluntarily consents to the proposed intervention.[12,13]

In the unique triadic relationship between the pediatric surgeon, parent, and child, surgeons bring the values and ethical principles of their profession, which give priority to the interests and well-being of their patients and families. In their landmark book, *Surgical Ethics*, McCullough and colleagues[14] present patients' rights related to the surgical encounter, each of which implies a key professional value. They remind us that "(patients have the right) . . . not to be killed intentionally or negligently by the surgeon, not to be harmed by intent or negligence of the surgeon . . . not to be deceived by the surgeon . . . to be adequately informed about the risks and benefits of surgery, to be treated by a knowledgeable, competent practitioner, to have his or her health and well-being more highly valued than the surgeon's own economic interest, and to decide whether to accept treatment under the conditions described."[14]

## Prenatal Surgical Consultation

Routine prenatal screening with ultrasonography and biochemical markers now permit detection of major fetal anomalies that may require operative intervention shortly after birth, or rarely, in utero. When a significant fetal malformation is detected by screening, consultation with the pediatric surgeon or other specialists is usually offered to prospective parents. Ethical issues that may arise during the course of a prenatal consultation include (1) the possibility of prenatal intervention or termination of pregnancy; (2) the timing, location, and mode of delivery; and (3) potential postnatal surgical intervention.[15]

The prenatal surgical consultation should be guided by the same ethical principles of autonomy (self-determination), beneficence, and justice, and in addition respect for the woman's choice and her reproductive freedom. The proper role of the pediatric surgeon is not only to give information but also to provide a supportive, caring environment for informed decision making. In theory, a value-neutral norm that promotes objectivity and client autonomy may be considered ideal, but such an approach usually proves insufficient as the moral basis for prenatal surgical consultation. Value neutrality and moral detachment on the part of the surgeon creates an obstacle to forming a professional relationship with prospective parents who are seeking compassion, honesty, and integrity, virtues cited by Pellegrino and Thomasma as being essential components of the physician-patient relationship.[3]

Very few prospective parents consider termination of pregnancy when they present for a prenatal surgical consultation.

**TABLE 15-1**

**Types of Minor Consent Statutes or Rules of Common Law That Allow for the Medical Treatment of a Minor Patient Without Parental Consent***

| *Legal Exceptions to Informed Consent Requirement* | *Medical Care Setting* |
|---|---|
| The "emergency" exception | Minor seeks emergency medical care |
| The "emancipated minor" exception | Minor is self-reliant or independent:<br>• Married<br>• In military service<br>• Emancipated by court ruling<br>• Financially independent and living apart from parents<br>In some states, college students, runaways, pregnant minors, or minor mothers also may be included |
| The "mature minor" exception | Minor is capable of providing informed consent to the proposed medical or surgical treatment—generally a minor 14 yr or older who is sufficiently mature and possesses the intelligence to understand and appreciate the benefits, risks, and alternatives of the proposed treatment and who is able to make a voluntary and rational choice (*in determining whether the mature minor exception applies, the physician must consider the nature and degree of risk of the proposed treatment and whether the proposed treatment is for the minor's benefit, is necessary or elective, and is complex)* |
| Exceptions based on specific medical condition | Minor seeks:<br>• Mental health services<br>• Pregnancy and contraceptive services<br>• Testing or treatment for human immunodeficiency virus infection or acquired immunodeficiency syndrome<br>• Sexually transmitted or communicable disease testing and treatment<br>• Drug or alcohol dependency counseling and treatment<br>• Care for crime-related injury |

From Committee on Pediatric Emergency Medicine: Consent for emergency medical services for children and adolescents. Pediatrics, 2003. 111: p. 703-706.
*These laws vary by state and the surgeon should refer to the applicable jurisdiction.

In fact, most are seeking the pediatric surgeon's knowledge and reassurance that their unborn fetus can be treated with a good outcome. These prospective parents typically provide the surgeon with their most current fetal ultrasonogram and other diagnostic tests, its gender, and its first and middle names. The stage is therefore set for the pediatric surgeon to forge an ongoing professional relationship that is centered on the care of the future infant and that both parties share in making ethically responsible and medically sound decisions for the fetus.

We suggest the following as guidelines for pediatric surgeons during a prenatal surgical consultation:

1. Empathize with the inevitable grief and sorrow that the prospective parents feel on the recent unexpected and frightening diagnosis of a fetal malformation.
2. Candidly disclose the benefits, harms, and alternatives for the given fetal condition and offer recommendations that balance maternal and fetal interests.
3. Foster an atmosphere that facilitates the exchange of medical information and help the prospective parents make decisions that are consistent with their own beliefs, goals, and values.
4. Promote responsible efforts to improve access to the full range of prenatal services available at high-risk perinatal centers for women from all socioeconomic, ethnic, and cultural groups.

On occasion, ethical conflict may arise if the pregnant woman, in the exercise of her reproductive freedom, chooses a course of action that is inconsistent with conventional pediatric surgical recommendations. For example, a decision on the part of the woman to terminate the pregnancy because of a nonlethal anomaly, such as gastroschisis, could provoke emotional, moral, and professional conflict with the pediatric surgeon. Sadly, termination rates for gastroschisis remain high, particularly in Europe, where 29% of prospective parents in the EUROSCAN study[16] and as much as 44% in another study[17] elected termination for a condition with such a favorable prognosis. Prenatal counseling, when successful, should allay parental anxiety and reduce the rate of unnecessary terminations. Fortunately, other European studies have reported termination rates for gastroschisis of 5% or less.[18,19]

When, despite the objective medical fact of the low lethality of the fetal malformation, the woman insists on termination or other action detrimental to the fetus, it is not clear whether the pediatric surgeon can interfere with her choice. Under usual circumstances, a pediatric surgeon might invoke the power of the state when they believe that a pediatric patient's best interests are not being protected by the parents. However, there is no similar authority to intervene on behalf of the fetus. There has also been some concern that in situations in which maternal and fetal interests diverge, the obstetrician and the pediatric surgeon might be drawn into an ethical conflict as they seek the best interests of the mother and fetus, respectively.[20]

## End of Life

Advances in technology and development of new diagnostic and therapeutic interventions have created new life-sustaining treatments that can prolong a patient's life. These "high tech" measures (e.g., renal dialysis, ventilators, and organ transplantation) as well as new applications of existing therapies (e.g., antibiotics, fluids and nutrition delivered by enteral tubes or intravenous means) and chemotherapy increase the potential to extend life after critical illness. Depending on the therapeutic goal, surgical treatment could correct a surgical anomaly, provide palliation of symptoms, or merely improve selected physiologic parameters. In many cases, attainment of the defined therapeutic goal can allow an infant to develop normally or a child to pursue a meaningful life. However, in some cases the price of success is a relatively poor quality of life and a burden of care that could overwhelm some families. The question therefore is no longer whether pediatric surgeons *can* save the life of an infant with severe malformation or other neonatal disease but whether they *should* save it.[20]

Determination of what constitutes an optimal quality of life and the threshold below which life-saving measures should not be undertaken is a difficult moral, ethical, spiritual, and legal problem. Decisions to withhold life-sustaining treatment are generally made in advance and agreed on by the parents and physicians. However, there are limits to parental authority to make end of life decisions for their children as illustrated in the United States by the Baby Doe case.[21] Baby Doe was born in Bloomington, Indiana in 1982 with Down syndrome and esophageal atresia. The infant died after 6 days when the obstetrician recommended, and the parents agreed, to no surgical intervention. The Surgeon General at the time, C. Everett Koop, himself a pediatric surgeon, publicly expressed disagreement with this decision, which he believed was made on the basis of the infant's mental retardation rather than on the prospect for success after surgery. Several months later, Dr. Koop was again drawn into opposition when the parents of a second infant, "Baby Jane Doe" born with spina bifida cystica, decided not to have operative treatment. This time, a "right-to-life" lawyer and subsequently the federal government brought a court action, but the court ruled that the parents refusal was "a reasonable one, based on due consideration of the medical options available, and on genuine concern for the best interests of the child."[22]

Although several courts upheld the parental decisions in these and subsequent cases, public outcry led to federal intervention. Congress passed the Baby Doe law that specified criteria under which withholding of life-saving treatment can be permissible as follows:

- Child is irreversibly comatose
- Treatment is "virtually futile" in terms of survival
- Treatment would only prolong dying

Although the Baby Doe rules were designed to protect the child's right to life-saving treatment, regardless of the parents' wishes, the intent was not to mandate unnecessary or inappropriate treatments. To the contrary, the Baby Doe law positively directs physicians to make treatment recommendations to parents based on "reasonable medical judgment." Unfortunately, the law has been widely misinterpreted and misunderstood among physicians. In a 1988 survey, one third of pediatricians stated that maximal life-prolonging treatment was not in the best interests of the infants, but because of the Baby Doe law they would provide such treatment.[23] Some critics of the law also complained about federal imposition of medical decisions that would lead to proliferation of severely handicapped children without assurance of the resources needed to care for them.[22]

In both infants and older children, medical advances have created ethical dilemmas in the initiation or withdrawal of medical care for conditions with poor prognosis, particularly in situations in which treatment may prolong survival with an unacceptable quality of life. Although many individuals believe it is "worse" to discontinue life-sustaining treatment than to never institute such treatment, ethicists, moral philosophers, and legal scholars find no ethical or legal distinction between not starting treatment and stopping treatment.

A common situation in the neonatal intensive care unit is when a premature infant with several comorbid factors, such as chronic lung disease and intraventricular hemorrhage, requires surgical exploration for necrotizing enterocolitis or midgut volvulus. Issues that may arise include the appropriateness of extensive small bowel resection and whether care should be withdrawn in the face of poor prognosis. If bowel resection leads to short-bowel syndrome, will the infant be a candidate for intestinal or liver transplantation, or both? This situation typifies an all too frequent ethical dilemma faced by pediatric surgeons. When making decisions to prolong life or to discontinue life-sustaining treatment for an infant with critical illness, the *best interests standard* is generally used to focus on issues that are patient centered and to assess the benefits and burdens of continued treatment for a *particular infant*. In this case the infant's best interests standard would include consideration of the following:

- Severity of the medical condition
- Availability of curative or corrective treatment
- Achievability of medical goals
- Presence of serious neurologic impairments
- All associated medical conditions
- Life expectancy
- Extent of suffering
- Proportionality of treatment benefits to burdens in both the short term and long term

In making these difficult decisions, the medical team must work cooperatively with the parents. and their wishes should be given due consideration. There is an emerging consensus that great discretion should be given to parents in making decisions on nonintervention or withdrawal of life-saving treatment.[24] The guidelines issued in 2007 by The American Academy of Pediatrics encourage a family-centered, patient-oriented approach.[25] When there is disagreement, continued engagement between physicians and parents will often lead to an agreement. Conflict resolution may require transfer of care to another physician or consultation with the institution's ethics committee.

With life-threatening illnesses, such as terminal cancer, in older children and adolescents, parental protective instincts may come into conflict with the child's autonomy to participate in end-of-life decisions. However, older children who are capable of giving assent in ordinary situations are equally competent to do so when forced to confront their mortality. In fact terminal illness may impact the developmental understanding of pediatric patients by accelerating their grasp of serious illness and by promoting their wishes to control decisions about their health care. The stresses of their illness may "make them grow up faster" and make them wiser than their same-age peer group. For example, a 12-year-old child with terminal cancer may ask to discontinue chemotherapy or other unpleasant treatments and request to have "one final special vacation."

Because children cannot give morally or legally valid consent to or refusal of treatment, practice among physicians in the past was to shelter dying children from the truth of their dire circumstances. Current practice, favored by The American Academy of Pediatrics, acknowledges that these patients usually have a much more mature understanding of their situation than previously realized by their physicians and parents and that they should be told the truth about their prognosis and included in discussions about their care.[26,27] These discussions should include the extent of desired life-sustaining treatments, whether a do-not-resuscitate (DNR) or an allow natural death (AND) status is to be invoked, the role of palliative procedures in granting a better quality of life, and their desire for hospice services.

## Ethical Issues in Pediatric Bariatric Surgery

Bariatric operations in the pediatric population are increasingly used as an effective means of achieving weight loss and thereby relieving comorbidities such as type 2 diabetes, cardiovascular dysfunction, hypertension, obstructive sleep apnea, and dyslipidemias. These and other unsuspected comorbidities are present in nearly one third of all patients treated at the Center for Healthy Weight and Nutrition at Nationwide Children's Hospital. Morbidly obese children are likely to remain so in adulthood and carry with them the increased risks of premature morbidity and mortality. From a public health perspective, there is a rising childhood obesity epidemic that could dramatically increase the cost of medical care and cause a decline in life expectancy, thereby eroding the gains in longevity achieved during the 20th century in developed countries.

A multidisciplinary approach is currently used in the treatment for morbid obesity. The range of success with these approaches varies, and research is needed to better assess them, particularly in the pediatric population. Medical therapy that includes a comprehensive program of exercise and diet has not been successful in adults over the long term. Few children's hospitals have developed comprehensive medical obesity programs. Thus there is scant evidence in the pediatric literature about the outcomes of such programs. For adults with morbid obesity, surgical therapy is quite popular because it has been successful in achieving weight reduction with acceptable morbidity and mortality rates. Based on the good results in the adult population, it is not surprising that pediatric surgeons are being asked by the public—in particular, eager patients and their parents—to provide bariatric surgery for children and adolescents with morbid obesity.

Roux-en-Y gastric bypass and gastric banding, both performed laparoscopically, are the two bariatric operations performed most frequently in North America and Europe. Although both achieve weight loss, gastric banding does not alter the anatomy and is reversible; gastric bypass alters the anatomy in an essentially irreversible manner. Gastric bypass is very effective in achieving weight loss not only because it reduces the size of the stomach but also because it causes malabsorption. Long-term studies in adults indicate that gastric banding is somewhat less effective in achieving major

weight loss but is successful in reducing the comorbid conditions of hypertension and diabetes.

As noted by Caniano,[28] both principle-based ethics (autonomy, beneficence, nonmaleficence, and justice) and virtue-based ethical considerations (trustworthiness, compassion, phronesis, fortitude, integrity, and self-effacement) must be included in order to fully capture the moral complexity of pediatric bariatric surgery. Also, because bariatric surgery remains an innovative treatment, insofar as its long-term consequences for pediatric patients remain unknown, there are additional ethical obligations for evaluation of outcomes and for clinical research. All of these factors must be considered when (1) a pediatric surgeon recommends a bariatric operation to an individual patient, (2) the pediatric patient and her or his family decide to have bariatric surgery, (3) hospitals establish pediatric bariatric programs, and (4) the major professional surgical organizations endorse the performance of pediatric bariatric interventions. The following discussion examines how various ethical principles apply specifically to bariatric surgery.

True *autonomy* for the morbidly obese adolescent considering bariatric surgery is reflected by adequate informed consent. More than most other cases, the balance between parental permission and the child's assent weighs heavily toward the latter. Unfortunately, true autonomy under these settings is under severe pressure from the flurry of information available in the media, lay publications, and the Internet, which often highlight former morbidly obese individuals who became svelte after their intervention. The desire to have a body that is socially acceptable and free of comorbidities may interfere with a deep understanding of the operative risks and the irreversible nature of some of the proposed procedures. The burden of providing informed consent to the adolescent patient and his or her family rests on the surgical team, which should include at the least medical specialists, psychologists, and pediatric surgeons. Interested readers are referred to the guidelines proposed by Raper and Sarwer on the elements of informed consent that constitute the minimum amount of information to be discussed with prospective adolescent patients interested in bariatric treatment and their families.[29]

*Beneficence* obliges physicians to seek to reverse the physical and psychological derangements that interfere with well-being in morbidly obese children. If nonsurgical interventions—such as calorie-restriction diets, exercise programs, and behavioral therapy—were effective in achieving substantial weight loss with reversal of comorbidities, beneficence would favor these approaches. However, adolescent patients whose body mass index (BMI) exceeds 40 $kg/m^2$ have only a 3% reduction in BMI after 1 year of intensive medical weight management, a result that is insufficient to reverse comorbidities.[30] However, given the risks associated with bariatric surgery, beneficence warrants that prospective patients undergo thorough assessment of their metabolic and psychological parameters, receive a "reasonable" trial of medical/behavioral weight loss treatment, and continue such treatment if it proves effective. For most patients who are unsuccessful with this approach, bariatric surgery upholds the principle of beneficence in enhancing health and well-being.

The well-known risks of harm during and after bariatric procedures impose an obligation of *nonmaleficence* in recommending treatment choices. Although reported rates of serious short-term risks of bariatric surgery are low, adolescent patients who are eager to lose weight may not appreciate the potential impact of such complications in terms of lengthy hospitalization, reoperative surgery, and other unanticipated problems. Furthermore, assessment of possible harm must include consideration of complications that may develop several years later. Wilde, in a 2004 law review article, observes that physicians trust that morbidly obese adult patients can put all the known risks and complications into perspective before agreeing to a bariatric operation, but it is not clear that pediatric patients and their families have that same perspective given the uncertainty of outcomes decades after the operation.[29a]

The principle of *justice* (also a virtue) requires that each person share equitably in the benefits and risks of health care. Studies have found significant disparities in access to adult bariatric surgery for African Americans, Hispanics, low-income individuals, and males.[30] Similarly, justice is threatened when disparities occur in the manner in which pediatric hospitals and their bariatric programs provide access to and participation in surgical treatments. The mission and values of pediatric hospitals generally include the provision of health care for all patients, regardless of their socioeconomic status. Pediatric obesity in the United States affects one in three socially disadvantaged children, with particularly high rates among African American girls and Hispanic and Native American children of both genders.[31] Children from socially and economically challenged families fare poorly on most childhood health indicators and may not have ready access to medical weight management and bariatric services. The "conscience" of the pediatric hospital system, within the context of its local and regional community, will be the driving force behind distributive justice relative to many children and adolescents with morbid obesity. Organized efforts to support costly multidisciplinary weight management and behavioral therapy programs, as well as bariatric programs, require professional leadership that advocates for equitable access for all children. Any pediatric bariatric program that excludes patients based on lack of insurance or financial resources would violate the principle as well as the virtue of justice.

## Surgeons and Industry

There are many benefits to patients and the general public when physicians work together with pharmaceutical, medical device, and biotechnology companies. Much of the development in new tests, drugs, and devices that have vastly improved the quality of medical care have been the direct outcome of industry support for medical education, research, and innovation. In fact, industry funds about 50% of the costs of continuing medical education (CME) programs and 60% of clinical research in the United States.[32,33] However, renewed focus on professionalism in medical education and practice has raised the concern that these relationships may create conflicts of interest (COI), potentially resulting in undue influence on professional judgments. Industry practices that cross the line between patient welfare and profit seeking can induce physicians to perform unnecessary tests and treatments that may be harmful to patients and contribute to rising health care costs.[34] Increasing scrutiny by the public, patient advocacy groups, and Congress has therefore led most

medical institutions and professional organizations to adopt stricter COI policies.

From an ethical standpoint, COIs are not inherently immoral or even unethical. However, COIs increase the potential for unethical physician behavior. There are three characteristics of a COI:[35]

1. A fiduciary relationship exists in which a physician acts in a fiduciary role in which they act primarily in the patient's best interest.
2. The fiduciary agent (physician) has self-interests that can be influenced and potentially override the agent's primary concern and obligation to the patient's interest.
3. A relationship with another entity (industry) exists that has the capacity to influence the physician to shift primacy of concern from the recipient of the fiduciary relationship (patient) to one that is motivated by direct or indirect self-interest.

It becomes readily apparent that COIs can exert a corrosive effect on several moral and ethical principles, particularly those of fidelity, beneficence, and nonmaleficence. Of these, fidelity is the most directly applicable to COI. The principle of fidelity establishes the physician's responsibility to carry out duties carefully and completely and in doing so demonstrate loyalty to, and in turn receive the trust of, the patient.[3] COIs erode the trust of the patient and compromise the physician's fiduciary role.

The ethical response to COI may take one or a combination of two forms: disclosure and avoidance. Disclosure of COI tends to dominate policies adopted by many institutions and professional bodies, in keeping with Brandeis' famous maxim that "sunshine is the best disinfectant."[36] However, there are distinct limitations to the power of disclosure alone as an effective antidote to COI. One possible reason is that full disclosure may not be attainable because the primary source of funding can be obfuscated through a labyrinthine maze that could involve front organizations or even accredited medical education companies.[37] Even a full disclosure, while raising the suspicion of bias, is too ambiguous to help the recipient of information from financially conflicted individuals to determine whether bias is present.[38] In fact, disclosure may allow some physicians to maintain or even strengthen their conflicts and has no inbuilt mechanism to actually eliminate bias. Therefore some have proposed that the only true way to eliminate industry bias in physician behavior is to avoid it whenever possible. Physicians, they argue, should avoid situations that unnecessarily introduce COI. However, avoidance is not always practical and may be impossible if physicians and investigators are going to pursue industry-funded research that has the potential to benefit patients.[38] This has produced somewhat of a backlash among those who complain that the new COI rules are too stringent and that the pendulum has swung far in the direction of stifling innovation and jeopardizing patient care.[39]

The 2009 report "Conflict of Interest in Medical Research, Education, and Practice" issued by the Institute of Medicine (IOM) has brought renewed urgency to this issue.[40] The IOM stresses the importance of preventing bias and mistrust rather than trying to remedy damage after it is discovered, and it encourages the enactment of policies and laws that identify, limit, and manage COI without negatively affecting constructive collaborations between the medical profession and industry.

## Multiculturalism

With the increasing diversity of modern society, pediatric surgeons are faced with the difficult task of providing care to children from culturally heterogeneous backgrounds. Many pediatric surgeons, like other physicians, may consider themselves culturally competent and perhaps take pride in their personal commitment to providing equitable care to all patients. However, an ever-increasing body of evidence continues to highlight disparities in several areas of health care delivered to ethnic minority populations.[41] A contributing factor to this problem might be a failure among physicians to appreciate and actively counter cultural bias in their own relationships with their patients.

*Culture* is a term that may have different meanings, but in this context we define culture as the common and accepted way of thinking, feeling, and acting for a group of people. This includes a set of shared beliefs, values, attitudes, patterns of meanings, and behaviors that characterize a group of people. However, we must not restrict the definition of a "group of people" to political borders, religious practices, or physical characteristics. Focusing on such distinctions risks objectifying those whose appearance, language, or national origin is different from the majority into overly simplistic categorical stereotypes.[42]

It may be tempting for physicians, who are socialized by traditional values inherent in Western medical training, to view with suspicion attitudes from other cultures that challenge deeply held normative values. Western attitudes to health are based on a set of assumptions and values about disease and well-being that are not necessarily shared by other cultures. For example, Western medicine views health in biologic terms, with disease being the consequence of disruption of anatomic form or malfunctioning in biologic processes. In contrast, some cultures may ascribe spiritual, superstitious, or metaphysical causes to various illnesses and may have less trust in Western medicine as they pursue an assorted variety of alternative medicine or natural cures. In meeting parents and children whose culture is different, the pediatric surgeon should inquire about their beliefs, goals of treatment, and concerns.[43]

Individuals from minority cultures differ in the extent to which they assimilate the values of the larger society. Some parents will be informed by Western values on some issues, whereas maintaining their own cultural beliefs in others, and individuals from a similar cultural background or even within the same families may disagree on specific issues. Therefore the pediatric surgeon must resist the tendency to assign stereotypes of beliefs or behavior to individuals based on their identification with a cultural group. For example, some immigrant Chinese-American patients and families base their disease management decisions on their concerns for family well-being, family face, and the reciprocal responsibilities required by varied family roles,[44] but not all Chinese-American patients will be motivated by such values.

Along with cultural diversity, language barriers are increasingly encountered in our health system and may contribute to disparities for patients with limited English proficiency (LEP).[45] U.S. Census data shows that, other than English, more than 100 other languages are spoken by 47 million

people in the United States, and the proportion of those with limited English proficiency nearly doubled from 4.8% in 1980 to 8.1% in 2000.[46] Fortunately, health disparities due to language barriers can be reduced or eliminated entirely when physicians use the services of trained interpreters.[47,48] Whenever possible, however, pediatric surgeons should avoid using family members or older siblings of the patient for translation to ensure accuracy of transmitted information both to and from the parents and child patient, to avoid translation bias, and to help in reading nonverbal and verbal cues about underlying concerns. A recent study identified specific risks of working with family interpreters, such as imposing their own agenda (rather than the patient's agenda) and controlling the consultation process.[49]

How then does a pediatric surgeon deal with cultural practices that are different from the norm, particularly when they affect parental acceptance of and compliance with recommended treatments? First we must consider that our patients (including children and their parents) experience illness as represented by their personal, interpersonal, and cultural reactions to the disease. Therefore the key is to understand *how* and *why* parents of a particular culture react in a certain way and hold certain attitudes when faced with illness in their children. We previously outlined the following strategies to reduce cross-cultural conflicts: asking questions about the parents' values and listening to their responses, indicating to the parents that their views are important, allowing enough time to deal with the parents whose culture is different, and seeking assistance from "experts" who understand the parents' cultural beliefs when significant differences arise in the course of treatment.[43]

## Surgical Error

The 1999 Institute of Medicine (IOM) report "To Err Is Human"[50] focused the spotlight on the high incidence of medical errors and alerted the health care community and general public in the United States on the significant impact medical errors have on patient outcomes. The IOM report estimated that as many as 98,000 patients die each year as a result of medical error. The report also noted that many more patients undergo serious harm from a medical error that prolongs their hospitalization, causes unnecessary suffering, and increases the cost of care. Common examples of errors encountered during surgical treatment include wrong diagnosis, wrong patient (or site) procedures, and retained foreign bodies.

The process of medical decision making may be considered in four phases (1) data gathering, (2) integration or processing of data, (3) confirmation of diagnosis, and (4) treatment.[51] Medical errors are often due to deficiencies in medical judgment rather than knowledge, but other contributing factors include inadequate experience, carelessness, and fatigue. The core problem is often a defect in medical decision making, whether in formulating a diagnosis, choosing an appropriate surgical technique, or in the initial response to an adverse outcome. An analysis of the process of data integration among physicians identified four common sources of error: (1) wrong synthesis (lack of knowledge leading to an incorrect conclusion), (2) premature closure (incomplete consideration of all disease processes), (3) inadequate synthesis (data do not support conclusions), and (4) omission (important diagnostic information was not obtained).[52]

Considerable effort has been directed at establishing patient safety practices that minimize the incidence of errors. In contrast, there has been relatively less attention to how to respond after an error has occurred. Historically in the United States, fear of malpractice litigation has fostered a "code of silence" among physicians that is detrimental to efforts to improve patient safety, breeds mistrust, and fractures the therapeutic relationship between physicians and their patients. However, concern regarding legal liability should not affect the pediatric surgeon's honesty with parents. There is also a "human dimension" to the problem, as the silence, shame, anger, and guilt exacts an emotional toll on everyone involved, including physicians.[53] Research indicates that patients want full disclosure, a sincerely framed apology, and clear admission of responsibility.[54] Most parents desire an explicit acknowledgment that an error had occurred, what the error was, how the error occurred, how the error will affect their child, and what efforts are being made to prevent occurrence of similar errors in the future. Studies indicate that patients were more likely to trust physicians who participated actively in disclosing a serious error. In addition, fears that disclosure of an error will increase the likelihood of a malpractice claim have not been substantiated.[55]

In the United States, most medical institutions, professional organizations, and regulatory agencies consider full disclosure of a surgical error to be an ethical imperative. When a surgical error has occurred, the pediatric surgeon should proceed to inform the patient and parents in clear language about the nature of the error, the anticipated consequences, and how the error will be managed in the patient. This conversation requires that the pediatric surgeon explain how the error occurred, offering an empathetic apology about the commission of the error. The offering of an apology with disclosure of the error is a key step in the process. The apology must acknowledge the error and its consequences; the pediatric surgeon must assume responsibility and communicate regret, shame, or humility for having caused harm and in some cases offer reparation.[56] Most parents want to know that specific action will be taken to prevent the same error from harming another child. In some situations, an offer of compensation or early settlement offers by hospitals can dramatically reduce malpractice claims. In countries with no-fault compensation systems, malpractice claims are much less common. There is a movement in the United States to encourage physicians to offer an apology to patients and families when medical error occurs. More than 30 states in the United States and several Canadian provinces have passed "apology laws" to enhance medical error reporting and medical safety. Such laws make it possible for physicians to be able to use the dreaded phrase "I am sorry," without the statement being construed as an admission of liability.

Now, more than a decade after "To Err is Human," the subject of medical errors has gained wide currency in our society. Language such as adverse events, root cause analysis, disclosure, and risk management are commonly used in the lay press. Medical schools and residency training programs are rapidly adopting simulation modules, virtual patients, and other novel educational strategies to minimize the risk of harm to patients, while meeting needs of educating the next

generation of physicians.[53] The opportunity seems ripe for competency-based medical education, initiated by the Accreditation Council for Graduate Medical Education (ACGME), to firmly embrace patient safety. In fact a proposal has been made that the identification of medical error recognition and disclosure be recognized as a *seventh* core competency to be adopted in our medical education.[57]

## Innovation and Research

Innovation involves the introduction of a new method, idea, treatment, medication, or device to benefit the individual patient.[58] A surgical innovator is motivated by the belief that the new technique or therapy, or modification of an existing procedure, will improve the care of an individual patient. Such innovations often proceed without prior study and occur in real time. Sometimes the surgeon employs the innovative procedure in a small series of patients, using an iterative process to perfect the technique one patient at a time. In contrast, clinical research involves formal testing of different approaches to treatment with the aim to discover new knowledge that will benefit humankind, although there may be no benefit to individual study subjects. Therefore the results of formal research are generalizable, but the results of innovation initially apply to only a single patient.[59] Despite these distinctions, innovation and research are intertwined, and one cannot proceed effectively without the other.[60]

In pediatric surgery, much advancement has been brought about by research and development of innovative surgical techniques. Pediatric surgeons have been among the most notable surgical innovators, and many of the procedures beneficial to children today, including appendectomy and pyloromyotomy, may never have passed the rigor of randomized trials. Even with the advent of randomized trials, many innovative procedures have been widely adopted without evidence to support their advantage over standard techniques. For example, minimally invasive surgery has become the preferred approach for treating many childhood conditions, although rigorous evaluation of its role has rarely been undertaken.[61] Yet too little regulation creates the potential for abuse and can be harmful and dangerous. For example, some innovative procedures that were intuitively appealing when first proposed such as sympathectomy for Hirschsprung disease and jejunoileal bypass for morbid obesity were subsequently abandoned and may never have been widely used in the first place if a stricter regulatory regimen were in place. Also, some operations have failed to withstand the process of rigorous research evaluation. Recent experience with fetal surgical treatment of congenital diaphragmatic hernia provides a case in point. Thus far all randomized trials comparing prenatal intervention to standard postnatal therapy for congenital diaphragmatic hernia have shown no benefit to prenatal intervention.[62]

The fundamental ethical question is how to balance the need for research and innovation to advance human progress against the potential risks to patients who are the first recipients of the new procedures or the subjects in a clinical trial. Current ethical standards for the conduct of clinical research in the United States are derived from several standards, including the Nuremberg Code, the Declaration of Helsinki, and the Belmont report. Similar standards are in place in most progressive societies. Recent implementation of the Privacy Rule now requires the investigator to protect not only the safety but also the privacy of the research subject. In most institutions, compliance with these requirements is promoted by the institutional review board (IRB). The editors of most pediatric surgery journals have joined a growing coalition of medical journals requiring IRB approval before publication of results of research studies. In contrast, patient protections in innovative surgery are informal and rely primarily on the surgeon's competence and integrity.[59] In considering a new procedure, the surgeon must balance competing ethical principles, and relevant questions include whether it should be performed outside of a formal research protocol, what level of disclosure is needed to achieve an adequate informed consent, what research design meets the desired standard of evaluation, and how the burdens and benefits of such research can be distributed fairly.[63]

Randomized clinical trials (RCTs) are the most effective method to evaluate new procedures, but the specialty of pediatric surgery has lagged behind some other surgical specialties in the numbers of RCTs that guide our practice. Although RCTs compose 3% to 6% of studies reported in adult surgical literature, Moss and colleagues found that a trivial 0.17% of pediatric surgical studies were RCTs.[64] A recurrent obstacle cited for the reluctance among pediatric surgeons to participate in RCTs is the lack of clinical equipoise.[64,65] The meaning of equipoise is often misunderstood. The concept of equipoise was introduced by Charles Fried to express the uncertainty that a physician may have in choosing the best treatment out of competing alternatives.[66] Although this definition is useful in guarding the physician's fiduciary relationship with his or her patient, it could intensify a physician's state of uncertainty about whether a patient should be enrolled in a clinical trial. Freedman subsequently proposed the notion of clinical equipoise (or community equipoise), a state of uncertainty or professional disagreement within a professional group or clinical specialty regarding the relative merits of competing treatments.[67] In declaring clinical equipoise as the basis for participating in a clinical trial, the physician acknowledges that there is a reasonable uncertainty within his profession about the best treatment, even though he or she may have a strong preference for one option. Acceptance of clinical equipoise as sufficient ethical and moral justification for RCTs will increase enrollment in such trials.

Ultimately pediatric surgeons must be conservative guardians in surgical innovation. We agree with McKneally that the terminology of innovation has a seductive connotation of added value that attracts patients seeking the "latest and greatest" treatment.[68] Instead it should be replaced by the term *nonvalidated* as proposed by Levine because it more accurately reflects the ethical and medical hazard entailed in new procedures.[69] The concept of a nonvalidated operation is more transparent and honest because it embodies the fact that the proposed operation has not been subjected to rigorous investigation. This awareness may nudge both parents and pediatric surgeons toward supporting the ideal of RCTs, when a state of clinical equipoise exists about the role of a new procedure, before it is widely imposed on vulnerable and trusting patients and their families.

# Conclusion

The ethical principles of beneficence, nonmaleficence, autonomy, and justice, and virtues such as trust, compassion, prudence, justice, courage, phronesis, fortitude, integrity, honesty, and self-effacement provide a sound basis to navigate the moral dilemmas we encounter in pediatric surgery practice and research. Although there is no universal solution to a given ethical problem, we think that an acceptable solution can be reached if these principles are followed. Formal teaching of clinical bioethics has been lacking in most pediatric surgery training programs.[70] Recently, a case-based, practice-oriented ethics curriculum was developed by the American Pediatric Surgical Association (APSA) for pediatric surgery training programs in North America. In addition to all the topics discussed in this chapter, these case studies cover important ethical concerns related to child abuse, conflict resolution, and the disruptive surgeon. The APSA curriculum is an invaluable clinical bioethics learning resource for both trainees and practicing pediatric surgeons and is available on the APSA web site.[71]

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 16

# Patient- and Family-Centered Pediatric Surgical Care

Sherif Emil

*"I am a mother of a child who was born with trisomy 13. My daughter died at home on April 13, 2010, at age 5, surrounded by her loved ones. She was not supposed to live that long, but she had great determination to beat the odds. During her last few months, I was introduced to the supportive/palliative care service. This program focused on helping her to live life to the fullest—her life, my life, our family's life. I wish there had been this program when she was born. By focusing on the quality of her life, rather than trying to fix things, my daughter would have had less hospitalizations and more special time with us at home. She would have had better pain management and would have been able to live life to the fullest, which I believe she did during those last few months."*

**Fundraising email sent by Rachel Llanos, mother of Kellie Llanos, a child with trisomy 13 who died at age 5 after a plethora of medical and surgical interventions.**

This is the first edition, in the long history of this illustrious textbook, that dedicates a chapter to patient- and family-centered care (PFCC). It is befitting, because the 21st century has seen the principles of PFCC quickly permeate through all areas of medicine, including pediatric surgery. Some may feel that these principles are self-evident, politically correct terms of what surgeons have always practiced. Although it is true that a competent, empathetic, ethical surgeon with good listening and communication skills is very likely to practice PFCC, the concept is far more than one of competency, empathy, or communication. Over the last 20 years, PFCC has evolved into a health care discipline, with a significant volume of research, publication, and programs. Systematic reviews show that PFCC increases adherence to management protocols, reduces morbidity, and improves quality of life for patients.[1] This chapter aims to introduce surgeons to this relatively new discipline and to emphasize the potential positive impact PFCC can have on pediatric surgical practice.

## Definition

The Institute for Patient- and Family-Centered Care (IPFCC) in Bethesda, Maryland is a non-profit organization that was founded in 1992 with a mission to advance the understanding and practice of PFCC and to partner with patients, families, and health care professionals to integrate PFCC concepts in all aspects of health care.[2] The institute defines PFCC as *an innovative approach to the planning, delivery, and evaluation of health care that is grounded in mutually beneficial partnerships among health care providers, patients, and families.* The core concepts of PFCC are (1) respect and dignity, (2) information sharing, (3) participation, and (4) collaboration.[2] In a recent technical report and policy statement, whose lead author is a pediatric surgeon, the American Academy of Pediatrics (AAP) deemed these same concepts essential to professionalism.[3,4] The Institute offers a plethora of resources on its Web site, and partners with practice groups and health care organizations to help integrate these concepts into the health care environment. Some of the contrasts between traditional medical care and PFCC are shown in Table 16-1.

## Background

In what is perhaps the oldest pediatric surgical textbook in the English language, published in 1895, D'Arcy Power wrote the following:

> "When an operation has been decided upon, it will generally be found that better results are obtained if the child be removed from its accustomed surroundings and is placed in the charge of those who have special experiences in nursing sick children. Only in very exceptional cases can a mother be trusted to nurse her own child after a serious operation, and in many instances the recovery of a spoilt and fractious child is seriously retarded by the presence of those who love it best. It is therefore acting in the best interests of the child, to recommend that it should be placed in a surgical home, or in the charge of an experienced children's nurse."[5]

This was essentially the paradigm for the surgical care of children in the first half of the 20th century. In 1953, Robert Gross included a section on "psychic preparation" for surgery in his seminal pediatric surgical textbook.[6] He challenged the paradigm of the child's separation from his family by emphasizing that abandonment "can seriously undermine the

**TABLE 16-1**

**Contrasts Between Traditional Care and Patient and Family-Centered Care**

| *Traditional Care* | *Patient- and Family-Centered Care* |
|---|---|
| Doctor knows what is best for the patient | Doctor and patient/parents together decide what is best for the patient |
| Exclusion of religious and cultural issues from medical decisions | Inclusion of religious and cultural issues in medical decisions |
| Psychosocial issues are ignored or approached separately | Psychosocial issues are included in the overall care plan of the patient |
| Parental role is minimized in overall care | Parental role is optimized in overall care |
| Parental absence during invasive procedures, resuscitation, or anesthetic induction | Parental presence during invasive procedures, resuscitation, or anesthetic induction |
| Withholding of information, particularly regarding poor outcomes or complications | Open and transparent information sharing, including admission of error or adverse events |
| Minimal preoperative preparation | Thorough preoperative preparation |
| Reactive approach to pain management | Proactive approach to pain management |
| Separate specialty clinics for complicated diseases | Multidisciplinary clinics for complicated diseases |
| Outcome studies analyze only physical or biological factors | Outcome studies also analyze quality of life factors pertaining to patient and family |

faith of the child in his mother or father."[6] He emphasized the importance of preoperative mental preparation at home and the role parents can play in the child's surgical experience. Dr. Gross's desire for an enhanced familial role probably was far ahead of the resources available at the time, because the same chapter shows a postoperative child shackled to the bed by her wrists and ankles in order to receive intravenous infusion.[6] As pediatric surgeons continued to tackle and win more surgical battles, their attention began to turn to psychosocial issues surrounding pediatric surgical care. In the mid-1990s, Caniano ushered in the field of pediatric surgical ethics, inevitably bringing attention to family dynamics and "the big picture" during fetal consultation, management of congenital anomalies, and pediatric surgical care in general.[7,8] In the last decade, outcome studies for a variety of pediatric surgical conditions started to look at emotional and developmental results on the child, in addition to the physical ones. Recently, these outcome studies have begun to investigate the effects of interventions on parents and caregivers. In one recent study, Zaidi and colleagues investigated the caregiver's perspective after esophagogastric dissociation in neurologically impaired children with severe gastroesophageal reflux disease, arguing for a greater role for this procedure because of the unexpectedly high caregiver satisfaction.[9] Another recent study looked past the typical outcomes of treatment, to analyze the child's emotional quality of life as well as the degree of parenting distress, in two arms of a randomized controlled trial for perforated appendicitis with abscess.[10] These types of studies are bringing to light the concept that successful physical outcomes may not necessarily translate into the best patient and family-centered outcomes. Finally, Paice and colleagues recently raised the possibility of parental presence in the operating theatre.[11] Pediatric surgery has come a long way in 100 years!

# Core Concepts

## RESPECT AND DIGNITY

All persons should be treated with respect and regard for individual worth and dignity, including sensitivity to gender, race, and cultural differences, as well as maintenance of patient confidentiality when appropriate.[4] Pediatric surgeons, particularly in developed countries, find themselves practicing in increasingly multicultural settings. The forces of immigration and globalization have created many international cities and communities, where people of diverse cultures, faiths, beliefs, and economic circumstances seek surgical care for their children. The parents' background and belief system, in turn, influences their interaction with the medical system; their expectations of medical personnel; and their decisions regarding their children's health care. At times, the surgeon may find himself or herself at odds with the approach or the decision of the child and/or the parents. The surgeon does not have to agree with the family. However, the principle of respect implies recognition that rational people may hold opposing and irreconcilable views.[8] The surgeon can demonstrate respect for the family and acknowledge their dignity by listening carefully, understanding their perspectives, and attempting to see beyond his or her own personal experience. Respect does not imply compromising the surgeon's primary responsibility to his or her patient's welfare. For example, the AAP has repeatedly called for the equal application of legal interventions whenever children are endangered or harmed, without exemption for actions based on religious beliefs.[12,13] It has also opposed religious or cultural practices, such as ritual genital cutting of female minors, that consistently harm children, and it has called on its members to actively dissuade families from carrying out these practices.[14]

## COMMUNICATION

We live in the age of information. Accurate and timely information sharing with patients and parents is one of the hallmarks of medical practice in the 21st century. Parents of children undergoing surgery desire comprehensive perioperative information. In fact, Fortier and colleagues recently reported that the vast majority of children older than 7 years also desire comprehensive information about their surgery.[15] The responsibility for providing this information lies mainly with the surgeon, because it has been shown that information acquired from elsewhere (general practitioner, books, popular magazines, Internet) does not necessarily improve the parents' understanding of the child's operative risk.[16] Clinicians may feel an impetus to withhold information, to decrease parental anxiety. This notion has been disproven by strong evidence.[17,18]

Information sharing is often used interchangeably with communication. However, effective communication goes well beyond information sharing, to include understanding, empathy, compassion, transparency, and advocacy. One of the few acts that require more trust than surrendering oneself to a surgeon is surrendering one's child to a surgeon. This intense trust is built on many factors, including the surgeon's reputation and competence, but none more important than effective communication. Good communication skills are essential core competencies that are associated with improved health outcomes, better patient adherence, fewer malpractice claims, and enhanced satisfaction with care.[19] Communication obviously serves the pediatric surgeon well on a daily basis, but certain situations require particular attention to communication if PFCC is to be provided. These include prenatal consultations, planning for correction of congenital anomalies, relaying a diagnosis of cancer, provision of end-of-life care, communicating the death of a child, and transmission of information regarding surgical errors and adverse events.

Prenatal consultation with pediatric surgeons by parents carrying a fetus with a congenital anomaly has become routine in the developed world. Although these consultations have not been proven to improve outcomes, they serve the vital purpose of relaying information to the parents before the stressful events of childbirth. They also help the surgeon establish early rapport with the parents and start building a trusting relationship. Parents are typically interested in more than a description of the anomaly, its treatment, and its potential outcome. They usually seek to learn what the future may hold for their baby, including his or her potential social function and interaction with family and society.[8] Caniano and Baylis stress the importance of compassion in such interactions, particularly in situations where couples may choose to end much-wanted (and sometimes difficultly acquired) pregnancies associated with life-threatening fetal malformations, for which there are no effective surgical interventions.[8] After examining prenatal surgical consultations for congenital diaphragmatic hernia (CDH), Aite and colleagues found that 70% of patients found it difficult to follow the surgeon's explanations or ask questions because of fear and other intense emotions.[20] Interestingly, consultations for lesions associated with better prognoses, such as congenital cystic adenomatoid malformation, were less effective in decreasing parental anxiety than consultations for CDH.[21] The reasons for this were uncertainty about prenatal outcome and lack of a defined management plan.[21] These data point to a possible deficiency in a single prenatal consultation, where the surgeon relays all the pertinent information. Follow-up by the surgeon or ancillary medical personnel after the initial consultation may enhance communication in this regard.

The setting of surgically correctable congenital anomalies, especially in the absence of prenatal diagnosis, presents another communication challenge for the pediatric surgeon. Families, even relatively sophisticated ones, often have never heard of the anomaly and are overwhelmed by the notion that their newborn baby can undergo and survive a major operation.[22] Provision of written and illustrated material can significantly enhance communication.[20–22] Before the operation, families are most interested in the description of the anomaly and its prognosis, whereas after the operation, they are most interested in the recovery process and assessment of the long-term quality of life.[22] Many congenital anomalies produce permanent and profound effects on the family dynamic, with potential marital, social, and financial implications. In an analogy to the five stages of grief described by Elizabeth Kubler-Ross, Drotar and colleagues described five stages of parental reaction after the birth of an infant with a congenital malformation (Table 16-2).[23] Understanding these stages can allow the pediatric surgeon to effectively relate to the family in the immediate perioperative period and beyond.

A new diagnosis of cancer presents a major crisis in the life of the patient and family. Fortunately, most pediatric solid and hematologic malignancies have better prognoses than their adult counterparts. This could be mentioned early in the discussion, because most parents will automatically remember a family member or loved one who died of cancer. The hospital and community resources available to the family should be clearly described, convincing the family that they will not be alone during this difficult experience. The emotional state of the parents is often associated with very poor receptiveness and comprehension on their part when the diagnosis is first relayed.[24] Repetition and constant clarifications of treatment plans and other details are typically necessary. Although information should be shared liberally with the parents, and often the child, the surgeon should remember that hope is not statistical. Hope is often recognized as an important component for healing; therefore, while remaining realistic in the expectation of cure, the surgeon should not try to remove all hope from the patient and family.

Communication with the family when the end of the child's life is in sight, or after the death of a child, presents particular challenges to the surgeon, who often has to deal with his or her own emotions. A sense of failing the child or family can interfere with the surgeon's ability to care for and comfort the family, when cure is no longer possible. The physician needs to find the strength to discuss life-threatening illnesses in an open, sympathetic, and direct manner, because families resent evasive or brief interactions.[25] Researchers at Children's Hospital Boston have identified six parental priorities for end-of-life care in the pediatric intensive care unit—namely, honest and complete information, ready access to staff, communication and care coordination, emotional expression and support by staff, preservation of the integrity of the parent–child relationship, and faith.[26] One can see that most of these priorities relate to communication. The pediatric surgeon's role does not end with the death of a child. The families a surgeon often bonds with the most are the ones whose children's funerals the surgeon has attended. A pillar of American pediatric surgery, Dr. Morton Woolley, chose the subject of a child's death as his last publication, in an attempt to help pediatric surgeons provide appropriate responses when confronted with the death of a child.[27]

Finally, communication, in general, and transparent communication, in particular, is exceptionally important in

**TABLE 16-2**
**Five Stages of Parental Reaction After the Birth of an Infant with a Congenital Malformation[23]**

| | |
|---|---|
| Stage I | Shock |
| Stage II | Denial |
| Stage III | Sadness and Anger |
| Stage IV | Adaptation |
| Stage V | Reorganization |

decreasing litigations.[28] The American College of Surgeons Closed Claims Study identified failure to communicate as the major cause of litigation in 22% of claims.[29] The adverse consequences of these failures included medical errors, escalation of the consequences of otherwise nonpreventable adverse events, and anger or mistrust even when the standard of care was met. A policy of transparent disclosure of error with an apology or expression of regret when preventable adverse events were identified, coupled with an offer of reasonable compensation, has been shown to dramatically decrease medicolegal costs.[30]

Effective communication between health care team members is also essential in providing PFCC to complex pediatric patients. In one study, Meltzer and colleagues found that physicians, faced with difficult patients or families, were more likely to distance themselves or refer the family to the psychosocial profession, while nurses were more likely to consult with colleagues.[31] Communication skills and relational abilities in pediatric health care can be significantly improved by formal training.[19]

## PARTICIPATION

Surgery is often described in terms of doing things *to* patients, and not *with* patients. It is not surprising, therefore, that the patient's and family's active participation in the surgical experience has constituted the most controversial aspect of PFCC over the past 2 decades, a period that has seen a flurry of research into issues such as preoperative family preparation, parental presence during induction of anesthesia (PPIA), and parental involvement in the choice of potentially anxiolytic preoperative and postoperative maneuvers. Preoperative anxiety in young children undergoing surgery is associated with more pain during the recovery period, as well as higher incidences of emergence delirium, postoperative anxiety and sleep disturbance, and postoperative maladaptive behavior.[32,33] The parents' preoperative anxiety may also influence outcomes. For example, many mothers who exhibit a high desire to be in the operating room are also very anxious, and their children are likely to exhibit high anxiety levels during induction of anesthesia.[34] Interventions to decrease the mother's anxiety during PPIA were found to also decrease the child's anxiety on entrance to the operating room and during introduction of the anesthesia mask.[35] Most of the research, therefore, is aimed at identifying maneuvers that may decrease child and parental anxiety during the perioperative period, outcomes that are understandably difficult to assess. Nevertheless, multiple scales, such as the Motivation for Parental Presence during Induction of Anesthesia (MPPIA),[34] the Yale Preoperative Anxiety Scale (mYPAS),[36] and the Child-Adult Medical Procedure Interaction Scale,[37] have been developed in an attempt to provide some objective data. Chorney and Kain have recently presented a comprehensive model of family-centered pediatric perioperative care.[38] This model covers the preoperative, intraoperative, and postoperative environments, and includes family factors, such as anxiety and previous medical experience, as well as provider and system factors, such as training and organizational policy.[38]

### Preoperative Preparation

Most children's hospitals currently have some type of preoperative preparation program for surgical patients. These programs generally include an orientation to the operating room (OR), a description of the anticipated events on the day of surgery, and, in some instances, psychological preparation of the parent and pediatric surgical patient.[39,40] Certain patient factors identified during the preoperative preparation, such as age, previous anesthesia, and anxiety level, have been found to predict poor behavioral compliance during inhaled induction.[41] These factors may help identify children who could benefit from behavioral or pharmacologic interventions. Targeting the parents in such programs is also important, because there is evidence that the parents' anxiety on the day of surgery is highly associated with the child's anxiety.[42] During the preoperative visit, options such as PPIA may be discussed, if available in the institution. These visits also afford the anesthesiologist an opportunity to assess the family as a whole and formulate a plan for induction. For example, a preoperative assessment of the anxiety level of parent and child, in addition to other specific factors, such as age, temperament, and coping style, were found to predict which child-parent pair is likely to benefit from PPIA.[43,44] Kain and colleagues have performed two randomized controlled trials to assess the value of preoperative preparation.[45,46] In the first study, an extensive preoperative program (OR tour + videotape + child-life preparation), produced limited anxiolytic effects, which were seen only in the preoperative period and did not extend to induction or postoperative recovery.[45] In a more recent study, an ADVANCE program (*A*nxiety reduction, *D*istraction, *V*ideo modeling and education, *A*dding parents, *N*o excessive reassurance, *C*oaching, and *E*xposure/shaping) was compared with three other arms: standard of care, PPIA, and oral midazolam. The ADVANCE program resulted in multiple improved outcomes for children and parents.[46] Children in the ADVANCE group exhibited a lower incidence of emergence delirium, required significantly less analgesia in the recovery room, and were discharged from the recovery room earlier than children in the three other groups.[46] A more recent Brazilian study also showed improvement in anxiety levels and behavior during the postoperative period in children who received preoperative psychological preparation prior to undergoing elective surgery.[40]

### Intraoperative Period

The main controversy surrounding PFCC during the intraoperative period is PPIA. PPIA was an almost natural extension of increased parental participation and presence during critical procedures on their children, including trauma resuscitations, emergency room resuscitations, bedside invasive procedures, and cardiopulmonary resuscitations. Many of these situations also involve the pediatric surgeon. This movement has significantly grown in strength in the last quarter century. Parental presence during these procedures, in many institutions, now occurs routinely. Although there are no research studies that point to a patient benefit if the family is present, there appears to be at least a major psychological benefit to the family. Research suggests that families want to be given the option to be present during invasive and resuscitative procedures, and they often choose that option.[47–49] Those who are present generally report favorable experiences.[47] Parents who witnessed a terminal medical event involving their child in the pediatric intensive care unit (PICU) were less distressed than those who did not and felt that their presence helped them cope with their child's death.[48,49] Family

presence has not been found to prolong time to computed tomography (CT) imaging or to resuscitation completion for pediatric trauma patients.[50] Uninterrupted care can be delivered with the family present.[51] Physicians and nurses have become increasingly comfortable with family presence in critical situations.[47,52–55] Major professional organizations, including the AAP and the American College of Emergency Physicians, have endorsed the practice.[56–58]

However, many do not see PPIA as a natural extension of parental presence during other clinical scenarios. Critics of PPIA cite decreased OR efficiency, additional staffing requirements, increased cost, and possible medico-legal implications as potential arguments against its practice. There are no data to support these arguments. On the other hand, data regarding positive outcomes of PPIA are also mixed. Kain and colleagues reported several randomized trials of PPIA over the past 15 years.[59–63] In the first study, published in 1996, PPIA did not reduce any behavioral or physiologic measures of anxiety during induction.[59] A benefit was seen in specific subgroups of children when cortisol levels were measured, an outcome of questionable clinical significance.[59] In another study, oral midazolam was superior to PPIA in reducing anxiety and increasing compliance of the child during the perioperative period.[60] Interestingly, that study also showed that parents of children in the midazolam group had lower anxiety scores after separation from their children.[60] In a study comparing oral midazolam alone to oral midazolam plus PPIA, children in both arms exhibited similar levels of anxiety.[61] However, parents in the PPIA arm had lower self-reported anxiety scores and higher satisfaction stores.[61] The physiologic effects of PPIA on parents were specifically investigated in another trial, which found that parents in the PPIA arms, regardless of whether a sedative was also given to their child, manifested a significantly higher physiologic stress response during induction (increased heart rate and skin conductance level), than parents in the control arm.[62] The most recent study investigated the presence of one versus two parents during induction.[63] The presence of two parents did not affect observed child anxiety, but reduced parents' self-reported anxiety.[63] Chundamala and colleagues recently published a comprehensive evidence-based review of the effects of PPIA on parent and child anxiety and concluded that, contrary to popular belief, PPIA does not appear to alleviate parents' or children's anxiety.[64] These authors, from Toronto's Hospital for Sick Children, raise the possibility that PPIA may be driven by market forces and hospital competition in the United States. The use of PPIA has certainly grown in the United States.[65] However, the practice is far more frequent in Britain, where support for PPIA is dramatically higher than in the United States among both anesthesiologists and pediatric surgeons.[66,67] In fact, the practice has become so routine in Britain, that some are raising the possibility of parental presence during the surgical procedure.[11] One would be hard pressed to cite the market as the driving force for PPIA in Britain. Chorney and Kain, with practices in very different health care settings (Halifax, Nova Scotia and Orange County, California), argue that the focus on efficacy data has misguided the debate over PPIA.[38] They stress that PPIA is overwhelmingly preferred by parents, increases parental satisfaction, and improves hospital public relations.[38] Some parents may see it as a basic right.

PPIA is an instrument that may work well for many, but not all, families. Medical personnel are therefore encouraged to respect the family's decisions and preferences.[38] There is undoubtedly a strong demand for this option. The number of parents in our practice who are asking for PPIA is exponentially increasing. The demand is particularly strong among parents whose children have undergone prior surgery with or without PPIA.[68] PPIA is therefore not a passing fad, but rather a practice well on its way to becoming a standard of care.

### Postoperative Care

Postoperative care and recovery are facilitated if adequate preoperative preparation is given and a positive intraoperative surgical experience ensues.[38,40,69] A quick reunion with the parents in the recovery room now occurs routinely. Daily, clear updates to the parents of hospitalized children are a must. When pediatric surgery fellows or other house staff are part of a surgical service, a special effort should be made to give the patient and parents clear and nonconflicting information. Inadequate pain management is of utmost concern to the child and parents. This should be addressed appropriately, and preemptively, when possible. If the child is on a treatment protocol or algorithm, the relevant details and end points should be clearly explained to the parents. Support for the parents and the child during recovery at home is also essential. Home health care resources should be mobilized as early as possible to allow the child to continue care at home, when it is deemed appropriate and safe. Clear and detailed discharge instructions should be given both directly and in writing. Some data suggest that many children do not receive optimal pain management at home after day surgery.[70] A follow-up phone call from the surgeon or nurse during the first 72 hours after day surgery is highly appreciated by the parents. In the late 1990s, reports of successful phone follow-up for select pediatric surgical operations, with the intent to provide convenient and cost-effective care, appeared in the literature.[71,72] Following these reports, our service began an active phone follow-up program for the majority of day surgery cases and many simple inpatient cases (e.g., nonperforated appendicitis, pyloric stenosis).[73] This has been extremely popular with parents, because it avoids an unnecessary postoperative visit, while identifying those patients who require or request follow-up. More recently, a 90% satisfaction rate has been reported with a similar strategy.[74]

## COLLABORATION

Collaboration can be best defined as a health care environment that regards the parents and family as health care team members, and not spectators. In fact, the family should be seen as the most consistent and permanent member of the health care team, because nurses, ancillary medical staff, social workers, and even the attending staff surgeon may change from time to time. This concept is often referred to in the literature as *partnership*—the physician and health care team partnering with the family to provide the best care possible to the patient. This is not such a new or modern concept. Surgeons who have practiced in missionary settings or underdeveloped countries will attest to the huge role the family plays in the active medical care of the patient.

Partnerships are formed when the health care team values the information given by parents, actively seeks their input in decisions affecting their child, acknowledges their positions

**TABLE 16-3**

**Montreal Children's Hospital Division of Pediatric General Surgery Pledge to Patients and Families**

| |
|---|
| We will treat every child and family with dignity, compassion, and respect. |
| We will draw on the expertise of the entire team and other hospital services to offer the best care to each child. |
| We will discuss with patients and families all relevant alternatives for treatment. |
| We will serve as advocates for each child within the health care system. |
| We will keep patients and families fully informed of the treatment plan, and address concerns in an open and honest manner. |

**TABLE 16-4**

**PFCC Best Practices in Pediatric Surgery**

| |
|---|
| A commitment to respect the culture, faith, and belief system of each family, while always advocating for the child's best interests |
| A commitment to keeping the patient and family united as long as possible during the perioperative period |
| Inclusion of family advisors as partners in facility design of surgical waiting rooms and perioperative areas |
| Inclusion of family advisors in the review and formulation of surgical documents, including preoperative instructions, consent, and discharge forms |
| Encouragement of families to ask questions, share concerns, and offer feedback to surgeons, anesthesiologists, and surgical staff |
| Open, honest, and continuous sharing with families of procedural risks and safety precautions |
| Provision of information to families on how they can actively partner with staff to reduce risks and optimize outcomes |
| Provision of information to families on pain management and recruitment of their feedback on its efficacy |
| Provision of information to families on the roles and responsibilities of the members of the surgery team, as well as clear instructions on who to contact for questions and concerns |
| Open and honest disclosure of surgical complications and adverse events |

and concerns, and acts on their feedback. The United States Maternal and Child Health Bureau defines a positive family–provider partnership as a core program outcome.[75] Denboba and colleagues found that a sense of partnership between the families of children with special health care needs and their physicians was associated with improved outcomes across a number of important health care measures.[75] However, poverty, minority racial and ethnic status, and absence of health insurance placed families at elevated risk of being without a sense of partnership.[75] An extra effort, therefore, is needed to build partnerships with certain at-risk populations. Partnerships are also created when parents feel that they have full access to the health care team. Parents who desire to meet with the entire tumor board, fetal diagnosis and treatment group, or any other multidisciplinary treatment team, to obtain comprehensive information, should be encouraged and invited. Partnerships can also be integrated into daily patient care. An example comes from Cincinnati Children's Hospital, where families can choose to be part of attending physician rounds.[76] Integration of the family into multidisciplinary rounds was found to require an additional 2.7 minutes per patient and affect the medical decision-making discussion in 90% of cases—an excellent investment![77] Collaboration is particularly important in the long-term care of pediatric surgical patients with congenital anomalies, such as imperforate anus or esophageal atresia, which become lifelong chronic medical conditions after repair. Rahi and colleagues recently offered a detailed and practical account of how a support program for children with a newly diagnosed lifelong disability can be built in collaboration with family, counselors, and health care personnel.[78]

# Putting It All Together: PFCC in Action

Many individual surgeons, surgical practices, and institutions apply the principles of PFCC intuitively. However, an intentional commitment to PFCC can have a transforming effect on pediatric health care. Our hospital, like most children's hospitals, saw itself as a child- and family-friendly hospital. However, after a visit from a national leader and advocate of PFCC in October 2009, the hospital made a firm commitment to examine its practices and traditions. Such examination showed ample potential for growth in PFCC. Specific actions included the formation of a PFCC working group, with representation from all areas of the hospital, stronger collaboration with the hospital's family advisory forum and their inclusion in planning and policy making, the hiring of a PFCC coordinator to act as a liaison between the hospital and families, and taking PFCC issues into account in the design and building of a new hospital. Within our Division of Pediatric General Surgery, we adopted a new mission statement that reflects a strong commitment to PFCC, as well as a pledge to patients and families (Table 16-3). The mission statement and pledge are included in a color brochure that provides core information about our services and our staff, which is given to all families who come in contact with our division. A color chart containing the names and pictures of all members of the pediatric surgical service, including students, residents, and fellows, is also given to all admitted patients so that families are always clear about the roles of each member of the team. Our surgery and anesthesia departments started to investigate the incorporation of PPIA into the OR culture and to explore other ways of enhancing the role of parents in the operative experience.

A list of 10 PFCC best practices, relating to pediatric surgery, is shown in Table 16-4. These are practical steps that can be taken to apply the principles discussed in this chapter. In addition, the Web site of the IPFCC has many additional concrete examples of PFCC in action from children's hospitals throughout the United States that have been leaders in the adoption of PFCC principles and practices.[2] These principles and practices are as important to the psychosocial aspects of pediatric surgical care in the 21st century as evidence-based medicine is to the biological aspects.

***Acknowledgments***

The author is grateful to Juliette Schlucter, who is a parent of two chronically ill children and a patient- and family-centered care consultant, for sharing her experience, inspiring this chapter, and reviewing the manuscript.

*The complete reference list is available online at www.expertconsult.com.*

# Part II

# TRAUMA

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CHAPTER 17

# Injury Prevention

Gina P. Duchossois and Michael L. Nance

*"If a disease were killing our children in the proportions that injuries are, people would be outraged and demand that this killer be stopped."*

**—C. Everett Koop**

Injury presents the greatest threat to life of all diseases in the pediatric population. More children die each year from injury than all other causes combined.[1] More than one in nine children will require medical attention for an injury each year. Many more children will be injured but not require or seek medical care (Fig. 17-1). The economic costs of injury are staggering. In addition to direct costs for care, there is the additional loss of future productivity as well as loss of productivity by parental caregivers who must provide for the injured child. For the year 2000, these costs were estimated to top $130 billion in total costs, with nearly $25 billion due to direct medical costs.[2] The significance of the costs of injury become even more provocative when one considers the potential financial savings that can be realized from injury prevention strategies (Table 17-1).

William Haddon, in the 1970s, reported his classic characterization scheme (the Haddon "matrix") and approach to injury prevention.[3] This system argued against the traditional idea that injury was an accident, leaving the burden of prevention on the individual. Rather, he suggested that injuries result from predictable events and thus offer an opportunity for systematic intervention and injury reduction. This strategy, which considers injury in pre-event, event, and post-event phases, each offering opportunity for intervention, is still relevant today (Table 17-2). Pre-event (primary) prevention measures seek to prevent the event leading to the injury through education, intervention, and/or safety design measures. For example, crosswalks and count-down timers are effective safety engineering actions to make our roadways safer for pedestrians. Measures aimed at altering the event (secondary) seek to lessen the severity of an injury if it occurs. For example, child safety seats are not designed to prevent a motor vehicle collision but rather minimize (or eliminate) the severity of any injuries if a collision occurs. Finally, post-event (tertiary) injury prevention is the strategy used by most health care providers. It seeks to mitigate the consequences of the injury once it has occurred. For example, management of intractable intracranial hypertension through hemicraniectomy is tertiary prevention. Advances in health care have led to marked improvements in outcome for children with traumatic injuries. However, quite clearly, primary prevention, averting the event altogether, is the optimal approach. Haddon provided 10 countermeasures to use when addressing the prevention of a particular injury (Table 17-3).[4] These concepts can be applied to most any injury and help break down the problem into potentially actionable steps.

## Prevention Priorities

Injury prevention resources are finite. As such, priorities for these prevention efforts must be established. These priorities may vary depending on the individual, the community, or perhaps the nation interested in prevention. A variety of factors are integral to the decisions regarding how best to deploy these limited resources. At the individual level, one might favor efforts to minimize in-home injury and "child-proof" the surroundings. A community might work toward pedestrian safety efforts in neighborhoods in which such injuries have been predominant. Finally, a nation (e.g., the United States) might focus efforts to reduce motor vehicle–related injuries, the leading cause of injury death. Simply counting the number of deaths from a particular injury mechanism may not provide an accurate or adequate representation of the burden of injury (by mechanism) in the geographic area of study. For instance, an injury mechanism that is highly lethal (e.g., hanging) but infrequent may not be an optimal prevention target. Nor might efforts to reduce an injury that is common but usually of limited severity (e.g., assault) be the ideal strategy. An injury that is both common and severe would, in most settings, represent the ideal target for mitigation efforts. To help define such injuries, Haider and colleagues used an injury prevention priority score.[5] This calculation takes into account both the frequency of an injury and the mean severity of an injury by mechanism. In a comparison of pediatric populations from two geographically distinct trauma centers, they noted differences in injury patterns. In the inner city, auto/pedestrian injuries achieved the highest priority score, while in the community center, motor vehicle–related injuries ranked highest. Wiebe and colleagues applied this methodology to a national trauma center population and demonstrated that motor vehicle–related injuries, falls, and firearm-related

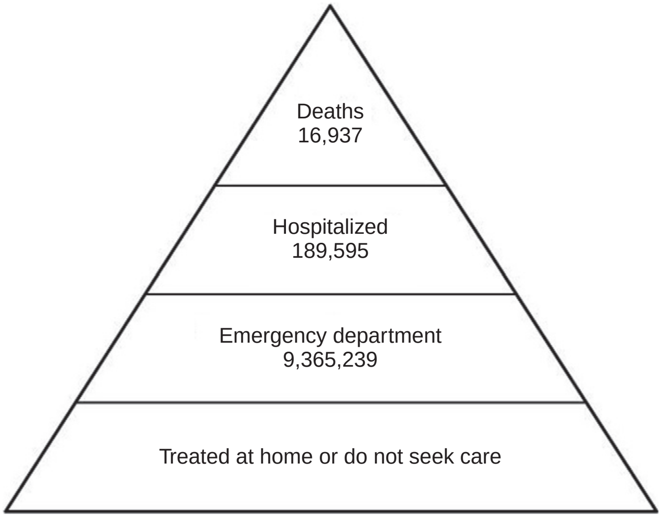


FIGURE 17-1 Injury pyramid demonstrating fatal injuries, injuries requiring hospitalization, and injuries resulting in an emergency department visit for children age 0 to 19 years, 2007. (Data from National Center for Injury Prevention and Control.[1])

TABLE17-1
**Potential Financial Savings from Selected Injury Prevention Initiatives**

| *Expenditure of $1 Each on:* | *Savings ($)* |
|---|---|
| Smoke alarms | 65 |
| Child restraints | 29 |
| Bicycle helmets | 29 |
| Prevention counseling by pediatricians | 10 |
| Poison control services | 7 |
| Road safety improvements | 3 |

From Peden M, OyegbiteK, Ozanne-Smith J, et al: World report on child injury prevention. Geneva, Switzerland, World Health Organization, 2004. Available at http://www.who.int/violence_injury_prevention/child/injury/world_report/en/index.html. Accessed November 12, 2010.

injuries, respectively, were the highest ranking injury mechanisms (Table 17-4).[7] In addition, Wiebe and colleagues also created additional scores that take into account the relative mortality of an injury mechanism (mortality priority score), the cost of an injury (hospital cost priority score), and the years of productive life lost (years of productive life lost priority score) to further characterize the burden of a particular injury. As suggested by Haider in his original publication, the methodology is easily applied to individual populations, such as that of a trauma center or a county or a state, to help determine how best to deploy prevention

TABLE 17-3
**Haddon Measures to Combat Injury and Their Application to Firearm Injury**

| *Haddon Countermeasure* | *As Applied to Firearm Injury Prevention* |
|---|---|
| Prevent the creation of the hazard in the first place | Eliminate handguns |
| Reduce the amount of the hazard brought into being | Limit the number of handguns allowed to be sold or purchased |
| Prevent the release of the hazard that already exists | Install locks on handguns |
| Modify the release of the hazard that already exists | Eliminate automatic handguns |
| Separate, in time and space, the hazard and that which is to be protected | Store handguns only at gun clubs rather than at home |
| Separate, by material barrier, the hazard and that which is to be protected | Keep guns in locked containers |
| Modify the relevant basic qualities of the hazard | Personalize guns so they can be fired only by the owner |
| Make that to be protected more resistant to damage from the hazard | Create and market bullet-proof garments |
| Counter damage already done by the hazard | Provide good access to emergency care in the prehospital period |
| Stabilize, repair, and rehabilitate the object of the hazard | Provide high-quality trauma care in hospitals |

TABLE 17-2
**Haddon Matrix Applied to Motor Vehicle Crashes in Children**

| | *Child Factors* | *Vehicle and Safety Equipment* | *Physical Environment* | *Socioeconomic Environment* |
|---|---|---|---|---|
| Pre-event | Age; gender; lack of supervision; risk-taking; impulsive behavior; disobedience; lack of police enforcement | Lack of roadworthiness of vehicle; poor lighting; poor state of brakes; speeding; overloading | Poor road design; lack of public transport; no enforcement of speed limits; no safety barriers; lack of alcohol laws; poor infrastructure for pedestrian safety | Poverty; single-parent family; large family size; poor maternal education; lack of awareness of risks among caregivers, childcare providers, and educators |
| Event | Size and physical development of child; lack of equipment to protect occupants, or equipment improperly used; underlying conditions in child | Child restraints and seat belts not fitted or incorrectly used; bicycle and motorcycle helmets not used; poor design of vehicle for protection in crashes; no rollover protection | Roadside objects such as trees and poles | Lack of safety culture in the car and on the road |
| Post-event | Child's lack of resilience; child's general condition; lack of access to appropriate health care; postinjury complications | Difficult access to victim; lack of trained health care and rescue workers | Lack of availability of adequate pre-hospital care, acute care and rehabilitation | Lack of culture of supporting injured people; no first aid given at scene |

From Peden M, Oyegbite K, Ozanne-Smith J, et al: World report on child injury prevention. Geneva, Switzerland, World Health Organization, 2004. Available at http://www.who.int/violence_injury_prevention/child/injury/world_report/en/index.html. Accessed November 12, 2010.

**TABLE 17-4**

**Incidence and Characteristics of 13 Injury Mechanisms Presenting to United States Trauma Centers, 2000-2004, and Priority Scores and Priority Rankings by Injury Mechanism**

| *Mechanism* | *Incidence and Characteristics* | | | | | | *Priority Scores and Rankings* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **Mortality** | | **Injury Severity** | | **Hospital Charges** | | **Years of Life Lost** | |
| | *N* | Median Age (Years) | Median ISS | Median Charges | Median YPLL | Mortality (%) | Mort PS§ | Rank | IPPS* | Rank | Charge PS† | Rank | YPLL PS‡ | Rank |
| Motor vehicle traffic | 378,029 | 32 | 9 | $15,941 | 37 | 5.0 | 69.7 | 1 | 72.0 | 1 | 74.0 | 1 | 74.6 | 1 |
| Suffocation | 1,314 | 28 | 1 | $12,754 | 48 | 23.0 | 63.4 | 2 | 38.5 | 12 | 48.5 | 6 | 53.3 | 4 |
| Firearm | 53,146 | 26 | 9 | $14,484 | 48 | 16.2 | 59.5 | 3 | 55.5 | 3 | 54.4 | 4 | 57.4 | 3 |
| Fall | 237,500 | 53 | 9 | $12,922 | 10 | 3.5 | 58.4 | 4 | 64.9 | 2 | 61.1 | 2 | 42.9 | 11 |
| Drowning/ submersion | 945 | 20 | 4 | $10,777 | 56 | 16.5 | 56.2 | 5 | 43.9 | 10 | 44.9 | 10 | 59.4 | 2 |
| Pedestrian, other | 3,100 | 32 | 9 | $15,936 | 36 | 5.9 | 44.8 | 6 | 53.0 | 5 | 54.4 | 3 | 44.3 | 9 |
| Transport, other | 45,151 | 29 | 9 | $14,240 | 42 | 2.9 | 44.5 | 7 | 55.1 | 4 | 53.5 | 5 | 51.2 | 5 |
| Fire/burn | 17,511 | 28 | 2 | $7,412 | 23 | 4.6 | 44.4 | 8 | 41.2 | 11 | 39.6 | 12 | 35.5 | 13 |
| Struck by, against | 61,962 | 30 | 5 | $10,367 | 35 | 1.5 | 44.1 | 9 | 48.8 | 6 | 47.3 | 8 | 48.2 | 7 |
| Cut/pierce | 40,574 | 31 | 4 | $10,477 | 42 | 1.9 | 43.0 | 10 | 45.9 | 8 | 46.4 | 9 | 51.8 | 6 |
| Machinery | 12,221 | 40 | 4 | $12,442 | 31 | 1.8 | 41.0 | 11 | 44.5 | 9 | 48.5 | 7 | 41.2 | 12 |
| Poisoning | 1,041 | 32 | 1 | $5,201 | 38 | 2.5 | 41.0 | 12 | 38.5 | 13 | 34.7 | 13 | 45.7 | 8 |
| Pedal cyclist, other | 13,934 | 17 | 6 | $9,277 | 34 | 0.9 | 40.1 | 13 | 48.2 | 7 | 42.8 | 11 | 43.6 | 10 |

From Wiebe DJ, Nance ML, Branas CC: Determining objective injury prevention strategies. Inj Prev 2005;12:347-350.
*Injury prevention priority score.
†Charge priority score.
‡Years potential life lost priority score.
§Mortality priority score.
Note: data based on trauma centers participating in the National Trauma Data Bank surveillance system.
ISS, injury severity score.

resources. Using data to better understand the scope of the problem is essential to designing effective prevention strategies.

## INJURY PREVENTION DESIGN STRATEGIES

Effecting behavior change is always a difficult task to accomplish in injury prevention. As the Haddon matrix suggests, a multifaceted approach is necessary when designing effective injury prevention programs. It is important to understand the injury problem, associated risk factors, and the target population. The most successful prevention strategies are those that combine comprehensive methods and models. Most prevention models employ a variety of methods, often referred to as the three "Es": education, engineering (modification of the environment), and enforcement (policy change).[8] The fourth "E" that is often incorporated into prevention strategies is encouragement (e.g., economic incentives).

Education is the most common prevention strategy employed, with the goal of affecting behavioral modification. It is hoped that with understanding of risk will come behavior change. However, increased knowledge through education does not always translate readily into a behavior change. For example, although an adult may realize that using a crosswalk is the safest way to cross a busy street, crossing midblock is much quicker. This strategy incorrectly assumes the public will voluntarily and preferentially adopt a safe behavior.

Enforcement (policy change) uses the force of the law to increase compliance and change behavior. This strategy is most effective when combined with education. There are many studies highlighting the positive impact that laws can have on injury prevention. As an example, the use of safety belts in motor vehicles increased by 15% after law enforcement agencies began issuing traffic citations.[9] Government regulations and industries have done much to offset poor behavior choices in order to save lives. Safety features have been introduced throughout our everyday lives, from air bags and crumple zones in cars to child-resistant caps on medicines to fire-resistant clothing for children. Other legislation requires an active response from the end user, such as the installation of smoke alarms in the home or wearing a bicycle helmet. Legislation is generally regarded as one of the most powerful tools in injury prevention, and has affected a positive behavior change.

Engineering (modification of the environment or product) is often used because this approach eliminates the need to change behavior in the individual. Effective engineering

modifications for pedestrians include the introduction of sidewalks, barriers, and pedestrian signs. Engineering is often the most expensive strategy and at times even cost prohibitive. To decrease the likelihood of crossing midblock, a roadway barrier can be put in place to eliminate crossing midblock. The cost to a governmental agency or to a product manufacturer must be weighed against the potential societal benefit in determining efficacy of such prevention strategies.

## SELECTED INJURY PREVENTION INITIATIVES

### Child Passenger Safety

One of the most dramatic examples of the efficacy of injury prevention strategies is that of child passenger safety efforts (Figure 17-2). Motor vehicle crashes are the leading cause of death for ages 3 to 14 in the United States. However, research has shown that lap/shoulder seat belts and child safety seats, when used, save lives. Vehicle seat belts reduce the risk of fatal injury to front seat occupants of passenger cars by 45%, while child safety seats reduce fatal injury by 71% for infants and 54% for toddlers in passenger cars.[10] The challenge is to make sure every passenger (regardless of age) is properly secured, every single ride.

Studies suggest that efforts to reduce injury risk to children in a motor vehicle should promote use of child restraint systems through a combination of education, distribution programs, and appropriate laws governing use.[11] Pierce and colleagues illustrate the importance of providing ongoing education combined with legislation and enforcement during a booster seat giveaway program in a Head Start program.[12] The program measured the knowledge level of Head Start providers, parents, and students regarding booster seats. It combined education along with the provision of age-appropriate restraints and direct observation following the program. The project was successful in increasing the use of booster seats, although the majority (66%), while restrained, were done so suboptimally. Despite the demonstrated efficacy, child passenger restraint misuse and inappropriate use is common (>72%) and offers additional room for prevention efforts.[13]

In a systematic review of five different interventions designed to increase child safety seat use, Zaza and colleagues demonstrated that the most successful interventions were those that did not stand alone but rather were multifactorial.[14] There was insufficient evidence for education-only programs. However, they identified strong evidence for effectiveness of child safety seat laws and distribution plus education programs. Also, community-wide information plus enhanced enforcement campaigns and incentive plus education programs had sufficient evidence of effectiveness.[14] Based on these findings, as well as other evidence-based programs designed to reduce injury risk to children in motor vehicles, efforts should promote use of child restraint systems through improved laws combined with education and disbursement programs.

### Fire Safety

Because the causes for residential fires are multifactorial, efforts to prevent fire-related morbidity and mortality should also consider multiple approaches. A smoke alarm is arguably the single most important piece of safety equipment to prevent fire-related morbidity and mortality. The risk of dying in a residential fire is cut in half when a functioning smoke alarm is present.[15] Two efforts thought to be essential in reducing fire-related injury are the use of smoke alarms and identifying an escape plan for use in the event of a fire; both require action on the part of the resident. Previous research has demonstrated that the most effective and cost-efficient method to distribute smoke alarms is through direct home visits.[16] Harvey and colleagues have proven that direct installation is much more effective than voucher distribution for a free fire alarm.[17]

There are other passive preventive techniques that are also as effective, such as flame-resistant clothing for children. Half of the persons who start reported fires by playing are 5 years of age and younger. Most child-playing home fires are started with matches or lighters.[18] Legislatively, there are a variety of laws and standards that are designed to save lives, such as the requirement of smoke alarms on every level of the home and in every bedroom, sprinkler systems in some dwellings, and cigarette lighter standards. The U.S. Consumer Product

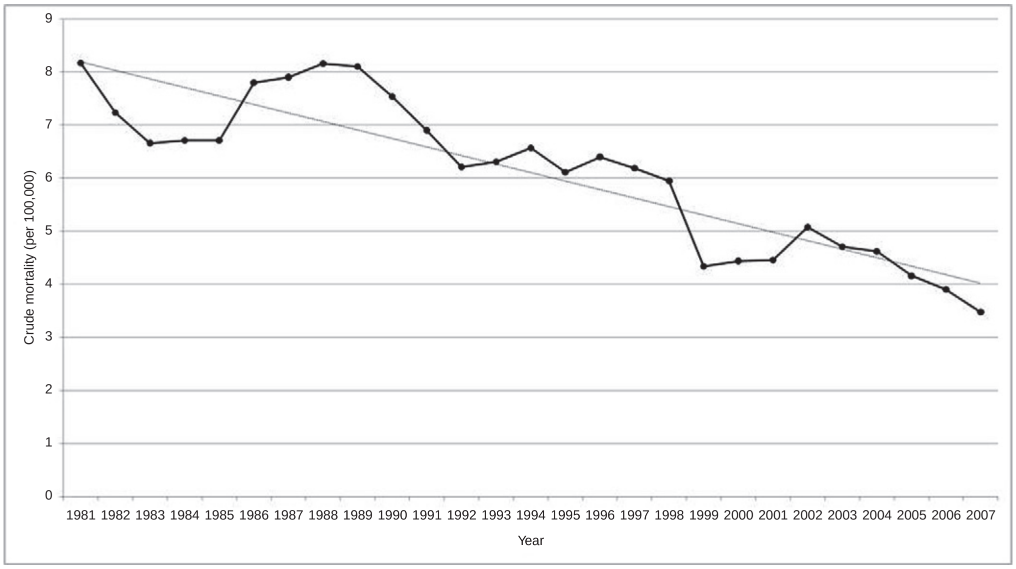


**FIGURE 17-2** Decline in crude mortality rate for child occupants (age 0 to 19 years) in motor vehicle crashes for the period 1981 to 2007. (Data from National Center for Injury Prevention and Control.[1])

Safety Commission has issued a safety standard for cigarette lighters, which requires that disposable cigarette lighters be resistant to operation by children younger than the age of 5. In an analysis of this standard, it has been proven to reduce fire injuries, deaths, and property loss by children playing with cigarette lighters and can be expected to prevent additional fire losses in subsequent years.[19] Some states are now enacting novelty cigarette lighter legislation to protect against lighters that are being mistaken for toys. Continued efforts are necessary to maximize prevention efforts.

### Firearm Storage

Firearm-related injuries have posed significant prevention challenges. With one of the highest case fatality rates of all injury mechanisms, prevention of the initial exposure is vital. However, with more than 250,000,000 firearms in circulation in the United States, that task is daunting.[20] The presence of a firearm in the home has been shown to increase the risk of unintentional firearm death (3.7-fold), suicide (3.4-fold), and homicide death (1.4-fold) versus households without firearms.[21,22] The effectiveness of educational programs geared to children and firearm use have been questioned. In a classical behavioral study, Hardy and colleagues demonstrated persistence of curious behaviors among children who encountered a firearm despite having undergone prior gun safety education.[23] Efforts to limit access to firearms by children have also had mixed results. A survey of parents visiting pediatrics practices revealed unsafe gun storage practices in 70% (gun unlocked 61%, gun loaded 15%, gun unlocked/loaded 7%, gun locked/unloaded 30%) of the homes.[24] The outcome of strategies geared toward parental firearm storage behaviors was summarized by McGee and colleagues, who did note an improvement in reported storage practices following counseling and education.[25] However, evidence to demonstrate a reduction in injury related to improved safety measures is limited. Grossman and colleagues were able to demonstrate that several factors were associated with a protective effect when examining the risk of youth unintentional and suicide firearm injuries: keeping a gun locked and unloaded, and storing ammunition locked and in a separate location.[26] Although firearm injury mitigation strategies have been of uncertain success, continued efforts are warranted given the ongoing risks that exist.

### Helmet Use

Bicycle riding is enjoyed by millions of children and adults every day. Learning to master the technical challenges of a two-wheeled bicycle is a rite of passage for most children. However, because of its popularity and widespread use, bicycle riding is also a common source of injury in the pediatric population. Helmet use has long been advocated to mitigate the risk of serious head injury. Helmet use has been demonstrated to reduce head injury of all types, serious head injury, and facial injury related to bicycle collisions.[27–29]

Both educational initiatives as well as legislative mandates have been used to encourage routine helmet use among pediatric riders. Educational programs promoting use of bicycle helmets have been shown to increase their routine use. Rivara and colleagues demonstrated an increase in helmet use from 5.5% baseline to 40.2% after introduction of a community-wide bicycle helmet campaign.[30] At the same time, the rate of bicycle-related head injuries decreased by 67%. The effects of bicycle helmet use campaigns seem to be most effective in the younger-aged children and in the higher socioeconomic status populations.[31,32] Parkin and colleagues demonstrated the efficacy of legislative approaches to improving helmet use in children, with a significantly increased observed rate of use from 46% to 68%.[33] Interestingly, the least impact of the legislation was noted in the highest socioeconomic groups. However, these groups also had the highest rates of baseline use, suggesting perhaps the efficacy of prior educational campaigns. A side benefit of mandatory laws may be heightened awareness of riders in areas not covered by helmet use laws. For example, in a Canadian study, the risk of bicycle-related head injury declined 45% in areas with mandatory use but also by 27% in areas without mandated use.[34]

Although a less common issue in the pediatric population, motorcycle helmet use has similarly been shown to reduce the incidence of serious head injury and death related to motorcycle accidents. A Cochrane collaborative reported a reduction in mortality of 42% and serious head injury of 69%.[35] Evidence was lacking regarding helmet use and risk of facial injuries. Mandatory motorcycle helmet use laws frequently are met with stiff opposition from riders, but such laws save lives and reduce serious head injuries.[36]

### Pedestrian Injury

Pedestrian injuries in children resulted in 573 deaths (2007) and more than 47,000 injuries (2009) in the United States.[1] The burden of injury globally is far greater where pedestrians represent the largest category of child road traffic casualties.[37] A Cochrane Collaboration review demonstrated the effectiveness of pedestrian education programs geared toward children.[38] Programs included direct education of the child by professionals as well as use of the parents as educators. An improvement in knowledge was exhibited along with changes in baseline pedestrian behaviors, but a correlation with risk reduction was not possible. Most studies have been carried out in developed nations. As pedestrian injuries are increasing in developing nations along with an increase in motor vehicle use, effective prevention strategies are warranted. Somewhat paradoxically, most pedestrian injuries in children occur in optimal driving conditions (daylight hours, dry road conditions, no adverse weather conditions).[39] The majority of child pedestrians struck were crossing the street at the time of injury, frequently obscured by an obstacle.[39,40]

Engineering modifications to vehicles offer tremendous hope. Improving sight lines, optimizing visualization of the area surrounding the vehicle (through mirror placement and use of rear-facing cameras), and design changes to mitigate energy transfer at common impact points (e.g., front bumper) may reduce the burden of injury.[41] Efforts to change the environment, such as “traffic calming” techniques, have demonstrated efficacy.[42,43] The calming measures might include the use of speed humps, lower posted speed limits, traffic circles, installation or enhancement of crosswalks, and use of crossing aids.

### Poisoning

Drug overdose death rates in the United States have never been higher. Rates of unintended ingestions have increased roughly fivefold since 1990, a leading cause of death in the pediatric population.[44] In addition, the Drug Abuse Warning Network (DAWN) reports the number of emergency

department (ED) visits for legal drugs is now comparable to visits from illegal drugs.[45] Most fatal poisonings in the United States are from drug misuse (i.e., overdose). Overdose may include attempts at self-harm (suicide), assault (intentional), and accidental ingestion (unintentional).[44]

Among children, ED visits for medication poisonings are most common in children less than 6 years of age.[46] Emergency department visits for medication poisonings are twice as common as poisonings from other household products.[47] One of the most effective injury prevention initiatives in poison prevention was the introduction of child-resistant packaging for aspirin and oral prescription medicine that went into effect in the early 1970s.[48]

For children, caustic agents such as household cleaners that are marked with clear warning labels are not the only items in the home that can be dangerous to children. Everyday items such as cleaning supplies and medicines can be poisonous as well and should be kept out of the reach of children. The national poison control hotline (800-222-1222) provides parents and practitioners with readily accessible information about the toxicity and treatments for specific ingestions.

## Measuring Success (Programmatic Evaluation)

Measuring the success of an injury prevention program or prevention initiative is imperative. There are many injury prevention programs in the community that appear to be effective. However, without adequate evaluation of the efforts, there is no way to verify if a program is actually achieving the goal of injury mitigation.

The most important aspect of evaluation is an adequate measurement of the problem conducted before, during, and after the intervention. The evaluation process should be dynamic. Assessment is started early, immediately after a program idea is conceived, and should continue through the intervention phase until the program is complete, when one determines whether the program has met its overall goal. In some cases, evaluation may continue for years after the intervention is complete to assess the durability of the desired outcome.

Evaluation is also critical to prove to funding agencies that their support is making a difference. A successful evaluation can also be used to strengthen funding proposals and to continue or replicate the program in other areas. A program that has rigorous, scientifically proven success is much more likely to receive continued funding. The same standards are necessary to publish the work in professional journals and disseminate prevention ideas to professionals in other communities.

Evaluation has four essential stages that are intertwined throughout the planning and intervention phase of a program. These stages are formative, process, impact, and outcome evaluation.[49] A well-designed formative evaluation will give the program a better chance at success, along with elucidating areas of improvement. In the formative stage, a targeted issue is identified (e.g., bicycle helmet use to lessen head injury) and may include an assessment of existing resources and deficiencies. During this stage, it is important to identify barriers to success (e.g., age, access to target population, education). Inclusion of community stakeholders at this stage increases the likelihood of long-term success.

Through process evaluation, the second stage, a plan is formulated to measure whether or not the program is reaching the desired audience. This stage typically requires documentation of the number of people reached during the educational or interventional program, for instance, the number of bicycle helmets distributed or the number of students taught bicycle safety. Such data will provide the foundation for sound assessment of the program.

Impact evaluation is a measure of how well the program is progressing toward its goals. It is a measurement of knowledge, attitudes, and beliefs. This assessment may be through direct observation of a particular behavior, or perhaps though survey or questionnaire. Preintervention and postintervention data collection (e.g., observed bicycle helmet use) will provide insight regarding the success of a program.

The final phase, outcome evaluation, measures whether or not the program met its goal of decreasing incidence of injury, morbidity, and/or mortality. Demonstrating long-term success (beyond the intervention stages) is ideal, but such study can be time consuming and resource intensive. However, demonstration of sustained injury reduction is likely to lead to dissemination of practices and ongoing funding.

Injury is the leading cause of death and disability in the pediatric population. Although trauma systems have evolved to provide optimal care, prevention is the preferred approach. Prevention strategies should be tailored to the target population and studied to ensure efficacy. For additional Internet-based injury prevention resources, see Table 17-5.

**TABLE 17-5**
**Selected Internet Resources for Injury Prevention**

| | |
|---|---|
| The American Association of Poison Control Centers | www.aapcc.org |
| National Fire Protection Association | www.nfpa.org |
| Safe Kids Worldwide | www.safekids.org |
| Centers for Disease Control and Prevention | www.cdc.gov |
| National Center for Injury Prevention and Control | www.cdc.gov/HomeandRecreationalSafety/Poisoning/index.html |
| Consumer Product Safety Commission | www.cpsc.gov |

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 18

# Infants and Children as Accident Victims and Their Emergency Management

Jeffrey R. Lukish and Martin R. Eichelberger

## Epidemiology of Childhood Injury

Preventable injuries take an enormous financial, emotional, and social toll on the injured children and their families, but also on society as a whole. Worldwide, childhood injuries are a growing problem. Every year, approximately 875,000 children are killed, and nonfatal injuries affect the lives of between 10 million and 30 million more globally (Fig. 18-1).[1] In the United States, unintentional injury is the leading cause of death among children ages 18 and younger, claiming more than 12,000 child lives annually, or an average of 30 children each day. In addition to the deaths, there were 9.2 million medical visits for unintentional injury among U.S. children, accounting for 151,319 hospitalizations.[2] More than 16% of all hospitalizations for unintentional injuries among children result in permanent disability.[3]

The unintentional injury fatality rate among children ages 14 years and younger declined 45% in the United States since 1987. Despite this decline, unintentional injury remains the leading cause of death among children ages 1 to 14 years in the United States. In fact, 5,162 children ages 14 years and younger died in 2005 from an unintentional injury, and 6,253,661 emergency room visits for unintentional injuries in this age group occurred in 2006.[4] From 2000 to 2005, the leading cause of fatal unintentional injury among children was transportation-related followed by drowning and airway obstruction injury. Falls were the leading cause of nonfatal, hospital emergency room–treated childhood injury and accounted for 2.8 million visits in 2005.[1]

Leading causes of unintentional injury-related death vary according to a child's age and are dependent on developmental abilities and exposure to potential hazards, in addition to parental perceptions of a child's abilities and injury risk. Falls were the leading cause of nonfatal injury for all age groups less than 15 years. The least progress in the injury death rate decline was among infants less than 1 year of age, who had a decline of only 10%, compared with children in the age groups 1 to 4 years (42%), 5 to 9 years (42%), and 10 to 14 years (40%). Children less than 1 year of age have the highest rate of unintentional injury-related death, with a rate more than twice that of all children. Airway obstruction is the leading killer in this age group. In children, ages 1 to 4 years of age, drowning was the leading cause of injury death followed by transportation-related injury. The lowest rate of unintentional death among children less than 14 years of age is in the group of children 5 to 9 years of age. The most common cause of death in this age group and those children aged 10 to 14 years was motor vehicle occupant injury (Fig. 18-2).[2]

In all age groups, male children are at higher risk for unintentional injury than females. This can be attributed to a variety of factors, including biology (differences in temperament), exposure to risky behavior, gender socialization, and cognitive differences.[3] Race and ethnicity are also important factors in the risk for unintentional injury in children. American Indian and Native Alaskan children have the highest unintentional injury death rate at 15.3 per 100,000, and Asian or Pacific Islanders have the lowest fatality rate at 4.24 per 100,000. African-American and white children have approximately the same fatality rate, which has declined 44% and 48%, respectively, in these groups since 1987. In 1990, Hispanic and non-Hispanic children had similar fatality rates from unintentional injury at approximately 12.11 and 12.48 per 100,000, respectively. Since then, the fatality rate has declined by nearly 40 percent for Hispanic children and only 30 percent for non-Hispanic children. In 2005, 4,229 non-Hispanic children and 922 Hispanic children in the United States died from unintentional injuries. Although the number of fatal injuries among Hispanic children increased, the rate of injuries declined because of the increased population size. These racial and ethnic disparities have more to do with economic conditions than with biologic differences, because living in impoverished communities is a primary predictor of injury. Fatality rates from unintentional injury declined in each of the four regions of

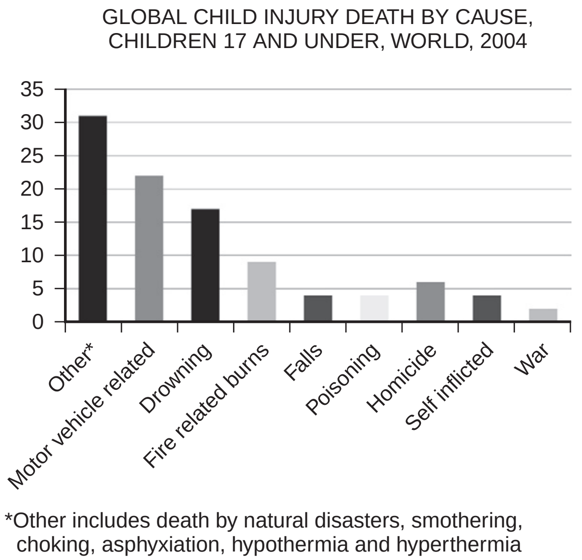


**FIGURE 18-1** Percentage of fatal injuries in children 17 years of age and younger worldwide in 2004. (From Peden MM, UNICEF, World Health Organization: Geneva, Switzerland, World Health Organization, 2008.)

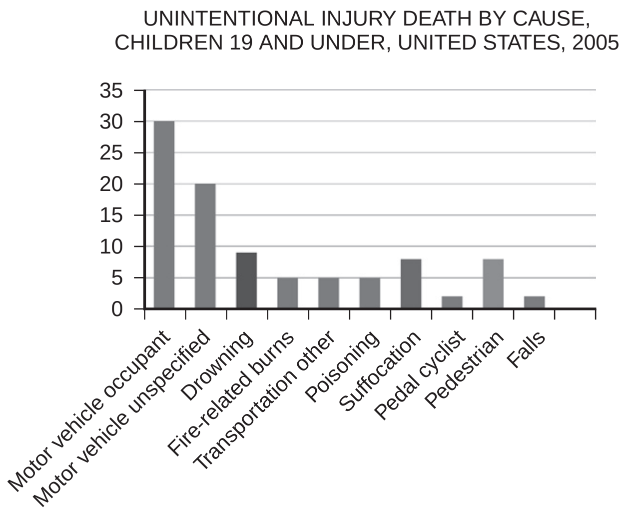


**FIGURE 18-2** Percentage of unintentional injury death in children 19 years of age and younger in the United States from 2000 to 2005. (From Borse NN, Gilchrist J, Dellinger AM, et al: CDC Childhood Injury Report: Patterns of unintentional injuries among 0-19 year olds in the United States, 2000-2006. Atlanta, Ga, Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2008.)

the United States between 1987 and 2005. The largest decrease, almost 60%, was in the Northeast, while the Midwest had the smallest decrease, 40%. Since 1987, the South has consistently had the highest rate of fatality, 10 per 100,000 in 2005, and the Northeast has had the lowest, 4.56 per 100,000. Geographic differences in injury fatality rates reflect demographic differences and different levels of exposure to hazardous activities. At the state level, rates of unintentional injury fatality tend to be highest in the South, potentially because of large rural populations with high rates of poverty and limited access to trauma care. Overall, states with the lowest injury death rates were in the Northeast. Fire and burn death rates were highest in some of the southern states. Death rates from transportation-

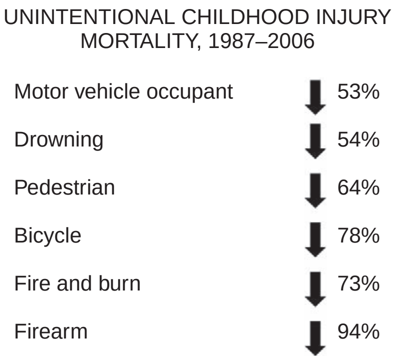


**FIGURE 18-3** Percentage decrease of unintentional injury mortality in children 19 years of age and younger in the United States from 1987 to 2006. (From Wallace AL, Cody BE, Mickalide AD: Report to the Nation: Trends in unintentional childhood injury mortality and parental views. Washington, DC, National Safe Kids Campaign, April 2008.)

related injuries were highest in some southern states and some states of the upper plains, while the lowest rates occurred in states in the northeast region.[1,4]

Over the last 20 years there has been a dramatic reduction in childhood injury death (Fig. 18-3). These extraordinary decreases in the injury death rate are due to multifaceted prevention strategies.

Intentional injury results in a fatal outcome from homicide, child abuse, or suicide. National and state efforts in this regard have led to continued reductions, and now these deaths represent a much smaller percentage of fatalities in children in the United States. Recognition of this intent requires referral to the child protection service for assessment. The resuscitation of these children is frequently a challenge, because abuse may be chronic, which results in a child with a limited physiologic reserve (refer to Chapter 27 on child abuse).[4]

## Resuscitation and Impact on Outcome

Resuscitation of the injured child includes the actions necessary to reverse and control the sudden alterations in physiologic homeostasis that occur as the result of injury. Children are remarkably resilient; however, the initial period of stability has been shown to be significantly shorter as age decreases.[5] Therefore, resuscitation is not complete until injuries have been definitively treated and the child displays physiologic stability without continued intervention.

Differences between children and adults with respect to patterns of injury, physiologic presentation, and management are important. Physicians who treat injured children must recognize and understand the important distinctions so that the resuscitation process addresses the special needs of the child.

The principle of a trimodal pattern of trauma-related mortality and morbidity in adults must be modified for children. In the trimodal model, the first group of injured children dies very rapidly after injury, within seconds or minutes, because of injuries to the central or peripheral nervous system and the central vasculature. Survival can only be improved in this group through prevention efforts, such as education, social awareness, and behavior modification. A second peak occurs from minutes to hours after the injury and is due to mass lesions in the central nervous system (CNS) (usually subdural

and epidural hematomas), solid organ injury, or collection of fluid in the pleural and pericardial space. These are the specific injuries that require rapid identification and treatment and are the focus of the advanced trauma life support (ATLS) protocol. Although initial physiologic compensation may have been sufficient to achieve some temporary accommodation, progressive dysfunction and exhausted reserves bring about a critical impairment of oxygen delivery and the child's eventual demise. Advances in the aggressive and systematic delivery of emergency medical services (EMSC) for children have a salutary effect upon preventable death in children. A third mortality peak occurs days to weeks after the initial injury and is the result of complications of injury, such as sepsis and systemic inflammatory response syndrome, leading to multiple organ failure syndrome.[6] This late peak in trauma-related mortality is less frequent in younger children.

# Resuscitation Principles

## PREHOSPITAL CARE

Systematic management following an injury to a child is essential to survival. The resuscitation process begins when emergency transport personnel first encounter the child in the field. The fate of any given child can turn on the decisions and interventions that transpire during these first crucial moments. In general, children fare worse than adults in the out-of-hospital phase of resuscitation. The injury-adjusted death rate for children is twice that of adults. Similarly, the survival rate for out-of-hospital cardiac arrest in children is only half that of adults.[7] Although part of this discrepancy results from the different causes of cardiac arrest in children and adults, unfamiliarity and inadequate training with children contributes to poor outcome. The failure rate for resuscitation interventions in the field is twice as high in children as adults; the failure rate for prehospital endotracheal intubation of children is close to 50%.[8] Unfamiliarity with pediatric resuscitation skills is understandable; trauma is the most common indication for pediatric ambulance transport, but accounts for less than 10% of total paramedic patient volume in most metropolitan areas.

The most important objectives for emergency personnel in the field are

- Recognition and treatment of immediate life-threatening dysfunction
- Assessment of the mechanism of trauma and extent of injuries
- Documentation of pertinent medical data
- Triage to the appropriate-level pediatric trauma facility

Add to these the additional challenges of comforting a terrified and hurt child, as well as a distraught parent, and the paramedic's task becomes formidable. Consequently, prehospital personnel function best by adopting strict protocols to treat the injured child. The priorities and techniques associated with pediatric field resuscitation are similar to those for emergency department care.

## PRIMARY SURVEY AND TREATMENT OF LIFE-THREATENING INJURIES

When the injured child encounters medical personnel, whether in the field or in the emergency room, events transpire in a rapid sequence that is dictated by a systematic protocol to recognize and treat acute injuries. This approach is designed to standardize diagnostic and treatment decisions so that individual variations in patterns of injury do not distract caregivers from recognizing and treating subtle injuries that can have a profound impact upon outcome. This systematic framework comprises a primary survey, a resuscitation phase, and a definitive secondary survey. The primary survey is the initial process of identifying and temporizing injuries that are potentially life-threatening and follows the "ABCDE" sequence (*A*irway, *B*reathing, *C*irculation, *D*isability, and *E*xposure). The system relies upon simple observations to assess physiologic derangement and immediate intervention to prevent death.

### Airway and Cervical Spine Control

Provision of airway control is perhaps the least controversial of all priorities in pediatric trauma management. The inability to establish and maintain a child's airway, leading to hypoxia and inadequate ventilation, continues to be a common cause of cardiorespiratory arrest and death. Significant clinical hypoxia is suspected when oxygen saturation is less than 95%.

Assessment of the airway includes inspection of the oral cavity; manual removal of debris, loose teeth, and soft tissue fragments; and aspiration of blood and secretions with mechanical suction. If a child is neurologically intact, phonates normally, and is ventilating without stridor or distress, invasive airway management is unnecessary. Airway patency can be improved in the spontaneously breathing child by use of the jaw-thrust or chin-lift maneuvers.

An airway that is unsecured because of coma, combativeness, shock, or direct airway trauma requires endotracheal intubation. A nasopharyngeal or oropharyngeal airway can improve management during bag mask ventilation but are temporizing measures until definitive control is established. In most cases, orotracheal intubation with in-line cervical spine stabilization is the preferred approach to airway control. Although nasotracheal intubation is recommended in nonapneic adult with potential cervical spine injury, this approach is not indicated and poorly tolerated in children.

The pediatric airway anatomy is unique and affects management technique. The child's larynx is anatomically higher and more anterior than that of the adult patient, necessitating an upward angulation of the laryngoscope to place the endotracheal tube properly. Removing the anterior half of the rigid cervical collar allows access to the neck for gentle cricoid pressure. The pediatric epiglottis is shorter, less flexible, and tilted posteriorly over the glottic inlet. Because of this, direct control of the epiglottis with a straight blade is usually necessary for proper visualization of the vocal cords. The vocal cords themselves are more fragile and easily damaged. The narrowest point in the pediatric airway is the subglottic trachea at the cricoid ring, as opposed to the glottis in adult patients. Therefore passage of the endotracheal tube through the vocal cords does not guarantee safe advancement into the trachea or avoidance of subglottic injury. The selection of an appropriate endotracheal tube is an important part of pediatric resuscitation. Internal diameter sizes can range from 3.0 to 3.5 mm in newborns to 4.5 mm at 1 to 2 years of age. After 2 years of age, internal diameter can be estimated by the following formula: internal diameter $=$ age/4 $+$ 4. Approximating the diameter of the patient's little finger is also useful. Because of the narrow subglottic trachea, an uncuffed endotracheal tube is indicated in children 8 years of age or younger (Fig. 18-4).[8,9]

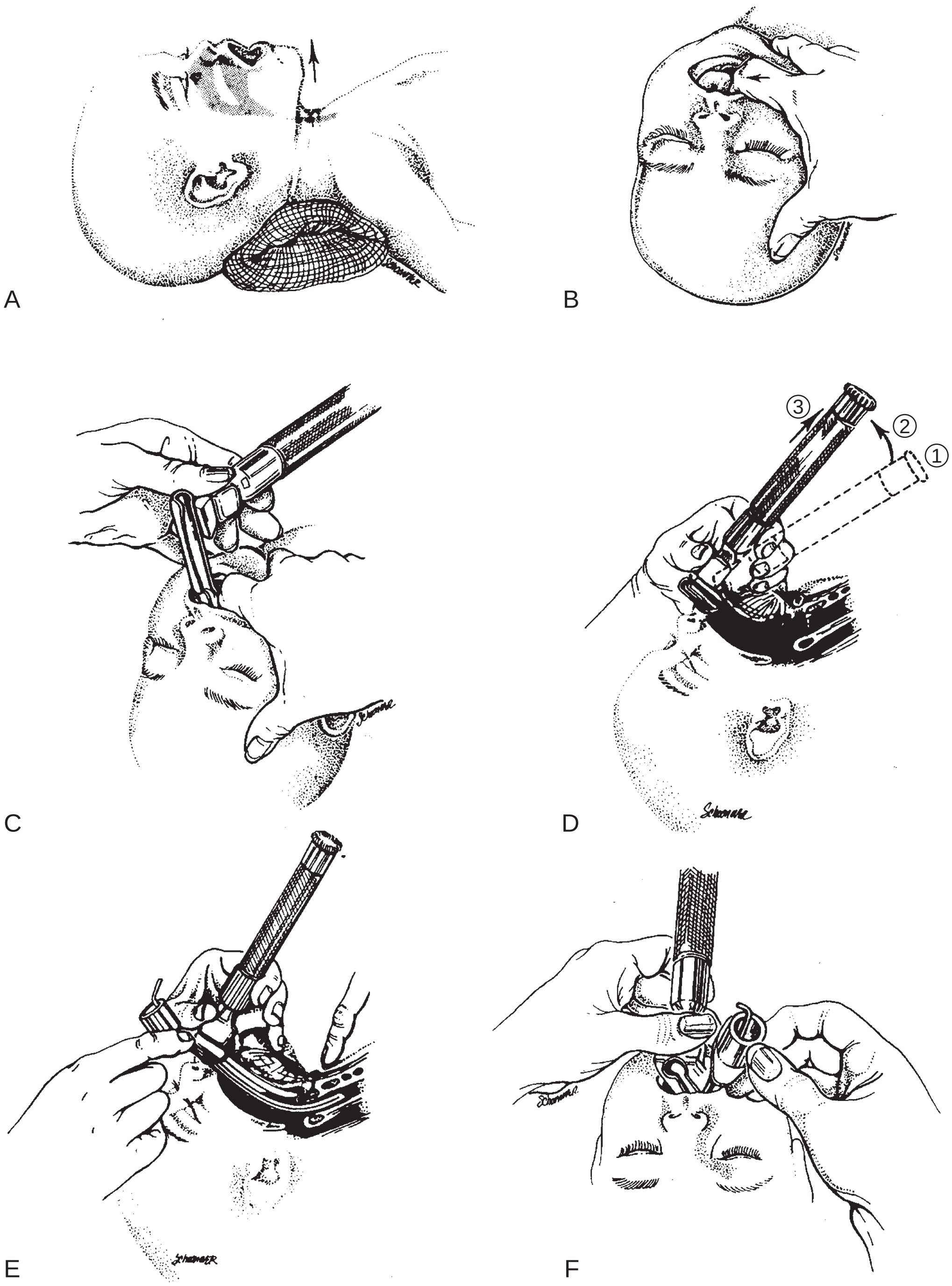


**FIGURE 18-4** Endotracheal intubation. **A,** The pediatric larynx and supraglottic space are anterior and angled cephaled compared with the position in adults. A posterior neck roll optimizes visualization of the vocal cords in children. **B,** The tongue is large relative to the space in a child's oral cavity. The tongue should be moved to one side of the oral cavity to facilitate exposure of the posterior pharynx and supraglottic area. **C,** The laryngoscope blade is inserted from the right side of the mouth and slides back along the vallecula. **D,** With the blade in the proper position and the child's neck slightly extended in the sniffing position, lifting the handle (positions 1, 2, and 3) raises the epiglottis and brings the vocal cords into direct vision. **E,** In all except newborns, the straight blade should be placed over the epiglottis to lift it, along with base of the tongue, to expose the larynx. A stylet with the tip curved within the endotracheal tube facilitates successful intubation. **F,** The endotracheal tube is held in place while the laryngoscope is removed and secured after verification of bilateral breath sounds. (From Eichelberger MR: Pediatric Trauma, Prevention, Acute Care, Rehabilitation. St Louis, Mosby, 1993.)

The technique of intubation depends on the urgency of establishing an airway. In the hypotensive, hypoxemic, comatose child, orotracheal intubation is accomplished without delay as an integral part of the resuscitation. In a more elective situation, more attention is given to adequate preoxygenation and premedication. An adequate oxygen saturation (i.e., more than 95%), as measured by pulse oximetry, is attempted by bag-mask ventilation with 100% oxygen. Thoracic trauma can preclude and make attainment of adequate oxygen saturation impossible before intubation. Inducing hypocarbia ($Pco_2$ = 28 to 32 torr) by hyperventilation is advantageous and can reduce intracranial hypertension.

Following preoxygenation using mask ventilation, children should receive atropine sulfate (0.1 to 0.5 mg) to ensure that the heart rate remains high during intubation. It is important to maintain heart rate, because this is directly proportional to cardiac output; stroke volume does not change in a child. Also, the child should be premedicated with intravenous sedatives and muscle relaxants. Appropriate sedatives include short-acting barbiturates, such as thiopental sodium (5 mg/kg), if volume status is normal, or a benzodiazepine, such as midazolam (0.1 mg/kg), if hypovolemia is suspected. Muscle relaxation is achieved with short-acting nondepolarizing agents (vecuroniurn bromide, 0.1 mg/kg) or shorter-acting depolarizing agents (succinylcholine chloride, 1 mg/kg). The presence of burns and devitalized tissue precludes the use of succiny1-choline because of the risk of hyperkalemia. Continuous monitoring of the intubated child with end-tidal carbon dioxide ($CO_2$) and pulse oximetry is essential to safe resuscitation.

In the rare circumstance, when tracheal intubation is not possible as a consequence of oral maxillofacial trauma or congenital anomaly, a surgical airway is indicated. A surgical crycothyrotomy is the preferred approach in older children (>10 years). Because this crycothyroid membrane is easily exposed through a transverse skin incision, placement of a small, uncuffed endotracheal tube via this incision is possible. The morbidity is less because of the superficial location of the crycothyroid membrane in contrast to an emergency tracheostomy. The crycothyrotomy should be converted to a formal tracheostomy, when the child is stabilized, to avoid subglottic stenosis.

In small children, the cricoid cartilage is a delicate structure and provides the majority of support to the trachea. Injury of this membrane during emergency cricothyrotomy can lead to significant morbidity and lifelong laryngotracheomalacia. To avoid this complication, children younger than 10 years of age should undergo needle cricothyrotomy and jet insufflation of the trachea. A 16- to 18-gauge intravenous catheter is used to access the tracheal lumen through the crycothyroid membrane, and is connected to a 100% oxygen source at a high flow rate of 10 to 12 L/min. Needle-jet ventilation is limited in children by hypercarbia that occurs in approximately 30 minutes; therefore this method is a temporary means of ventilation. Following stabilization of the child, endotracheal intubation or formal tracheostomy is necessary.[9]

### Breathing

Compromised breathing and ventilation in the injured child usually results from either head injury (impaired spontaneous ventilatory drive), or thoracic injury (impaired lung expansion). Recognition of the head-injured child is usually clear, while recognition of a thoracic injury that impairs lung expansion requires a detailed survey. The potential seriousness of these injuries is underscored by the fact that mortality rates for thoracic trauma in children approach 25%.[10]

Following thoracic trauma, air, fluid, or viscera can occupy the pleural space. Compression of the pulmonary parenchyma can result in impairment of gas exchange sufficient to produce respiratory distress. In the case of traumatic rupture of the diaphragm, loss of muscular integrity also has a direct effect on lung expansion. The pediatric mediastinum is extremely mobile; as pressure increases in the pleural space, the mediastinum is displaced to the opposite side, causing compression of the contralateral lung. The distortion of mediastinal vascular structures, along with the elevated intrathoracic pressure, can result in a critical reduction of venous return to the right atrium.

Loss of chest wall integrity from flail chest impairs ventilation and oxygenation. Consequently, paradoxical chest wall movement occurs during inspiration preventing complete lung expansion; treatment is best by assisted positive-pressure breathing. The force required to fracture multiple ribs in a child is enormous and is transmitted to the underlying lung parenchyma, resulting in a pulmonary contusion. Regions of parenchymal hemorrhage and edema impair ventilation-perfusion matching; the decrease in pulmonary compliance can dramatically increase the work of breathing, which can precipitate ventilatory failure.

Recognition of ventilatory compromise is usually not difficult, especially with a high index of suspicion. The sound of air movement at the mouth and nares is assessed, as are the rate, depth, and effort of respirations. On inspection, asymmetric excursion of the chest wall suggests a ventilatory abnormality. Percussion elicits dullness or hyper-resonance, depending on the presence of fluid or air in the pleural space, while breath sounds are decreased. With tension hemopneumothorax, mediastinal shift may be detected by tracheal deviation, displacement of the point of maximal impulse, and distention of neck veins caused by impaired venous return to the heart.

Mechanical ventilatory failure is life threatening and requires immediate treatment during the primary survey. All children require supplemental oxygen by nasal cannula, mask, or endotracheal tube. Endotracheal intubation and assisted ventilation are sufficient to treat hypoventilation caused by head injury, pain from rib fractures, flail chest, and pulmonary contusion. Simple hemopneumothorax may be well tolerated with supplemental oxygen until tube thoracostomy can be performed after the primary survey (Fig. 18-5). In cases of hemopneumothorax, which results in compromised ventilation or hypotension, a thoracostomy tube is required, often combined with endotracheal intubation and intravenous access for rapid fluid infusion. If tension is present, the hemodynamic derangements can be minimized by needle thoracostomy in the second intercostal space at the midclavicular line, followed by definitive thoracostomy tube. When endotracheal intubation has been performed, the child should receive 100% $Fio_2$, with a tidal volume of 10 to 12 mL/kg at a respiratory rate of 15 to 20 cycles/min. Oxygenation and ventilation should be manipulated to maintain an arterial $Po_2 > 80$ mm Hg and a $Pco_2$ of 28 to 32 torr, with a positive end-expiratory pressure (PEEP) not to exceed 5 cm $H_2O$. The goal is to prevent secondary brain injury by optimizing oxygenation and cerebral perfusion by minimizing intracranial pressure. Children with head trauma are best managed by moderate hyperventilation and hypocarbia ($Pco_2 = 30$ to 35 mm Hg) to reduce intracranial pressure.[6,9,11]

Tube thoracostomy is accomplished during this phase of resuscitation for symptomatic hemopneumothorax. A chest tube of adequate caliber to evacuate blood and air is inserted into the pleural cavity. The narrow intercostal space of a small child usually limits the size of the tube, but the largest caliber tube that can be placed is preferable (18° F to 20° F). The tube should be placed in the midaxillary line at the nipple level (fourth or fifth intercostal space) to avoid intra-abdominal

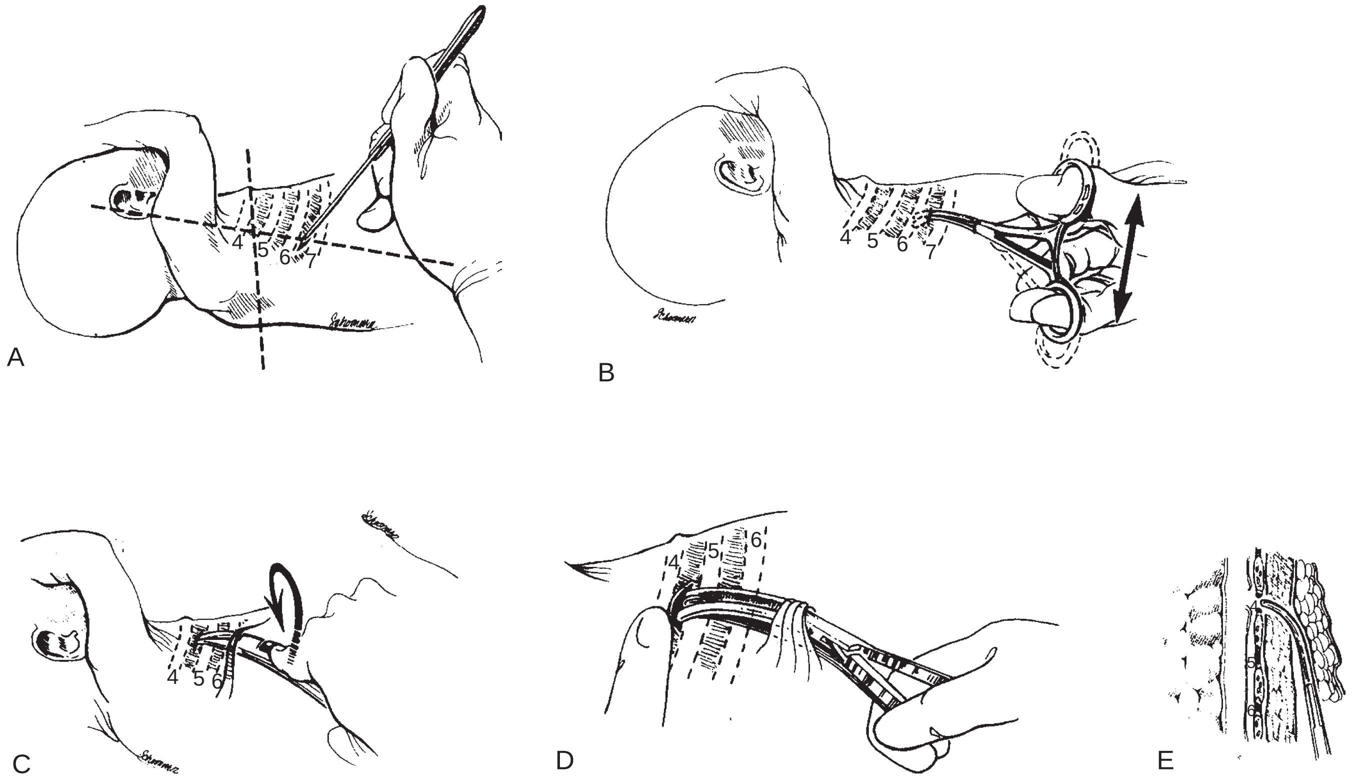


**FIGURE 18-5** Thoracostomy tube insertion. **A,** An incision is made in the midaxillary line just below the nipple in a male or inframammary fold in a female (fourth intercostals space). **B,** The dissection is carried out in a cephalad direction, subcutaneously over two ribs. A long subcutaneous track is preferable in a child to minimize air leak around the tube. **C,** The fourth intercostal space is the ideal place for thoracostomy tube placement. **D,** The entrance into the pleural space should be made just over and superior to the rib to avoid injury to intercostal vessels. **E,** Lateral view of the technique. (From Eichelberger MR: Pediatric Trauma, Prevention, Acute Care, Rehabilitation. St Louis, Mosby, 1993.)

placement through an elevated diaphragm. The tube should be directed posterior and cephalad to evacuate both blood and air. The tube is connected to a pleurovac closed-suction drainage system set at −15 cm $H_2O$. Persistent hemorrhage from a thoracostomy tube is uncommon in children; however, drainage of 1 to 2 mL/kg/hour is a sign of ongoing significant bleeding from a vascular or mediastinal injury that requires thoracotomy to identify the source of blood loss and to secure hemorrhage.

### Circulation and Vascular Access

The third priority in the sequence of the primary survey is the rapid assessment of circulation and the establishment of venous access. Seriously injured children often have normal vital signs, even with significantly decreased circulating volume as a result of a remarkable cardiovascular reserve. This compensation that occurs in the injured child delays the early hemodynamic signs of hypovolemia until relatively late in their physiologic decline. A high index of suspicion based on the mechanism of injury and continuous careful scrutiny of physiologic parameters and clinical signs is necessary to minimize morbidity.

A reliable sign of adequate perfusion is a normal mental status. As the child is resuscitated, clinical signs of the efficacy of resuscitation should be monitored. Improvement in the following parameters is consistent with hemodynamic stability and success of resuscitation:

- Slowing of the heart rate (<100 beats/min)
- Increased pulse pressure (>20 mm Hg)
- Return of normal skin color
- Increased warmth of extremities
- Clearing of the sensorioum (improving Glasgow Coma Scale [GCS] score)
- Increase in systolic blood pressure (>80 mm Hg)
- Urinary output of 1 to 2 mL/kg/hour in infants and 1 mL/kg/hour in adolescents

After establishing an adequate airway, provision of venous access in a hypovolemic child is often a challenge. Two functioning catheters are best in all cases of significant injury. Optimal circumstances would be to achieve venous access above and below the diaphragm, given the potential for extravasation of resuscitation fluids from occult intra-abdominal venous injuries. Nevertheless, in children any peripheral venous access is useful.

Two attempts should be made to place large-bore peripheral IVs in the upper extremities. If percutaneous placement is unsuccessful, insertion of an intraosseous (IO) line is useful in a child less than 6 years of age. If more than 6 years of age, a venous cutdown performed at the ankle is best. The greater saphenous vein is easily exposed through short transverse incisions, 0.5 to 1 cm proximal and anterior to the medial malleoli. The exposed vein can be suspended over a silk ligature, and the largest appropriate intravenous catheter is introduced into the vessel lumen under direct vision. Trans-section or ligation of the vein is not necessary (Fig. 18-6).

Because central venous catheterization can result in significant complications, such as laceration of the subclavian or

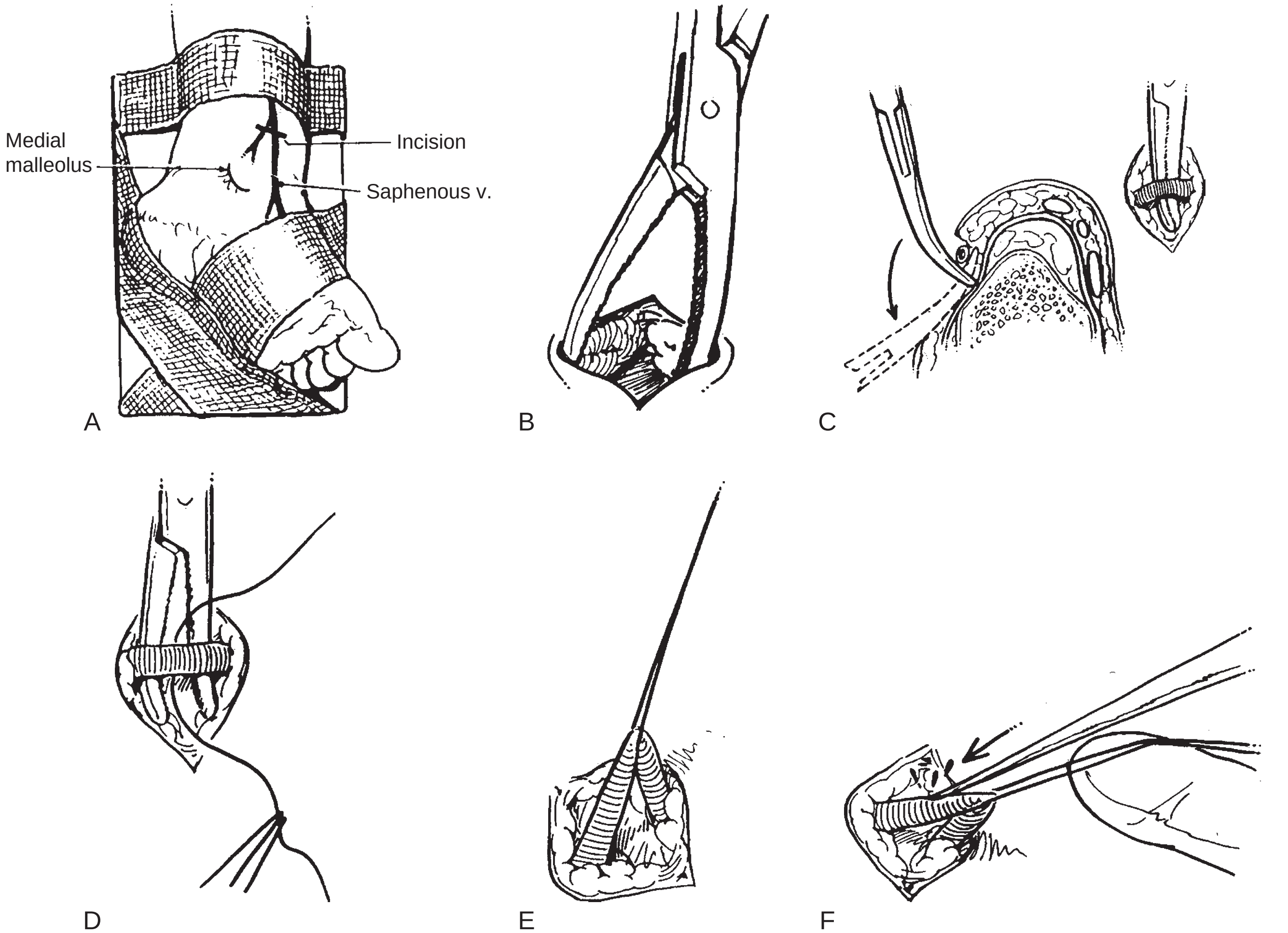


**FIGURE 18-6** Greater saphenous vein cannulation. **A,** Consistent emergency venous access is achieved at the ankle, anterior to the medial malleolus via the saphenous vein. **B,** A transverse incision is made anterior to the medial malleolus (1 cm anterior and 1 cm cephalad). Perpendicular dissection in the incision exposes the saphenous vein. **C,** The vein is dissected circumferentially. **D,** A suture ligature is passed around the vessel. **E** and **F,** Gentle traction on the suture facilitates catheterization of the vein. (From Eichelberger MR: Pediatric Trauma, Prevention, Acute Care, Rehabilitation. St Louis, Mosby, 1993.)

femoral artery, this technique is less useful. The femoral route is preferred because of ease of access. If subclavian venous access is necessary, the child should be positioned in the Trendelenberg position, with the head maintained in a neutral position without the placement of a posterior shoulder roll. This position provides optimal cross-sectional area of the subclavian vein in both children and adults.[12]

An intraosseous (IO) line is a simple, reliable, and a safe route for administration of fluids, blood products, and medication. The technique is applicable in children 6 years of age and younger, because of the well-perfused marrow of early childhood. The preferred site for IO insertion is through the flat anteromedial surface of the tibia, about 2 to 3 cm below the tibial plateau. The needle is angled 60 degrees from horizontal and pointed toward the foot. The cortex is penetrated and the marrow cavity detected by aspirating blood and particulate material. Alternative sites include the midline distal femur, 3 cm above the condyles directed cephalad in small children, and the distal tibia above the medial malleolus or the proximal humerus in the adolescent. Specially designed IO needles should be available in the pediatric resuscitation room to facilitate this maneuver; however, a 14- to 16-gauge needle can be used. The complication rate of IO is low but includes osteomyelitis, cellulitis, fracture, growth plate injury, fat embolism, and compartment syndrome.

As soon as vascular access is established, fluid resuscitation with a bolus of fluid is begun. Generally, isotonic crystalloid solution, such as lactated Ringer solution, is administered in 20 mL/kg increments. If evidence of hypovolemia persists after 40 mL/kg has been given, transfusion of ABO-matched packed red blood cells (RBCs) is initiated in a bolus of 10 mL/kg. Packed RBCs have the desirable qualities of raising colloid oncotic pressure and effecting a more rapid and sustained intravascular expansion than crystalloid. In addition, the red blood cell provides hemoglobin to increase oxygen-carrying capacity. All fluids (crystalloid, colloid, and blood) should be warmed during infusion. This is accomplished by use of a microwave to heat crystalloid solutions and use of a warming device.

It is important to reassess the child's response to resuscitation continually to characterize the nature and extent of the injuries and to avoid the complications of excessive fluid resuscitation. As perfusion is restored, the rate of fluid infusion is gradually reduced to avoid unnecessary fluid administration. Pulmonary edema rarely occurs in normal lungs, but considerable morbidity results from fluid

sequestration in a region of pulmonary and cerebral contusion. If hemodynamic stabilization does not occur with crystalloid and blood resuscitation, hemorrhage is likely from an intra-abdominal or pelvic source, cardiac dysfunction because of tamponade, contusion, or tension hemopneumothorax; cerebrospinal injury, such as atlantooccipital disassociation; and profound hypothermia.[9,13]

### Disability

A rapid neurologic evaluation is included in the primary survey to identify serious injuries that may have immediate consequences for airway management. A rapid method for describing gross cerebral function is the AVPU pneumonic: alert, voice responsive, pain responsive, or unresponsive. An assessment of pupillary responsiveness and symmetry is also useful. Transtentorial herniation secondary to an expanding intracranial hematoma causes ipsilateral pupillary dilation and loss of light reflex. Direct trauma to the eye is an equally common cause of unilateral anisocoria. Characterization of extremity posturing as decorticate or decerebrate indicates the loss of cortical or global brain function, respectively. In the comatose child with a unilateral fixed and dilated pupil, measures to reduce intracranial pressure (ICP) are imperative. These include early controlled endotracheal intubation to keep the $Pco_2$ regulated (30 to 35 mm Hg) with moderate hyperventilation, which causes cerebral vasoconstriction and decreases cerebral blood flow. This lowers brain volume and ICP with resulting increase in cerebral perfusion pressure (CPP). The reverse Trendelenburg position, in which the head is slightly elevated by 30 degrees, can also reduce intracranial hypertension but should be employed in children with normal cardiac function.

### Exposure

Complete exposure of the child is essential to facilitate a thorough examination and identification of injury. A conscious child does not understand the need for such action, so exposure must be done carefully. A thorough primary survey on a stable child with a normal GCS score can be performed without removing all items of clothing simultaneously. Children are particularly apprehensive about exposing an injury that had previously been covered. Attention to the special sensitivities of the child in this regard frequently results in a more efficient resuscitation.

In a child, hypothermia affects physiologic parameters, such as cognitive function, cardiac activity, and coagulation. It is important to maintain core temperature above 35 to 36 degrees Celsius. A warm resuscitation room preserves core body temperature and minimizes heat loss. Similarly, resuscitation fluid and inhaled gases should be warmed and humidified. Overhead and bed warmers are essential but a radiant warmer is best for the injured infant.

## RESUSCITATION PHASE

The cornerstone of resuscitation is continuous reappraisal of the child's response to therapeutic intervention. Deterioration at any point requires repetition of the primary survey. After the ABCs are completed and life-threatening injuries are stable, place a gastric tube and urinary catheter, followed by removal of blood for analysis and establishment of a cardiac monitor.

In children, acute gastric dilation can cause both respiratory compromise and vagus-mediated bradycardia. Gastric decompression to evacuate the stomach and reduce the risk of vomiting and aspiration is important in all injured children, especially those with a decreased level of consciousness. Assessment for a stable midface and for presence of cerebrospinal fluid (CSF) rhinorrhea are important before placement of nasogastric tube for decompression. If abnormal, gastric tube placement is contradicted.

A urinary catheter is also placed following a thorough perineal assessment, including a rectal exam prior to placement. In instances of a high-riding prostate, meatal bleeding, perineal or scrotal ecchymosis, or unstable anterior pelvic fracture, a retrograde urethrogram is indicated before insertion of the catheter.

An electrocardiogram (ECG) is essential to monitor cardiac rhythm, which is rarely abnormal. Secondary abnormalities are occasionally seen and include sinus bradycardia because of advanced shock; or electromechanical dissociation from hypovolemia, tension pneumothorax, or pericardial tamponade; and ventricular fibrillation because of hypothermia or acidosis. Ventricular ectopy, low voltages, and signs of ischemia can accompany myocardial contusion. Beyond evaluating the actual rhythm, diffuse low voltage may be the first indication of hemopericardium.

After vascular access, blood and urine is obtained for laboratory analysis, hemoglobin, urinalysis, and arterial blood gas analysis. Blood alcohol level and a toxicology screen are not routine in children but reasonable in adolescents. Blood should be drawn for typing and crossmatching for possible transfusion.[13,14]

## NEURORESUSCITATION

Brain injury is the most common cause of acquired disability and mortality during childhood. It is estimated that 1 in 500 children in the United States sustains a brain injury, 7000 children die from head injury, and 28,000 children become permanently disabled.[15,16] Largely a result of prevention strategy and of regional trauma systems, the overall mortality from severe traumatic brain injury has decreased from approximately 50% in the 1970s to 36% in 2006. In children, the current overall mortality from injury is 3%; the primary cause of death in 70% of the cases is CNS injury. Overall, the outcome for children older than 3 years of age is better than for adults with comparable injuries; however, outcome in young children (<3 years) is often poor.[6,9,17]

Traumatic brain injury can be defined as either primary or secondary. Primary brain injury is the structural derangement of cerebral architecture that occurs from direct, mechanical impact, resulting in cellular and vascular disruption, infarction, or tissues loss. The child's brain is susceptible to injury of deep white matter shear, punctate hemorrhage, brain swelling, and linear, nondepressed skull fractures rather than a mass lesion, such as subdural, epidural, intracerebral hematoma, and depressed skull fractures, which are more frequently encountered in adults. Children, however, have a higher incidence of epidural hematoma, perhaps because the thinner, less rigid skull is more apt to fracture and lacerate the meningeal artery. The proportionately larger size of the cranium in children, along with a less muscular and more flexible ligamentous cervical spine, may account for the increased incidence of diffuse axonal injury in the injured child.

Primary brain injury responds only to prevention efforts, while the secondary brain injury is the target of clinical neuroresuscitation. Secondary brain injury occurs as a result of decreased cerebral perfusion after the traumatic event. Both diffuse and regional brain swelling impair oxygen and substrate delivery largely as a result of increasing intracranial pressure (ICP) and its effect upon cerebral perfusion pressure (CPP). CPP, ICP, and mean arterial pressure (MAP) are related by the following formula: $CPP = MAP - ICP$. Resuscitation should optimize CPP by controlling ICP and maintaining MAP. When ICP exceeds venous outflow pressure (as a result of brain swelling), it acts as a Starling resistor and determines the pressure gradient for cerebral blood flow. Normal CPP values and the ideal range of ICP in children with severe brain injury are not clear.[17] Favorable outcomes in children are possible by maintaining the ICP less than 20 mm Hg in all ages and a CPP greater than 45 mm Hg in children younger than 8 years of age and 70 to 80 mm Hg in older childen.[18]

Efforts to reduce secondary brain injury focus upon maintaining a therapeutic ICP and CPP and the normalization of MAP. The most expeditious method is intubation and controlled hyperventilation—initially, by reducing $Pco_2$ to a range of 30 to 35 mm Hg, while maintaining $Po_2$ greater than 100 mm Hg, and pH to $7.40 \pm 0.05$. Hypocarbia and alkalosis promote cerebral vasoconstriction, limiting cerebral blood volume and lowering ICP. The effect is rapid but can be limited in duration by re-equilibration of cerebrospinal fluid (CSF) pH balance. The maximal duration of the effect is unknown but may range from several hours to several days. Current therapy maintains the $Pco_2$ in the range of $35 \pm 5$ mm Hg. This regimen avoids excessive hyperventilation, which has been found to be deleterious in severe brain injury by converting borderline regions of cerebral ischemia into infarction.[17] A ventriculostomy is usually placed to allow CSF to drain to further optimize CPP. Repeat computed tomography (CT) of the head is indicated 24 to 48 hours after injury to assess the extent of brain edema, to identify new infarcts, or to demonstrate the development of a new hematoma or large contusion, which may require evacuation. The ventilation and fluid hydration status are reassessed and optimized.

If measures fail to control ICP, then osmotherapy with 20% mannitol rapid bolus intravenous infusion is administered: 0.25 gm/kg to 0.5 gm/kg/dose every 4 to 6 hours. Mannitol is withheld if the serum sodium concentration is greater than 145 meq/L, serum osmolarity is greater than 310 mOsm, urine output is less than 0.5 mL/kg/hour, or blood pressure is low. Mannitol exerts a therapeutic effect by creating a hyperosmolar environment in the cerebral microcirculation; this improves brain oxygen delivery by exerting a diuresis of free water from the cerebral interstitium, which improves red blood cell rheology.[17]

The induction of mild to moderate hypertension may reverse abnormal ICP and raise CPP by improving brainstem microvascular perfusion.[19] Therapy is begun with dopamine 5 to 20 μg/kg/min intravenous infusion with avoidance of cerebral edema.

Hyperthermia and seizures are common after traumatic brain injury and adversely affect efforts to normalize ICP and CPP. Both fever and seizures promote further secondary brain injury by increasing metabolic demand of the compromised brain. Therefore core temperature in children is maintained in the normal range (35° to 36° C) with acetaminophen, 10 mg/kg/dose every 4 to 6 hours. Cooling blankets may be necessary for recalcitrant fever. A single seizure in a child after the injury and resultant normal neurologic assessment does not require treatment. Seizures that occur within 1 week after injury is treated with phenobarbital in children less than 1 year of age, and with dilantin in children greater than 1 year of age. Either drug is administered by one-time intravenous therapy of 10 to 20 mg/kg, followed by daily dosage of 5 mg/kg/day. Treatment is discontinued after 7 days. Children who develop a late seizure require long-term anticonvulsant medication. Whether the comatose child who has not demonstrated seizure activity requires anticonvulsant prophylaxis during the resuscitation process is controversial.[20]

## COAGULOPATHY

Dysfunctional coagulation related to injury occurs in several circumstances: extreme hypothermia, massive transfusion, and severe brain injury. Hypothermia causes excessive bleeding by reducing the efficiency of enzymatic processes that cause coagulation. Massive transfusion, defined as the acute administration of blood products equal to or greater than one blood volume (65 to 80 mL/kg) causes coagulopathy by hypothermia. Another mechanism results from storage of blood in anticoagulants containing ethylenediaminetetraacetic acid or citrate (citrate-phosphate-dextrose), both of which chelate calcium and inhibit the calcium-dependent steps of the coagulation cascade. Acute hypocalcemia is another consequence of massive transfusion.

The most common mechanism by which massive transfusion causes coagulopathy, is dilutional thrombocytopenia. Coagulopathy resulting from dilution of clotting factors is much less common because of a much greater functional reserve of these components. As continued hemorrhage depletes circulating platelets and blood is replaced with RBCs, a progressive reduction in the platelet count ensues. With acute injury, a decrease of platelet count to 50,000 can produce surgical bleeding. Such drastic reductions in platelet levels requires a massive transfusion of at least two blood volumes. Platelet levels less than 100,000 signify impending coagulopathy, and levels of 50,000 or less require platelet transfusion. Administration of ABO-matched platelets at an initial dose of 0.1 U/kg raises the platelet level by about 40,000.

Severe head injury is also associated with a coagulopathy unrelated to platelet dilution. Presumably, large concentrations of procoagulant tissue thromboplastin are released from cerebral laceration. These thromboplastins initiate disseminated intravascular coagulation, resulting in a consumptive coagulopathy in which clotting factors and fibrinogen are depleted as well as platelets. Coagulopathy after head injury is a grim prognostic sign. Treatment requires administration of matched fresh frozen plasma at a dose of 15 to 30 mL/kg. Cryoprecipitate contains large amounts of fibrinogen, factor VIII, factor X111, and von Willebrand factor and can be given at a dose of 0.1 U/kg in addition to fresh frozen plasma. Administration of fresh frozen plasma, cryoprecipitate, or both may also be required in the setting of preexisting coagulopathies, such as hemophilia, von Willebrand disease, and advanced liver disease.[9]

It is clear that the coagulopathy associated with traumatic injury is a result of multiple independent but interacting

mechanisms. Early coagulopathy is driven by shock and requires thrombin generation from tissue injury as an initiator. Following initiation and further activation of anticoagulant and fibrinolytic pathways, the acute coagulopathy of trauma-shock is propagated by events associated with the care of the traumatically injured child, specifically acidemia, hypothermia, and dilution.[21]

## Damage Control

The goal of "damage control" is to reverse the sequelae of shock. Severely traumatized children who require operative intervention are at risk for hypothermia, acidosis, and coagulopathy. In these circumstances, the child may require emergent completion of the surgical procedure using a process of damage control surgery. The fundamentals of damage control in children are the following:

1. Exposure and control of vascular or solid organ hemorrhage
2. Control of contamination from hollow-viscus injury
3. Packing of the abdomen
4. Temporary abdominal closure
5. Transport to the pediatric intensive care unit (PICU)

All measures available for core rewarming should be used in these children. Efficient and rapid abdominal closure is critical. Since the early descriptions of the wound vacuum-assisted closure (VAC) technique, commercially produced products have been developed for managing these open abdominal wounds by temporary abdominal closure.[22] The VAC allows for a rapid abdominal closure as well as minimizing the risk of abdominal compartment syndrome post-operatively in the PICU during the physiologic and biochemical restoration phase. The VAC has also been shown to be of benefit in children with head injury by optimizing cerebral blood flow.

During damage control, blood products should be used in a 1:1:1 ratio of RBC to plasma to platelets. The decision to return to the operating room for formal closure occurs when all aspects of physiology have been restored.[23]

## Pain Management

The primary goal of acute pain management is to reduce the stress of the injured child and to improve outcome. Acute pain serves as a noxious stimulus that leads to the activation of the physiologic stress response. The result is a disruption in the neuroendocrine response, which has a profound and deleterious effect upon metabolism, thermoregulation, wound healing, and immunity.

The following are critical elements in the pain management of injured children:

- An experienced interdisciplinary team, lead by a clinician devoted to pain management
- Ensuring the least possible pain
- Recognizing that effective pain management requires constant adjustment
- Recognizing that anxiety needs to be considered and treated, because it may alter the effectiveness of pain treatment
- The ability and knowledge to effectively use all pain therapy in real-time coordination with the rest of the child's supportive care and treatment plans

A team-oriented, protocol-based algorithm that attempts to control pain in this environment will further enhance the overall success of the emergency management of these children.[24]

## Conclusion

A systematic approach to the injured child saves lives. Nevertheless, prevention of injury is essential to children.

The unintentional childhood injury death rate has declined nearly 48% during the past 25 years.[4] Among the most notable advances in childhood injury prevention are the declines in death rates for unintentional firearm (94%) and bicycle-related injury (78%). The death rate from fire and burn injury declined 53%, while that of pedestrian injury dropped 64%. Unfortunately, the motor vehicle occupant death rate, particularly among children ages 5 to 9 years, has been slow to decline, and the death rate from airway obstruction injury among infants remains unchanged.

Many factors have contributed to the overall dramatic decline in the unintentional childhood injury death rate. It is clear that the highest priority should be on injury prevention with particular emphasis placed on minimizing injury risk to minorities, younger children, and motor vehicle occupants. Once injury occurs, proper resuscitation can save lives.

*The complete reference list is available online at www.expertconsult.com.*

# CHAPTER 19

# Thoracic Injuries

David E. Wesson and Charles S. Cox, Jr.

## Epidemiology and Prevention

Injuries to the chest wall, diaphragm, lungs, and mediastinal structures occur in about 25% of children treated in level I pediatric trauma centers, usually after high-energy blunt or penetrating trauma. Change in velocity, $\Delta V$, is a strong predictor of significant injury for children in motor vehicle crashes.[1] Low-energy mechanisms, such as simple falls from playground equipment, seldom cause chest injury. Thoracic injuries range in severity from minor to rapidly fatal, but virtually all chest injuries can be treated successfully if they are promptly diagnosed and appropriately treated. Although chest injuries are less common than injuries to the abdomen, soft tissues, and extraaxial skeleton, they are more lethal. Because of the impact required, patients who have sustained such injuries have a significant risk of mortality. In fact, thoracic injuries account for a high proportion of all trauma deaths not caused by central nervous system (CNS) injury.

As with most types of pediatric trauma, the male-to-female ratio is between 2:1 and 3:1. Thoracic injuries can be classified by anatomic site (e.g., rib fracture, pulmonary contusion, bronchial laceration), mechanism (blunt or penetrating), or threat to life (immediate or potential). Although most serious blunt injuries to the chest are motor vehicle–related in all age groups, the proportion of children injured as pedestrians is much higher than in adults. The causes of penetrating thoracic injuries in teenagers mimic those in adults—mostly knife and gunshot wounds. BBs or pellets fired from air guns, although often considered to be relatively innocuous, may also be life threatening.[2] The causes of penetrating injuries in preadolescent children include a number of other unusual mechanisms, such as impalement by shards of broken glass or metal rods.[3]

The most common thoracic injuries seen clinically are listed in Table 19-1. Autopsy series, which include prehospital and emergency department deaths, reveal a higher proportion of rapidly fatal, major vascular and cardiac injuries.[4] In adults, rib fractures are by far the most common type of blunt trauma to the chest. In children, pulmonary contusions are the most frequent.[5,6] Tracheobronchial lacerations are more common in children than in adults, whereas the opposite is true for traumatic rupture of the aorta.[7]

The most common thoracic injuries are lung contusion, pneumothorax, hemothorax, and fractures to the ribs, sternum, or scapula. Injuries to the heart, aorta, trachea, bronchi, and diaphragm are much less common but potentially more dangerous. The most common *immediately* life-threatening injuries to the chest are airway obstruction, tension pneumothorax, massive hemothorax, and cardiac tamponade. Open pneumothorax and massive flail chest are rare. The most common *potentially* life-threatening injuries of the chest are myocardial contusion, aortic disruption, ruptured diaphragm, and tracheobronchial disruption. Esophageal rupture is rare.

The relative incidence of blunt and penetrating thoracic trauma varies widely, depending on the amount of violence in the community. Peterson and colleagues[3] reported a large series of adults and children with thoracic trauma. Blunt injuries comprised 81% of thoracic injuries in children 12 years of age or younger; penetrating injuries accounted for 58% of chest injuries in adolescents. In Nakayama's series, 97% of thoracic injuries in children up to 17 years of age were blunt.[6] Meller[8] reported a series in which nearly all wounded teenagers had penetrating injuries. The National Pediatric Trauma Registry reflects the combined experience of many pediatric trauma centers across North America. From 1985 to 1991, more than 25,000 cases were reported to the National Pediatric Trauma Registry, including 1553 cases with thoracic injury.[5] Eighty-six percent of injuries were blunt (mostly motor vehicle related). The remaining 14% were penetrating (mostly stab or gunshot wounds).

The overall mortality rates for blunt and penetrating cases were almost identical at 15% and 14%, respectively.[5] Mortality increases with the number of associated injuries. Most of the deaths in the group that had blunt trauma were caused by associated head injuries, whereas most of the deaths in the group with penetrating injuries resulted from the chest injuries themselves. Overall, thoracic injuries were second only to CNS injuries as the cause of death in the National Pediatric Trauma Registry. Most deaths from chest injuries occur at the scene of the accident or in transit to the hospital and result from fatal injuries to vital organs. Patients with thoracic injuries who reach the hospital alive are potentially salvageable.

Although the ratio of blunt-to-penetrating injuries varies in adults and children, the spectrum of chest injuries and the basic principles of diagnosis and treatment are the same for all ages. The most common injuries—pulmonary contusion, rib fracture, pneumothorax, and hemothorax—can be treated with simple measures, such as tube thoracostomy, oxygen, and analgesia. Approximately 20% of patients with these injuries also require endotracheal intubation and

**TABLE 19-1**
**Epidemiology of Pediatric Chest Injuries**

| | *Hospital for Sick Children* | *Memorial Hermann Children's Hospital* |
|---|---|---|
| Ribs/sternum | 26% | 24% |
| Pneumothorax/ hemothorax | 26% | 30% |
| Heart | 1% | 1% |
| Great vessel | 1% | 1% |
| Lung | 44% | 43% |
| Bronchus/esophagus/ diaphragm | 2% | 2% |

Percentage of the total patients with chest injuries with each type of injury from the trauma registries of two leading pediatric trauma centers: the Hospital for Sick Children, Toronto, Ontario and Memorial Hermann Children's Hospital, Houston, Tex.[101,102]

mechanical ventilation, often for the management of associated head injuries.

Several thoracic injuries virtually always require operation: major airway lacerations, aortic injuries, structural cardiac and pericardial injuries, and esophageal perforations. One of the greatest challenges in thoracic trauma is to recognize the rare cases that need an operation as early as possible during the course of treatment. In Nakayama's series, 2 of 3 patients with penetrating injuries and only 3 of 83 patients with blunt injuries had chest operations.[6] In Peterson's report, 15% of the children with blunt injuries required thoracotomy (about the same as in adult series). Forty percent of those with penetrating injuries required surgery (far higher than in adult series).[3]

Although clinicians are naturally concerned with the needs of individual patients, no consideration of chest injuries in children would be complete without mentioning prevention. Motor vehicle accidents and gunshot wounds cause the vast majority of severe pediatric thoracic injuries. These injuries are all preventable. Increasing the use of seat belts and child restraints would substantially reduce the risk for injury to motor vehicle occupants. Reducing the illegal use of firearms would also have major benefits, especially for teenagers. Chest protectors may be effective in reducing the incidence of chest injuries, including *commotio cordis* in young athletes.[9,10] In combination, these measures would substantially reduce the incidence and severity of pediatric thoracic trauma and the deaths and disabilities which result from it.

## Clinical Presentation

The pathophysiology of thoracic trauma and the anatomy and physiology on which management strategies are based differ significantly between children and adults. The most important anatomic factors that distinguish children are the relatively narrow airway, which is prone to obstruction, the anterior and superior position of the glottis, which makes nasotracheal intubation difficult and therefore inappropriate in an emergency, and the short trachea, which increases the risk of endobronchial intubation. The increased oxygen consumption and low functional residual capacity of children predispose them to hypoxia. Because young children rely largely on their diaphragm to breathe, any increase in intra-abdominal pressure compounds the problem by restricting diaphragmatic excursion.

Children with significant thoracic injuries may present with minimal signs and symptoms. A large adult series from the Maryland Institute of Emergency Medical Services Systems (MIEMSS) found that two thirds of patients with thoracic injuries arrived with stable vital signs.[11] This same finding was reported in children.[8] About 25% of the patients with significant intrathoracic injuries in the MIEMSS series did not have a rib fracture. These "occult" injuries included pneumothorax, hemothorax, myocardial contusion, cardiac rupture, tracheobronchial injury, pulmonary laceration, ruptured diaphragm, and ruptured aorta.

The ribs of a child are more pliable than those of an adult. Consequently, rib fractures are much less common in children. However, it is important to note that because of the elasticity of the chest wall in childhood, severe thoracic injuries may occur without injury to the chest wall or external signs of injury. In Nakayama's series, less than half of the children with significant thoracic injuries had rib fractures.[6] The compressibility of the chest wall may also explain why traumatic asphyxia is almost unique to children and why major airway trauma is so much more common in children than in adults.

The mediastinal structures are more mobile in children than in adults. Therefore tension pneumothorax is more likely to shift the mediastinum, compromising ventilation of the contralateral lung and impairing return of venous blood to the heart.

## Diagnosis and Initial Resuscitation

Diagnosis and initial treatment of patients with traumatic chest injury must proceed simultaneously. Although the manifestations of thoracic injury may be immediate or delayed by hours or days, the initial goal should be to rule out injuries that are immediately life threatening, such as airway obstruction, tension pneumothorax, massive hemothorax, and cardiac tamponade.

All injury victims should be managed according to the principles of the Advanced Trauma Life Support (ATLS) Program of the American College of Surgeons.[12] The overall plan is as follows:

1. Primary survey
2. Resuscitation of vital functions
3. Detailed secondary survey
4. Definitive care

All children with thoracic trauma must have supplemental oxygen, two large-bore intravenous lines, and a nasogastric (NG) tube to prevent gastric distention. A NG tube may also reveal an abnormal position of the esophagus or stomach, thereby indicating aortic injury or a ruptured diaphragm. Children with thoracic trauma should be observed closely. Vital signs and oxygen saturation in arterial blood ($SaO_2$) should be continuously monitored. If the child is intubated, end-tidal carbon dioxide should be monitored continuously or checked frequently. Blood should be available for transfusion. The equipment and skilled personnel needed to address

breathing problems and to manage the airway with suction, oral airways, endotracheal tubes, laryngoscopes, and a bag-valve-mask apparatus must always be on hand, especially during transport and diagnostic procedures.

Life-threatening injuries should be identified *and* treated during the initial resuscitation phase of the ATLS protocol. The first priority is to clear and secure the airway. Endotracheal intubation may be required. After intubation, the position of the endotracheal tube must be checked by observing chest excursion, listening for bilateral air entry, monitoring end-tidal carbon dioxide, and obtaining a chest radiograph. A colorimetric carbon dioxide detector may be used to verify endotracheal tube position, especially in the prehospital setting.[13]

The second priority is to ensure adequate ventilation. Tension pneumothorax, if present, should be treated before a radiograph is obtained. Occasionally, open pneumothorax or massive flail chest requires intubation and assisted ventilation during the initial resuscitation. Persistent shock despite adequate fluid administration usually indicates ongoing (most likely abdominal) blood loss. However, if no obvious cause of hypovolemia can be found, the possibility of acute pericardial tamponade should be considered; this disorder can be relieved, at least temporarily, by pericardiocentesis.

The indications for urgent thoracotomy may become obvious at any stage (Table 19-2). The most common indications are massive bleeding, massive air leak, and cardiac tamponade. Emergency room (ER) or resuscitative thoracotomy is a controversial technique that does not seem to have clear indications or contraindications. In the report from MIEMSS,[11] none of 39 adult patients who presented without vital signs in the ER survived after emergency thoracotomy. However, emergency thoracotomy may be lifesaving in children, especially those with penetrating cardiac injuries. Powell and colleagues reported a 26% survival rate in a series of children and adolescents who had ER thoracotomy.[14] These authors recommended thoracotomy in the ER for post-traumatic arrest, or near arrest, in the following three situations:

1. All cases of penetrating thoracic trauma
2. Blunt trauma with acute deterioration but signs of life in the ER
3. Blunt trauma with signs of life at the scene when the scene is in proximity to the hospital

The incision for emergency thoracotomy should be on the left anterolateral chest wall in the fifth interspace. A rib spreader should be used. If evidence of pericardial tamponade exists, the pericardium should be opened longitudinally, anterior to the phrenic nerve. Cardiac wounds should be controlled by direct pressure and simple suture. If cardiac tamponade is not present, the descending aorta should be cross-clamped. If the patient has massive lung injury, the hilum should be clamped or twisted off (see Treatment later). Patients who respond to these measures should then have definitive repair performed in the operating room.

**TABLE 19-2**
**Indications for Emergency Thoracotomy**

1. Penetrating wound of the heart or great vessels
2. Massive or continuous intrathoracic bleeding
3. Open pneumothorax with major chest wall defect
4. Aortogram indicating injury to aorta or major branch
5. Massive or continuing air leak, indicating injury to a major airway
6. Cardiac tamponade
7. Esophageal perforation
8. Diaphragmatic rupture
9. Impalpable pulse with cardiac massage

In most cases of thoracic trauma, the child is physiologically stable. After initial resuscitation, the next step is the detailed secondary survey. To avoid missing a significant injury, a complete and careful assessment is essential. In nearly all cases, a history that suggests significant impact to the chest can be elicited. Therefore it is crucial to obtain as much information as possible regarding the details of the accident. Children involved in motor vehicle accidents, occupants and pedestrians alike, demand especially careful assessment. A history of difficulty breathing also indicates significant thoracic injury.

A systematic physical examination of the chest by inspection, percussion, palpation, and auscultation is the next step of the secondary survey. Tachypnea and tenderness and abrasions of the chest wall are predictive of intrathoracic injury.[15,16] One should look for cyanosis, dyspnea, noisy breathing, tracheal deviation, hoarseness or stridor, subcutaneous emphysema, open or sucking chest wounds, reduced or absent breath sounds, venous engorgement, pulsus paradoxus, and hypotension. Dyspnea and cyanosis suggest inadequate oxygenation. Noisy breathing may result from an injury to the airway or the presence of foreign material, such as blood, mucus, or vomitus. Tracheal deviation implies tension pneumothorax or massive hemothorax. Hoarseness, stridor, or other difficulty with phonation suggests direct laryngeal or tracheal injury. Surgical emphysema suggests a tracheal or bronchial laceration or, on rare occasions, an esophageal perforation. Jugular venous engorgement, hypotension, and pulsus paradoxus greater than 10 mm Hg imply cardiac tamponade. The patient should also be checked for signs of acute aortic coarctation, which can be caused by injury to the thoracic aorta. The most sensitive sign of a significant cardiac injury is hypotension or a large fluid requirement that is not explained by bleeding. A cardiac injury may also cause a loud systolic murmur. Acute congestive heart failure may result from valvular injury or a traumatic ventricular septal defect.

Holmes and colleagues developed a set of clinical predictors for the presence of chest injuries in a group of children less than 16 years old with blunt torso trauma.[17] The strongest predictors were hypotension, increased respiratory rate, abnormal physical examination of the thorax, associated femur fracture, and Glasgow Coma Scale (GCS) less than 15. Ninety-eight percent of proven cases had at least one of these predictors. Inspection and palpation were the most sensitive, but abnormalities detected on auscultation had the highest positive predictive value. This confirms the importance of clinical assessment in children with blunt trauma. The most common injuries were lung contusion, pneumothorax, and rib fracture, in that order.

In recent years, bedside surgeon–performed ultrasonography (US) has proven helpful in assessing abdominal trauma, and US is now a routine part of the clinical assessment of all major trauma cases.[18] US also has a role in chest trauma. It is sufficiently accurate to be clinically useful in diagnosing

pneumothoraces, hemothoraces, and pericardial effusions.[18–20] Recent reports document that surgeon-performed ultrasonography in the emergency department (ED) is an accurate screening test for the presence of a pneumothorax.[19,21]

Because it lacks sensitivity and specificity, clinical assessment is routinely supplemented by diagnostic imaging, usually the key step in identifying those children who need an operation.[22] Plain chest radiographs are routine, although Bokhari suggests that they are not necessary in blunt trauma cases with a completely normal chest physical examination.[15,23] A standard posteroanterior and lateral examination is best, but a supine anteroposterior film will suffice. The chest radiograph should be repeated on arrival at the trauma center even if the patient has been transferred from another hospital. The important signs of chest injury on plain chest radiographs include subcutaneous emphysema, fractures to the rib or other bony structures, hemothorax, pneumothorax, contusion or other parenchymal lesion (e.g., aspiration pneumonia), mediastinal shift or widening, and diaphragmatic rupture.

Computed tomography (CT) gives greater detail than plain radiographs and is more sensitive in the diagnosis of pneumothorax, rib fracture, and pulmonary contusion. It may also help in the diagnosis of ruptured diaphragm. Because chest films are not 100% sensitive, some groups have recommended that CT be used to screen all patients suspected of having a chest injury. However, this is not proven, and plain chest radiographs are still the standard screening tool for chest trauma.[24] The most common injuries identified by CT are pulmonary contusions and lacerations.[25] Many pneumothoraces revealed by CT are either not evident or underestimated on plain films. CT gives greater detail than plain radiographs in pulmonary contusions.[25] Manson concluded that plain radiographs, especially those obtained in the trauma resuscitation room, are only “a gross screening examination” for thoracic injury and recommended dynamically enhanced CT in all cases of significant thoracic trauma diagnosed clinically or by plain radiograph. In such cases, CT will give better definition of the injuries already recognized and may well reveal occult injuries not visible on plain radiographs. Exadaktylos and colleagues support this view.[26] In their experience, CT revealed potentially life-threatening aortic injuries, even when the plain chest radiographs were normal. They recommended routine chest CT in all patients with major chest trauma. Renton and colleagues studied the question of whether CT should replace routine chest radiograph as the initial diagnostic imaging test of choice.[27] They concluded that it should not, mainly because the increased cost was not justified by the relatively few changes in management that resulted from the use of CT scans. They estimated that 200 CTs would have to be done for each clinically significant change in management. In summary, CT should not be used liberally in cases of suspected chest injury.

Occasionally, other diagnostic tests, including ultrasonography, transthoracic or transesophageal echocardiography, bronchoscopy, radionuclide bone scan, angiography, and even video-assisted thoracic surgery are also helpful. Ultrasonography is more sensitive than supine anteroposterior (AP) chest radiographs and equally sensitive to CT in the diagnosis of traumatic pneumothorax.[28] Recent case reports document the use of video-assisted thoracic surgery to diagnose pericardial rupture and herniation of the heart.[29] In cases of suspected child abuse, a radionuclide bone scan helps to detect recent and long-standing rib fractures. Although impractical in most emergencies, MR is very helpful in defining injuries to the thoracic spine, especially when spinal cord involvement is suspected. It may also help identify diaphragmatic injuries in equivocal cases.[30]

For many years angiography has been the gold standard for the diagnosis of injuries to the aorta and its main branches. However, there is a clear trend to use helical CT as the initial test for suspected aortic injury, reserving aortography for proven cases to guide the repair, or, in some reports, eliminating aortography entirely.

Transthoracic echocardiography is a very useful way to diagnose all types of structural heart injury and ventricular dysfunction caused by contusion. Transthoracic echocardiography may reveal intracardiac injuries or pericardial tamponade. Transesophageal echocardiography is a useful screening test for traumatic rupture of the aorta. It can identify the cause of mediastinal hematomas seen on plain radiographs or CT scan.[31]

Pericardiocentesis may be used for diagnosis when cardiac tamponade is suspected and echocardiography is unavailable. All patients with thoracic trauma should have continuous echocardiographic monitoring during assessment in the ER. A full 12-lead echocardiogram should be obtained in cases of suspected cardiac contusion to rule out an arrhythmia. Bronchoscopy should be done in the operating room under general anesthesia in cases of suspected major airway trauma.

## Treatment

The treatment of thoracic injuries varies from supportive only (oxygen, analgesia), to simple interventions (endotracheal intubation, ventilation, tube thoracostomy) to operation (minimally invasive, open thoracotomy), depending on the specific structures injured and the severity of the injuries. However, most patients do not require an operation and can be managed with supportive measures, with or without tube thoracostomy.[32]

The ideal location for the incision when an operation is indicated varies depending on the preoperative diagnosis. An anterolateral incision in the fifth interspace, which can be extended across the midline, is best in an emergency. A trapdoor incision, which may be best, has been described for vascular injuries in the upper mediastinum. For esophageal injuries, a right posterolateral thoracotomy gives adequate exposure, except for the most distal thoracic esophagus, which is best viewed from the left. Median sternotomy is best for cardiac injuries. Heart–lung bypass is only rarely needed emergently for such injuries as coronary artery laceration and laceration of the thoracic aorta. Intracardiac injuries to the atrioventricular valves or the atrial or ventricular septae do require bypass, but they can be repaired semielectively. Injuries to the root of the neck or shoulder can be approached through a supraclavicular extension of a median sternotomy.

The concept of damage control, which is now well established for intra-abdominal trauma, can also be applied in selected cases of intrathoracic injury. Nonanatomic resection of the lung to control bleeding and massive air leak, pulmonary tractotomy with a gastrointestinal anastomosis (GIA) stapler

for through and through wounds of the lung, en masse pneumonectomy, and hilar twist[33] all may be lifesaving. The latter has been reported in cases of uncontrollable bleeding or air leak from the lung. The inferior pulmonary ligament is divided, and the lower lobe is twisted anteriorly over the upper lobe. This controls the situation so that the patient can be taken back to the intensive care unit (ICU) for stabilization and returned to the operating room (OR) later for definitive control, usually by pneumonectomy. The EndoGIA stapler (Covidien, Mansfield, MA) with vascular staples is very useful for rapid control of major pulmonary vessels in damage control.

## BLUNT INJURIES

### Chest Wall

***Soft Tissue*** Although seldom clinically important, injuries to the soft tissue of the chest wall suggest the possibility of more serious associated intrathoracic injuries. Soft tissue injuries to the chest wall should be managed according to accepted principles of wound care.

***Rib Fractures*** In childhood, the ribs are strong and pliable. Therefore rib fractures are less common than in adults and flail chest is quite rare. Because rib fractures require a great deal of force, they are an indication of severe injury. Fractures of the first rib suggest the possibility of a major vascular injury, especially to the subclavian artery.[34] First rib fractures may also be complicated by Horner syndrome and thoracic outlet syndrome.

The goal of treatment is to prevent atelectasis and pneumonia while optimizing patient comfort. The treatment of rib fractures includes rest and analgesia. Oral or intravenous narcotics are usually sufficient for pain control. Intercostal nerve blocks may also be helpful. Children rarely experience pulmonary atelectasis from splinting of the chest wall. Rib fractures usually heal spontaneously within 6 weeks. The overall mortality rate for children with rib fractures in the National Pediatric Trauma Registry was 10%.[5]

Rib fractures in infants and toddlers less than 3 years old are often caused by child abuse.[35,36] The likelihood of nonaccidental injury in children with one or more rib fractures decreases with increasing age.[36] In cases of child abuse, the typical site of fracture is the neck of the rib near the costotransverse process articulation. Kleinman and colleagues[37] described fractures of the head of the rib in abused infants, which are usually undetectable on radiographs because the head is cartilaginous. Cystic lesions of the ribs that are located posteriorly are another indication of child abuse,[38] as are multiple rib fractures at varying stages of healing.

***Flail Chest*** Flail chest is relatively uncommon in children. It occurs when a segment of the chest wall is destabilized when several adjacent ribs are fractured. The injured chest wall moves paradoxically—*in* during inspiration and *out* during expiration. Ventilation is inefficient because of the paradoxical movement. Flail chest is usually associated with a lung contusion. Chest wall splinting and ineffective coughing often compound the primary injury. This leads to consolidation and collapse of the affected lung, which, in turn, result in a ventilation/perfusion (V/Q) mismatch and hypoxia.

Initial treatment of flail chest includes supplemental oxygen, pain relief (intercostal nerve blocks, oral or intravenous narcotics, or an epidural blockade given as a continuous infusion), and physiotherapy. Fluid therapy must be carefully monitored to avoid pulmonary edema, and intensive care monitoring is advisable. Children with isolated flail chest and no other significant injuries seldom require ventilation. If respiratory failure develops, endotracheal intubation and positive-pressure ventilation with positive end-expiratory pressure may be required for several days. Tracheotomy is rarely necessary. In the National Pediatric Trauma Registry, the overall mortality rate for patients with flail chest was 40%.[5]

***Sternal Fractures*** Sternal fractures are less common in young children than in adults, because the sternum is cartilaginous.

### Lung and Airway

***Pneumothorax*** Pneumothorax can result from an injury to the chest wall, the lung parenchyma, the tracheobronchial tree, or the esophagus. High energy is required to produce a pneumothorax; so, it must be considered a marker for other occult injuries.

**Simple Pneumothorax** Simple pneumothorax may cause chest pain, respiratory distress, tachypnea, decreased air entry on the affected side, and oxygen desaturation. Careful examination may reveal an abrasion of the chest wall, crepitus, or tracheal shift. However, many patients show no clinical signs or symptoms. This underscores the importance of routine chest radiographs for all trauma cases. The radiographic signs include unilateral or asymmetric lucency, a sharp outline of the mediastinum, mediastinal shift, and a visible visceral pleural border away from the chest wall. The diagnosis of simple pneumothorax should be confirmed by chest radiography before treatment.

Simple pneumothoraces should be treated by intercostal chest tube drainage (Fig. 19-1). The best location for chest tube insertion is the fourth or fifth intercostal space (nipple level) in the anterior axillary line. The recommended chest tube sizes are as follows: newborns, 12 to 16 Fr; infants, 16 to 18 Fr; school-age children, 18 to 24 Fr; and adolescents, 28 to 32 Fr. Safe chest tube insertion requires training and experience to minimize complications.[39,40] The chest tube should be connected to an underwater seal on gentle suction and removed when the air leak stops. For most cases, this is the only treatment necessary. A continued or massive air leak suggests injury to the tracheobronchial tree.

A small, asymptomatic pneumothorax may be observed in carefully selected cases. If the patient is to be transferred to another hospital or intubated and ventilated for any reason, or if the pneumothorax exceeds 15%, it should be drained. When in doubt, a chest tube should be inserted.

**Open Pneumothorax** Open pneumothorax is rare in children. In cases of open pneumothorax, the intrapleural pressure is equal to that of the atmosphere. As a result, the lung collapses and alveolar ventilation decreases. Sucking wounds should be recognized clinically. They may be treated by insertion of a Heimlich valve or applying an occlusive dressing to the wound, taping the dressing on three sides only so that it can act as a flutter valve, and inserting a chest tube in the usual location.

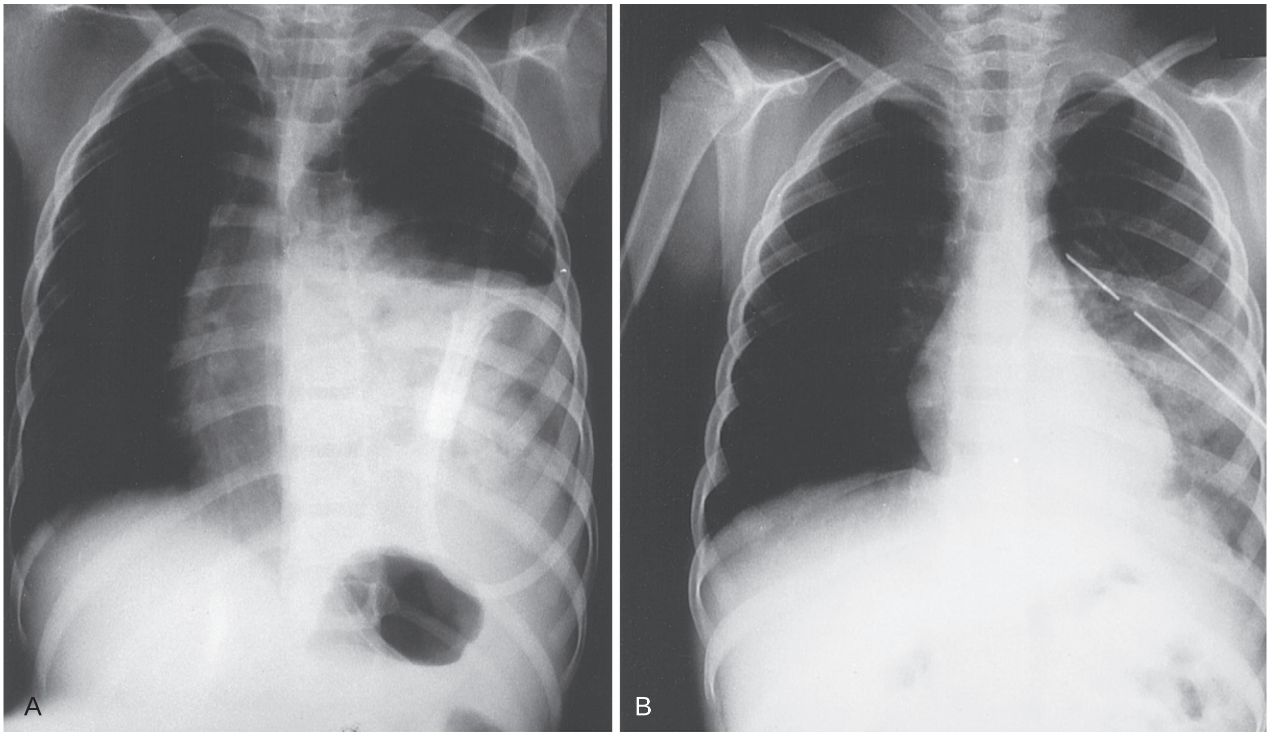


FIGURE 19-1 **A,** Left hemopneumothorax; note the nasogastric tube in situ. **B,** Same patient after insertion of intercostal drain; no other treatment was required. (From Wesson DE: Trauma of the chest in children. Chest Clin North Am 1993;3:423-441. Used with permission.)

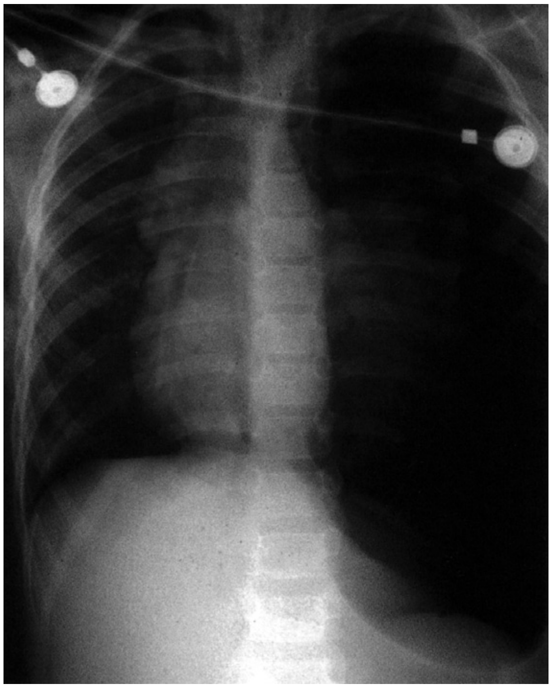

FIGURE 19-2 Tension pneumothorax. Pneumothorax resulting from blunt thoracic trauma in a 4-year-old boy run over by a school bus. He was unconscious when seen in the emergency department, and no breath sounds could be heard in the right chest. The trachea was shifted toward the left. The suspected pneumothorax on the right was treated initially with needle aspiration and then a chest tube inserted. (From Haller JA Jr, Shermeta DW: Acute thoracic injuries in children, Pediatr Ann 1976;5:71-79. Used with permission.)

**Tension Pneumothorax** Tension pneumothorax may develop when a one-way valve effect occurs, allowing air to enter the pleural space but not to escape (Fig. 19-2). The underlying cause is usually a pulmonary laceration or an injury to the trachea or a large bronchus. The intrapleural air pressure exceeds that of the atmosphere, collapses the ipsilateral lung, pushes the mediastinum to the opposite side, flattens the diaphragm, impairs ventilation of the opposite lung, and reduces return of venous blood to the heart. The pulse and respiratory rate increase, and the patient becomes severely distressed. The trachea is usually deviated away from the involved side, and the neck veins may become engorged. The ipsilateral side of the chest is hyperresonant to percussion with diminished breath sounds. Frank cyanosis is a late sign. The most important differential diagnosis is pericardial tamponade. However, this disorder can be distinguished from tension pneumothorax, because the trachea is not displaced and the chest is normal to percussion. Tension pneumothorax should be considered when an injured patient, especially one on a mechanical ventilator, suddenly deteriorates for no apparent reason. Both acute gastric dilation and right mainstem intubation may result in diminished breath sounds on the left, and should not be confused with a tension pneumothorax.

The treatment for tension pneumothorax is immediate needle-catheter drainage (without waiting for chest radiographs) through either the second intercostal space in the midclavicular line or the fourth or fifth interspace in the axilla, followed by insertion of a chest tube.

***Hemothorax*** When enough blood is lost into the thorax to cause shock, the term massive hemothorax is used. Massive hemothorax is more common after penetrating than blunt trauma.

Hemothorax may result from a laceration of an intercostal or internal mammary artery, the lung, or a mediastinal blood vessel. Free bleeding into the pleural space from a major vessel, such as the aorta or one of the pulmonary hilar vessels, is usually rapidly fatal. Most bleeding from the lung stops spontaneously because of the low pressure in the pulmonary circulation. Bleeding from a systemic vessel, such as an intercostal artery, is more likely to cause massive hemothorax producing signs of hypovolemia, mediastinal shift, diminished breath sounds, and dullness to percussion on the affected side. Hemothorax is often associated with pneumothorax (see Fig. 19-1). The treatment is intercostal drainage to prevent a clotted hemothorax and to monitor the rate and total volume of blood loss. It is wise to establish two large-bore intravenous catheters, begin treatment for shock, if present, and obtain blood for transfusion before draining a massive hemothorax, because it may precipitate further bleeding. However, drainage and reexpansion of the lung usually stop the bleeding.

In most cases, intercostal drainage is the only treatment needed. However, thoracotomy may be indicated for the following reasons:

1. Initial drainage exceeds 20% to 25% of estimated blood volume
2. Continued bleeding exceeds 2 to 4 mL/kg/hour
3. Bleeding is increasing
4. The pleural space cannot be drained of blood and clots

Hoth and colleagues reported an increased likelihood of nontherapeutic exploration when thoracotomy is performed for increased chest tube output of blood in blunt trauma.[41] Auto-transfusion may be helpful during surgery for massive intrathoracic bleeding.

### Lung

***Hematoma and Contusion*** Pulmonary contusion is the most common type of blunt injury to the chest in children. Direct force to the lung causes disruption of the parenchyma, bleeding, and edema in a nonanatomic distribution, often without obvious injury to the chest wall. Specific clinical signs or symptoms are seldom evident at presentation, although rib fractures and abrasions over the chest may be present.

Because of the lack of specific physical features, routine chest radiographs are the key to the diagnosis of hematoma and contusion. Pulmonary contusions are usually obvious on plain radiographs taken at admission (Fig. 19-3) and are even more striking on CT, which has shown that they usually lie posteriorly or posteromedially.[25] However, there is no need for a CT when a contusion is obvious on plain films. Pulmonary contusions may be progressive, especially when compounded by edema and atelectasis. Children with pulmonary contusions seldom require mechanical ventilation and almost never develop adult respiratory distress syndrome. The differential diagnosis includes aspiration pneumonia, which can result from aspiration at the scene, en route, during intubation, or with vomiting after admission. It affects the right lower lobe most frequently.

Patients with extensive lung hematomas or contusions should be monitored carefully with continuous $SaO_2$ measurements, preferably in an intensive care unit. The treatment for these disorders is supportive, with analgesia, physiotherapy, supplemental oxygen, and fluid restriction. Endotracheal intubation and mechanical ventilation are less likely to be needed for children than for adults. Deterioration after admission is unusual.[42] It is important to guard against overhydration and aspiration of gastric content. The most common complication is infection of the lung. Most pulmonary hematomas and contusions clear within 10 days, unless the lung becomes infected.

Pulmonary contusions may be complicated by pneumothorax, hemothorax, or pleural effusion, all of which may require intercostal drainage. These secondary phenomena are much more common in the presence of concomitant fractures of the bones of the chest wall and may be delayed as long as 48 hours. Therefore serial chest radiographs should be obtained in cases of pulmonary contusion (see Fig. 19-3).

Occasionally, a post-traumatic pneumatocele forms when the injured lung cavitates during healing. Because pneumatoceles usually resolve spontaneously in a few months, treatment is seldom necessary.

### Laceration

Pulmonary lacerations are most often seen after penetrating injuries and usually result in a pneumothorax or hemothorax. They may also be caused by rib fractures.

Air embolus is the most serious complication of pulmonary laceration. This diagnosis should be suspected in all children with thoracic trauma who suddenly deteriorate, especially while receiving positive-pressure ventilation in the absence of a pneumothorax. Air embolus may cause focal neurologic deficits. Frothy blood aspirated from an arterial cannula is a telltale sign. Emergency thoracotomy, clamping of the pulmonary hilum, and aspiration of the air from the heart or right ventricular outflow tract may be lifesaving.[43]

***Trachea and Bronchi*** Injuries to the major airways are uncommon in children. Nearly all are caused by blunt trauma.[5] The most common specific lesions are partial or complete transections of one of the main bronchi and tears of the membranous trachea. Airway injuries usually occur within 2 to 3 cm of the carina and may be rapidly fatal if not recognized and treated promptly.

Some patients with major airway injuries die from respiratory failure before reaching the hospital or shortly thereafter. Most present with dyspnea, which is often caused by tension pneumothorax. Other characteristics of patients with major airway injuries are voice disturbance, cyanosis, hemoptysis, massive subcutaneous and mediastinal emphysema, and failure of expansion of the lung or continuing large-volume air leak despite properly functioning chest tubes. Failure of the lung to expand or a continuous massive air leak after intercostal drainage strongly suggests a major airway injury (Fig. 19-4). Although not common, "dropped lung," in which the lung actually falls to the lower half of the pleural cavity below the level of the injured bronchus, is virtually diagnostic of a major airway injury. Finally, some patients present late with chronic collapse and infection of the involved lung from bronchial obstruction.

Initial management in the trauma room depends on the clinical situation. The initial treatment of airway injuries is to control the airway and breathing according to the ATLS protocol. This may require endotracheal intubation and intercostal drainage. If the patient has a good airway and is well oxygenated, it is prudent not to manipulate the airway by attempting intubation before taking the patient to the OR. Flexible bronchoscopy may facilitate endotracheal intubation

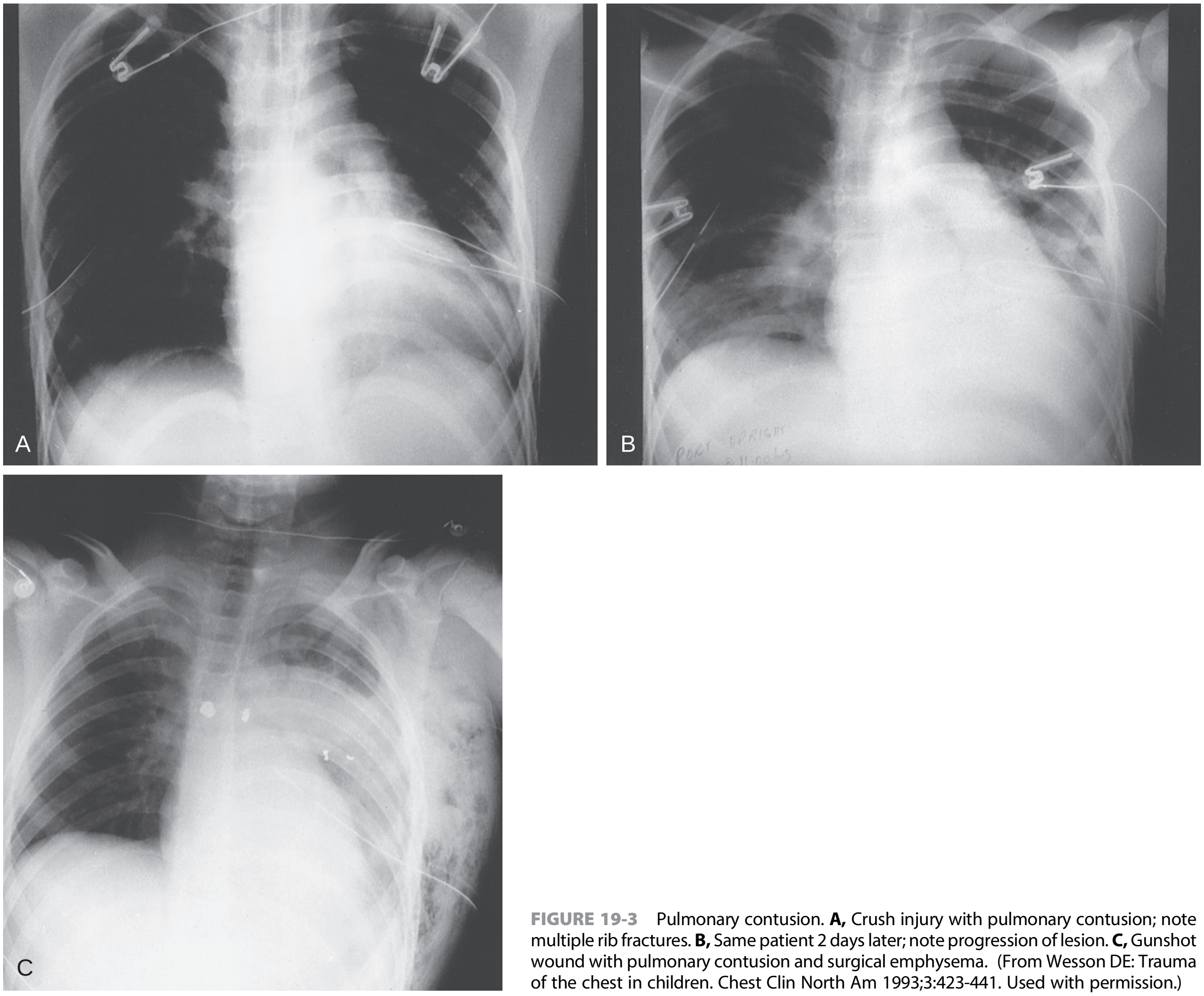


**FIGURE 19-3** Pulmonary contusion. **A,** Crush injury with pulmonary contusion; note multiple rib fractures. **B,** Same patient 2 days later; note progression of lesion. **C,** Gunshot wound with pulmonary contusion and surgical emphysema. (From Wesson DE: Trauma of the chest in children. Chest Clin North Am 1993;3:423-441. Used with permission.)

beyond the site of the injury or selective intubation of the uninjured bronchus. High-frequency ventilation may be more effective than conventional methods in the presence of a massive air leak and may facilitate stabilizing the patient for surgical repair.[44]

Helical CT may be a good initial test in stable patients with suspected major airway injuries, but bronchoscopy is more reliable. Bronchoscopy is indicated whenever the lung fails to expand or a massive air leak continues after intercostal drainage. It should be done in the operating room under general anesthesia; a rigid, ventilating bronchoscope should be used. If possible, the patient should be allowed to breathe spontaneously during induction of anesthesia and passage of the bronchoscope. Staff and equipment for thoracotomy must be at hand. In unstable patients or those with possible or confirmed cervical spine injuries, flexible bronchoscopy with the patient awake or through an endotracheal tube may also reveal the lesion. At bronchoscopy, a defect in the wall of the airway may be visible. Other bronchoscopic signs of injury include mucosal disruption or exposed cartilage.

Spontaneous healing is the rule for small lacerations in the membranous trachea and some partial bronchial tears involving up to one third of the circumference.[45] These may be treated nonoperatively. For larger lacerations of the trachea or bronchi, primary surgical repair through a posterolateral thoracotomy is the best way to ensure good long-term results. Distal injuries to a lobar or segmental bronchus may be treated by lung resection rather than direct repair. The right side of the chest allows the best exposure of the trachea, carina, and right main bronchus; the left side gives better exposure for injuries to the distal left main bronchus. In the presence of a massive air leak, it may be necessary to clamp the hilum before attempting to repair the airway. Advancing the endotracheal tube or passing a sterile tube across the surgical field into the distal airway may also be helpful during the repair. Simple, interrupted sutures after debridement of the margins work best. Although lobectomy or pulmonary segmentectomy may be necessary, pulmonary resection is done only as a last resort in unstable patients or when the lung is extensively damaged. The late functional results of pulmonary resection or bronchial repair are usually excellent.[46]

**FIGURE 19-4** This patient had a sustained air leak associated with blunt thoracic injury despite adequate chest tube drainage. Blood was noted in the right upper lobe bronchus, and contrast injection demonstrated the location and extent of the leak, which was controlled by the injection of fibrin glue and chest tube drainage. Operative closure or resection is sometimes required.

Asymptomatic pneumomediastinum is often detected on chest CT during the evaluation of the multiple injury patient. Recent studies have demonstrated that there is an exceedingly low incidence of aerodigestive tract injuries presenting with pneumomediastinum alone.[47–49]

Bronchial injuries that are missed initially may seal spontaneously, but there is a risk of stenosis. After months or years, children with spontaneously sealed bronchial injuries may have persistent atelectasis often with pneumonia or frank bronchiectasis in the involved lung caused by a bronchial stricture. The diagnosis can be confirmed by bronchography or bronchoscopy. This type of stricture can be dilated in some cases. Open repair or even resection of the involved lung is usually necessary. One report illustrates that late repair of a completely transected main stem bronchus with preservation of the lung is possible.[50]

***Esophagus*** The most common causes of esophageal injury are ingestion of caustic liquids and penetrating trauma, which includes iatrogenic instrumentation. Forceful vomiting and retching rarely cause esophageal tears in childhood. External blunt trauma rarely causes esophageal injury. The mechanism of esophageal injury from blunt trauma is believed to be a sudden increase in intraesophageal pressure caused by expulsion of gas from the stomach through the gastroesophageal (GE) junction.

Esophageal perforations cause fever, chest pain, and tachycardia. Occasionally, subcutaneous emphysema develops in the neck. Mediastinal or intrapleural air may be visible on routine chest radiographs or CT. If esophageal injury is suspected, a water-soluble contrast swallow, endoscopy, or both should be done.

When diagnosed within the first 12 hours, esophageal injuries are best treated by primary closure, and drainage. When diagnosed later and for more destructive lesions, they may require salivary diversion by means of a cervical esophagostomy and gastrostomy in addition to thoracic drainage. Alternatively, the repair can be buttressed by a neurovascular intercostal muscle pedicle flap. The flap can be secured akin to a modified Graham closure after primary repair, or it can be used to augment the extramucosal repair.[51] There has been a growing, favorable experience with endoscopic stenting of esophageal perforations/leaks in adults, and this may be an alternative to standard approaches in some circumstances.[52]

***Diaphragm*** Although rare in children, diaphragmatic injuries can be caused by a forceful impact to the abdomen or by a penetrating missile. It is important to recognize these injuries, because the stomach and bowel may herniate through the defect and strangulate. Ninety percent of diaphragmatic injuries occur on the left side. In blunt trauma, tears are usually in or near the central tendon and oriented radially.

Diaphragmatic injuries are easily missed at initial presentation, especially because they are often associated with other severe injuries. They may be asymptomatic or cause abdominal, thoracic, or ipsilateral shoulder tip pain. Physical examination is rarely helpful in the diagnosis of diaphragmatic injuries. The diagnosis is usually based on the plain chest radiograph, which is the most important diagnostic test (Fig. 19-5). Table 19-3 summarizes the radiographic signs of diaphragmatic injury. Basically, any abnormality of the diaphragm or near the diaphragm on plain chest radiography should arouse suspicion. Chest radiographs are initially normal in 30% to 50% of cases.[53] Therefore repeat radiographs should be obtained if a diaphragmatic injury is suspected.

Because other injuries often dominate the clinical picture, delayed diagnosis of a diaphragmatic injury is common. At first, herniation of abdominal viscera into the chest may not have occurred, especially in patients receiving mechanical ventilation. However, the negative intrathoracic pressure of normal breathing may gradually draw the stomach and bowel up into the chest. This can be recognized on plain radiographs, especially if the stomach herniates with a nasogastric (NG) tube in place. In the absence of an NG tube, acute dilation of the herniated stomach may develop leading to severe respiratory distress.

The diagnosis may be confirmed, if necessary, by contrast upper- or lower-intestinal studies. However, these studies may not be possible in patients with multiple acute injuries. Here, CT with multiplanar reconstruction may be helpful. The signs of diaphragmatic injury on CT include discontinuity of the diaphragm, herniation of intra-abdominal viscera into the chest, and constriction of the stomach as it passes through the defect.[54] In stable patients, MR may also help to establish the diagnosis.

Some patients present late with obstruction or strangulation of the herniated gut. This causes severe abdominal or chest pain (or both), nausea, and vomiting. Primary repair through an abdominal incision is indicated. The usual repair is by open laparotomy, but several recent reports of laparoscopic repair demonstrate the feasibility of this approach.[55,56]

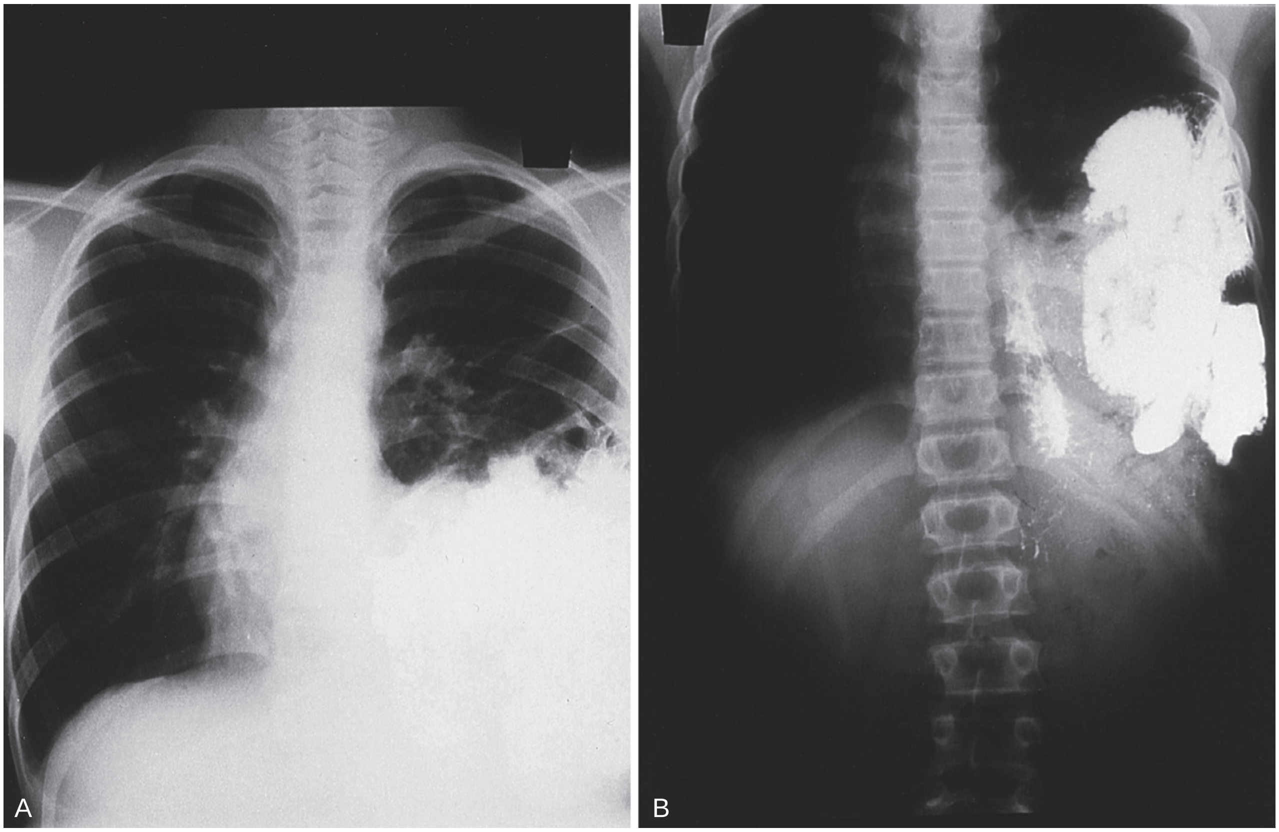


**FIGURE 19-5** Ruptured diaphragm. **A,** Plain chest radiograph. **B,** Herniated bowel on gastrointestinal contrast study.

**TABLE 19-3**
**Radiographic Signs of Diaphragmatic Injury**

1. Obscured hemidiaphragm
2. Elevated hemidiaphragm
3. Herniated viscera causing abnormal gas pattern above the diaphragm
4. Tip of nasogastric tube curled up into the chest
5. Atypical pneumothorax
6. Platelike atelectasis adjacent to the diaphragm

## Heart and Pericardium

Blunt trauma to the heart can produce several types of injury: concussion, contusion, or frank rupture of the myocardium, a valve, or septum.[57,57a] Although rare, disruption or thrombosis of a coronary artery may also occur. A tear of the pericardium may allow herniation of the heart into the pleural space, thereby impairing cardiac function and causing a low output state. Occasionally, blunt trauma to the chest produces occult structural cardiac injuries without gross impairment of cardiac function, bleeding, or cardiac tamponade.[58] These injuries include atrial or ventricular septal defects, mitral or tricuspid insufficiency, and ventricular aneurysm formation. Often, the only sign is a new murmur or a change on the electrocardiogram. The diagnosis can be confirmed by echocardiography or cardiac catheterization. These injuries may be repaired electively once the patient is stable.[58] Follow-up echocardiography should be arranged in all cases of known or suspected injury to the heart.

Several case reports have appeared documenting sudden cardiac arrest in children after a direct blow to the chest. The term *commotio cordis* has been applied to this entity.[9,10] *Commotio cordis* occurs most often during organized sporting events such as baseball. No contusion or other sign of injury can be found at autopsy, and death has usually been attributed to ventricular fibrillation.

When performing emergency surgery for cardiac trauma, the surgeon should bear in mind a few simple rules:

1. Prepare and drape the entire chest.
2. Place the incision in the left fourth or fifth interspace in an anterolateral direction (except for stable patients undergoing elective repair of known cardiac injuries, which should be repaired through a median sternotomy).
3. Avoid the phrenic nerve when opening the pericardium.
4. Apply direct pressure to control the bleeding.
5. Suture the heart using pledgets as required, avoiding the main coronary arteries.
6. Leave the pericardium open.

Some authors have reported the use of skin staples to control cardiac wounds. Direct suture is preferable. A Foley catheter may be introduced through the defect to control the bleeding during repair.

Although most cardiac injuries can be repaired without cardiopulmonary bypass, this option should be available. During the operation, the surgeon should always check for a thrill, which might indicate a ruptured valve or traumatic ventricular septal defect. Intraoperative trans-esophageal echocardiography may be a useful adjunct to diagnose traumatic septal and valve injuries as well as monitor the integrity of any repair. It is also important to check for intracardiac lesions by listening for new murmurs and performing

echocardiography in the postoperative period. Follow-up echocardiography should also be done after discharge.

***Myocardial Contusion*** Myocardial contusion is the most common type of blunt cardiac injury. It produces focal damage to the heart that can be identified histologically. It can cause life-threatening arrhythmias and cardiac failure. Treatment is aimed primarily at these complications.

Contusion can be distinguished from concussion and *commotio cordis* because the latter do not produce any structural change, even at the microscopic level. Contusions are usually, but not always, associated with an injury to the chest wall. Myocardial contusions may be completely silent or cause an arrhythmia (supraventricular tachycardia or ventricular fibrillation) or hypotension secondary to reduced cardiac output.

Unfortunately, although many tests have been proposed, including electrocardiography, echocardiography, myocardial enzyme determinations (creatine kinase–myocardial band [CKMB], cardiac troponin I, and troponin T), and radionuclide scans, there is no definitive diagnostic test for cardiac contusion. This makes it difficult to define the indications for any of the currently available diagnostic tests and even more difficult to decide on treatment. Tellez and colleagues concluded that a "comprehensive diagnostic evaluation of the heart in all children sustaining multiple injuries from blunt trauma cannot be justified."[59] The simplest test is a 12-lead electrocardiogram, which may reveal reversible changes to ST segments and T waves. Echocardiography may show reduced ejection fraction, localized systolic wall motion abnormality, or an area of increased end-diastolic wall thickness and echogenicity. Swaanenburg and colleagues found that cardiac troponin I and T levels were more accurate and reliable than any of the other diagnostic tests in selecting patients for ICU monitoring.[60–62] They recommended a repeat analysis after admission for patients suspected of having myocardial contusion who have normal values at admission.

A prospective study of 41 children with blunt thoracic trauma, which used a battery of tests that included serum enzyme levels, electrocardiography, echocardiography, and pyrophosphate myocardial scanning, revealed a high incidence of abnormal tests. However, there was little correlation among the tests or between any of the tests and the clinical course.[63] The authors concluded that myocardial contusion is rarely clinically significant in pediatric thoracic trauma. For practical purposes, significant myocardial contusion can be ruled out when findings on 12-lead electrocardiography and echocardiography are normal.

Treatment of myocardial contusion includes electrocardiographic monitoring for 12 to 24 hours, frequent blood pressure determinations and inotropic support as indicated. Complications tend to occur early in the disorder or not at all.[64] Tellez and colleagues recommended cardiac monitoring in the emergency room and intensive care unit to identify arrhythmias and, in patients with arrhythmias and obvious thoracic injuries, serial electrocardiograms and cardiac enzyme tests.[59] Rarely, patients may suffer profound myocardial dysfunction after myocardial contusion. Extracorporeal circulatory support has been useful in isolated cases with marked cardiac dysfunction after blunt trauma.[65] Consideration must be given to left ventricular decompression at the time of circulatory support to prevent distention and subendocardial ischemia.

***Myocardial Rupture*** Rupture of the heart is usually rapidly fatal. In fact, myocardial rupture is the most common cause of death from thoracic injury. In a population-based autopsy series, Bergman and colleagues found that two thirds of these patients died at the scene of the accident, and one third died in the emergency room.[4] Most cases of cardiac rupture result from high-energy impacts, such as those sustained in motor vehicle accidents or falls from great heights. The atria tend to rupture from impact occurring during late systole; ventricles rupture from impact during late diastole. The right ventricle is the most commonly ruptured site.

Children with myocardial rupture usually present with pericardial tamponade (discussed later). Myocardial necrosis, aneurysm formation, and delayed rupture may also occur.[66] Those with a traumatic atrial septal defect or ventricular septal defect may present with a new murmur without obvious cardiac failure. All patients with chest trauma should be checked carefully for a new murmur before discharge. Any new murmur is an indication for echocardiography. Occasionally, with early diagnosis and repair, patients can survive myocardial rupture.

***Valve Injury*** Valve injuries are rare but well recognized after blunt trauma.[67,68] Atrioventricular valves are most commonly injured, causing incompetence by damage of the annulus or rupture of the chordae tendinae or papillary muscle (Fig. 19-6). A diastolic murmur, and worsening pulmonary failure out of proportion to the initial pulmonary injury should prompt echocardiography and/or pulmonary artery catheterization to investigate the possibility of a valve injury. This is one type of blunt cardiac injury that can be repaired semielectively.

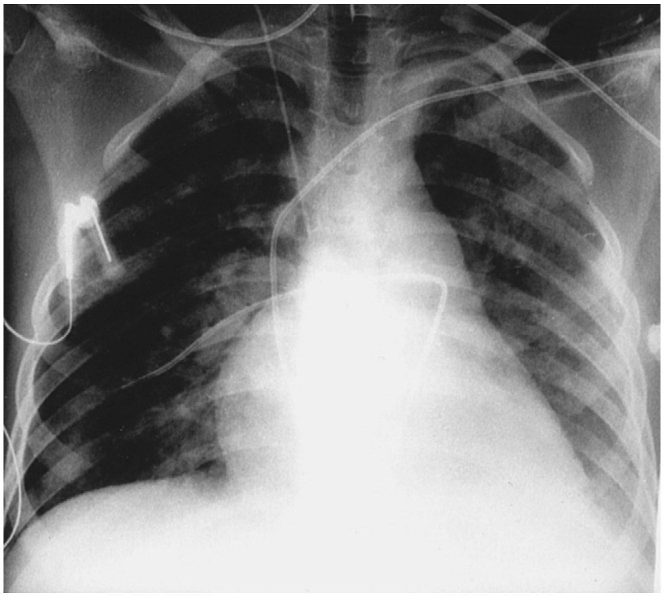

**FIGURE 19-6** Cardiomegaly and pulmonary edema 2 days after blunt chest trauma; note Swan-Ganz catheter. Torn mitral valve annulus and chordae tendinae were successfully repaired. (From Wesson DE: Trauma of the chest in children. Chest Clin North Am 1993;3:423-441. Used with permission.)

***Pericardial Tamponade*** Pericardial tamponade can result from an accumulation of blood in the pericardial sac after blunt trauma. The full spectrum of pericardial tamponade—pulsus paradoxus and the Beck triad (elevated jugular venous pressure, systemic hypotension, and muffled heart sounds)—rarely develops in patients with acute trauma. Pericardial tamponade is usually associated with tachycardia, peripheral vasoconstriction, jugular venous distention, and persistent hypotension, regardless of aggressive fluid resuscitation. In fact, pericardial tamponade should be suspected in all cases of unexplained hypotension, especially when it is associated with elevated jugular venous pressure. The best way to confirm the diagnosis is by transthoracic echocardiography, which can be performed by the surgeon at the bedside in conjunction with the FAST (focused abdominal sonography trauma) examination.[20,69]

Treatment of suspected pericardial tamponade begins with control of the airway and breathing plus restoration and expansion of the circulating blood volume. The diagnosis should be confirmed by echocardiography, which is the single best diagnostic tool. However, if the patient is in severe shock, needle-catheter drainage of the pericardial space may be lifesaving (Fig. 19-7). Therefore, in emergency situations or when echocardiography is not available, immediate pericardiocentesis is indicated. The needle should be inserted by the subxiphoid approach at a 45-degree angle upward and toward the left shoulder. A successful tap is confirmed by aspiration of nonclotting blood. A catheter should be inserted and left for repeated aspirations, if necessary, pending definitive treatment. Pericardiocentesis may be complicated by bleeding or damage to the left anterior descending coronary artery. If pericardiocentesis is positive, and does not stabilize the patient, immediate thoracotomy should be performed to relieve the tamponade and control the bleeding.

***Pericardial Laceration*** The pericardium may be torn by blunt trauma. The most common site is on the left, anterior to the phrenic nerve. The heart may herniate through the defect, impairing its function and reducing cardiac output. This type of injury may be recognized on CT or by video-assisted thoracic surgery.[54,70,71]

## Aorta and Great Vessels

Traumatic rupture of the aorta and its major branches is uncommon in children.[72] Eddy and colleagues reported that aortic injuries caused 2.1% of all traumatic deaths in children in King County, Washington.[73] Traumatic rupture of the aorta causes a higher proportion of traumatic deaths in adults (approximately 10%) than in children, probably because adult aortas are more brittle and easily torn. Predictors of aortic injury include hypotension, head injury, unrestrained motor vehicle occupant, pelvic fracture, extremity fracture, and other chest injuries. However, it is not clear which mechanism is a reliable predictor. Dyer found mechanism of injury to be "imperfect" and "subjective."[74] Horton found that $\Delta V$ greater than or equal to 20 mph and near-side passenger compartment intrusion of greater than or equal to 15 inches correlated strongly with aortic injury.[75]

Traumatic rupture of the aorta occurs with rapid deceleration, which applies shear stress to the wall of the aorta. The most common sites of injury are near the ligamentum arteriosum, the root of the aorta or one of the other main branch points, such as the take-off of the innominate, vertebral or carotid artery. Tears of the distal arch are usually located on the anteromedial aspect of the aorta and oriented horizontally. Children with Marfan syndrome are at risk for aortic dissection following blunt torso trauma.

Although it is usually rapidly fatal, in some cases, the adventitia and pleura contain the blood and prevent

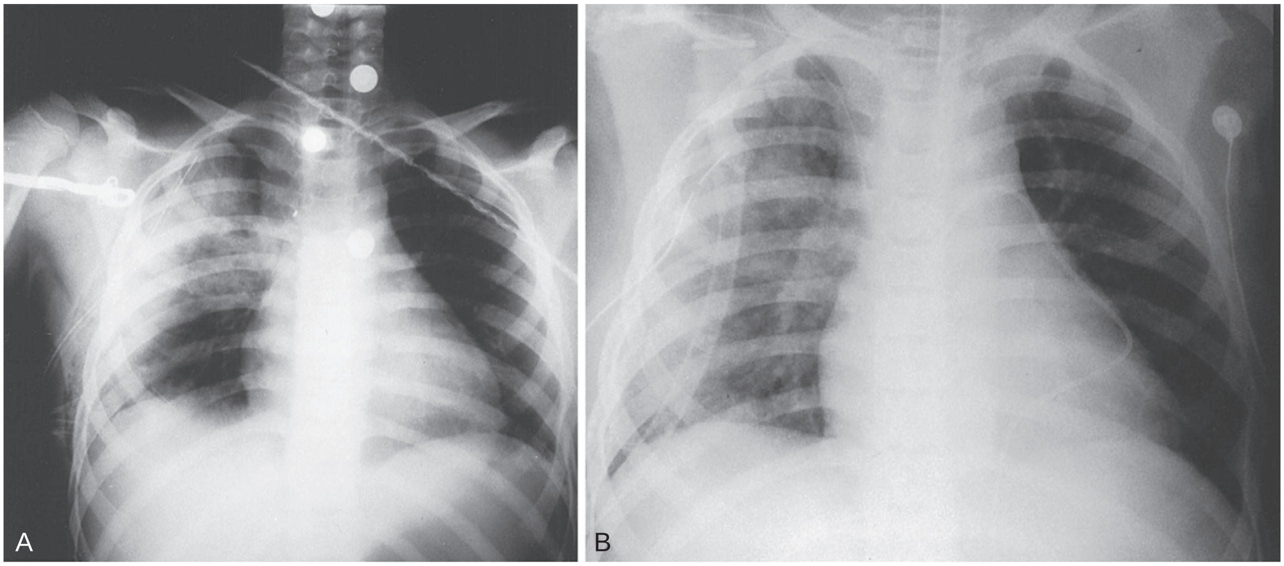


**FIGURE 19-7** Pericardial tamponade from blunt chest trauma. The patient was a rear seat passenger in a high-speed frontal collision. Seat belt mark over lower sternum. Shock unresponsive to fluid. Pericardial effusion on transthoracic echocardiography. **A,** Normal heart on plain chest radiograph with evidence of pulmonary contusion. **B,** Chest radiograph after catheter drainage of bloody pericardial effusion. No further treatment was required. (From Wesson DE: Trauma of the chest in children. Chest Clin North Am 1993;3:423-441. Used with permission.)

exsanguination. The natural history of patients who do not exsanguinate immediately is unknown, but imminent rupture in these patients is unlikely. Therefore it is unnecessary to rush them to the OR before stabilization, a full diagnostic workup, and treatment of other injuries. This may require laparotomy, craniotomy, or both before repair of the aorta.

The management of aortic injuries in children is essentially the same as in the adult.[76,77] Diagnosis is difficult, because there may be no clinical evidence of thoracic injury. The acute coarctation syndrome—upper limb hypertension, a difference in blood pressure between the upper and lower limbs, and a loud murmur over the precordium or back—is rare. DelRossi and colleagues reported a series of 27 cases of aortic injury without a single case of coarctation syndrome.[78]

The diagnosis is most often suggested by plain chest radiography, which is sensitive (false negatives, 2% to 7%) but not specific (false positives, 80%). The radiographic signs of traumatic rupture of the aorta are the same as described for adults (Table 19-4 and Fig. 19-8). Nearly all reported cases demonstrate widening of the mediastinum (mediastinum: chest ratio $> 0.25$) and an abnormal aortic contour.

Until recently, most authors referred to aortography as the gold standard diagnostic test. Many now believe that contrast-enhanced multislice helical CT, which is equally sensitive to aortography, has become the definitive test for diagnosing aortic injury (Fig. 19-9).[74,79–81] If the helical CT is normal, an aortogram is unnecessary. This has substantially reduced the number of negative aortograms done for patients with blunt chest trauma and suspicious plain radiographs. The techniques of helical CT and CT angiography have been reviewed by Melton and Rubin.[79,82] Timing of the contrast injection, as well as the volume and rate of infusion must be carefully controlled to yield optimal results. Helical CT costs about half as much as aortography.[80]

There is still a role for aortography in equivocal cases or to provide more anatomic detail before repair in proven cases.[83] However, many authorities now argue that helical CT alone is sufficient for management of aortic injuries.[79]

Transesophageal echocardiography (TEE) also has a role in the diagnosis of injuries to the descending thoracic aorta, especially for unstable patients in the ICU not able to go to radiology. It is not useful for injuries to the ascending aorta or its branches. Unfortunately, TEE is operator dependent and not universally available. Le Bret and colleagues noted three signs on TEE that are sensitive enough to screen patients for aortic injury.[31] These are increased distance (>3 mm) between the probe and the aorta, double contour of the aortic wall, and an ultrasonographic signal between the aorta and the visceral pleura. The sensitivity for diagnosing traumatic rupture of the aorta by transesophageal echocardiography in this report was 100%; the specificity was 75%. Le Bret proposed that TEE should be done in all cases of severe chest trauma. TEE is also useful in cases with equivocal findings on CT or aortography to avoid an unnecessary thoracotomy.[84]

**TABLE 19-4**

**Radiographic Signs of Aortic Injury**

1. Widened mediastinum (mediastinum:chest ratio $> 0.25$)
2. Loss or abnormal contour of aortic knob
3. Depression of left main bronchus (>40 degrees below horizontal)
4. Deviation of trachea (left margin to right of T4 spinous process)
5. Deviation of esophagus (nasogastric tube to right of T4 spinous process)
6. Left pleural cap
7. Left hemothorax

Once the diagnosis is proven the treatment options include open repair, endovascular stent graft, or even nonoperative observation in some cases. Aortic surgery carries a significant risk of complications, including intracranial hypertension, which may exacerbate bleeding, left ventricular strain, renal failure, and spinal cord ischemia. When used, heparin may increase the likelihood of bleeding at remote sites of injury.

A small intimal flap may heal spontaneously, but surgical repair after the patient has been stabilized (the bleeding at other locations should be repaired first) through a left posterolateral thoracotomy is the treatment of choice. Surgery may be safely delayed pending repair or control of associated severe injuries to the CNS, extensive burns, septic or contaminated wounds, solid organ injuries likely to bleed with heparinization, and respiratory failure.[85] In such cases, beta blockade to control mean arterial blood pressure and ICU monitoring are essential until repair can be safely accomplished. Esmolol is the preferred beta blocker.

Cardiopulmonary bypass (CPB) should always be available during repair in the event that the injury extends to the aortic root. The left lung should be collapsed and retracted. Care is required when dissecting the aorta for cross-clamping to avoid injury to the branches of the aorta that supply the spinal cord and to the vagus nerve and its recurrent branch. Some partial tears can be repaired primarily; however, repair usually requires placement of a woven Dacron graft, especially when the tear is circumferential. There are three basic ways to perform the operation:

Clamp and sew
Intraoperative shunt
Mechanical circulatory support

The simplest is to “clamp and sew” without a shunt or CPB. This is the fastest method and requires the shortest cross-clamp time; it is adequate if the injury is not too extensive. Razzouk and colleagues reported that the “clamp and sew” technique “is feasible in the majority of patients without increased mortality or spinal cord injury.”[86,87] Kwon and colleagues also believe that the clamp technique does not increase mortality or morbidity.[88] However, others strongly disagree. Hochheiser and colleagues reported a lower incidence of postoperative paraplegia after repair with mechanical circulatory support.[89]

Another option is intraoperative shunting with a heparin-bonded shunt. This may reduce the risk of ischemic damage to the spinal cord without the risks of systemic heparinization. However, no controlled studies to prove this exist. The third method is to use mechanical circulatory support during the repair. The most common choice is CPB from the left superior pulmonary vein or left atrium to the femoral artery.[90] Femoral–femoral bypass with direct perfusion of the distal descending thoracic aorta has also been used. CPB is thought by some authorities to reduce the risk of paraplegia, but conventional circuits require systemic heparinization, which can increase the incidence of intracranial hemorrhage; heparin-bonded circuits (including cannulas) are available, and short-term use at higher flows does not require anticoagulation.[91]

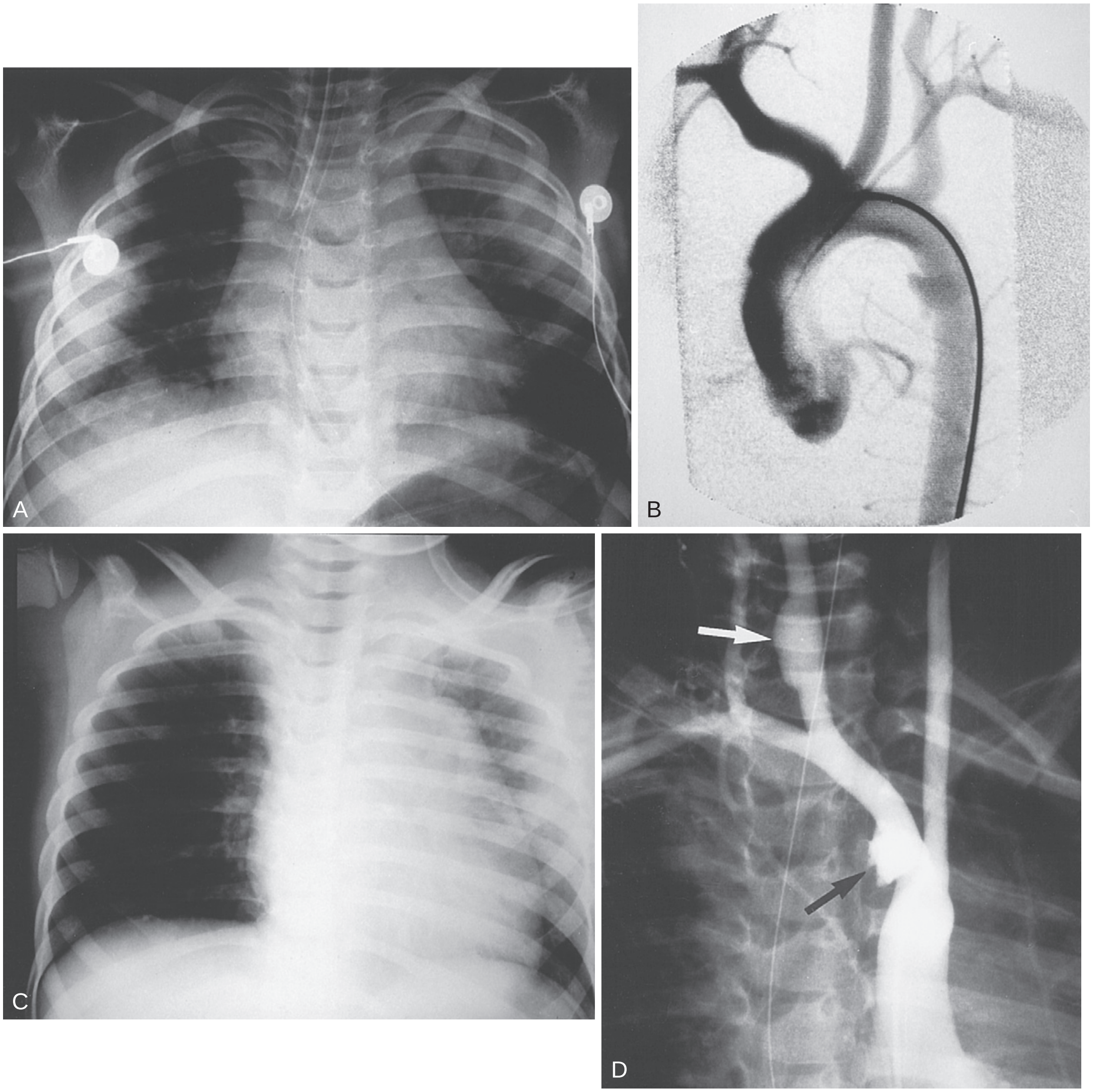


**FIGURE 19-8** Traumatic rupture of the aorta and branches. **A,** Widened mediastinum with deviation of the endotracheal and nasogastric tubes to the right. **B,** Same patient as in **A.** Aortic injury was confirmed by aortogram. **C,** Widened mediastinum in a patient who sustained blunt trauma to the chest. **D,** Same patient as in **C.** Innominate artery laceration at its origin (*arrow*). (From Wesson DE: Trauma of the chest in children. Chest Clin North Am 1993;3:423-441. Used with permission.)

The rate of paraplegia after repair of traumatic rupture of the aorta is about 5% to 10%. Individual variations in spinal cord blood supply, cross-clamp time, and intraoperative hypotension are important determinants of spinal cord injury.

There have been several recent reports of transfemoral stent insertion (endovascular stent grafting–thoracic endovascular aortic repair [EVSG–TEVAR]) for injuries to the thoracic aorta in adults. Early results indicate that the results may be better than with standard open repair. Three case series have appeared with remarkably low incidences of paraplegia.[92–94] EVSG–TEVAR has been reported in a small series of children, but there are no reports of long-term results.[77]

Only 1 of 13 patients in Eddy's report, a population-based study that included prehospital deaths, survived traumatic rupture of the aorta.[73] In contrast, DelRossi reported a 75% survival rate in a clinical series.[78] Three of the 21 survivors in Del Rossi's series were paraplegic after repair, but two recovered later. DelRossi found no evidence to support one technique of repair versus the others. However, Fabian and colleagues reported that the clamp and sew technique is more likely to result in paraplegia than repair with bypass, especially if the cross-clamp time is greater than 30 minutes.[95] As is true for many types of injury, outcome also depends on associated injuries.[91] Hormuth reported excellent overall

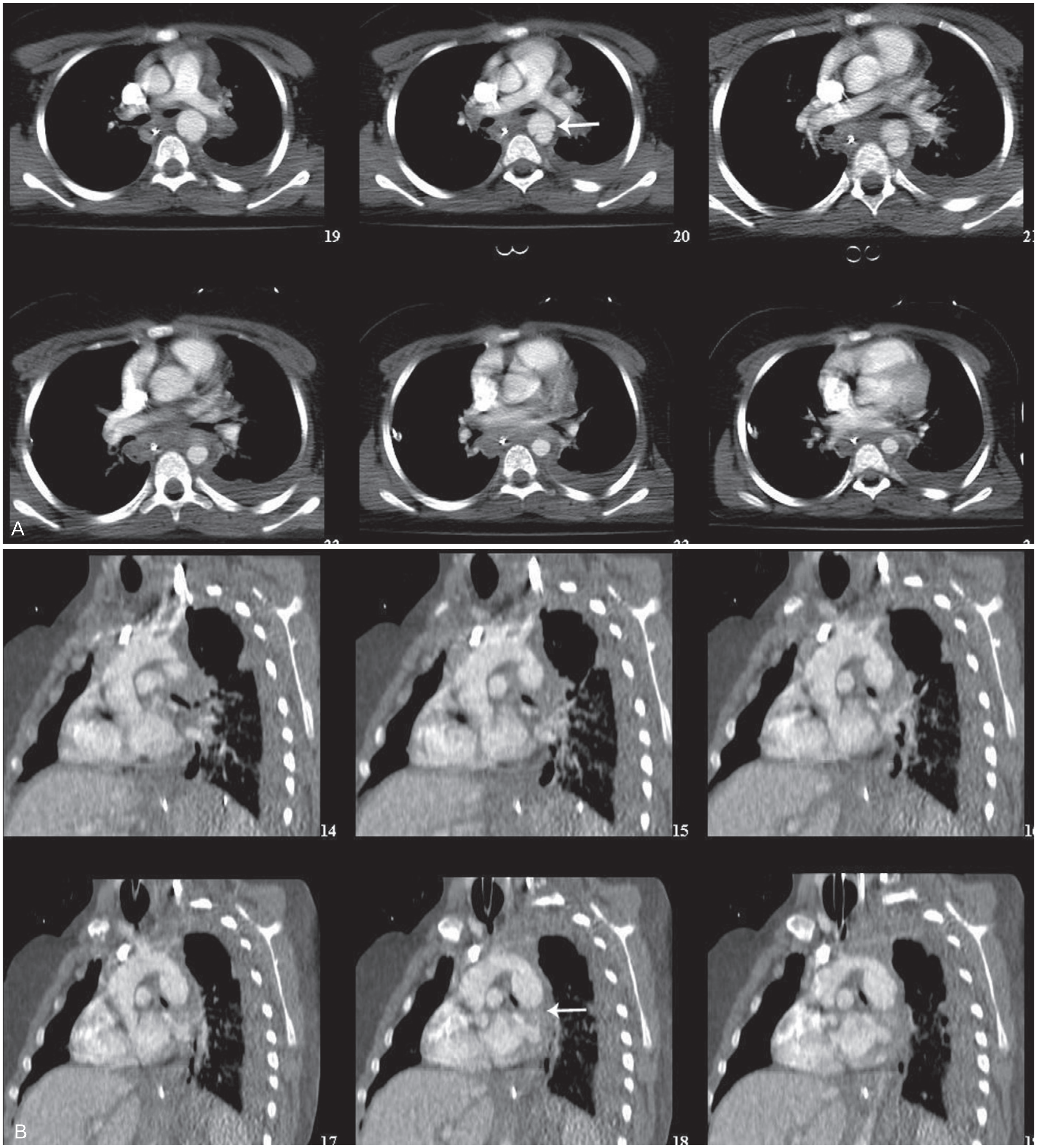

FIGURE 19-9 Helical computed tomography (CT) scan reconstruction showing traumatic rupture of the aorta in a 14-year-old boy. **A,** Transaxial view. Note periaortic hematoma at the isthmus. **B,** Three-dimensional reconstruction. Note interruption of flow at the isthmus.

results in a series of 11 children with thoracic aortic injuries.[76] They repaired isthmus injuries with left heart bypass with direct perfusion of the distal thoracic aorta and arch injuries with hypothermic arrest.

Other thoracic vascular injuries in children are rare, and the majority of injuries are in older children, resulting from penetrating mechanisms.[87] The standard vascular exposure for right subclavian vessel/innominate vessel injuries is a median sternotomy with a supraclavicular or anterior sternocleidomastoid-type neck extension. The choice depends on the injury complex and the potential need for extension distally toward the axilla on more distal injuries. Traditionally,

the left subclavian artery was approached through an anterior third intercostal space thoracotomy for proximal control with a supraclavicular approach for exposure of the middle-distal vessel. The proximal left subclavian artery can be controlled by a sternotomy as well, with a type of extension similar to that of right-sided injuries. Alternatively, hemodynamically stable patients have had thoracoscopic proximal control and direct repair performed. More recently, adolescents have undergone endovascular repair/stenting of these injuries. Caution must be exercised in considering the site of injury, because most grafts are not suitable for crossing joints because of an increased risk of thrombosis.

### Chylothorax

Injury to the thoracic duct, although rare, causes chylothorax. Most cases resolve spontaneously with nutritional support (total parenteral nutrition or elemental diet with medium-chain triglycerides). Occasionally, ligation of the thoracic duct is necessary.

### Traumatic Asphyxia

Traumatic asphyxia, a clinical syndrome that is unique to children, occurs with sudden compression of the abdomen or chest (or both) against a closed glottis.[96] This event causes a rapid rise in intrathoracic pressure, which is transmitted to all the veins that drain into the valveless superior vena cava. Extravasation of blood occurs into the skin of the upper half of the body, sclerae, and possibly the brain. The brain may also be damaged by hypoxia during and after the injury. The clinical features of this disorder include seizures, disorientation, petechiae in the upper half of the body and conjunctivae, and respiratory failure (Fig. 19-10). The treatment is supportive. Most patients recover uneventfully.

**FIGURE 19-10** Traumatic asphyxia. Two-year-old boy who was run over by truck wheel, causing typical plethoric appearance of "traumatic asphyxia." (From Haller JA: Thoracic injuries. In Welch KJ, Randolph JG, Ravitch M, et al (eds): Pediatric Surgery, ed 4. St Louis, Mosby-Year Book, 1986. Used with permission.)

## PENETRATING INJURIES

The initial management of penetrating injuries is the same as for blunt trauma: Clear the airway, give oxygen and intravenous fluids, carefully assess the patient, and obtain a plain chest radiograph in every case. An attempt should be made to determine the path of the injury by marking the entry and exit wounds on the plain films. Endotracheal intubation and chest tube insertion should be done as needed during the initial resuscitation. It is important to remember the possibility of a concomitant abdominal injury with any wound below the nipple line. Bronchoscopy is indicated for suspected injury to the major airways; esophagoscopy and water-soluble contrast studies are indicated for suspected esophageal wounds. Echocardiography can be used in stable patients to diagnose suspected heart injuries.

Treatment is also the same as described for blunt trauma. Most of these patients do not require thoracotomy. The most common indications for surgery are massive bleeding, massive air leak, and pericardial tamponade.

Penetrating injuries are more likely to involve the heart, especially with anterior wounds medial to the midclavicular line. These injuries may cause pericardial tamponade or, if the pericardium has a defect, exsanguinating hemorrhage into the chest. Shock is a clear indication for urgent thoracotomy in cases of penetrating wounds to the chest. However, the management of patients who present with normal physiologic parameters and with wounds near the heart is problematic. The most conservative and safest approach is to take all such patients to the operating room for a subxiphoid pericardial window followed by thoracotomy through a median sternotomy, if necessary. Recent reports suggest that early echocardiography may be a very sensitive test for occult cardiac injuries and that this technique may be used to select patients who require a pericardial window, thereby minimizing unnecessary invasive procedures.[20,57,69] In this report, only patients with pericardial effusions on echocardiography underwent subxiphoid pericardial window; if blood was found, a median sternotomy followed. Patients with normal echocardiographs were observed clinically. Harris and colleagues reported a large experience with penetrating cardiac injuries and recommended cardiac ultrasonography in the diagnosis of these injuries in stable patients.[34]

When an operation is required for a penetrating cardiac injury, a Foley catheter placed through the defect may control the bleeding temporarily to facilitate suture of the defect. Median sternotomy is best for known cardiac injuries.

## THORACOABDOMINAL INJURIES

Thoracoabdominal injuries can be vexing because of the high mortality from multiple injuries and the need for combined procedures with appropriate sequencing for optimal results. Inappropriate sequencing of thoracic versus abdominal exploration occurs 20% to 40% of the time. The pitfalls are related to the unreliability of abdominal examination, inaccuracy of chest tube output as an indicator of ongoing thoracic bleeding, miscalculation of bullet/knife trajectory, and unreliability of central venous pressure as an index of preload. All of these pitfalls are managed by maintaining a high index of suspicion

of occult or underappreciated blood loss in the nonexplored cavity. Prompt changes in initial approaches minimizes delayed intervention, despite initial exploration of the less critical cavity.[97,98]

### TRANSMEDIASTINAL INJURIES

Transmediastinal injuries are initially managed according to hemodynamic status. Unstable patients are explored without extensive imaging or diagnostic studies. Stable patients should undergo initial chest radiography; then subsequent imaging or diagnostics depend on those findings/trajectory of the missile. CT imaging of the chest using helical scanners can diagnose most vascular injuries and give high-resolution images of potential aerodigestive tract injuries. Further localization depends on the findings and degree of certainty of the imaging studies.

## Complications

Very little information can be found in the literature on the morbidity of chest injuries or the complications after surgery for thoracic injuries in children. The two most common complications of thoracic surgery are pulmonary atelectasis and pneumonia. The most serious is paraplegia, which occurs in 5% to 10% of cases of injury to the thoracic aorta.

## Outcome

The risk for death from thoracic injury varies with the type of injury and the number and severity of associated injuries, particularly to the central nervous system. Roux and Fisher reported a series of 100 consecutive children with motor vehicle–related chest trauma in South Africa.[99] Ninety-one pedestrians comprised the largest subgroup. Eight died with a mean Injury Severity Score of 34 compared with 25 among the survivors. Seven of the 8 children who died had fatal head injuries. Thus in blunt injuries to the chest in children, the level of injury reflected in the Injury Severity Score and the presence of concomitant head injuries are the main determinants of survival. Deaths from thoracic injury in children tend to occur in the first few days after the injury, usually from other injuries and not from respiratory failure or sepsis, as is the case in adults.

The overall mortality for chest injuries was 15% in the National Pediatric Trauma Registry—virtually identical to most adult series.[5] Mortality increases with each individual chest injury: 30% for a ruptured diaphragm, 40% for cardiac injury, and 50% for injury to a major vessel.

The morbidity among survivors is remarkably low. DiScala[100] reported that 90% of survivors in the National Pediatric Trauma Registry had no impairment at the time of discharge.

## Summary

The following points summarize the management of thoracic injuries in children:

1. Most thoracic injuries can be diagnosed by a combination of clinical assessment and plain chest radiographs.
2. Most heal with medical (not surgical) treatment.
3. Life-threatening thoracic injuries are relatively uncommon.
4. A few thoracic injuries require surgery, but even the most severe can be managed successfully if recognized and treated expeditiously.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 20

# Abdominal Trauma

Steven Stylianos and Richard H. Pearl

Who could have imagined the influence of Simpson's 1968 publication on the successful nonoperative treatment of select children presumed to have splenic injury?[1] Initially suggested in the early 1950s by Warnsborough, then chief of general surgery at the Hospital for Sick Children in Toronto, the era of nonoperative management of splenic injury began with the report of 12 children treated between 1956 and 1965. The diagnosis of splenic injury in this select group was made by clinical findings, along with routine laboratory and plain radiographic findings. Keep in mind that this report predated ultrasonography (US), computed tomography (CT), or isotope imaging. Subsequent confirmation of splenic injury was made in one child who required laparotomy years later for an unrelated condition, when it was found that the spleen had healed in two separate pieces. Nearly half a century later, the standard treatment of hemodynamically stable children with splenic injury is nonoperative, and this concept has been successfully applied to most blunt injuries of the liver, kidney, and pancreas as well. Surgical restraint is now the norm, based on an increased awareness of the anatomic patterns and physiologic responses of injured children. Our colleagues in adult trauma care have slowly acknowledged this success and are applying many of the principles learned in pediatric trauma to their patients.[2]

Review of multiple large trauma databases indicates that 8% to 12% of children suffering blunt trauma have an abdominal injury.[3] Fortunately, more than 90% of them survive. Although abdominal injuries are 30% more common than thoracic injuries, they are 40% less likely to be fatal. The infrequent need for laparotomy in children with blunt abdominal injury has created a debate regarding the role of pediatric trauma surgeons in their treatment. Recent analyses of the National Pediatric Trauma Registry (NPTR) and the National Trauma Data Bank emphasize the overall "surgical" nature of pediatric trauma patients, with more than 25% of injured children requiring operative intervention.[4,5] Clearly, a qualified pediatric trauma surgeon would be the ideal coordinator of such care.

Few surgeons have extensive experience with massive abdominal solid organ injuries requiring immediate surgery. It is imperative that surgeons familiarize themselves with current treatment algorithms for life-threatening abdominal trauma. Important contributions have been made in the diagnosis and treatment of children with abdominal injury by radiologists and endoscopists. The resolution and speed of computed tomography (CT), the screening capabilities of focused abdominal sonography for trauma (FAST), and the percutaneous, angiographic, and endoscopic interventions of nonsurgeon members of the pediatric trauma team have all enhanced patient care and improved outcomes. This chapter focuses on the more common blunt injuries and unique aspects of care in children. Renal and genitourinary injuries are covered separately in Chapter 21.

## Diagnostic Modalities

The initial evaluation of an acutely injured child is similar to that of an adult. Plain radiographs of the cervical spine, chest, and pelvis are obtained after the initial survey and evaluation of the ABCs (airway, breathing, and circulation). Other plain abdominal films add little to the acute evaluation of pediatric trauma patients. As imaging modalities have improved, treatment algorithms have changed significantly in children with suspected intra-abdominal injuries. Prompt identification of potentially life-threatening injuries is now possible in the vast majority of children.

### COMPUTED TOMOGRAPHY

CT has become the imaging study of choice for the evaluation of injured children owing to several advantages. CT is now readily accessible in most health care facilities; it is a noninvasive, accurate method of identifying and qualifying the extent of abdominal injury, and it has reduced the incidence of nontherapeutic exploratory laparotomy. CT can be particularly helpful in diagnosing abdominal injuries in intubated, multi-injured children.[6]

Use of intravenous contrast is essential, and "dynamic" methods of scanning have optimized vascular and parenchymal enhancement. The importance of a contrast "blush" in children with blunt spleen and liver injury continues to be debated and is discussed later in the chapter (Fig. 20-1).[7] Head CT, if indicated, should be performed first without contrast, to avoid concealing a hemorrhagic brain injury. Controversy remains regarding the benefits of enteral contrast for diagnosis of gastrointestinal (GI) tract injuries. Many authors conclude that CT with enteral contrast does not

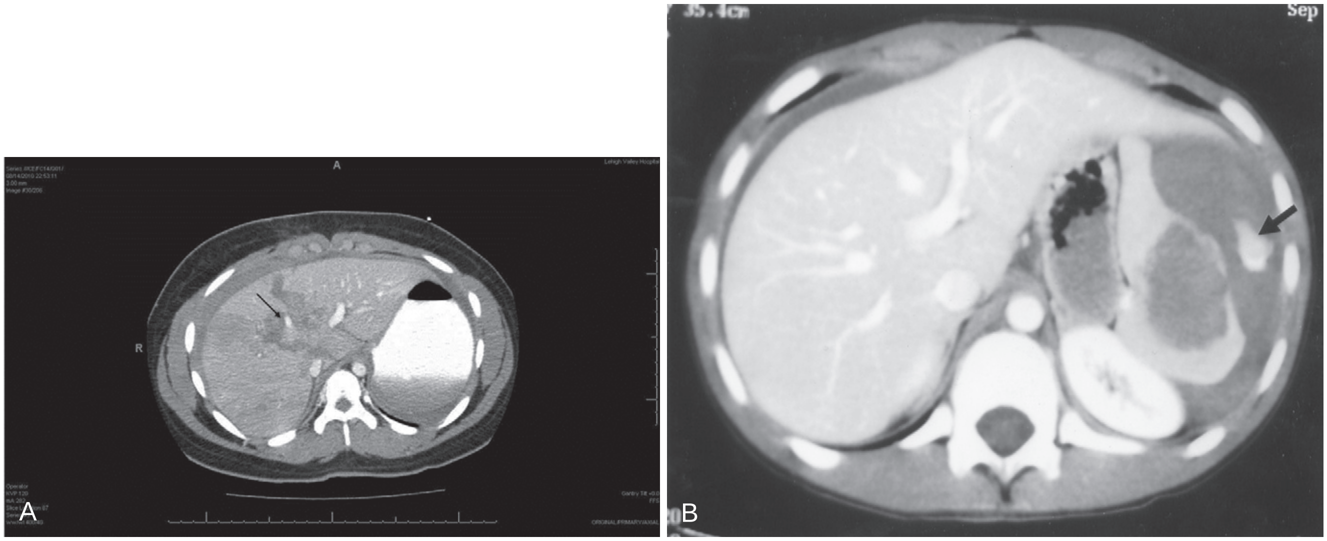


FIGURE 20-1 **A,** Abdominal computed tomography scan demonstrating a significant injury to the right hepatic lobe with intravenous contrast "blush" (*arrow*). This patient had successful angiographic embolization and avoided operation. **B,** Abdominal computed tomography scan demonstrating a significant injury to the spleen with intravenous contrast blush (*arrow*). The patient remained hemodynamically stable and avoided operation.

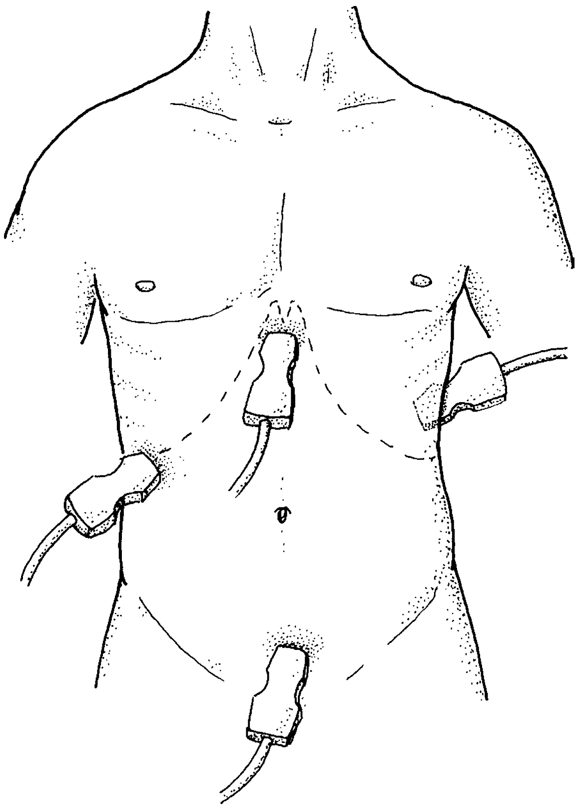

FIGURE 20-2 Schematic of a focused abdominal sonography for trauma (FAST) examination, with emphasis on views of the subxiphoid, right upper quadrant and pouch of Morrison, left upper quadrant and left paracolic region, and pelvic region and pouch of Douglas. (Original illustration by Mark Mazziotti, MD.)

improve diagnosis of GI injuries in the acute trauma setting and can lead to delays in diagnosis and aspiration.[8–12]

Not all children with potential abdominal injuries are candidates for CT evaluation. Obvious penetrating injury often necessitates immediate operative intervention. A hemodynamically unstable child should not be taken out of an appropriate resuscitation room for the performance of CT. These children may benefit from an alternative diagnostic study, such as peritoneal lavage or FAST, or urgent operative intervention. The greatest limitation of abdominal CT in trauma is the inability to reliably identify intestinal rupture.[13] Findings suggestive but not diagnostic of intestinal perforation are pneumoperitoneum, bowel wall thickening, free intraperitoneal fluid, bowel wall enhancement, and dilated bowel.[14] A high index of suspicion should exist for the presence of bowel injury in a child with intraperitoneal fluid and no identifiable solid organ injury on CT.[10] The diagnosis and treatment of bowel injury are reviewed in detail later.

## FOCUSED ABDOMINAL SONOGRAPHY FOR TRAUMA

Clinician-performed sonography for the early evaluation of an injured child is currently being evaluated to determine its optimal use. Examination of the pouch of Morrison; the pouch of Douglas; the left flank, including the perisplenic anatomy; and a subxiphoid view to visualize the pericardium is the standard four-view FAST examination (Fig. 20-2). This bedside examination may be a good rapid screening study, particularly in patients too unstable to undergo an abdominal CT scan. Early reports have found FAST to be a helpful screening tool in children, with a high specificity (95%) but low sensitivity (33%) in identifying intestinal injury. However, a lack of identifiable free fluid does not exclude a significant injury.[15] FAST may be useful in decreasing the number of CT scans performed for "low-likelihood" injuries. Repetition of the study may be necessary, depending on clinical correlation, and the finding of free fluid by itself is not an indication for surgical intervention. A recent meta-analysis of FAST in pediatric blunt trauma patients revealed modest sensitivity for hemoperitoneum.[16] The authors concluded that a negative FAST may have questionable utility as the sole diagnostic test to rule out the presence of an intra-abdominal injury. A hemodynamically stable child with a positive FAST should undergo CT.

## DIAGNOSTIC PERITONEAL LAVAGE AND LAPAROSCOPY

Diagnostic peritoneal lavage (DPL) has been a mainstay in trauma evaluation for more than 3 decades. However, its utility in pediatric trauma is limited. Because up to 90% of solid organ injuries do not require surgical intervention, the finding of free blood in the abdomen by DPL has limited clinical significance. Hemodynamic instability and the need for ongoing blood replacement are the determinants for operation in patients with solid organ injury in the absence of blood in the abdominal cavity. Additionally, the speed and accuracy of CT have further decreased the indications for DPL in pediatric trauma. The sensitivity of CT in diagnosing solid organ injuries and more subtle injuries to the duodenum, pancreas, and intestines continues to improve. This has relegated DPL to the evaluation of patients with clinical findings suggestive of bowel injury and no definitive diagnosis on CT. In this setting, the presence of bile, food particles, or other evidence of GI tract perforation is diagnostic. Recent literature has suggested that laparoscopy can both diagnose and, in some cases, allow definitive surgical management without laparotomy, further limiting the usefulness of DPL.[17]

Large series using laparoscopy in adults have demonstrated increased diagnostic accuracy, definitive management of related injuries, decreased nontherapeutic laparotomy rates, and a significant decrease in hospital length of stay, with an attendant reduction in costs.[18,19] The extent of feasible operations is directly related to the surgeon's skill with advanced laparoscopic techniques and the patient's overall stability. At the Children's Hospital of Illinois, our two most recent handlebar injuries causing bowel perforation were successfully treated laparoscopically. As with elective abdominal surgery, the role of laparoscopy in trauma will increase substantially as trauma centers redirect their training of residents to this modality and as more pediatric centers report outcome studies for laparoscopic trauma management in children.[20–22]

# Solid Organ Injuries

## SPLEEN AND LIVER

The spleen and liver are the organs most commonly injured in blunt abdominal trauma, with each accounting for one third of the injuries. Nonoperative treatment of isolated splenic and hepatic injuries in stable children has been universally successful and is now standard practice; however, there is great variation in the management algorithms used by individual pediatric surgeons.[23]

Controversy exists regarding the utility of CT grading and the finding of contrast blush as a predictor of outcome in liver and spleen injury.[24–26] Several recent studies reported contrast blush in 7% to 12% of children with blunt spleen injury (see Fig. 20-1).[27–29] The rate of operation in the blush group approached or exceeded 20%. The authors emphasized that CT blush was worrisome but that most patients could still be managed successfully without operation. The role and impact of angiographic embolization in adults is still debated and has yet to be determined in pediatric spleen injury.[30,31] Initial retrospective studies have found angiographic embolization to be safe and effective in children; however, selection criteria remain undefined.[32]

The American Pediatric Surgical Association (APSA) Trauma Committee analyzed a contemporary multi-institution database of 832 children treated nonoperatively at 32 centers in North America from 1995 to 1997 (Table 20-1).[33] Consensus guidelines on intensive care unit (ICU) stay, length of hospital stay, use of follow-up imaging, and physical activity restriction for clinically stable children with isolated spleen or liver injuries (CT grades I to IV) were defined based on this analysis (Table 20-2). The guidelines were then applied prospectively in 312 children with liver or spleen injuries treated nonoperatively at 16 centers from 1998 to 2000.[34] Patients with other minor injuries, such as nondisplaced, noncomminuted fractures or soft tissue injuries, were included as long as the associated injuries did not influence the variables in the study. The patients were grouped by severity of injury defined by CT grade. Compliance with the proposed guidelines was analyzed for age, organ injured, and injury grade. All patients were followed for 4 months after injury. It is imperative to emphasize that these proposed guidelines assume hemodynamic stability. The extremely low rates of transfusion and operation document the stability of the study patients.

Specific guideline compliance was 81% for ICU stay, 82% for length of hospital stay, 87% for follow-up imaging, and 78% for activity restriction. There was a significant improvement in compliance from year 1 to year 2 for ICU stay (77% versus 88%, $P < 0.02$) and activity restriction (73% vs. 87%, $P < 0.01$). There were no differences in compliance by age,

**TABLE 20-1**
**Resource Use and Activity Restriction in 832 Children with Isolated Spleen or Liver Injury by Computed Tomography Grade**

| | *Grade I* ($n = 116$) | *Grade II* ($n = 341$) | *Grade III* ($n = 275$) | *Grade IV* ($n = 100$) |
|---|---|---|---|---|
| Admitted to ICU (%) | 55.0 | 54.3 | 72.3 | 85.4 |
| No. hospital days (mean) | 4.3 | 5.3 | 7.1 | 7.6 |
| No. hospital days (range) | 1-7 | 2-9 | 3-9 | 4-10 |
| Transfused (%) | 1.8 | 5.2 | 10.1* | 26.6* |
| Laparotomy (%) | 0 | 1.0 | 2.7† | 12.6† |
| Follow-up imaging (%) | 34.4 | 46.3 | 54.1 | 51.8 |
| Activity restriction (mean wk) | 5.1 | 6.2 | 7.5 | 9.2 |
| Activity restriction (range wk) | 2-6 | 2-8 | 4-12 | 6-12 |

From Stylianos S, APSA Trauma Committee: Evidence-based guidelines for resource utilization in children with isolated spleen or liver injury. J Pediatr Surg 2000;35:164-169.
*Grade III vs. grade IV, $P < 0.014$
†Grade III vs. grade IV, $P < 0.0001$
CT, Computed tomography; ICU, intensive care unit.

**TABLE 20-2**

**Proposed Guidelines for Resource Use in Children with Isolated Spleen or Liver Injury by CT Grade**

| | *Grade I* | *Grade II* | *Grade III* | *Grade IV* |
|---|---|---|---|---|
| ICU days | 0 | 0 | 0 | 1 |
| Hospital stay (days) | 2 | 3 | 4 | 5 |
| Predischarge imaging | None | None | None | None |
| Postdischarge imaging | None | None | None | None |
| Activity restriction (wk)* | 3 | 4 | 5 | 6 |

From Stylianos S, APSA Trauma Committee: Evidence-based guidelines for resource utilization in children with isolated spleen or liver injury. J Pediatr Surg 2000;35:164-169.

*Return to full-contact, competitive sports (e.g., football, wrestling, hockey, lacrosse, mountain climbing) should be at the discretion of the individual pediatric trauma surgeon. The proposed guidelines for return to unrestricted activity include "normal" age-appropriate activities.

CT, Computed tomography; ICU, intensive care unit.

gender, or organ injured. Deviation from the guidelines was the surgeon's choice in 90% of cases and patient-related in 10%. Six patients (1.9%) were readmitted, although none required operation. Compared with the previously studied 832 patients, the 312 patients managed prospectively by the proposed guidelines had a significant reduction in ICU stay ($P < 0.0001$), hospital stay ($P < 0.0006$), follow-up imaging ($P < 0.0001$), and interval of physical activity restriction ($P < 0.04$) within each grade of injury.

From these data, it was concluded that prospective application of specific treatment guidelines based on injury severity resulted in conformity in patient management, improved use of resources, and validation of guideline safety. Significant reductions in ICU stay, hospital stay, follow-up imaging, and activity restriction were achieved without adverse sequelae when compared with the retrospective database. The pendulum continues to swing toward less hospitalization of stable children with solid liver or spleen injury. Retrospective and prospective studies suggest that the APSA guidelines for hospital length of stay can be reduced further.[35,36]

Authors from the Arkansas Children's Hospital reported on an abbreviated protocol based on hemodynamics while "throwing out" the CT grade of injury in 101 patients with isolated spleen or liver injury. Their protocol resulted in a significant reduction in length of stay (3.5 vs. 1.9 days, $P < 0.001$) from that predicted by APSA guidelines.

The attending surgeon's decision to operate for spleen or liver injury is best based on evidence of continued blood loss, such as low blood pressure, tachycardia, decreased urine output, and falling hematocrit unresponsive to crystalloid and blood transfusion. The rates of successful nonoperative treatment of isolated blunt splenic and hepatic injury now exceed 90% in most pediatric trauma centers and in adult trauma centers with a strong pediatric commitment.[35–37] A study of more than 100 patients from the NPTR indicated that nonoperative treatment of spleen or liver injury is indicated even in the presence of associated head injury if the patient is hemodynamically stable.[38] Rates of operative intervention for blunt spleen or liver injury were similar with and without an associated closed head injury.

Not surprisingly, adult trauma services have reported excellent survival rates for pediatric trauma patients; however, an analysis of treatment for spleen and liver injuries reveals alarmingly high rates of operative treatment.[39–41]

This discrepancy in operative rates emphasizes the importance of disseminating effective guidelines, because the majority of seriously injured children are treated outside of dedicated pediatric trauma centers. Mooney and Forbes[37] reviewed the New England Pediatric Trauma Database in the 1990s and identified 2500 children with spleen injuries. Two thirds were treated by nonpediatric trauma surgeons, and two thirds were treated in nontrauma centers. After allowing for multiple patient- and hospital-related variables, the authors found that the risk of operation was reduced by half when a surgeon with pediatric training provided care to children with splenic injuries. In a similar review using the Kids' Inpatient Database (KID) 2000 administrative data set, Mooney and Rothstein[42] found that despite adjustment for hospital- and patient-specific variables, children treated at an adult general hospital had a 2.8 greater chance ($P < 0.003$), and those treated at a general hospital with a pediatric unit had a 2.6 greater chance ($P < 0.013$), of undergoing splenectomy than those cared for at a freestanding pediatric hospital.

Several recent studies provide a basis for ongoing concern regarding disparity of treatment in children with blunt spleen injury.[37,40,42–45] Using large nonselected databases and adjusting for risk, these studies indicate that the disparity is substantial and continuing on a regional and national basis (see Table 20-5).

Todd and colleagues analyzed the Healthcare Cost and Utilization Project's National Inpatient Sample (HCUP-NIS), which contains a sample of discharges from 1300 hospitals in 28 states (representing 20% of all hospital discharges in the United States).[43] Children with splenic injury treated at rural hospitals had a risk-adjusted odds ratio for laparotomy of 1.64 (95% CI, 1.39 to 1.94) when compared with those treated at an urban teaching hospital. The APSA Center on Outcomes compared the treatment of pediatric splenic injury using discharge datasets from four states.[41] The authors found a risk-adjusted odds ratio for laparotomy of 2.1 (95% CI, 1.4 to 3.1) when comparing treatment at nontrauma centers versus centers with trauma expertise. Mooney and colleagues reviewed more than 2600 children with splenic injury from the New England Pediatric Trauma Database and found that similarly injured patients treated by nonpediatric surgeons had a risk-adjusted odds ratio for laparotomy of 3.1 (95% CI, 2.3 to 4.4) when compared with those treated by pediatric surgeons.[37] The last two studies found even greater disparity when comparing the treatment of children with isolated splenic injury as contrasted with those with multiple injuries. Bowman and colleagues used data from the Kids Inpatient Database (KID 2000) of the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality.[44] This administrative database represents an

80% sample of non-newborn discharges from 2784 hospitals in 27 states (2.5 million pediatric discharges). The authors found a risk-adjusted odds ratio for laparotomy of 5.0 (95% CI, 2.2 to 11.4) when comparing treatment at general hospitals versus children's hospitals in pediatric patients with splenic injury. Davis and colleagues reviewed discharge data from 175 hospitals in Pennsylvania and found the risk-adjusted odds ratio for laparotomy to be 6.2 (95% CI, 4.4 to 8.6) when comparing treatment at adult trauma centers versus pediatric trauma centers.[45] Although these studies suggest marked differences in the processes of care, administrative datasets do not readily allow risk adjustment for differences in physiologic status at presentation, a potential major limitation (Table 20-3).

Sims and colleagues surveyed 281 surgeons (114 pediatric, 167 adult) regarding their treatment of children with solid organ injury (SOI).[40] For all clinical scenarios, adult surgeons were more likely to operate or pursue interventional radiologic procedures than their pediatric colleagues (relative risk [RR]: 8.6 with isolated SOI, $P < 0.05$; 14.8 SOI with multiple SOI, $P < 0.001$; 17.9 SOI with intracranial hemorrhage, $P < 0.0001$). Adult surgeons were also more likely to consider any transfusion a failure (13.3% vs. 1.2%, $P < 0.01$) and had a much lower transfusion threshold.

The importance of these data is further amplified by the fact that the overwhelming majority (68% to 87%) of pediatric patients were treated at the facilities or by physicians with the higher likelihood of operation.[37,44,45] In contrast, Stylianos and colleagues found that nearly two thirds of children with splenic injury were treated at institutions with trauma expertise.[41] Trauma centers had a significantly lower rate of operation for both multiple-injury patients (15.3% vs. 19.3%, $P < 0.001$) and those with isolated injury (9.2% vs. 18.5%, $P < 0.0001$) when compared to nontrauma centers (see Table 20-6). The operative rates at both trauma centers and nontrauma centers exceeded published APSA benchmarks (Tables 20-4 and 20-5) for all children with splenic injury (3% to 11%) and those with isolated splenic injury (0% to 3%).

Thus trauma centers and their corresponding state or regional trauma systems may represent rational targets for dissemination of current pediatric trauma guidelines and benchmarks. Broad application of existing APSA guidelines for splenic injury should

**TABLE 20-3**
**Studies Comparing Operative Rates for Pediatric Blunt Splenic Injury**

| *First Author* | *Study Period* | *No. Patients* | *Database* | *Adjusted Odds Ratio (95% CI) for Operation* | *Ratio* | *P value* |
|---|---|---|---|---|---|---|
| Todd[43] | 1998-2000 | 2569 | HCUP-NIS | 1.64 (1.39-1.94) RH vs. UTH | n/a | n/a |
| Stylianos[41] | 2000-2002 | 3232 | State UHDDS | 2.1 (1.4-3.1) NTC vs. TC | 34:66 | <0.0001 |
| Mooney[37] | 1990-1998 | 2631 | NEPTD | 3.1 (2.3-4.4) NPS vs. PS | 68:32 | <0.0001 |
| Bowman[44] | 2000 | 2851 | KID 2000 | 5.0 (2.2-11.4) GH vs. CH | 87:13 | <0.001 |
| Davis[45] | 1991-2000 | 3245 | State UHDDS | 6.2 (4.4-8.6) ATC vs. PTC | 84:16 | <0.0001 |

ATC, Adult trauma center; CH, children's hospital; GH, general hospital; HCUP-NIS, Healthcare Cost and Utilization Project's National Inpatient Sample (1300 hospitals in 28 states; 20% of all hospital discharges in United States); KID 2000, Kids' Inpatient Database of the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality (2784 hospitals in 27 states; 2.5 million pediatric discharges); n/a, not available; NEPTD, New England Pediatric Trauma Database; NPS; nonpediatric surgeon; NTC; nontrauma center; PS, pediatric surgeon; PTC, pediatric trauma center; RH, rural hospital; TC, trauma center; UHDDS, Uniform Hospital Discharge Data Set; UTH, urban teaching hospital.

**TABLE 20-4**
**Operative Rate in Children with Splenic Injury[41]**

| | *Trauma Center* | *Nontrauma Center* | *P value* | *APSA Benchmarks* |
|---|---|---|---|---|
| Multiple injuries ($n$ = 1299) | 15.3% | 19.3% | <0.001 | 11%-17% |
| Isolated spleen injuries ($n$ = 1933) | 9.2% | 18.5% | <0.0001 | 0%-3% |
| TOTAL ($n$ = 3232) | 12.1% | 18.8% | <0.0001 | 5%-11% |

APSA, American Pediatric Surgical Association.

**TABLE 20-5**
**Pediatric Surgery Benchmarks for Operative Rate in Children with Splenic Injury**

| *First Author* | *Database* | *Study Period* | *No. Patients* | *Operative Rate: Pediatric Surgeon and/or Children's Hospital-PTC* | *Splenic Injuries* |
|---|---|---|---|---|---|
| Bowman[44] | KID 2000—AHRQ | 2000 | 363 | 3% | All |
| Davis[45] | Pennsylvania Trauma Outcome Study-UHDDS | 1991-2000 | 507 | 5% | All |
| Mooney[37] | New England Pediatric Trauma Database-UHDDS | 1990-98 | 866 | 11% | All |
| Stylianos[33,34] | APSA Trauma Committee Multicenter Registry | 1995-2000 | 652 | 3% | Isolated |
| Mooney[46] | Children's Hospital-Boston Trauma registry | 1993-99 | 82 | 0% | Isolated |

KID2000, Kids' Inpatient Database of the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality (AHRQ) (2784 hospitals in 27 states; 2.5 million pediatric discharges); PTC, Pediatric Trauma Center; UHDDS, Uniform Hospital Discharge Data Sets.

encourage conformity of care and result in reduced rates of operative intervention and diminished resource use.

Failure of nonoperative management (NOM) can have serious consequences; therefore patient selection is important.[47] Two recent multi-institutional reviews sought to evaluate the time line and the characteristics of patients who fail NOM.[48,49] There was operation in 120 of 1813 (6.6%) children with solid organ injury in a median time of 2.4 hours with 90% of patients having surgery within 24 hours. Pediatric patients who sustained pancreatic injuries were more likely to fail nonoperative management (odds ratio [OR] 7.49; 95% CI, 3.74 to 15.01) compared with those who suffered other injuries. The patients who failed had higher injury severity scores (ISS; $28 \pm 17$) than those who underwent successful NOM ($14 \pm 10$, $P < 0.001$). Severely head-injured patients (Glasgow Coma Scale [GCS] = 8) had a higher failure rate for NOM (OR 5.09; 95% CI, 3.04 to 8.52). Factors associated with increased failure rate include bicycle-related injury mechanism, isolated pancreatic injury, more than one solid organ injury, and an isolated grade 5 solid organ injury. The time to failure of NOM peaked at 4 hours and then declined over 36 hours from admission. Thus continued surgical evaluation and assessment during the entire hospital stay is required to limit morbidity and mortality of the pediatric trauma patient.

### Summary

If care is to be optimally provided at centers outside of the tertiary pediatric setting, health care providers in these environments need to reassess their approach to the management of pediatric splenic injury, recognizing that the operative rate is presently 4 to 6 times lower for children with splenic injury treated by pediatric surgeons at pediatric facilities than in other environments. It is incumbent upon pediatric trauma centers to do a better job of educating trauma colleagues in nonpediatric trauma centers regarding the optimal care of pediatric patients with splenic injury, so that these results are not limited to highly selected centers. Focusing educational programs and evidence-based management guidelines on centers with higher rates of splenectomy may be the next step to improve the rate of splenic conservation. Although the impact on in-hospital mortality might not be a relevant end point, because it is infrequent, these patients are at higher risk for overwhelming postsplenectomy sepsis and complications related to laparotomy, such as adhesive small bowel obstruction and incisional hernia.

Adult trauma surgeons caring for injured children must consider the anatomic, immunologic, and physiologic differences between pediatric and adult trauma patients and incorporate these differences into their treatment protocols.[50] The major concerns are related to the potential risks of increased transfusion requirements, missed associated injuries, and increased length of hospital stay. Each of these concerns has been shown to be without merit.[51–53]

## ASSOCIATED ABDOMINAL INJURIES

Advocates of surgical intervention for splenic trauma cite their concern about missing associated abdominal injuries if no operation is performed. Morse and Garcia reported successful nonoperative treatment in 110 of 120 children (91%) with blunt splenic trauma, of whom 22 (18%) had associated abdominal injuries.[51] Only 3 of these 120 patients (2.5%) had GI injuries, and each was discovered at early celiotomy done for a specific indication. There was no morbidity from missed injuries or delayed surgery. Similarly, a review of the NPTR from 1988 to 1998 revealed 2977 patients with solid abdominal visceral injuries; only 96 (3.2%) had an associated hollow visceral injury.[52] Higher rates of hollow visceral injury were observed in assaulted patients and in those with multiple solid visceral injuries or pancreatic injuries. Differences in mechanism of injury may account for the much lower incidence of associated abdominal injuries in children with splenic trauma. There is no justification for an exploratory celiotomy solely to avoid missing potential associated injuries in children.

## COMPLICATIONS OF NONOPERATIVE TREATMENT

Nonoperative treatment protocols have been the standard for most children with blunt liver and spleen injuries for the past 3 decades. This cumulative experience has allowed us to evaluate both the benefits and the risks of the nonoperative approach. Fundamental to the success of a nonoperative strategy is the early, spontaneous cessation of hemorrhage. Transfusion rates for children with isolated spleen or liver injuries have fallen below 10%, confirming the lack of continued blood loss in the majority of patients.[33,34,53] Rare anecdotal reports of significant delayed hemorrhage with adverse outcomes after solid organ injury continue to appear and cause concern.[47,54–56] Shilyansky and colleagues[56] reported two children with delayed hemorrhage 10 days after blunt liver injury. Both children had persistent right upper quadrant and right shoulder pain despite normal vital signs and stable hematocrits. The authors recommended continued in-house observation until symptoms resolve. The incidence of delayed bleeding after blunt splenic injury was 1 (0.33%) in 303 children reported from the Hospital for Sick Children in Toronto and resulted in a fatality.[47] These rare occurrences lead to caution when determining a minimum safe interval before the resumption of unrestricted activities.

Routine follow-up imaging studies have identified pseudocysts and pseudoaneurysms following splenic injury.[57] Splenic pseudoaneurysms often cause no symptoms and appear to resolve with time. The true incidence of self-limited, posttraumatic splenic pseudoaneurysms is unknown, because routine follow-up imaging after successful nonoperative treatment has been largely abandoned. Once identified, the actual risk of splenic pseudoaneurysm rupture is also unclear. Angiographic embolization techniques can successfully treat these lesions, obviating the need for open surgery and loss of splenic parenchyma (Fig. 20-3).[58] Splenic pseudocysts can achieve enormous size, leading to pain and GI disturbance (Fig. 20-4). Simple percutaneous aspiration leads to a high recurrence rate. Laparoscopic excision and marsupialization are highly effective (Fig. 20-5).

## SEQUELAE OF DAMAGE-CONTROL STRATEGIES

Even the most severe solid organ injuries can be treated without surgery, if there is a prompt response to resuscitation.[59,60] In contrast, emergency laparotomy, embolization, or both are

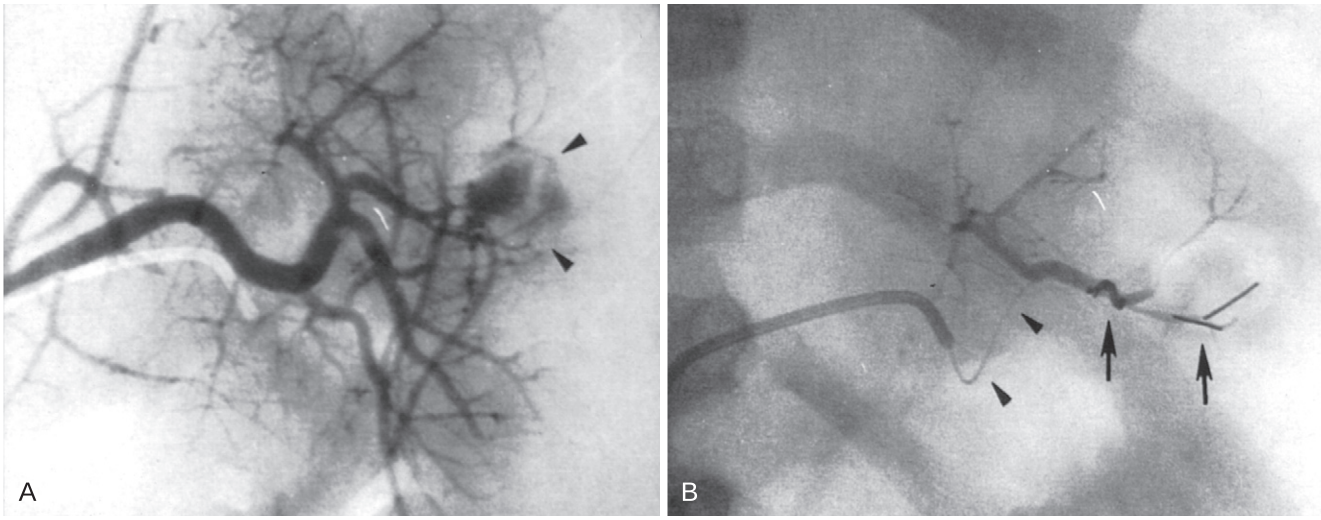


FIGURE 20-3 **A,** Splenic pseudoaneurysm (arrowheads indicate contrast within the pseudoaneurysm) after nonoperative treatment of blunt splenic injury. **B,** Successful angiographic embolization (*arrows* show occlusion of ruptured vessels).

indicated in patients who are hemodynamically unstable despite fluid and red blood cell transfusion (Fig. 20-6). Most spleen and liver injuries requiring operation are amenable to simple methods of hemostasis using a combination of manual compression, direct suture, topical hemostatic agents, and mesh wrapping. In young children with significant hepatic injury, the sternum can be divided rapidly to expose the suprahepatic or intrapericardial inferior vena cava, allowing for total hepatic vascular isolation (Fig. 20-7). Children can tolerate periods of vascular isolation for 30 minutes or longer, as long as their blood volume is replenished. Venovenous bypass may be useful but is rarely available for such rare injuries.[61] With this exposure, the liver and major perihepatic veins can be isolated and the bleeding controlled, permitting direct suture repair or ligation of the offending vessel. Although the cumbersome and dangerous technique of atriocaval shunting has been largely abandoned, newer endovascular balloon catheters can be useful

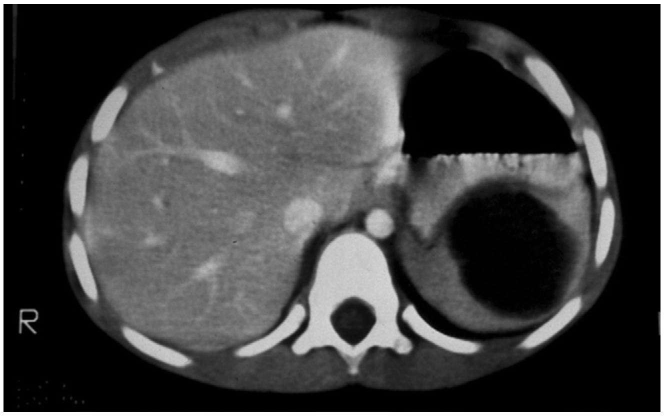


FIGURE 20-4 Computed tomography scan of post-traumatic splenic pseudocyst.

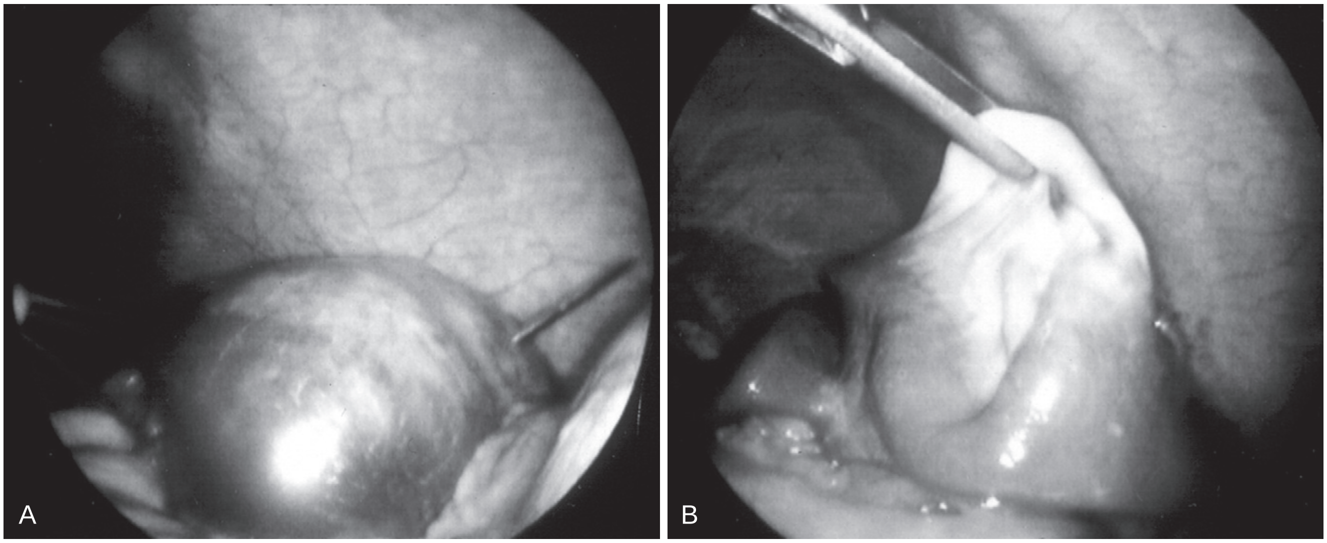


FIGURE 20-5 **A,** Laparoscopic view of splenic pseudocyst capsule. **B,** Appearance of cyst wall after laparoscopic aspiration and before marsupialization.

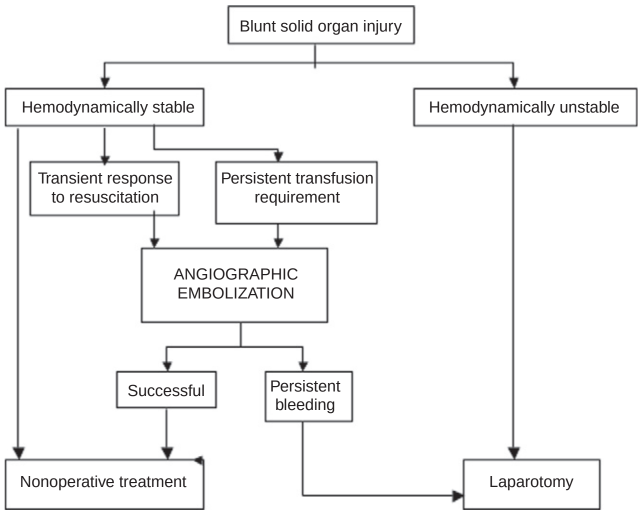


FIGURE 20-6 Algorithm for selected use of angiographic embolization in patients with blunt solid organ injury. (Modified from M. Nance, Children's Hospital of Philadelphia.)

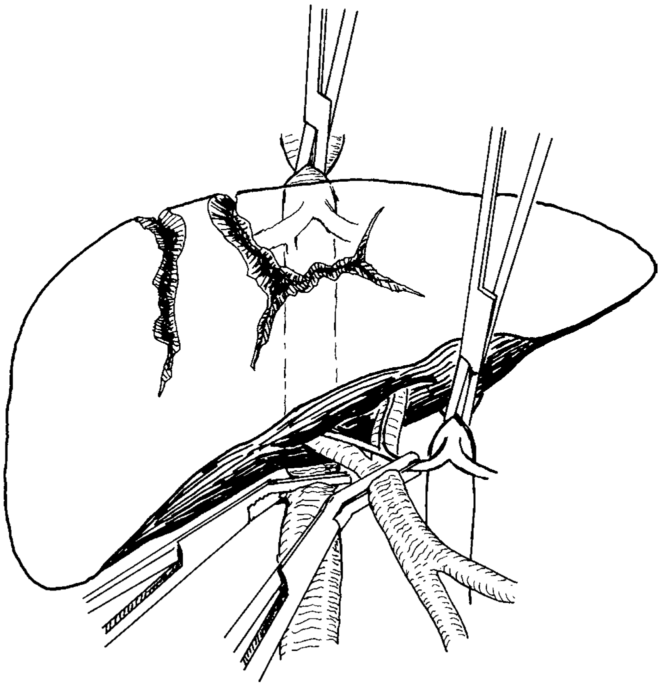

FIGURE 20-7 Total hepatic vascular isolation with occlusion of the portahepatic, suprahepatic, and infrahepatic inferior vena cava and supraceliac aorta (optional). (Original illustration by Mark Mazziotti, MD.)

for temporary vascular occlusion to allow access to the juxtahepatic vena cava.[62]

The early morbidity and mortality of severe hepatic injuries are related to the effects of massive blood loss and replacement with large volumes of cold blood products. The consequences of prolonged operations with massive blood-product replacement include hypothermia, coagulopathy, and acidosis. Although the surgical team may keep pace with blood loss, life-threatening physiologic and metabolic consequences are inevitable, and many of these critically ill patients are unlikely to survive once their physiologic reserves have been

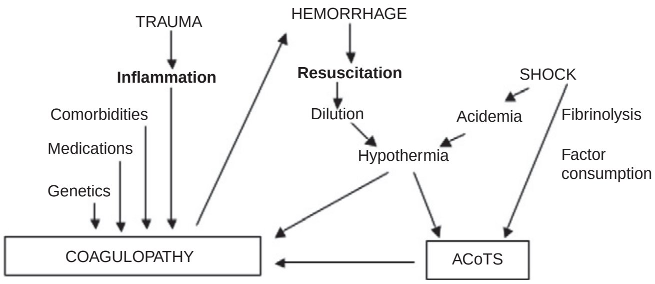


FIGURE 20-8 Acute coagulopathy of trauma and shock (ACoTS). (From Hess JR, Brohi K, Duton RP, et al: The coagulopathy of trauma: A review of mechanisms. J Trauma 2008;65:748-754.)

exhausted. A multi-institutional review identified exsanguination as the cause of intraoperative death in 82% of 537 patients at eight academic trauma centers.[63] The mean pH was 7.18, and the mean core temperature was 32° C before death. Moulton and colleagues reported survival in only 5 of 12 (42%) consecutive operative cases of retrohepatic vascular or severe parenchymal liver injury in children.[64]

Maintenance of physiologic stability during the struggle for surgical control of severe bleeding is a formidable challenge even for the most experienced surgical team, particularly when hypothermia, coagulopathy, and acidosis occur. This triad creates a vicious circle in which each derangement exacerbates the others, and the physiologic and metabolic consequences often preclude completion of the procedure. Lethal coagulopathy from a combination of tissue injury, dilution, hypothermia, and acidosis can rapidly occur (Fig. 20-8).[65] Experimental studies have defined the alterations in procoagulant and anticoagulant enzyme processes, platelet activation, and platelet adhesion defects with varying degrees of hypothermia.[66] The infusion of activated recombinant factor VII in children with massive hemorrhage has been promising in several case reports, and experimental studies suggest that recombinant factor VII maintains its effectiveness at hypothermic temperatures[67–70]

Increased emphasis on physiologic and metabolic stability in emergency abdominal operations has led to the development of staged, multidisciplinary treatment plans, including abbreviated laparotomy, perihepatic packing, temporary abdominal closure, angiographic embolization, and endoscopic biliary stenting.[71–74] Asensio and colleagues[75] reported on 103 patients with mostly penetrating grade IV or V hepatic injuries treated between 1991 and 1999. Mean blood loss was estimated at 9.4 L, and mean volume infusion in the operating room was 15 L. Packing of the hepatic injuries was used in 50% of patients at the first operation. Forty percent of patients who survived the initial operative control of hemorrhage had postoperative angiographic embolization (Fig. 20-9). Survival was 63% in grade IV patients and 24% in grade V patients, emphasizing the lethality of such injuries despite a well-choreographed, staged, multidisciplinary approach. Trauma surgeons treating critically injured children must familiarize themselves with these lifesaving techniques.

Hepatic angioembolization can clearly be an important adjunct in the treatment of patients with major liver injury. However, evidence of significant hepatic necrosis and biliary leaks occur in 30% to 40% of patients, thus emphasizing the need for cautious patient selection.[76,77]

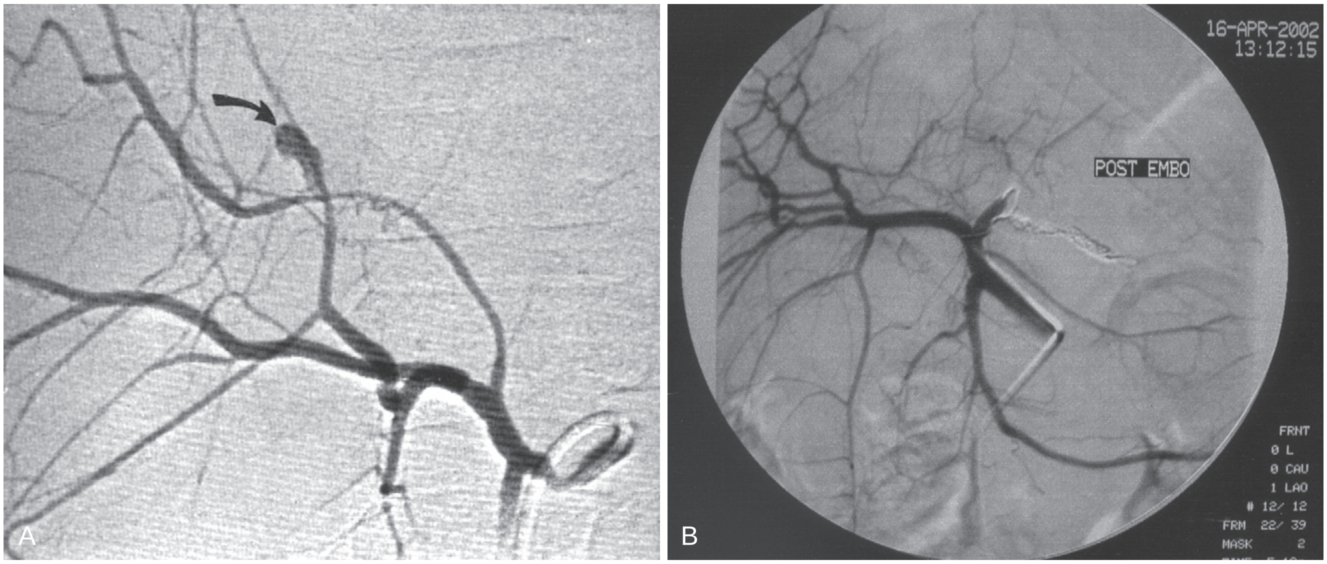


**FIGURE 20-9** **A,** Hepatic artery angiogram in a patient with persistent hemorrhage after initial damage-control laparotomy. The bleeding vessel is identified (*curved arrow*). **B,** Successful embolization was performed.

Abbreviated laparotomy with packing for hemostasis, allowing resuscitation before planned reoperation, is an alternative in unstable patients in whom further blood loss would be untenable. This damage-control philosophy is a systematic, phased approach to the management of exsanguinating trauma patients.[78–80] The three phases of damage control are detailed in Table 20-6. Although controversial, several resuscitative end points have been proposed beyond the conventional vital signs and urine output, including serum lactate, base deficit, mixed venous oxygen saturation, and gastric mucosal pH. Once a patient is rewarmed, coagulation factors are replaced, and oxygen delivery is optimized, he or she can be returned to the operating room for pack removal and definitive repair of injuries. A review of nearly 700 adult patients treated by abdominal packing from several institutions demonstrated hemostasis in 80%, survival of 32% to 73%, and abdominal abscess rates of 10% to 40%.[81,82] Although abdominal packing with planned reoperation has been used with increasing frequency in adults during the past 2 decades, there is little published experience in children.[61,83–88] Nevertheless, we believe that this technique has a place in the management of children with massive intra-abdominal bleeding, especially after blunt trauma. As an example, we reported a 3-year-old child who required abdominal packing for a severe liver injury, making closure of the abdomen impossible.[88] A Silastic silo was constructed to accommodate the bowel until the packing could be removed. The patient made a complete recovery. The combined technique of packing and a silo allowed time for correction of the hypothermia, acidosis, and coagulopathy without compromise of respiratory mechanics. One review reported 22 infants and children (age 6 days to 20 years) with refractory hemorrhage who were treated with abdominal packing.[87] The anatomic site of hemorrhage was the liver or hepatic veins in 14, retroperitoneum or pelvis in 7, and pancreatic bed in 1. Primary fascial closure was accomplished in 12 patients (55%), and temporary skin closure or prosthetic material was used in the other 10. Packing controlled hemorrhage in 21 of 22 patients (95%). Removal of the packing was possible within 72 hours in 18 patients (82%). No patient rebled after the packing was removed; however, 2 patients died with the packing in place. Seven patients (32%) developed an abdominal or pelvic abscess, and all were successfully drained by laparotomy (6 patients) or percutaneously (1 patient); 6 of the 7 patients with abdominal sepsis survived. Overall, 18 patients (82%) survived. Two deaths were due to multisystem organ failure, one to cardiac failure from complex cardiac anomalies, and one to exsanguination after blunt traumatic liver injury. There were no differences in the volume of intraoperative blood product transfusion, time to initiate packing, physiologic status, or type of abdominal closure between survivors and nonsurvivors.

**TABLE 20-6**
**Damage-Control Strategy in Exsanguinating Trauma Patients**

| | |
|---|---|
| Phase 1 | Abbreviated laparotomy for exploration |
| | Control of hemorrhage and contamination |
| | Packing and temporary abdominal wall closure |
| Phase 2 | Aggressive ICU resuscitation |
| | Core rewarming |
| | Optimization of volume and oxygen delivery |
| | Correction of coagulopathy |
| Phase 3 | Planned reoperation(s) for packing change |
| | Definitive repair of injuries |
| | Abdominal wall closure |

ICU, Intensive care unit.

Preperitoneal pelvic packing for hemodynamically unstable patients with pelvic fracture is another unique use of pack tamponade in life-threatening hemorrhage.[89]

Although the success of abdominal packing is encouraging, it may contribute to significant morbidity, such as intra-abdominal sepsis, organ failure, and increased intra-abdominal pressure. Intra-abdominal packs are contaminated by skin and gut flora, but these organisms are not those implicated in

subsequent patient sepsis.[90] Adams and colleagues[91] evaluated fluid samples from 28 patients with abdominal packing and found peritoneal endotoxin and mediator accumulation even when cultures were sterile. The authors concluded that laparotomy pad fluid accumulating after damage-control laparotomy can contribute to neutrophil dysfunction by enhancing neutrophil respiratory burst and inhibiting neutrophil responses to specific chemotactic mediators needed to fight infection. Thus the known propensity of such patients to both intra-abdominal and systemic infection may be related to changes in neutrophil receptor status and effector function related to the accumulation of inflammatory mediators in the abdomen. Early washout, repetitive packing, and other efforts to minimize mediator accumulation deserve consideration.

It is essential to emphasize that the success of the abbreviated laparotomy and planned reoperation depends on an early decision to use this strategy before irreversible shock occurs. When used as a desperate, last-ditch resort after prolonged attempts at hemostasis have failed, abdominal packing has been uniformly unsuccessful. Physiologic and anatomic criteria have been identified as indications for abdominal packing. Most of these focus on intraoperative parameters, including pH ($\approx$7.2), core temperature ($<$35° C), and coagulation values (prothrombin time $>$16 seconds), in a patient with profuse hemorrhage requiring large volumes of blood product transfusion.

The optimal time for reexploration is controversial, because neither the physiologic end points of resuscitation nor the increased risk of infection with prolonged packing are well defined. The obvious benefits of hemostasis provided by packing are also balanced against the potential deleterious effects of increased intra-abdominal pressure on ventilation, cardiac output, renal function, mesenteric circulation, and intracranial pressure. Timely alleviation of the secondary abdominal compartment syndrome may be a critical salvage maneuver for patients. Temporary abdominal wall closure at the time of packing can prevent the abdominal compartment syndrome. We recommend temporary abdominal wall expansion in all patients requiring packing, until hemostasis is obtained and visceral edema subsides.

A staged operative strategy for unstable trauma patients represents advanced surgical care and requires sound judgment and technical expertise. Intra-abdominal packing for control of exsanguinating hemorrhage is a lifesaving maneuver in highly selected patients in whom coagulopathy, hypothermia, and acidosis render further surgical procedures unduly hazardous. Early identification of patients likely to benefit from abbreviated laparotomy techniques is crucial for success.

## ABDOMINAL COMPARTMENT SYNDROME

The abdominal compartment syndrome is a term used to describe the deleterious effects of increased intra-abdominal pressure.[92] The syndrome includes respiratory insufficiency from worsening ventilation-perfusion mismatch, hemodynamic compromise from preload reduction resulting from inferior vena cava compression, impaired renal function resulting from renal vein compression, decreased cardiac output, intracranial hypertension resulting from increased ventilator pressures, splanchnic hypoperfusion, and abdominal wall overdistention. The causes of intra-abdominal hypertension in trauma patients include hemoperitoneum, retroperitoneal or bowel edema, and use of abdominal or pelvic packing. The combination of tissue injury and hemodynamic shock creates a cascade of events, including capillary leak, ischemia-reperfusion, and release of vasoactive mediators and free radicals, which combine to increase extracellular volume and tissue edema. Experimental evidence indicates that there are significant alterations in cytokine levels in the presence of sustained intra-abdominal pressure elevation.[93,94] Once the combined effects of tissue edema and intra-abdominal fluid exceed a certain level, abdominal decompression must be considered.

The adverse effects of abdominal compartment syndrome have been acknowledged for decades; however, abdominal compartment syndrome has only recently been recognized as a life-threatening but potentially treatable entity.[95,96] The incidence of this complication has increased markedly in recent years due to high-volume resuscitation protocols. Measurement of intra-abdominal pressure can be useful in determining the contribution of abdominal compartment syndrome to altered physiologic and metabolic parameters.[97,98] Intra-abdominal pressure can be determined by measuring bladder pressure. This involves instilling 1 mL/kg of saline into the Foley catheter and connecting it to a pressure transducer or manometer through a three-way stopcock. The symphysis pubis is used as the zero reference point, and the pressure is measured in centimeters of water or millimeters of mercury. Intra-abdominal pressures in the range of 20 to 35 cm $H_2O$ or 15 to 25 mm Hg have been identified as an indication to decompress the abdomen. Many prefer to intervene according to alterations in other physiologic and metabolic parameters rather than a specific pressure measurement. Chang and colleagues[97] reported 11 adult trauma patients with abdominal compartment syndrome in whom abdominal decompression using pulmonary artery catheters and gastric tonometry improved preload, pulmonary function, and visceral perfusion. Anecdotally, decompressive laparotomy has been used successfully to reduce refractory intracranial hypertension in patients with isolated brain injury without overt signs of abdominal compartment syndrome.[99]

Experience with abdominal decompression for abdominal compartment syndrome in children is limited.[*] Nonspecific abdominal CT findings in children with abdominal compartment syndrome include narrowing of the inferior vena cava, direct renal compression or displacement, bowel wall thickening with enhancement, and a rounded appearance of the abdomen.[100] Neville and colleagues[101] reported the use of patch abdominoplasty in 23 infants and children, only 3 of whom were trauma patients. These authors found that patch abdominoplasty for abdominal compartment syndrome effectively decreased airway pressures and oxygen requirements. Failure to respond with a decrease in airway pressures or fraction of inspired oxygen was an ominous sign in their series. Several authors have found that abdominal decompression resulted in decreased airway pressures, increased oxygen tension, and increased urine output in children with abdominal compartment syndrome.[95,98,101]

Many materials have been suggested for use in temporary patch abdominoplasty, including Silastic sheeting, Gore-Tex sheeting, intravenous bags, cystoscopy bags, ostomy appliances, and various mesh materials. The vacuum-pack

* References 87, 88, 95, 98, 100, 101.

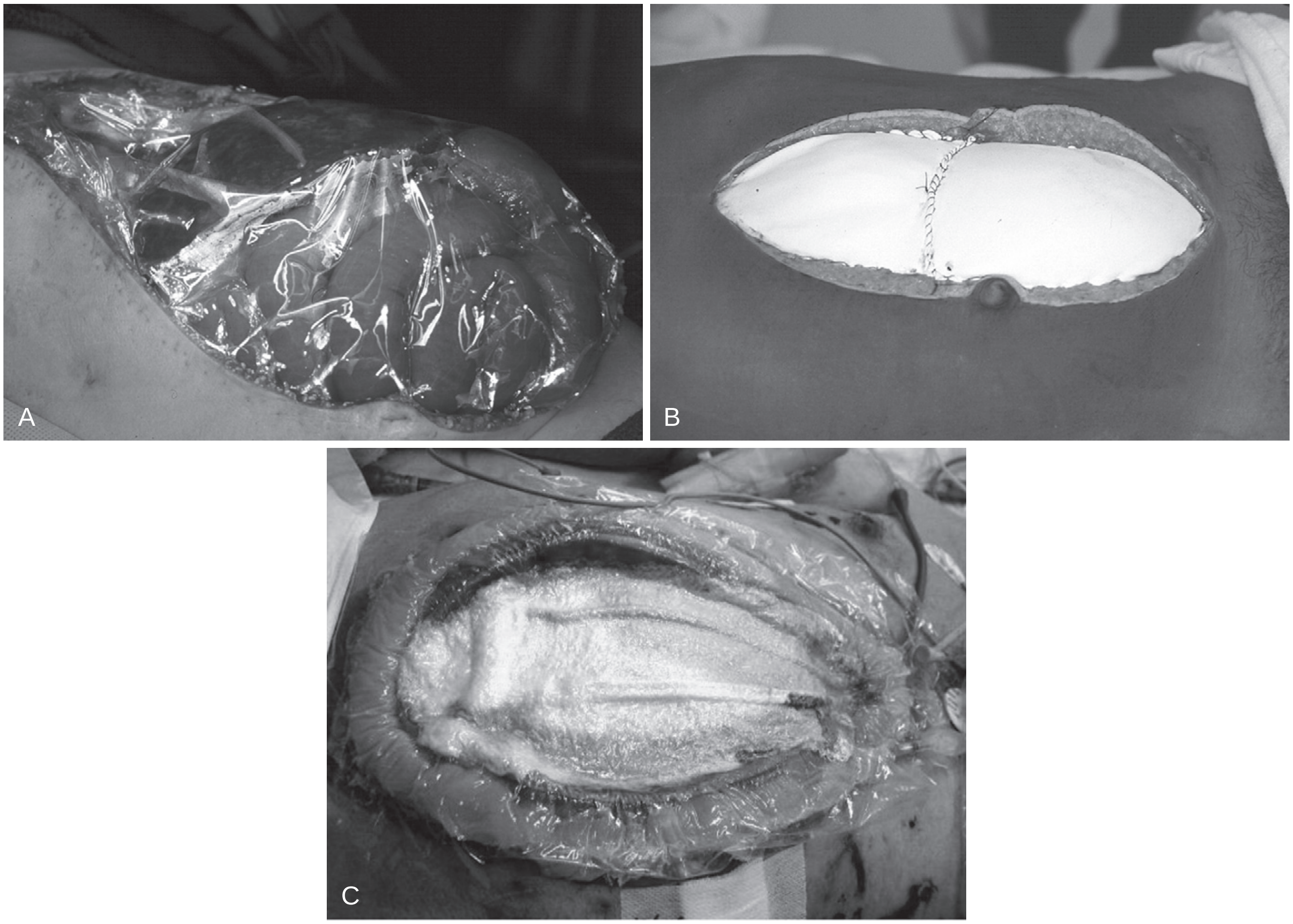

FIGURE 20-10 **A,** Abdominal wall expansion with Silastic sheeting. **B,** Abdominal wall expansion with a Gore-Tex patch. **C,** Vacuum-pack technique.

technique, used successfully in adults, has been an outstanding addition in children (Fig. 20-10).[78,85,102] Use of the vacuum-pack technique at the first trauma laparotomy may limit the early benefits of the open abdomen by resulting in a lower volume reserve capacity.[103]

### BILE DUCT INJURY

Nonoperative management of pediatric blunt liver injury is highly successful but is complicated by a 4% risk of persistent bile leakage.[104,105] Radionuclide scanning is recommended when biliary tree injury is suspected.[106] Delayed views may show a bile leak even if early views are normal. Several reports have highlighted the benefits of endoscopic retrograde cholangiopancreatography (ERCP) with placement of transampullary biliary stents for biliary duct injury following blunt hepatic trauma. Although ERCP is invasive and requires conscious sedation, it can pinpoint the site of injury and allow treatment of the injured ducts without open surgery (Fig. 20-11). Endoscopic transampullary biliary decompression is a recent addition to the treatment options for patients with persistent bile leakage. The addition of sphincterotomy during ERCP for persistent bile leakage following blunt liver injury has been advocated to decrease intrabiliary pressure and encourage internal decompression.[105–108] It is important to note that endoscopic biliary stents may migrate or become obstructed and require specific treatment.

## Injuries to the Duodenum and Pancreas

In contrast to the liver and spleen, injuries to the duodenum and pancreas are much less frequent, accounting for less than 10% of intra-abdominal injuries in children sustaining blunt trauma. Isolated duodenal and pancreatic injuries occur in approximately two thirds of cases, with combined injuries to both organs occurring in the remainder. The severity of the duodenal or pancreatic injury and associated injuries determines the necessity for operative versus nonoperative management. The “protected” retroperitoneum both limits the chance of injury and increases the difficulty of early diagnosis. Added to this diagnostic dilemma is the frequency of associated intra-abdominal or multisystem injuries, which can mask subtle physical and radiographic diagnostic signs of injury to the duodenum and pancreas.

### DUODENUM

In a report on blunt duodenal rupture, Ballard and colleagues[109] reviewed a 6-year statewide (Pennsylvania) experience. Of 103,864 patients registered from 28 trauma centers, blunt injury to the duodenum occurred in 206 (0.2%), of whom only 30 (14%) had full-thickness rupture. The mechanism of injury was car crash in 70%, which included both adults

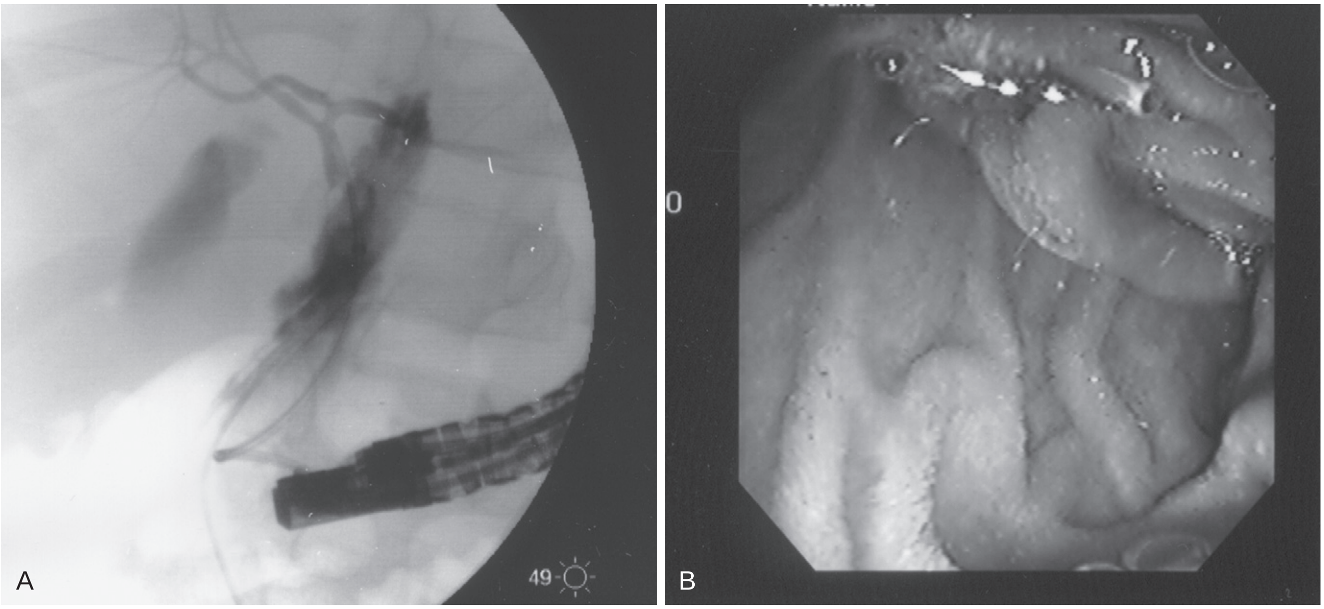

**FIGURE 20-11** **A,** Endoscopic retrograde cholangiopancreatography demonstrating several bile leaks after blunt liver injury. **B,** Endoscopic view of transampullary biliary stent.

and children. Of those without significant head injury (26 of 30), 92% either reported abdominal pain or had tenderness or rebound on physical examination. CT was performed in 18 patients; retroperitoneal air or extravasation of contrast was seen in only 26% of scans; an equal number were interpreted as normal. Mortality was 13% and was not affected by a delay in diagnosis or treatment. This study emphasizes the difficulty of analyzing this injury because of the low numbers reported by individual centers (and surgeons). Additionally, the investigators reviewed the range of repairs performed—from duodenal closure to the Whipple procedure—but commented that no definitive recommendations could be made because of the small number of patients and the many centers reporting.

In contrast, a group from Toronto reported a single-center experience in a series of 27 children (mean age, 7 years) sustaining blunt duodenal injuries and treated over a 10-year period.[110] Thirteen children had duodenal perforations (mean age, 9 years), and 14 sustained duodenal hematomas (mean age, 5 years). Associated injuries were seen in 19 patients (10 pancreas, 5 spleen, 4 liver, 2 long bone fracture, 1 central nervous system, 1 renal contusion, 1 jejunal perforation, and 1 gastric rupture). Seventeen patients were transferred from other facilities, with a 4-hour median time to transfer. The median interval from injury to surgery in those sustaining perforation was 6 hours. A comparison of the clinical presentation, laboratory evaluation, and radiographic findings in those with duodenal hematoma versus perforation is presented in Table 20-7. Most patients had abdominal CT scans performed with oral and intravenous contrast (Figs. 20-12 and 20-13). A comparison of CT findings in these patient groups is presented in Table 20-8. These data demonstrate that the clinical presentation is strikingly similar in both groups, with only age and injury severity score achieving statistical significance (but of little clinical relevance in individual patients). However, extravasation of air or enteral contrast into the retroperitoneal, periduodenal, or prerenal space was found in every child with a duodenal perforation (9 of 9) but in none of the 10 who had duodenal hematoma. The authors noted that few previous reports in the literature described these specific CT findings with duodenal injuries in general, and in particular, no previous series of pediatric patients had been reported. The CT scans (or upper GI contrast studies in equivocal cases) showing duodenal narrowing, corkscrewing, or obstruction without extravasation were diagnostic in all cases. In the current series of 14 patients treated nonoperatively, the duration of nasogastric decompression was 12 days (mean), and the length of total parenteral nutrition administration was 18 days (mean). Symptoms resolved in 13 of 14 patients an average of 16 days after injury. The remaining child developed a chronic fibrous stricture requiring operative duodenoplasty 49 days after injury. This child also had a pancreatic contusion.

Desai and colleagues,[111] from St. Louis Children's Hospital, reviewed their experience with 24 duodenal injuries from blunt abdominal trauma. There were 19 duodenal hematomas (15 diagnosed by CT, and 4 by upper GI studies), 17 of which were treated nonoperatively. In those with perforation, 4 of 5 were amenable to simple suture repair. The experiences from Salt Lake City and Pittsburgh emphasize an alarming finding that a common cause of duodenal trauma is child abuse, especially in younger patients.[112,113] Therefore isolated duodenal injures should raise suspicion if the history or mechanism of injury described is inconsistent with the actual injury.

In all these series, patients sustaining duodenal perforation were treated operatively in a variety of ways, depending on the injury severity and the surgeon's preference. We recommend primary closure of a duodenal perforation (whenever possible). Primary closure can be combined with duodenal drainage and either pyloric exclusion with gastrojejunostomy (Fig. 20-14) or gastric drainage with feeding jejunostomy. These surgical options decrease the incidence of duodenal fistula, reduce the time to GI tract alimentation, and shorten hospital stay. When faced with complicated

**TABLE 20-7**

**Presenting Symptoms and Signs in Children with Duodenal Hematoma and Duodenal Perforation**

| *Patient* | *Duodenal Hematoma* | *Duodenal Perforation* |
|---|---|---|
| Number | 14 | 13 |
| Age (yr) | 5 | 9* |
| ISS score | 10 | 25* |
| Seat belt worn: number (%) | 6 (100) | 5 (71) |
| Presentation | | |
| Pain or tenderness: | 10 (71) | 12 (92) |
| number (%) | | 11 (85) |
| Bruising: no. (%) | 6 (43) | |
| GCS score | 15 | 15 |
| Associated injuries | | |
| Pancreatic: number (%) | 7 (50) | 3 (23) |
| Lumbar spine: no. (%) | 1 (7) | 4 (31) |
| Total: number (%) | 11 (79) | 8 (62) |
| Laboratory evaluation | | |
| Hgb: mg %/Hct | 12.3/0.36 | 12.1/0.37 |
| Amylase: units (%) | 678 (64) | 332 (46) |

From Shilyansky J, Pearl RH, Kroutouro M, et al: Diagnosis and management of duodenal injuries in children. J Pediatr Surg 1997:32:880-886.
*Statistically significant difference.
GCS, Glasgow Coma Scale; Hct, hematocrit; Hgb, hemoglobin; ISS, Injury Severity Scale.

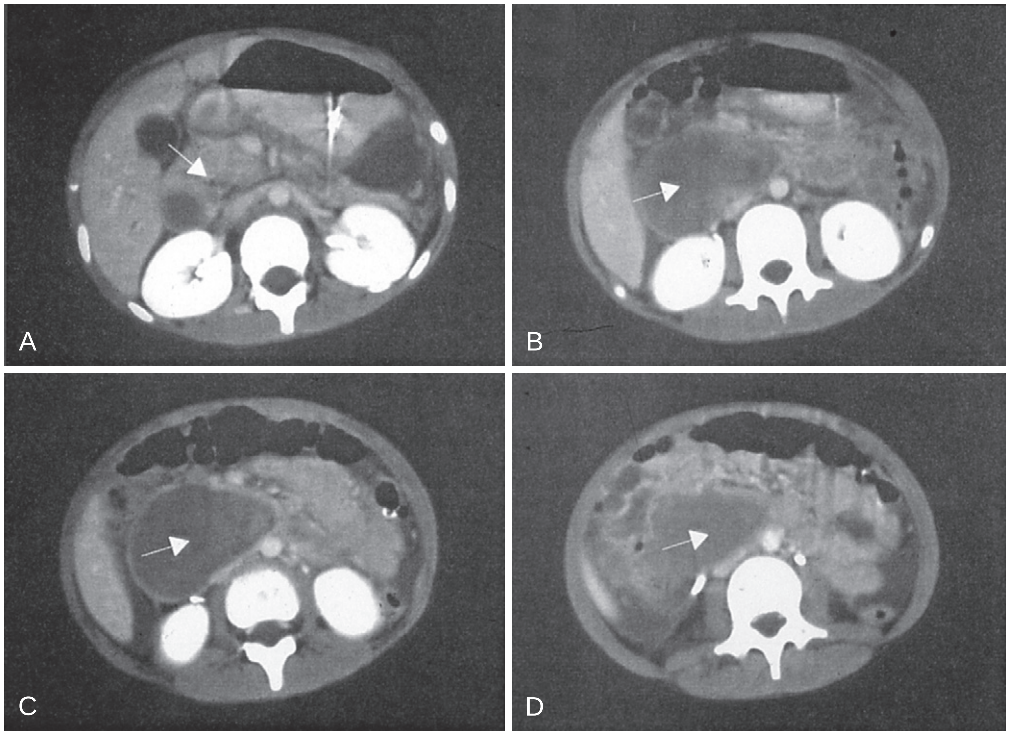


FIGURE 20-12 Abdominal computed tomography findings in an 8-year-old girl who sustained a duodenal hematoma after a fall at a playground. **A,** The *arrow* points to the markedly narrowed duodenal lumen. **B** to **D,** The *arrows* point to the large intramural hematoma. The child was treated with nasogastric suction and total parenteral nutrition. She was eating a regular diet 24 days after her injury.

duodenal trauma, an effective combination is the three-tube technique: duodenal closure (primary repair, serosal patch, or anastomosis) with duodenal drainage tube for decompression (tube 1), pyloric exclusion with an absorbable suture through gastrotomy and gastric tube placement (tube 2), and feeding jejunostomy (tube 3). Several closed suction drains are placed adjacent to the repair. When the duodenum is excluded (by an absorbable suture for temporary closure of the pylorus), complete healing of the injury routinely occurs before the spontaneous reopening of the pyloric channel (Fig. 20-15). Bioprosthetic repair of complex duodenal injury in a porcine model has been reported and could add to operative strategies.[114]

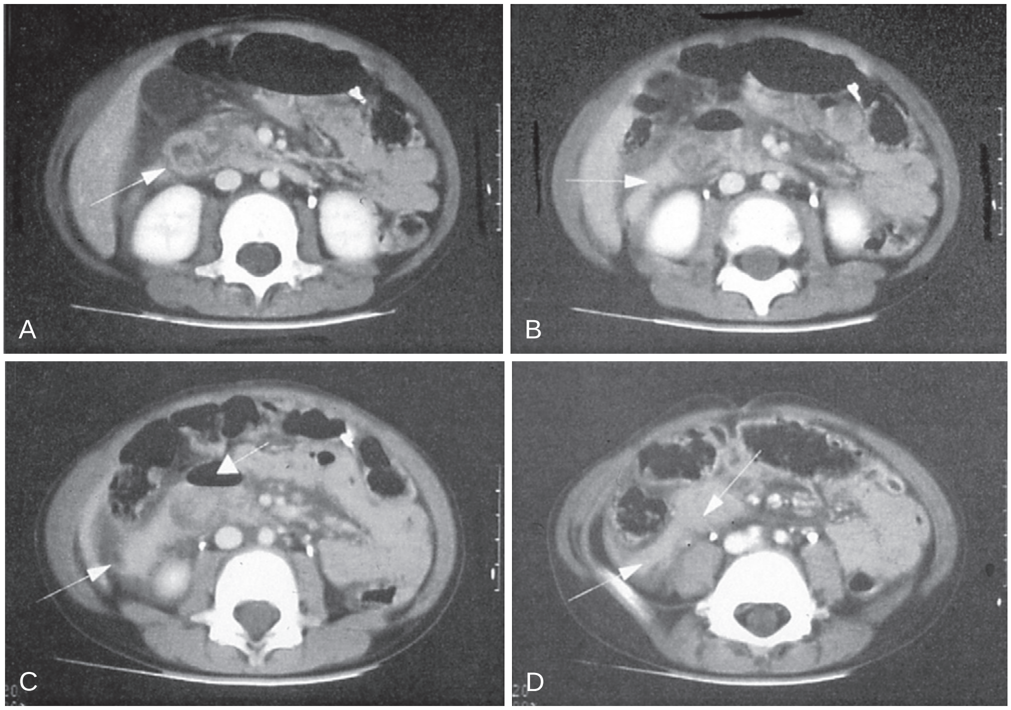


FIGURE 20-13 Abdominal computed tomography findings in a 4-year-old boy with duodenal perforation caused by a motor vehicle accident. **A,** The *arrow* points to the disrupted duodenal wall. **B** to **D,** Arrows point to extravasated retroperitoneal enteral contrast and extraluminal retroperitoneal air. A large defect involving the second and third portions of the duodenum was found. Primary repair, pyloric exclusion, tube duodenostomy, and gastrojejunostomy were performed. The child resumed eating 5 days after injury and went home 4 days later.

**TABLE 20-8**
**Comparison of Computed Tomography Findings in Children with Duodenal Hematoma and Duodenal Perforation**

| *Finding* | *Duodenal Hematoma (n = 10) Number (%)* | *Duodenal Perforation (n = 9) Number (%)* |
|---|---|---|
| Free air | 1 (10)* | 2 (22) |
| Free fluid | 8 (80) | 9 (100) |
| Retroperitoneal fluid | 9 (90) | 9 (100) |
| Bowel wall and peritoneal enhancement | 2 (20) | 4 (44) |
| Duodenal caliber change | 4 (40) | 3 (33) |
| Thickened duodenum | 10 (100) | 8 (89) |
| Mural hematoma | 10 (100) | 0 |
| Retroperitoneal air | 0 | 8 (89) |
| Retroperitoneal contrast† | 0 | 4 (57) |
| Retroperitoneal air or contrast | 0 | 9 (100) |

From Shilyansky J, Pearl RH, Kroutouro M, et al: Diagnosis and management of duodenal injuries in children. J Pediatr Surg 1997:32:880-886.
*The child had an associated jejunal perforation.
†Enteral contrast was not administered in two children.

However, no matter what repair the surgeon selects, a summary of the literature demonstrates that protecting the duodenal closure (drain and exclusion) and a route for enteral feeding (gastrojejunostomy or feeding jejunostomy) reduces morbidity and hospital length of stay.[115,116]

The surgical options are listed in Table 20-9 and illustrated in Figures 20-14 and 20-16. Of note, pancreaticoduodenectomy (the Whipple procedure) is rarely required. Although occasionally reported in the literature, pancreaticoduodenectomy should be reserved for the most severe injuries to the duodenum and pancreas in which the common blood supply is destroyed and reconstruction is impossible.

## PANCREAS

Injuries to the pancreas are slightly more frequent than duodenal injuries, with estimated ranges from 3% to 12% in children sustaining blunt abdominal trauma. As with duodenal injuries, individual centers frequently have small patient numbers and thus are unable to evaluate their results

critically. Recently, two centers (Toronto and San Diego) reported their experience with divergent methods of managing blunt traumatic pancreatic injuries in a series of reports.[117–121] Here we compare these papers and excerpt other authors' experience to make management recommendations.

Canty and Weinman (San Diego)[118] reported 18 patients with major pancreatic injuries over a 14-year period. The mechanism of injury was car or bike crashes. Sixteen of the 18 patients had CT scans on admission. Of these, 11 suggested injury; in 5, the injury was missed. Distal pancreatectomy was performed in 8 patients (44%). In 5 of 6 patients with either proximal duct injuries or injuries missed on the initial CT scan, pseudocysts developed; pseudocysts also occurred in 2 other children who had minimal initial symptoms and no admission CT scans. Of these 7 pseudocysts, 2 resolved and 5 were treated by cystogastrostomy. Two patients, treated more recently, received endoscopic retrograde cholangiopancreatography (ERCP) with duct stenting and experienced resolution of symptoms and complete healing. The authors concluded that distal injuries should be treated with distal pancreatectomy, proximal injuries with observation, and pseudocysts with observation or cystogastrostomy. They also concluded that acute ERCP management with stent placement is safe and effective, and that CT is suggestive but not always diagnostic for the type and location of pancreatic injuries.[117,118]

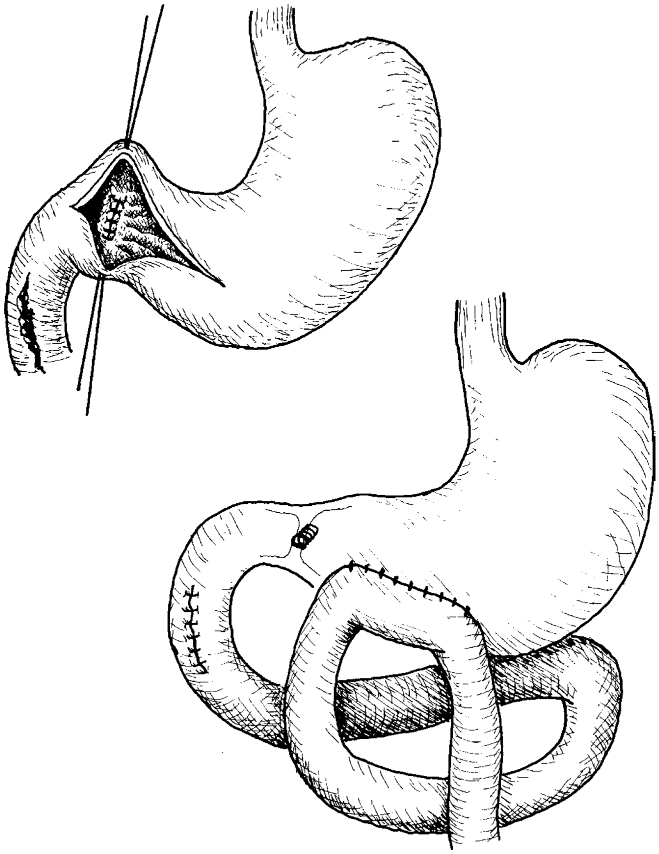

FIGURE 20-14 Lateral duodenal injury treated by primary duodenal repair and pyloric exclusion consisting of closing the pylorus with an absorbable suture and gastrojejunostomy. Closed suction drainage of the repair is not depicted. (Original illustration by Mark Mazziotti, MD.)

The experience summarized in three reports from Toronto is markedly different.[119–121] The extensive CT findings suggestive of pancreatic injury are detailed in Table 20-10. In the first brief report, 2 patients with documented duct disruption (by ERCP or cathetergram) had complete duct healing without operative intervention.[119] This was followed by a summary report of 35 consecutive children treated over 10 years (1987 to 1996).[120] Twenty-three had early diagnosis (<24 hours), whereas diagnosis was delayed (2 to 14 days) in 12 patients. Twenty-eight children were treated nonoperatively, and the other 7 had operations for other injuries. In the 28 cases treated nonoperatively, CT was diagnostic, revealing five patterns of injury: contusion, stellate fragmentation, partial fracture, complete transection, and pseudocyst (Fig. 20-17). The patients were placed in three clinical groups based on CT grade (Table 20-11). In these 28 patients, pseudocysts occurred in 10 (2 of 14 in group 1, 5 of 11 in group 2, and 3 of 3 in group 3). No patients in group 1 required drainage, whereas 4 in group 2, and all 3 in group 3 required intervention. These drainage procedures occurred 10 to 14 days after injury. Average time for the initiation of oral feeding was 15 days (11 days for group 1, 15 days for group 2, and 23 days for group 3). Mean hospital stay for all patients treated nonoperatively was 21 days.

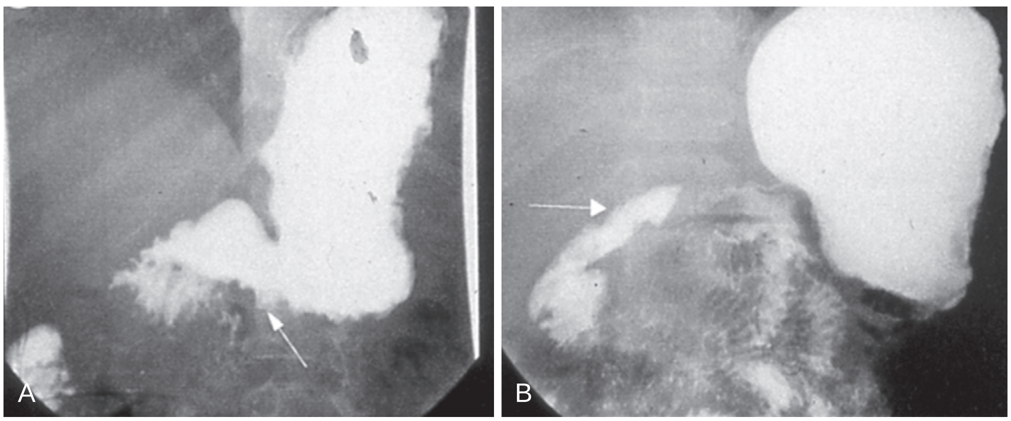


FIGURE 20-15 Upper gastrointestinal study of a 7-year-old girl with duodenal perforation resulting from a motor vehicle accident. Primary repair, pyloric exclusion, retrograde tube duodenostomy, gastrojejunostomy, and feeding gastrostomy were performed. The child tolerated jejunal feeds 6 days after the injury and oral feeds 12 days after the injury. **A,** Six weeks postinjury, an upper gastrointestinal study demonstrated spontaneous closure of the gastrojejunostomy (*arrow*). **B,** A patent pylorus is evident (*arrow*).

**TABLE 20-9**
**Surgical Options in Duodenal Trauma**

| |
|---|
| Repair of the duodenum |
| Diversion of the gastrointestinal tract (pyloric exclusion or duodenal diverticularization) |
| Gastric decompression (gastric tube insertion or gastrojejunostomy) |
| Gastrointestinal tract access for feeding (jejunostomy tube or gastrojejunal anastomosis) |
| Decompression of the duodenum (duodenostomy tube) |
| Biliary tube drainage |
| Wide drainage of the repaired area (lateral duodenal drains) |

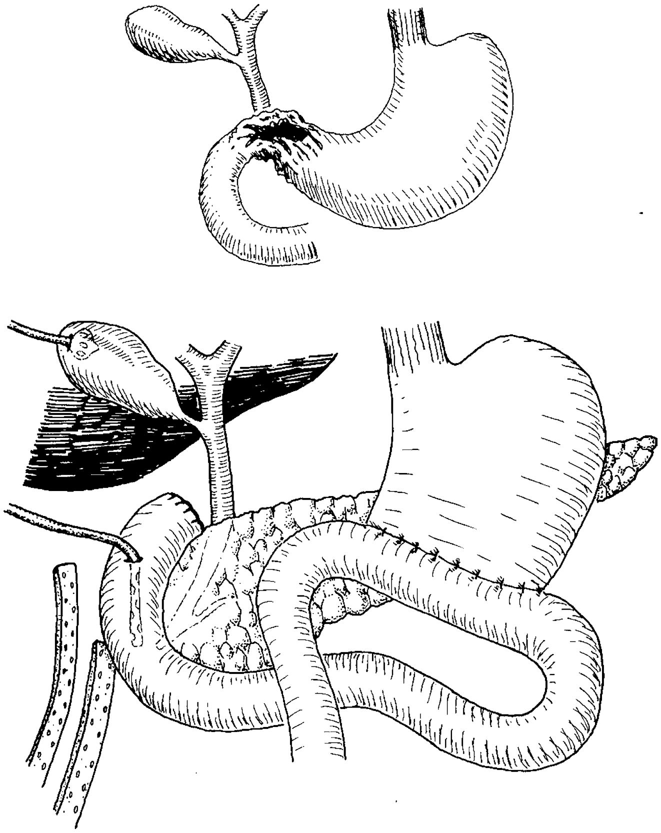

**FIGURE 20-16** Duodenal diverticularization for combined proximal duodenal and pancreatic injury. Resection and closure of the duodenal stump, tube duodenostomy, tube cholecystostomy, gastrojejunostomy, and multiple closed suction drains are depicted. A feeding jejunostomy should be strongly considered (not depicted). (Original illustration by Mark Mazziotti, MD.)

A comparison of the San Diego and Toronto protocols is depicted in Figure 20-18. The striking differences in these series are the 100% diagnostic sensitivity of CT in Toronto versus 69% in San Diego and the 44% operative rate in San Diego versus 0% in Toronto. A subsequent study from Toronto reviewed the follow-up on 10 patients with duct transections.[121] Four of these children (40%) developed pseudocysts, three of which were drained percutaneously (Fig. 20-19). The mean hospital stay was 24 days, and all recovered. Follow-up CT in eight of nine patients revealed atrophy of the distal pancreas in six and completely normal glands in two. There was no exocrine or endocrine dysfunction in a mean of 47 months of follow-up. The authors concluded that

**TABLE 20-10**
**Summary of Associated CT Findings in Children with Pancreatic Injuries**

| *Associated Finding* | *Number of Children* |
|---|---|
| Intraperitoneal fluid | 21 |
| Lesser sac fluid | 20 |
| Focal peripancreatic fluid | 20 |
| Retroperitoneal fluid | 20 |
| Right anterior pararenal fluid | 16 |
| Left anterior pararenal fluid | 15 |
| Thickened Gerota fascia (right and left) | 16 |
| Mesenteric fluid or hematoma | 13 |
| Left posterior pararenal fluid | 9 |
| Fluid separating SV and pancreas | 7 |
| Fluid surrounding SMV and PV | 7 |
| Fluid separating pancreas and duodenum | 6 |

Data from references 119-121.
CT, Computed tomography; PV, portal vein; SMV, superior mesenteric vein; SV, splenic vein.

following nonoperative management of pancreatic blunt trauma, atrophy (distal) or recanalization occurs in all cases with no long-term morbidity.

Reports from Dallas and Seattle favor early distal pancreatectomy for transection to the left of the spine to shorten hospital stay.[122,123] However, long-term sequelae of adhesive intestinal obstruction and endocrine and exocrine dysfunction were not assessed. Other reports document the efficacy of magnetic resonance pancreatography as a diagnostic tool, early ERCP intervention for diagnosis and treatment with ductal stenting, and the use of somatostatin to decrease pancreatic secretions and promote healing.[124–128] Of note, a large single-center series from Japan reported nonoperative management in 19 of 20 children with documented pancreatic injury (9 contusions, 6 lacerations, and 5 main duct disruptions).[129] In all cases, recovery was complete without surgery. That center's experience with pseudocyst formation and treatment and overall outcome virtually mirrors that of the Toronto report. A recent report from Denver documents their experience with pediatric pancreas injury over an 11-year period.[127] All ($n = 18$) with grade I injuries were treated nonoperatively. Children with grades II to IV received operative treatment in 14 and nonoperative in 11 cases. They concluded that children undergoing operative treatment had fewer pseudocysts but similar length of stay because of nonpancreatic complications.

These reports from major pediatric trauma centers are clearly in conflict. Some favor and document the efficacy and safety of observational care for virtually all pancreatic injuries, including duct disruption; others advocate aggressive surgical management with debridement or resection. Because proponents supply compelling data for each of these treatments, algorithms reflecting individual hospital or surgeon preference will probably determine which treatment plan is selected. However, it is clear that with simple transection of the pancreas at or to the left of the spine, spleen-sparing distal pancreatectomy can provide definitive care for this isolated injury, with short hospitalization and acceptable morbidity (Fig. 20-20). Laparoscopic techniques may limit perioperative morbidity.[128]

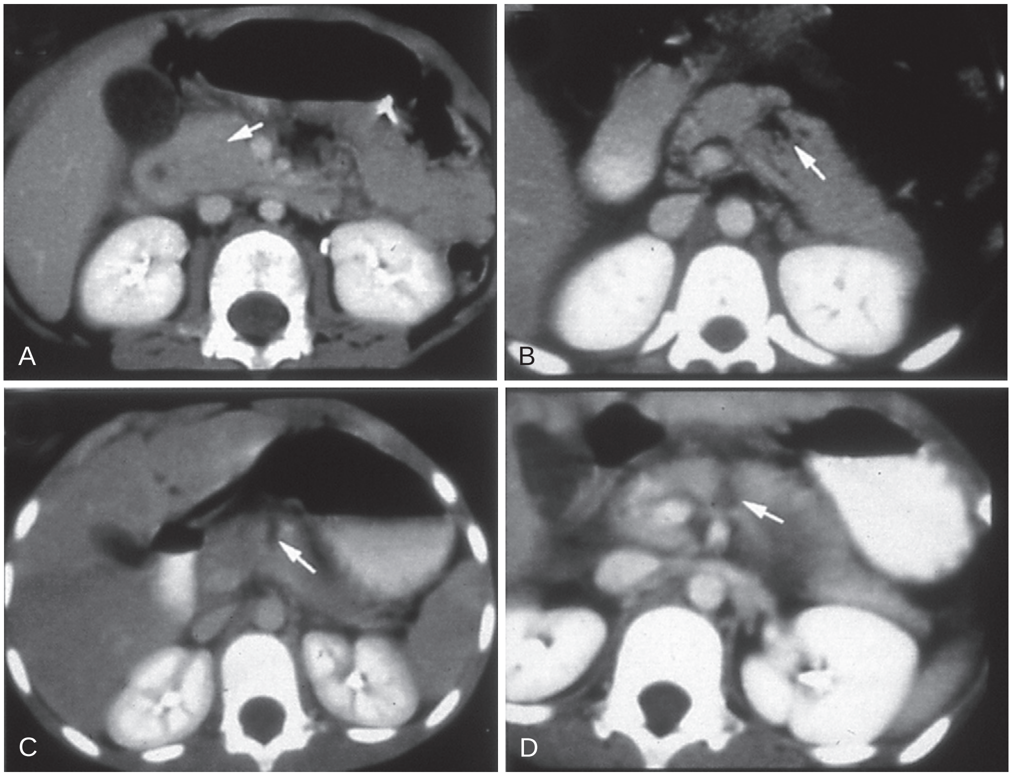


**FIGURE 20-17** Computed tomography findings in children with pancreatic trauma. **A,** Contusion. **B,** Stellate fragmentation. **C,** Partial fracture. **D,** Transection. Arrows indicate the specific pancreatic injury.

**TABLE 20-11**
**Proposed Classification of CT Findings in Children with Pancreatic Injuries**

| *Group (Clinical)* | *Grade (CT)* | *Pancreatic Injury* | *Description* | *Number of Children* |
|---|---|---|---|---|
| 1 | I | Contusion | Diffuse or focal swelling of the pancreas | 14 |
| 2 | II | Stellate fragmentation | Fluid or blood dissecting within pancreatic parenchyma | 2 |
| | III | Partial fracture | Incomplete separation of two portions of the pancreas | 1 |
| 3 | IV | Complete transection | Complete separation of two portions of the pancreas | 8 |
| | V | Pseudocyst | Persistent peripancreatic fluid collection | 3 |

Data from references 119-121.
CT, Computed tomography.

With this controversy in mind, we favor conservative therapy whenever possible, including the following:

1. Early spiral CT with oral and intravenous contrast in all patients who, by history, physical examination, or mechanism of injury, may have blunt trauma to the pancreas
2. Documentation of injuries and early ERCP to provide duct stenting in selected cases
3. Nonoperative management with total parenteral nutrition
4. Expectant management of pseudocyst formation
5. Percutaneous drainage for symptomatic, infected, or enlarging pseudocyst (Fig. 20-21)

# Injuries of the Stomach, Small Intestine, and Colon

Several different mechanisms cause distinct patterns of injury to these hollow organs. First is a crush injury that occurs as the stomach, jejunum, ileum, or transverse colon is compressed violently against the spine. Hematomas, lacerations, or partial or complete transections can occur with instantaneous or delayed perforation or obstruction. Second, burst injury occurs when rapid compressive forces are applied to a filled and distended hollow viscus, without direct mechanical compression. Shoulder-belt and seat-belt injuries to the GI tract can occur in this fashion. Third is shear injury caused by rapid acceleration–deceleration of an organ that is tethered at one end, such as the ligament of Treitz, ileocecal region, or rectosigmoid junction. With deceleration, the injury is caused by the tearing of tissue at the point of fixation.

Regardless of the mechanism of injury, a perforated viscus causes rapid contamination of the abdominal cavity. On the initial trauma assessment, virtually all neurologically intact patients have some symptoms (pain) and physical findings (tenderness, guarding, rebound). In fact, many reports have documented that the initial and serial physical examinations have a higher degree of diagnostic specificity than US or CT for these injuries.[130–132] In a series from New Mexico

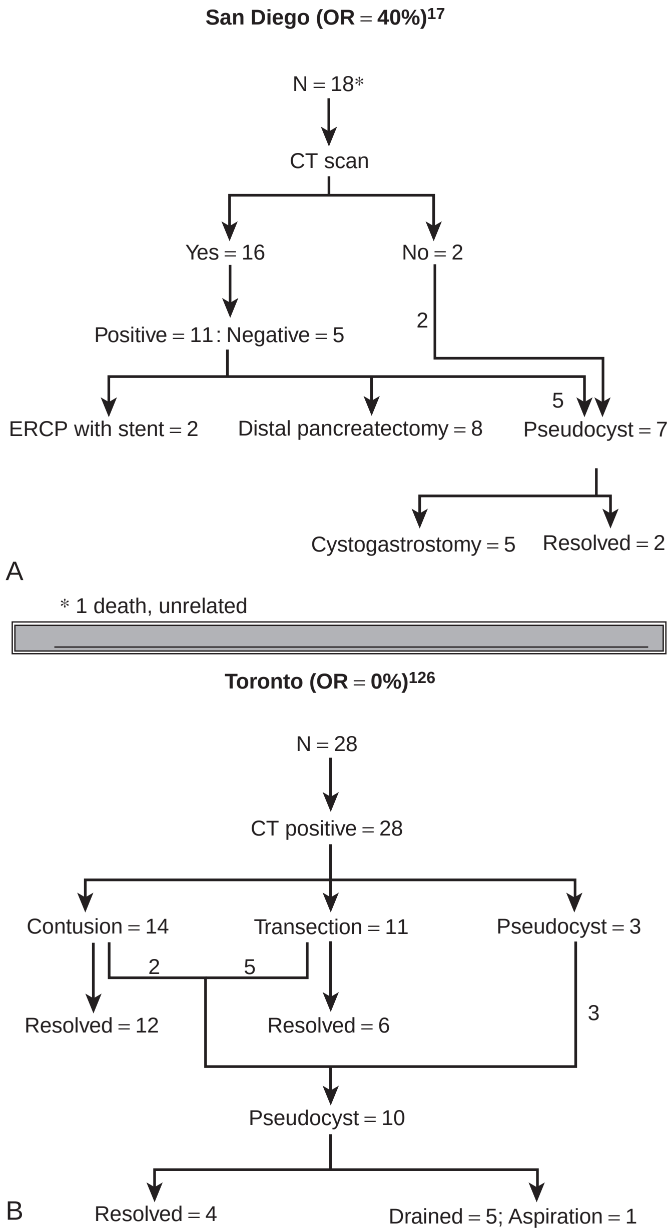


**FIGURE 20-18** Comparison of protocols in the management of blunt pancreas injury in children. **A,** San Diego. **B,** Toronto. CT, Computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; OR, operating room. (**A,** From Canty TG Sr, Weinman D: Management of major pancreatic duct injuries in children. J Trauma 2001;50:1001-1007; **B,** from Shilyansky J, Sen LM, Kreller M, et al: Nonoperative management of pancreatic injuries in children. J Pediatr Surg 1998;33:343-345.)

reporting 48 patients with small bowel injury, all conscious patients had abnormal physical findings either on presentation or after serial physical examinations.[131] Other diagnostic tests (US, CT, DPL, laboratory tests) were of comparatively less value. These findings were confirmed by a similar series from North Carolina involving 32 children with intestinal injury confirmed at laparotomy; 94% had physical findings suggestive of intestinal injury on admission, with 84% having diffuse abdominal tenderness (peritoneal signs).[132] Prompt diagnosis of these injuries is possible when free air and GI contrast extravasates into the abdominal cavity at the time of the initial injury. However, when partial-thickness lacerations, hematomas, or avulsed

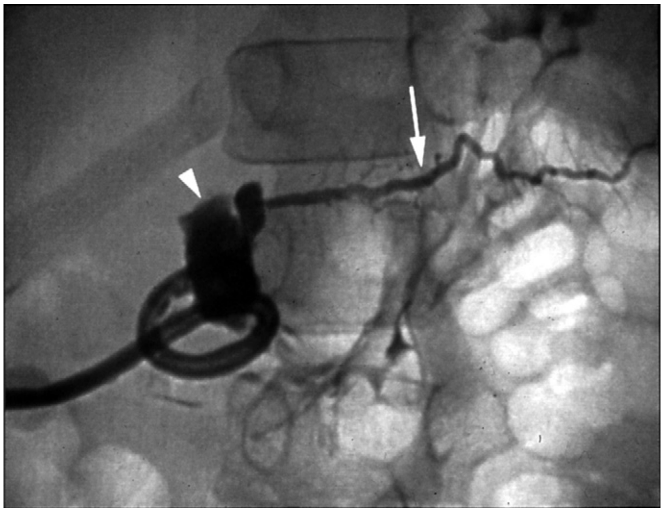

**FIGURE 20-19** Contrast study through a percutaneous drain placed into a pancreatic pseudocyst (*arrowhead*) after blunt trauma in a child. Communication with the main pancreatic duct (*arrow*) is demonstrated. The pseudocyst resolved without fistula formation or operative intervention.

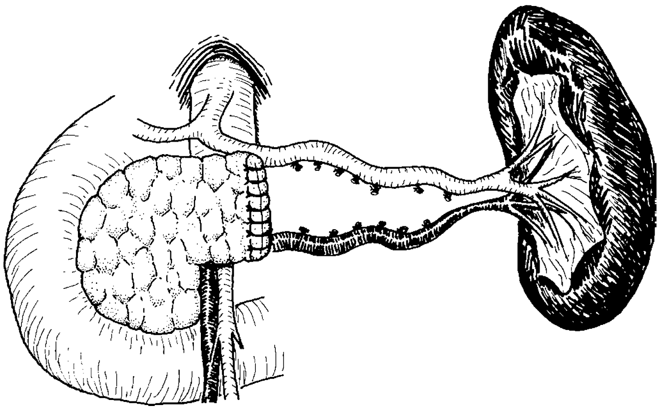

**FIGURE 20-20** Spleen-sparing distal pancreatectomy. (Original illustration by Mark Mazziotti, MD.)


**FIGURE 20-21** Post-traumatic pancreatic pseudocyst with extension into the mediastinum causing respiratory distress.

FIGURE 20-22 Small bowel mesentery avulsion with ischemic bowel.

mesenteric blood vessels occur, progression to full-thickness defects with leakage can be delayed over hours to days (Fig. 20-22). A high index of suspicion is indicated, along with the liberal use of serial physical examinations.

The APSA Trauma Committee recently performed a multi-institutional, retrospective review to determine whether delay in treatment of blunt intestinal perforation adversely affected outcome.[133] Their data in 214 patients suggested that delay in operative treatment up to 24 hours did not have a significant effect on prognosis after pediatric blunt intestinal injury, even when there is peritoneal contamination secondary to perforation.

Injuries to the stomach and small intestine are straightforward to repair. A full stomach usually ruptures at the greater curvature with a blowout or stellate configuration. Debridement with direct repair is virtually always sufficient. Small intestinal injuries run the gamut from simple laceration to transection to complete avulsion with larger segments of compromised bowel. However, unless the contamination is massive (or other injuries require extensive repair), debridement or resection with anastomosis is usually sufficient. In colon injuries, particularly if there is a delay in diagnosis and significant fecal contamination, colostomy with a defunctionalized distal mucous fistula or a Hartmann pouch is in order. If isolated colon injuries occur and are repaired early, on-table bowel irrigation, bowel anastomosis, and perioperative antibiotic coverage are safe and effective and avoid the complications caused by stomas and reoperation. The critical factors with injuries to the intraperitoneal GI tract are early recognition of the injury; prompt resuscitation; expeditious surgery, with complete removal of contaminated and devitalized tissue; reconstruction or diversion of the GI tract, as clinically indicated; and broad-spectrum antibiotics, with the duration of therapy dependent on the degree of contamination and postoperative clinical course (e.g., normalization of white blood cell count, absence of fever, return of GI tract function). Laparoscopic techniques may limit perioperative morbidity.[17]

## SEAT-BELT SIGN

Seat belts, when compared with no restraint, reduce serious injury and death by 50%.[134] Frequent physical examinations and vigilance are required for the subset of injuries caused by lap-belt restraints when children are passengers in high-speed automobile crashes.[130] These children present with visible seat-belt signs on physical examination of the abdomen (Fig. 20-23). Multiple studies have documented increased abdominal injuries to both solid and hollow organs with this finding.[135–137] However, a large retrospective review of 331 child occupants in motor vehicle crashes found that the seat-belt sign had relative risk of only 1.7 for an abdominal injury.[138] An interesting triad of injuries has been noted: abdominal wall contusions or herniation, chance fractures of the lumbar spine, and isolated jejunal or ileal perforations. One report reviewed 95 patients admitted with abdominal trauma, all of whom were wearing seat belts at the time of injury; in 60 of 95, there was a seat-belt sign.[137] Nine (15%) of the 60 patients with the seat-belt sign had intestinal injuries, compared with none of the 35 without the seat-belt sign. The more common injuries described earlier can distract both the patient and the trauma team, causing delay in the diagnosis of serious vascular injuries involving the aorta and iliac vessels.[139–141]

FIGURE 20-23 Seat-belt sign across the lower abdomen.

In recent reports from Philadelphia, a database created by the State Farm Insurance Company was used to review 147,985 children who were passengers in motor vehicle crashes.[142,143] In that series, 1967 children (1.33%) had abdominal bruising from seat-belt restraints. Although abdominal wall bruising was infrequent, those with this finding were 232 times more likely to have a significant intra-abdominal injury than were those without a bruise. These data further revealed that 1 of 9 children with an abdominal seat-belt sign had a significant intra-abdominal injury. Therefore, although the seat-belt sign is rare, CT scanning (admission and serial) is mandated when it is present. Optimal ($n = 881$) and suboptimal ($n = 1086$) use of seat-belt restraints was noted. After adjusting for age and seating position, optimally restrained children were more than 3 times less likely (odds ratio 3.51) than suboptimally restrained children to suffer an abdominal injury.

Our recommendation is to admit all children involved in a motor vehicle crash who present with a seat-belt sign, even in the setting of a “normal” FAST and/or abdominal CT. Progression of an intestinal wall crush should be detected with serial examinations with or without repeat imaging.

## IMAGING FOR GASTROINTESTINAL INJURY

Imaging of the GI tract has evolved over the past decade, with spiral CT or FAST examinations done by surgeons in the emergency department directly impacting diagnostic accuracy and

decision making. Some of the strengths and weaknesses of CT diagnosis have already been discussed. However, the ability to diagnose and treat blunt abdominal trauma in children has clearly been enhanced by this modality. Two studies from Toronto examined these issues. The first, reviewed 12 patients with blunt abdominal trauma evaluated by CT and found that bowel wall enhancement was a sign of either global GI tract ischemia associated with fatal central nervous system injury or bowel perforation when seen with bowel wall thickening and free peritoneal fluid.[144] A follow-up study reviewed 43 patients evaluated over 10 years with surgically confirmed GI tract perforation.[14] Extraluminal air was seen in 47%, with one false-positive. Five CT findings were found to be suggestive but not diagnostic of GI tract perforation: extraluminal air, free intraperitoneal fluid, bowel wall thickening, bowel wall enhancement, and bowel dilation. In every patient who had all five of these findings, bowel perforation was confirmed. However, this occurred in only 18% of the study population. All patients had at least one of these five specific CT findings. There were no false-negative studies. As mentioned previously, although CT scanning is a reliable modality for assessing GI tract perforations, it should not replace and does not improve on diligent serial clinical evaluations. A similar study from Calgary reviewed 145 children with blunt abdominal trauma.[145] CT scans were interpreted as positive for GI tract injury in 20 and negative in 152 (several children had more than one study). The sensitivity of abdominal CT scan was determined to be 0.93 for mesenteric or intestinal injuries requiring surgery, with a negative predictive value of 0.99 in this study population. Therefore CT rarely misses significant mesenteric or intestinal injuries.

The significance of isolated free intraperitoneal fluid in the absence of solid organ injury has frequently been heralded as a sign of intestinal trauma. Hulka and colleagues[146] reported a series of 259 CT scans (all with oral and intravenous contrast) and found only 24 patients (9%) with isolated free intraperitoneal fluid. Among the 16 patients with only a “small amount” of isolated fluid, only 2 required laparotomy. However, 4 of 8 patients (50%) with fluid in more than one location had a bowel injury requiring exploration. These authors also noted that enteral contrast is rarely present to aid in the diagnosis of bowel injury. Similar findings were reported by Holmes and colleagues,[147] with small quantities of intraperitoneal fluid having little clinical significance. In their report, only 8% of abdominal CT scans were positive for isolated intraperitoneal fluid, and in only 17% of these cases was there an identifiable injury. This represented only 7 of the 542 children (1.3%) studied.

Finally, FAST was found to be useful as a screening tool, with high specificity (95%) but low sensitivity (33%), in evaluating intestinal injury.[15] In that study of 89 FAST-negative children, only 20 went on to have CT scans performed, all at the surgeon’s request. Without this finding, they all might have had abdominal CT scans. Clearly, FAST can decrease the number of unnecessary CT scans performed, but it cannot detect the specific abdominal organs injured. FAST is therefore of limited value in assessing these injuries. Finally, to come full circle, in a large study from Pittsburgh, 350 children with abdominal trauma were reviewed, with 30 requiring laparotomy (8.5%).[148] There were five false-negative CT scans (26%) in 19 patients who underwent delayed laparotomy (3.5 hours or longer after injury). Those authors concluded that serial physical examination, not CT scanning, is the gold standard for diagnosing GI tract perforations in children. We concur.

## Injuries to the Perineum, Anus, and Genitalia

Children present with injuries to the perineum, anus, and external genitalia primarily from two mechanisms: accidental falls and sexual abuse. Accidental injuries are sustained by falling onto blunt or sharp objects in a straddled fashion. These injuries are characterized by bruising, contusion, laceration, or penetration, depending on the object struck and the height of the fall. Accidental injuries frequently involve the external genitalia, urethra, perineal body, and anus but rarely involve the rectum. Conversely, injuries sustained by sexual abuse are commonly rectal or vaginal penetrations from violent, nonconsensual acts or the purposeful insertion of objects into these orifices. Therefore, when examining a child with injuries to the perineum, isolated rectal or vaginal trauma should always be considered child abuse until proved otherwise; conversely, polytrauma to the perineum with genital, perineal, and anal involvement is typically accidental.[149]

Diagnosis of the extent of perineal injury frequently requires examination under anesthesia by means of proctoscopy, sigmoidoscopy, and retrograde urethrogram. After assessing the degree of injury, surgical strategies include repair of urethral injuries (directly or by stenting), urinary diversion with a suprapubic cystostomy, repair of rectal tears, rectal irrigation, placement of drains when required, and, in more complex injuries, fecal diversion by colostomy. After recovery, detailed radiologic confirmation of complete healing (e.g., by intravenous pyelogram, cystogram, urethrogram, contrast enemas) must be performed before reconstruction of fecal continuity or removal of urinary stents or urinary undiversion.

Colorectal and vaginal injuries in personal watercraft passengers highlight another mechanism which should create suspicion and concern.[150] Although rare, pediatric fatalities can occur with rectal impalement from abuse. However, more commonly, rectal insertion of thermometers, Hegar dilators, or enema tubes can cause significant rectal injuries in newborns, requiring surgical repair. We recently treated a 3-day-old infant with perforation of the rectosigmoid junction from frequent enemas required for the treatment of obstipation from cystic fibrosis; laparotomy and colostomy were required. Therefore, in newborns, apparently innocuous rectal manipulation can cause severe injuries requiring surgical evaluation and intervention.

## Diaphragmatic Injuries

Traumatic injury to the diaphragm is infrequently observed, even at the largest pediatric trauma centers. At Children’s Hospital of Illinois, only two traumatic diaphragmatic injuries were treated from 1998 to 2002 out of more than 800 admissions requiring level I pediatric trauma evaluation. At the Hospital for Sick Children in Toronto, only 15 children with this injury were seen from 1977 to 1998.[151,152] In a similar report, covering 1992 to 2002 at Denver Children’s Hospital,

1397 children were admitted and observed for blunt abdominal trauma, 387 had intra-abdominal injuries, but there were only 6 diaphragmatic ruptures (0.5%).[153] The injury is caused by massive compressive forces to the abdominal cavity, creating acceleration of abdominal contents cephalad, rupturing the diaphragmatic muscle. Occasionally, penetrating trauma causes this injury; however, in these cases, the injury is often found incidentally at exploration for other injuries. In the series reported from Toronto, 13 of 15 patients had diaphragmatic rupture from blunt trauma; the mean age was 7.5 years, with the right and left diaphragm equally involved.[152] The diagnosis was made with only a chest radiograph in more than half the patients. Three injuries were missed at the initial evaluation. Because of the force required to cause this injury, multiple associated injuries should be expected. In this report, 81% of patients had multiple injuries, including liver laceration (47%), pelvic fracture (47%), major vascular injury (40%), bowel perfusion (33%), long bone fracture (20%), renal laceration (20%), splenic laceration (13%), and closed head injury (13%). As expected, there were many complications, five deaths, and a mean hospital stay of 20 days. Emergent surgery in children with this constellation of associated injuries should include palpation of both diaphragms as a routine part of the abdominal exploration. Direct suture repair is usually possible after debridement of any devitalized tissue. Pledgeted sutures can be used to buttress the repair and prevent tearing of the muscle, making the closure more secure. If sufficient diaphragm tissue is destroyed, a tension-free closure is optimal using intercostal muscle or a prosthetic patch can be used, similar to the repair of congenital diaphragmatic hernias in newborns.[153] Reports of laparoscopic or thoracoscopic repair of this injury include delayed repairs on stable patients without associated injuries.[154,155] Delayed diagnosis of this injury in infants has been reported, as has renal avulsion into the chest through a traumatically ruptured diaphragm.[156] Because of the infrequent presentation of this injury, one must have a high index of suspicion when the mechanism of injury and the degree and location of other injuries support the possibility of diaphragmatic injury.

Recent advances in the treatment of trauma and the provision of critical care in children have resulted in improved outcomes following major injuries. Much has changed in our understanding of transfusion strategies and coagulation since the previous edition of this textbook.[65,157,158] It is imperative that pediatric surgeons familiarize themselves with current treatment algorithms for life-threatening abdominal trauma. Important contributions have been made in the diagnosis and treatment of children with abdominal injury by radiologists and endoscopists. Clinical experience and published reports addressing specific concerns about the nonoperative treatment of children with solid organ injuries and recent radiologic and endoscopic contributions have made pediatric trauma care increasingly nonoperative. Although the trend is in this direction, the pediatric surgeon should remain the physician of record in the multidisciplinary care of critically injured children. Lucas and Ledgerwood recently posed the provocative question of how we can meet the inherent challenge of teaching the psychomotor skills required for operative hemostasis in an era of nonoperative therapy for most solid organ injuries.[159] As we struggle to meet this challenge, the fact remains that the decision not to operate is always a surgical decision.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 21

# Genitourinary Tract Trauma

Rebeccah L. Brown, Richard A. Falcone, Jr., and Victor F. Garcia

## Epidemiology

Injury is the leading cause of death in children and young adults in the United States, with injury to the kidney from either blunt or penetrating trauma being the most common genitourinary tract injury.[1] Almost 50% of genitourinary tract injuries involve the kidney.[2] Blunt abdominal trauma is responsible for 90% of pediatric genitourinary tract injuries,[3] with the kidney being injured in 10% to 20% of all blunt trauma cases.[2,4] Renal injury occurs in about 3% to 6% of patients with penetrating trauma.[5,6] Serious renal injuries are most often associated with injuries to other organs, with multiple organ involvement occurring in 80% to 95% of patients with blunt or penetrating renal trauma.[6,7] The majority of associated injuries are closed-head injuries and extremity fractures.[8] Associated abdominal injuries occur in 42% to 74% of patients and primarily involve the spleen and liver in blunt trauma and the bowel in penetrating trauma.[4,9–12] The majority of isolated renal injuries can be classified as relatively minor injuries. Mortality is rare from isolated renal trauma and is more often attributed to the combined effects of major multisystem trauma.

## Mechanisms of Injury

Most blunt renal injuries are due to sudden deceleration forces. Confined within the Gerota fascia, the kidney may be crushed against the ribs or the vertebral column, resulting in laceration or contusion. Direct injury to the renal parenchyma and collecting system may also occur from penetration of sharp, bony fragments of adjacent fractured ribs. Rapid deceleration may cause arterial or venous stretching of the fixed renovascular pedicle.[13] Because the intima of the renal artery is less elastic than that of the media, it is predisposed to laceration, which may lead to subintimal dissection and arterial thrombosis.[14] Mechanisms of blunt renal injury include pedestrian/motor vehicle crashes (60%), falls (22.5%), sports injuries (10%), assault (3.5%), and other causes (4%).[15] Most children who sustain renal injury in motor vehicle accidents are unrestrained;[4] however, violent deceleration with severe flexion-extension as seen with lap belts is a well-recognized mechanism of renal injury associated with a higher risk of renal pedicle avulsion and ureteropelvic junction (UPJ) injury. It is of interest that bicycle crashes are the most common sports-related cause of renal injury in children and are associated with a significant risk of high-grade renal injury.[16] Although there is a perception among pediatric surgeons and urologists that contact sports such as football, hockey, and martial arts incur the greatest risk for renal injury in children,[15] a review by McAleer and colleagues[17] demonstrated that bicycle crashes accounted for 24% of injuries compared with only 5% for contact sports. This may have some impact on the type of counseling that should be provided regarding activity for children after severe renal injury and for those with solitary kidneys. Penetrating genitourinary tract injuries are becoming more common in children and should be suspected with any penetrating injuries to the chest, abdomen, flank, and lumbar regions. Penetrating renal injuries, most commonly due to gunshot wounds (86%) and stab wounds (14%),[6] are more frequently associated with multiorgan injury, higher grades of injury, and higher rates of surgical exploration.[1] For example, in patients with penetrating renal injury, nearly 70% will have grade III or higher injury, whereas with blunt trauma, only about 4% will sustain grade III or higher injury.[1]

## Anatomic Considerations

Children are considered to be at increased risk for genitourinary tract trauma owing to unique anatomic differences between children and adults.[3,13,18] In children, the kidneys are larger relative to the size of the child's body and are positioned lower in the abdomen, making them more exposed and vulnerable to injury. They are also less protected because of decreased perirenal fat, weaker abdominal wall musculature, and a poorly ossified thoracic rib cage. Because many pediatric kidneys retain their fetal lobulations, the risk for renal parenchymal disruption and lower pole amputation is increased. Furthermore, the renal capsule and Gerota fascia are less developed than in adults, creating a greater potential for laceration, nonconfined bleeding, and urinary extravasation. Because of the relative mobility of a child's kidney, rapid deceleration is more likely to result in renal pedicle injury and UPJ

disruption. In a comparative series of children and adults who sustained blunt renal trauma, Brown and colleagues[3] concluded that although the likelihood of major renal injury was significantly higher in the pediatric population, the severity of trauma was significantly lower.

For similar reasons, preexisting renal disease or congenital renal anomalies may predispose children to an increased risk of genitourinary tract injury from blunt trauma. The reported incidence of preexisting renal disease or congenital genitourinary anomalies in children sustaining renal trauma varies from 1% to 23%.[19–24] Underlying congenital anomalies associated with hydronephrosis (UPJ obstruction), abnormal kidney position (horseshoe kidneys, crossed fused renal ectopia), abnormal kidney consistency (polycystic kidney disease, urinary reflux), and renal tumors such as Wilms' tumor may predispose the kidney to significant injury despite relatively minor forces.[20] Gross hematuria associated with an ostensibly minor trauma should alert the physician to the possibility of an underlying pathologic lesion of the urinary tract and should prompt further radiologic imaging. Although underlying congenital genitourinary anomalies may produce an increased risk of injury in children, they do not appear to be associated with any increased morbidity or long-term disability.[17]

# Clinical Features

The evaluation of possible injury to the genitourinary tract is part of the systematic and expeditious assessment required in all seriously injured patients. The mechanism of injury is important to know in order to assess the risk of injury. Direct blows to the abdomen or flank and significant deceleration forces as may occur in motor vehicle crashes and falls should alert the physician to the possibility of renal injury. Penetrating injuries to the abdomen, flank, back, chest, and pelvis should also raise suspicion for injury to the genitourinary tract. Although the presence of abdominal or flank tenderness and flank ecchymosis or mass suggests renal injury, up to 25% of patients with severe renal injury have unremarkable abdominal examinations. Indeed, only 55% of children with significant renal injuries present with tenderness over the injured kidney. Conversely, only about half of children with renal tenderness on examination have a condition more serious than minor renal trauma.[25]

Perineal/scrotal ecchymosis, swelling, laceration, and bleeding are highly suggestive of genitourinary trauma. The presence of blood at the urinary meatus or a boggy mass or upward displacement of the prostate on digital rectal examination in boys requires formal urethrography to evaluate possible injury to the urethra before any attempts at urethral catheterization. However, it should be recognized that the sensitivity of the digital rectal examination for identifying urethral disruption may be quite low (2%),[26] especially in children in whom the prostate may not be fully developed.

Gross hematuria is indicative of genitourinary trauma and mandates further radiologic imaging. Conversely, the absence of hematuria, either gross or microscopic, does not exclude the possibility of significant genitourinary trauma. In fact complete avulsion of the renovascular pedicle and disruption of the UPJ have both been described in the absence of hematuria.[1,8,11,21,27–29]

Fractures of the lower ribs and lumbar spine may be associated with renal trauma, whereas fractures of the pelvis may be associated with bladder and urethral injuries. In a large study using data from the National Trauma Data Bank, Bjurlin and associates[30] reported that about 5% of more than 31,000 patients with pelvic fractures had an associated lower urinary tract injury involving the bladder or urethra, or a combination of both. Aihara and associates[31] found that certain types of pelvic fractures were associated with increased risk for rectal, bladder, or urethral injuries. Rectal injury was associated with widening of the symphysis pubis. Bladder injuries were most commonly associated with widening of the sacroiliac joint, symphysis pubis, and fractures of the sacrum, with widening of the symphysis pubis being the strongest predictor of bladder injury. Urethral injuries were most commonly associated with widening of the symphysis pubis and fractures of the inferior pubic ramus. Fractures involving these locations should heighten suspicion of associated rectal and lower urinary tract injuries and prompt directed diagnostic studies. Gross hematuria in the presence of a pelvic fracture strongly suggests a bladder perforation. Any degree of hematuria in the presence of a pelvic fracture is an indication for cystography.

# Diagnostic Evaluation

Although findings on urinalysis (either gross hematuria or microhematuria) may be suggestive of genitourinary tract trauma, the decision to proceed with imaging to assess for injury is usually made before performing urinalysis and is based instead on the clinical scenario and hemodynamic status of the patient. Thus findings on urinalysis are more often than not corroborative rather than diagnostic because imaging usually precedes urinalysis. If, however, urinalysis is obtained early in the course of trauma evaluation, there is great debate regarding the need for further imaging based on this parameter alone. Although most would agree that gross hematuria is an indication for formal diagnostic evaluation, much controversy exists as to whether microscopic hematuria as an isolated finding on urinalysis warrants further radiologic imaging.[9,12,32–41]

It remains unclear what degree of microscopic hematuria, if any, warrants radiographic evaluation in children. Several studies have attempted to answer the question as to whether the adult criteria for imaging of renal trauma, including findings of gross hematuria, microscopic hematuria (>5 red blood cells [RBCs] per high-power field [HPF]) with shock, major associated injuries, significant deceleration injury, and penetrating injury can be applied to children. Although degrees of microhematuria ranging from any degree[36,37] to 20 RBCs per HPF[42] to 50 RBCs per HPF[39] have been reported as significant in the literature, a careful analysis of published reports on 382 children with renal injuries reveals that the application of adult criteria for imaging would have identified 98% to 100% of all renal injuries.[41] One of the pitfalls in applying adult criteria for the imaging of renal trauma in children with regard to the presence or absence of shock is that children are unique in their ability to maintain normal blood pressure in the face of significant hypovolemia and blood loss. In fact only 5% of children with major renal injury have clinical signs of shock.[25] Therefore hypotension itself is not a reliable indicator of the severity of renal injury in the pediatric population. Tachycardia typically precedes

hypotension as an early indicator of shock in children and may be a worrisome sign. Accordingly the decision on imaging in children, as in adults, should be based not on isolated findings but rather on the whole clinical picture, including mechanism of injury (direct blow, major deceleration, flexion-extension injury, penetrating trauma), vital signs (tachycardia or hypotension), physical examination findings (abdominal/ flank tenderness, contusion, penetrating injury in vicinity of genitourinary tract), urinalysis (microhematuria or gross hematuria), and associated injuries. In most cases, microhematuria is not an isolated finding. Most children with microhematuria have some other factor, such as mechanism of injury, physical findings, or other associated injuries, that would warrant further imaging, therefore decreasing the likelihood of missed injury.

Abdominal computed tomography (CT) is the standard for radiographic evaluation of abdominal trauma in children and is the most accurate imaging and staging modality for evaluation of renal injury.[43,44] CT with intravenous contrast is highly sensitive and specific for detection of parenchymal contusions/lacerations, perinephric/retroperitoneal hematoma, urinary extravasation, and segmental or major arterial injuries; delineation of nonviable, nonperfused tissue or segmental infarction; and demonstration of other associated intra-abdominal injuries. Since images with multidetector helical CT are obtained before the contrast medium is excreted in the urine, injury of the collecting system may be missed. In patients with significant renal injury detected on the initial images, delayed images 5 to 20 minutes after the contrast injection may identify urine extravasation associated with injury to the collecting system. A plain radiograph may also be suggestive. Delayed images may be omitted to minimize radiation dose if the kidneys are normal or with injury unlikely to be associated with injury to the collecting system and in the absence of retroperitoneal or pelvic fluid.[43,45,46]

CT has replaced the intravenous pyelogram (IVP) in the hemodynamically stable patient. However, a one-shot IVP still remains useful in the hemodynamically unstable patient before emergent surgical exploration to determine the presence of two functional kidneys, the presence and extent of urinary extravasation, and the presence of renal pedicle injury. In children, 2 to 3 mL/kg of nonionic contrast is injected intravenously, followed by an abdominal radiograph immediately and 10 minutes later.[38] It should be recognized that the IVP provides only very basic information and is not useful in staging of renal injuries. In fact, some studies have shown that as many as 20% of patients with significant renal injuries have a normal IVP. Likewise, nonvisualization of the kidney on the IVP does not necessarily correlate with arterial occlusion or injury. Other factors, including renal contusion with vascular spasm, overhydration, and hypotension or hypoperfusion, may produce similar findings in up to half of patients.[47]

Arteriography has been largely supplanted by CT and CT angiography for the diagnosis and staging of renal injury. More invasive than CT, arteriography requires the expertise of an experienced interventional radiologist and may be associated with a formidable risk for arterial injury in small children whose vessels may be prohibitively small, fragile, and difficult to access or cannulate. The current role of arteriography is in the diagnosis of delayed or ongoing renal hemorrhage, renovascular injury, or delayed arteriovenous fistula or pseudoaneurysm formation in which interventional techniques such as selective embolization[48–53] or endovascular stenting[54,55] may be therapeutic.

Ultrasonography, although used extensively in Europe for the assessment of acute renal trauma, has not found widespread acceptance in the United States. Ultrasonography in the trauma patient in the United States is mostly limited to the focused assessment with sonography for trauma (FAST) examination, which is performed primarily to detect the presence of free intraperitoneal fluid. The focused assessment with sonography for trauma examination has not been particularly useful in children except perhaps in the hemodynamically unstable patient with an associated closed-head injury to rapidly exclude the presence of intra-abdominal hemorrhage. In the hemodynamically stable child, CT provides more useful information. Ultrasonography is not particularly sensitive for detecting parenchymal injuries, except in the most experienced hands, and only with close color and pulsed Doppler interrogation can a vascular injury be diagnosed. Therefore, its utility in the acute setting at present remains limited. Ultrasonography may, however, have utility in follow-up of acute renal injuries staged initially by CT to exclude complications of injury, including urinomas, expanding hematomas, abscesses, or pseudoaneurysms, thus reducing radiation exposure.[56]

CT cystography has been found to be equivalent to conventional cystography in terms of sensitivity (95%-100%), specificity (99%-100%), negative predictive value (100%), and positive predictive value (100%) for the detection of the presence or absence of bladder injury and has largely replaced conventional cystography in most major trauma centers.[57–59] An absolute indication for CT cystography is gross hematuria with a pelvic fracture. Other relative indications include gross hematuria alone, microscopic hematuria with pelvic fracture, or microscopic hematuria alone in the context of other clinical indicators of bladder rupture such as suprapubic pain, inability to void, or significant perineal trauma.[60] It is critical that the bladder be fully distended in order to accurately detect bladder injury. Simply clamping a Foley catheter after intravenous contrast agent administration for CT is not adequate and will result in an unacceptably high rate of missed injuries.[59,61] For CT cystography, the bladder is filled in a retrograde fashion by gravity drainage before or after routine abdominal/pelvic CT. The bladder of adolescents should be filled with 300 to 400 mL of contrast medium. The bladder of smaller children should be filled by gravity infusion until the patient becomes uncomfortable or the bladder capacity is reached. In children younger than 2 years of age, the bladder capacity is 7 mL/kg. In children 2 to 11 years of age, the bladder capacity is age in years plus 2 times 30 mL.[62,63] Multiplanar reformatted images are essential to assess the bladder fully for potential injury. If CT cystography is equivocal in any way for either the presence of extravasation of contrast or in differentiating intraperitoneal versus extraperitoneal extravasation, it should be followed by conventional cystography to confirm or exclude injury.[56]

Retrograde pyelography may play a role in the assessment of ureteral and renal pelvic integrity when UPJ injury is suspected. Failure of opacification of the distal ureter on CT should raise suspicion for a ureteral injury[64]; and if insufficient detail is provided by CT, retrograde pyelography is indicated.

Retrograde urethrography is indicated when urethral injury is suspected.[43] A Foley catheter with a minimally inflated

balloon is inserted into the fossa navicularis of the distal urethra, and approximately 30 mL of contrast medium is instilled under fluoroscopic vision. A normal retrograde urethrogram should demonstrate complete filling of the intact urethra with passage of contrast medium into the bladder. The presence of filling defects or extravasation of the contrast agent indicates urethral disruption. In the presence of hematuria, a cystogram should follow the retrograde urethrogram, even if the retrograde urethrogram is normal, because 10% to 15% of patients with urethral disruption from a pelvic fracture will have a concomitant bladder injury.[47]

# Injury Grading and Scoring Systems for Genitourinary Injuries

In 1989, the American Association for the Surgery of Trauma (AAST) Organ Injury Scaling Committee devised and published a classification or grading system for genitourinary tract injuries (Table 21-1) to standardize injury descriptions for research and data collection purposes.[65] Figure 21-1 illustrates this grading system. Injuries are graded on a scale from I to V ranging from the most minor injury (grade I) to the most complex (grade V). For the kidney, this grading system has proved highly applicable, and its usefulness as a measure of the seriousness of renal injury and as a predictor of clinical outcomes and nephrectomy has been validated in several subsequent studies.[66–70] For example, patients with a grade I injury require observation only, whereas those with a grade V injury are more likely to require nephrectomy. Those with intermediate injuries (grades II to IV) require individualized therapy, with a trend toward more invasive therapy as injury grade increases. It should be noted, however, these validation studies were composed primarily of adult patients. Thus extrapolation of results may not be entirely applicable to children. Furthermore, the AAST system has been criticized for grouping complex parenchymal injury with major renovascular injury in the grade IV and V categories, because management may be quite different for the same grades of injury. Modifications addressing this issue have been proposed for future iterations of the scaling system. The AAST scaling systems for ureteral, bladder, and urethral injuries (see Table 21-1) have not gained as widespread acceptance and have been used less consistently.

**TABLE 21-1**
**Urologic Injury Scale of the American Association for the Surgery of Trauma**

| *Grade** | *Injury Description†* |
|---|---|
| **Renal Injury Scale** | |
| I: Contusion | Microscopic or gross hematuria; urologic studies normal |
| Hematoma | Subcapsular, nonexpanding without parenchymal laceration |
| II: Hematoma | Nonexpanding perirenal hematoma confined to the renal retroperitoneum |
| Laceration | <1 cm parenchymal depth of renal cortex without urinary extravasation |
| III: Laceration | >1 cm parenchymal depth of renal cortex without collection system rupture or urinary extravasation |
| IV: Laceration | Parenchymal laceration extending through the renal cortex, medulla, and collecting system |
| Vascular | Main renal artery or vein injury with contained hemorrhage |
| V: Laceration | Completely shattered kidney |
| Vascular | Avulsion of renal hilum that devascularizes kidney |
| **Ureter Injury Scale** | |
| I: Hematoma | Contusion of hematoma without devascularization |
| II: Laceration | ≤50% transection |
| III: Laceration | >50% transection |
| IV: Laceration | Complete transection with 2 cm devascularization |
| V: Laceration | Avulsion of renal hilum that devascularizes kidney |
| **Bladder Injury Scale** | |
| I: Hematoma | Contusion, intramural hematoma |
| Laceration | Partial thickness |
| II: Laceration | Extraperitoneal bladder wall laceration ≤2 cm |
| III: Laceration | Extraperitoneal (>2 cm) or intraperitoneal (≤2 cm) bladder wall lacerations |
| IV: Laceration | Intraperitoneal bladder wall laceration >2 cm |
| V: Laceration | Intra- or extraperitoneal bladder wall laceration extending into the bladder neck or ureteral orifice (trigone) |
| **Urethra Injury Scale** | |
| I: Contusion | Blood at urethral meatus; urethrography normal |
| II: Stretch injury | Elongation of urethra without extravasation on urethrography |
| III: Partial disruption | Extravasation of urethrographic contrast medium at injury site, with contrast visualized in the bladder |
| IV: Complete disruption | Extravasation of urethrographic contrast medium at injury site without visualization in the bladder; <2 cm of urethral separation |
| V: Complete disruption | Complete transection with >2 cm urethral separation, or extension into the prostate or vagina |

From Moore EE, Shackford SR, Pachter HL, et al: Organ injury scaling: Spleen, liver, and kidney. J Trauma 1989;29:1664.
*Advance one grade for multiple injuries to the same organ.
†Based on most accurate assessment at autopsy, laparotomy, or radiologic study.

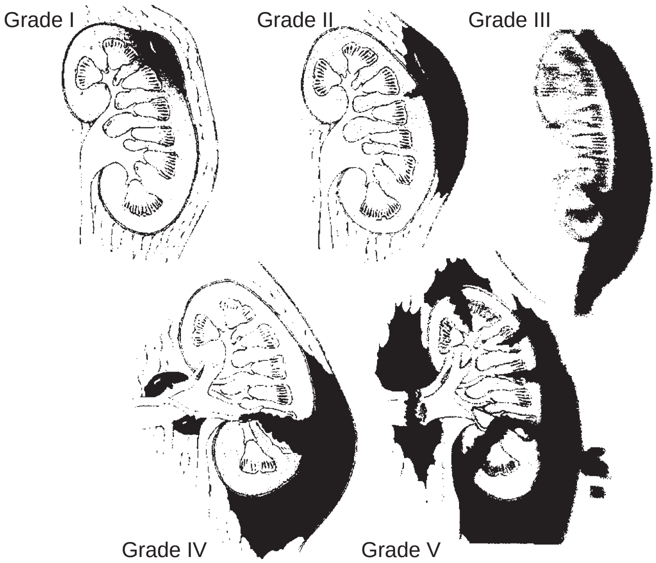


**FIGURE 21-1** Artist's rendition of the American Association for the Surgery of Trauma grading system for genitourinary tract trauma. (Reproduced with permission from Coburn M: Genitourinary trauma. In Moore E, Feliciano DV, Mattox KL [eds]: Trauma, 5th ed. New York, McGraw-Hill, 2004.)

# Management of Specific Injuries

## KIDNEY

### Blunt Injuries

As with traumatic injuries to the spleen and liver, the vast majority of blunt renal trauma in children can be safely managed nonoperatively.[8,11,35,71–82] Nonoperative management of hemodynamically stable children with blunt renal injury has become the standard of care in most centers, with success rates up to 98%.[77] About 85% of pediatric blunt renal injuries are considered low grade (grades I-III). Since the collecting system remains intact in these lower grade renal injuries, they will invariably heal without further sequelae. Because of disruption of the collecting system and/or vascular pedicle, high-grade injuries (grades IV and V) are associated with increased morbidity and mortality. Grade IV injuries account for about 15% of pediatric renal injuries, whereas grade V injuries with major disruption of the renal pedicle occur in the remaining 5% of children.[*]

Children with minor renal injury (grades I and II) may require brief hospitalization for observation or may be discharged home with clear follow-up instructions. Children with higher grade renal injury (grades III-V) or gross hematuria, or both, are hospitalized and placed on bed rest with close monitoring of vital signs and serial physical examinations and blood cell counts. Traditionally, ambulation is begun once the patient is fully resuscitated and hemodynamically stable, blood cell counts have stabilized, and gross hematuria has resolved. It is not unusual for the bladder outlet or Foley catheter to become occluded with clot in patients with gross hematuria. Decreased urine output, bladder distention, or bladder spasms should alert the clinician to this possibility. Placement of a Foley catheter or irrigation or replacement of an existing Foley catheter should remediate the problem. Although it is generally suggested that patients maintain a decreased level of activity until the microscopic or gross hematuria resolves, there are no evidence-based guidelines in the literature addressing appropriate length or type of activity restrictions for renal trauma. The time at which healing is adequate to allow return to full activity without risk has not yet been defined. A multi-institutional prospective study is currently under way to address this issue, allowing for immediate ambulation and discharge based on standard criteria rather than on the resolution of hematuria.[83]

Most pediatric and adult series report successful nonoperative management of even the most complex grade IV and grade V injuries, including shattered but perfused kidneys and complex lacerations with extensive perinephric hematoma and urinary extravasation. Although the AAST grading scale appears to have some predictive value on the need for surgery, indications for surgery are based more on hemodynamic stability of the patient and associated injuries, rather than on grade of renal injury based on imaging criteria. The only absolute indication for surgery is hemodynamic instability with ongoing bleeding and transfusion requirements. Radiographic signs of ongoing renal bleeding include an expanding or uncontained retroperitoneal hematoma or complete avulsion of the main renal artery or vein with extravasation as demonstrated by CT or arteriography. Although not an absolute indication for surgical intervention, active extravasation and pooling of contrast-enhanced blood in the arterial phase of the computed tomographic scan should be considered a relative indication for surgical intervention depending on the clinical status of the patient, and the clinician should maintain a low threshold for prompt exploration in patients with this computed tomographic finding. Recent studies would suggest that about 90% of grade IV injuries with urinary extravasation can be successfully managed nonoperatively in the hemodynamically stable patient.[73,78,80,81,84–87]

Although complications are more common with high-grade renal injuries, most complications associated with urinary extravasation are easily treated by percutaneous drainage or endoscopic stent placement, thereby achieving higher rates of renal salvage.[73,84,86,88] Selective nonoperative management of blunt grade V renal injury in both adults[89] and children[80,82] has also been shown to be feasible for hemodynamically stable patients. Henderson and colleagues[80] reported a 73% kidney salvage rate with nonoperative management of 15 patients with grade V injury, whereas Eassa and colleagues[82] reported a 78% kidney salvage rate with nonoperative management of 18 patients with grade V injury. Superselective embolization was used as adjunctive therapy for nonoperative management in a minority of patients with ongoing bleeding and transfusion requirements, thus permitting salvage of traumatized kidneys with a minimally invasive procedure and avoiding a major surgical procedure. An algorithm for the management of blunt renal injuries in children is presented in Figure 21-2.

### Penetrating Injuries

Penetrating renal injuries are rare in children. Although there is a role for selective nonoperative management, most gunshot wounds to the abdomen require abdominal exploration because of associated injuries from the blast effect. Retroperitoneal dissection and exploration is indicated only if preoperative or intraoperative assessment suggests a major renal injury

*References 47,73,76,77,79,83.

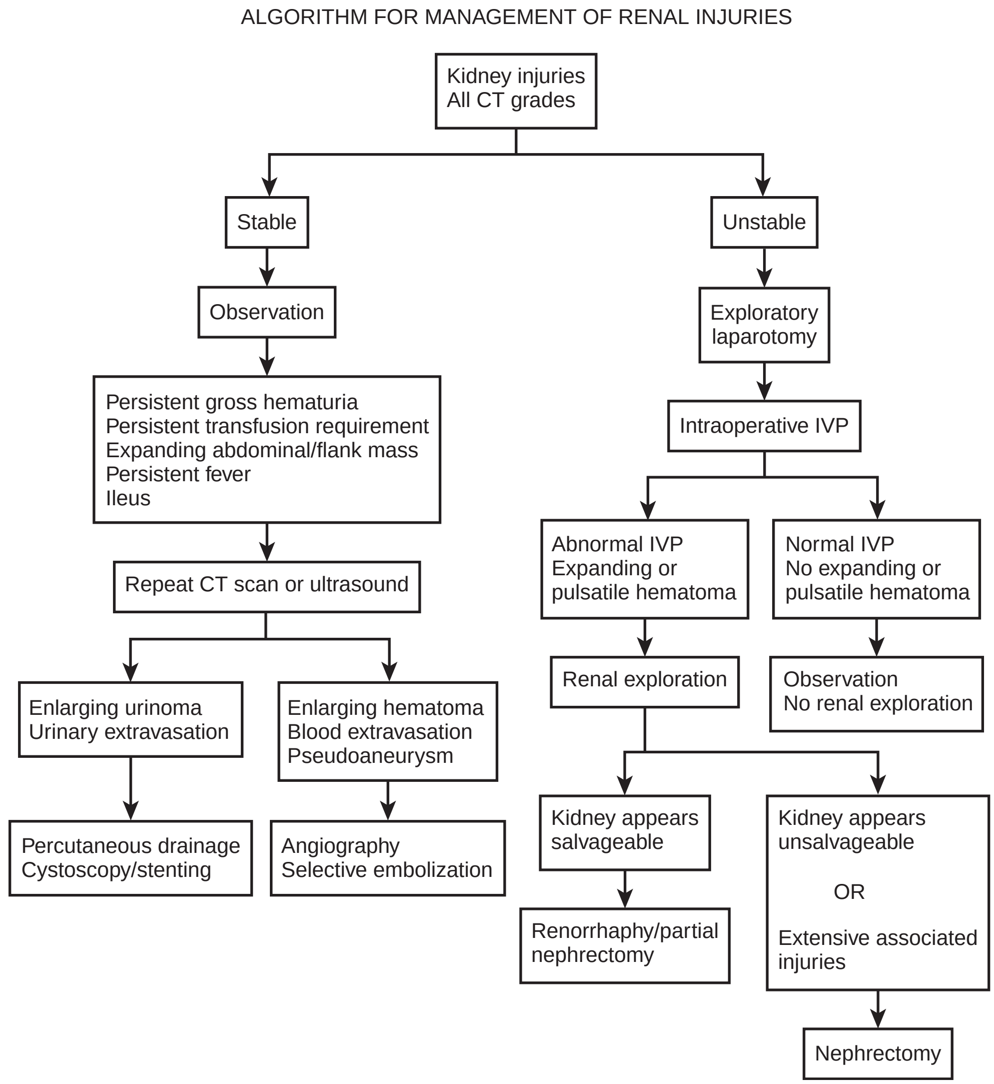


**FIGURE 21-2** Algorithm for the management of renal injuries in children. CT, computed tomography; IVP, intravenous pyelogram.

(grade IV or grade V), there is suspicion of significant nonurologic retroperitoneal injury (great vessels, duodenum, pancreas, colon), inspection reveals an expanding or pulsatile retroperitoneal hematoma, or a combination of these conditions exists.[90] McAninch and co-workers[91] classified gunshot wounds involving the kidney into five categories: (1) contusions (18.4%), (2) minor lacerations (13.8%), (3) major lacerations (50.5%), (4) vascular injuries (6.9%), and (5) lacerations combined with vascular injury (10.3%). In a large study of gunshot wounds seen in 206 renal units in 201 patients over a 30-year period, Voelzke and McAninch[92] reported an overall renal salvage rate of 85.4% using a combination of selective observation/bedrest (25%) and various operative techniques including exploration only, mesh repair, omental flap repair, peritoneal patch, renorrhaphy, vascular repair, and partial nephrectomy. The nephrectomy rate was 14.6%. Nonoperative management of renal injury due to gunshot wounds is evolving. In a 4-year prospective study by Navsaria and Nicol,[93] 34% of 95 patients with gunshot injuries to the kidney were managed nonoperatively without laparotomy with a 91% success rate. Selection criteria for nonoperative management included hemodynamic stability, CT for grading of kidney injury and excluding other associated injuries requiring exploration, and a clinically evaluable patient.

For renal-proximity stab wounds, nonoperative treatment is appropriate in hemodynamically stable patients without associated injuries who have been staged appropriately by triple-contrast CT.[5,94] However, a high index of suspicion for missed ureteral and other associated injuries must be maintained if a nonoperative pathway is chosen.

In a retrospective review by McAninch and co-workers,[95] 55% of renal stab wounds and 24% of renal gunshot wounds were successfully managed nonoperatively with an acceptable complication rate. In the hemodynamically unstable patient with penetrating trauma or in the patient with a retroperitoneal hematoma at laparotomy, a one-shot IVP may be useful to identify renal injury and confirm the presence and function of two renal units to further guide management.

## Renovascular Injuries

Major renovascular injuries are rare in children. Carroll and colleagues[96] and Turner and associates[97] reported penetrating trauma as a cause of renovascular injuries in 64% and 68% of

their patients, respectively. Conversely, Cass and co-workers[98] identified blunt external trauma as the cause of renovascular injury in 76% of patients. Regardless of the mechanism, these patients tend to have high injury severity scores, large transfusion requirements, and associated life-threatening multisystem injury,[96,98] the management of which supersedes that of renal injury. Knudson and colleagues[99] reported that factors associated with a poor outcome after renovascular injuries include blunt trauma, grade V injury, and attempted arterial repair. Elliott and colleagues[100] similarly demonstrated dismal outcomes for vascular repair of main or segmental renal artery injuries, with functional outcomes similar to nephrectomy. Grade V injuries are associated with severe major parenchymal injuries which contribute to poor function of the revascularized kidney. Patients with grade V main renal artery injuries with severe parenchymal disruption may be better served by immediate nephrectomy provided that a functional contralateral kidney is present. Bruce and associates[101] compared 12 patients with blunt renal artery injuries who underwent operative intervention (9 nephrectomies; 3 revascularizations) with 16 patients who were managed nonoperatively, 1 of whom underwent endovascular stent placement. They concluded that nonoperative management of unilateral blunt renal artery injuries is safe and often successful, with a 6% risk of the development of post-traumatic renovascular hypertension.

The pathogenesis of renovascular injuries due to blunt trauma is thought to be caused by rapid deceleration, which results in stretching of the renal vasculature, disruption of the arterial intima, and arterial thrombosis.[96] Blunt arterial injury occurs more commonly on the left side than on the right side because the right renal artery is longer than the left and may be better able to withstand the stretching caused by deceleration.[96]

Although hematuria may be absent or microscopic in 13% to 56% of patients with renovascular injuries,[1,8,11,96,98] most patients have other symptoms or signs that raise suspicion of a major renal injury and prompt further diagnostic imaging.[11,96] Renovascular injury is suggested on CT by (1) lack of renal enhancement or excretion, often in the presence of normal renal contour; (2) vein enhancement; (3) central hematoma; (4) abrupt cutoff of an enhanced renal artery; and (5) nonopacification of the pelvicaliceal system.[11,96]

The approach to this type of injury depends on the time to diagnosis, the type and extent of the vascular injury, and the extent of the associated injuries.[11,96] Repair of the right renal vein may be difficult owing to its short length and proximity to the inferior vena cava. Nonetheless, injuries to the main renal vein can be repaired in most cases.[96] Laceration of the left renal vein at its origin can be managed by ligation because collateral circulation supplied by gonadal and adrenal veins usually allows for adequate venous drainage.[96,102]

Segmental arteries are difficult to repair and may be managed by ligation with accompanying partial nephrectomy if the area of infarction encompasses more than 15% of the kidney. However, nonoperative management should be considered in any patient with segmental artery occlusion that is not associated with uncontrolled retroperitoneal hemorrhage, extensive urinary extravasation, or other intra-abdominal indications for surgery. This management strategy has been associated with an acceptably low incidence of complications.[96,100,103]

Arterial repair is most appropriate and most successful for renovascular injuries caused by penetrating trauma. Notwithstanding occasional reports of successful revascularization in patients 19 hours after injury,[102] the success of the procedure greatly diminishes after 8 hours of renal ischemia.[96,104,105] Ivatury and co-workers[106] reviewed 40 penetrating renovascular injuries and concluded that salvage of a kidney with a renovascular injury is determined primarily by the nature and extent of associated injuries. Furthermore, they reported that although attempts at renal artery repair are often futile, renal vein injuries are more amenable to repair and have a better prognosis. Nephrectomy, however, remains the procedure of choice in the hemodynamically unstable patient with multiple trauma.

Blunt injuries to the main renal artery are associated with the lowest success rate for complete renal preservation.[11,96,97] Renal artery thrombosis due to blunt trauma is often diagnosed by nonvisualization of the affected kidney on CT. Options for treatment include observation with delayed nephrectomy for complications or attempted vascular repair depending on the timing of the injury.[87] Haas and associates[107] reviewed the management of 12 patients with complete renal artery occlusion secondary to blunt trauma. Renal artery revascularization was attempted in 5 patients with a median warm ischemia time of 5 hours (range: 4.5 to 36 hours). Although 4 of 5 revascularizations were deemed technically successful at the time of operation, 3 patients demonstrated no function and 1 showed minimal function on postoperative renal function scans. Two patients required delayed nephrectomy because of complications, and of the 7 patients who received nonoperative management, significant hypertension developed in 3 patients requiring nephrectomy for blood pressure control. Based on these results, the authors were unable to advocate emergency revascularization for unilateral renal artery occlusion in the presence of a normal functional contralateral kidney unless the patient is hemodynamically stable and warm ischemia time is less than 5 hours. Patients with unilateral injury, complete arterial thrombosis, extensive associated injuries, and a prohibitively long period of renal ischemia may be managed either by primary nephrectomy or expectant nonoperative management depending on the hemodynamic stability of the patient. There are reports of successful endovascular stenting for traumatic renal artery dissection and thrombosis in both children[54] and adults.[55] An attempt should be made to revascularize all patients with bilateral renal artery injury or solitary kidneys.[96,108,109] An algorithm for the management of renovascular injuries is presented in Figure 21-3.

## Complications

Although most renal injuries in children can be managed nonoperatively, this type of management is not without complications. If a nonoperative course is chosen, the patient must be carefully monitored. Falling blood counts, ongoing transfusion requirements, and persistent gross hematuria may be indicative of ongoing bleeding. A repeated computed tomographic scan or arteriogram is warranted. An arteriogram may be especially useful because some injuries with ongoing bleeding may be amenable to selective embolization to control the bleeding. Indeed, the success of nonoperative management may be enhanced by angiographic embolization in select

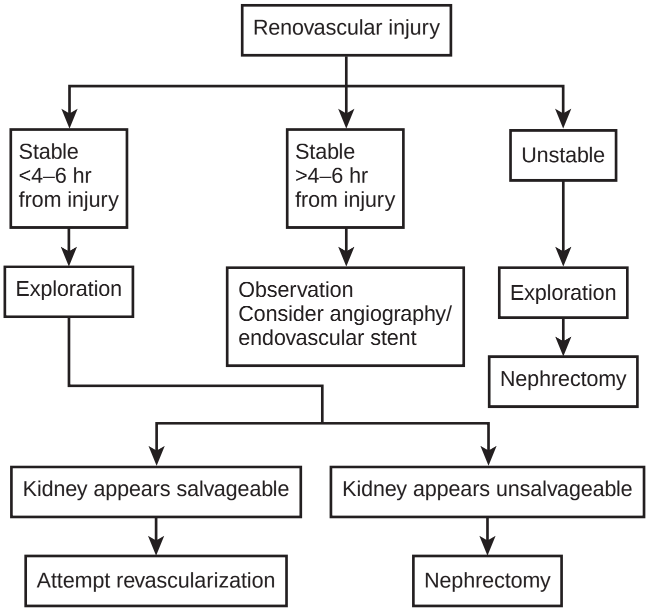


FIGURE 21-3 Algorithm for the management of renovascular trauma in children.

patients.[53,110–112] However, profuse bleeding not amenable to embolization requires emergent operative exploration.

Prolonged ileus, fevers, and an expanding abdominal/ flank mass or discomfort may be indicative of persistent urinary extravasation or urinoma, which is the most common complication after renal trauma. Ultrasonography may be used for diagnosis in patients with suggestive symptoms to reduce radiation exposure associated with CT.[56] Most urinomas are asymptomatic and will resolve spontaneously over time in 67% to 90% of patients.[73,81,84,86,87] Accordingly, small, noninfected, stable collections require no treatment other than observation, whereas larger, expanding collections may be managed by percutaneous drainage[73] or endoscopic placement of ureteral stents.[73,81,84,86,87] Traditionally broad-spectrum antibiotics are administered intravenously on an empirical basis, although this practice is not necessarily evidence based.

Delayed renal bleeding is unusual and most commonly occurs within 2 weeks of injury. However, Teigen and coworkers[113] reported two children in whom massive life-threatening hemorrhage developed several weeks after the initial injury diagnosed by arteriography and successfully treated by percutaneous transcatheter embolization.

Perinephric abscesses may be associated with ileus, high fevers, and sepsis. Ultrasonography or CT are diagnostic. Most of these abscesses are successfully treated with intravenous broad-spectrum antibiotics and percutaneous drainage. Multiloculated abscesses not amenable to percutaneous drainage may require operative drainage.

Late complications may include hydronephrosis, arteriovenous fistula, pseudoaneurysm, pyelonephritis, calculus formation, and delayed renal hypertension. Post-traumatic arteriovenous fistula and pseudoaneurysm may be successfully managed by percutaneous endovascular embolization.[48–50,110,111]

The incidence of renal hypertension after trauma is low, occurring in fewer than 5% of patients.[99,114,115] The incidence is thought to be even lower in children. Although hypertension usually occurs anytime from 2 weeks to several months after injury,[107,115] long-term follow-up is essential because onset may be delayed up to 10 to 15 years after injury.[109]

## Follow-Up and Outcomes

Evidence-based guidelines for follow-up of children after renal injury are conspicuously lacking in the literature. El-Sherbiny and colleagues[116] studied 13 children with grades III (6 children), IV (4 children), and V (3 children) renal injuries managed nonoperatively with a mean follow-up of 3 years with clinical measures (serial blood pressure measurements, urinalysis, and creatinine determinations), renal scintigraphy and/or CT angiography. Although there were residual morphologic changes noted on imaging in 92% of patients, no patient was hypertensive; all had normal urinalysis results and creatinine levels; and there was no significant functional loss, with all kidneys having a split function of 41% to 50% at final follow-up.

A study by Keller and co-workers[117] similarly evaluated the functional outcome of nonoperatively managed renal injuries in 16 children (grades I-III—4 children; grade IV—9 children; grade V—3 children) as measured by blood urea nitrogen (BUN) and creatinine levels, blood pressure, and technetium-99m-dimercaptosuccinic acid (DMSA) renal scans at 3-month and 1-year follow-up. All injuries were noted to be healed radiographically by ultrasonography or CT at 3 months. Normal to mild impairment (>40% split function) was noted in 56% of injured kidneys, with moderate impairment (30% to 40% split function) noted in 31% of injured kidneys. Severe impairment (< 30% split function) was noted in only 3 children—2 of 9 with grade IV injuries, and 1 of 3 with grade V injury. Furthermore, functional outcome did not change significantly from the 3-month to 1-year follow-up period, and all children, regardless of functional outcome on DMSA scan, remained asymptomatic and normotensive and had normal BUN and creatinine levels.

More recently, Eassa and colleagues[82] performed follow-up CT at a mean time of 8 months in 13 of 14 adult patients with grade V injuries managed nonoperatively and noted reapproximation of shattered parenchymal fragments with separation of individual fragments by thin hypoperfused scars. DMSA scans were obtained in 9 of the 14 patients at a mean time of 3 years—4 patients (44%) showed preserved renal function (>40% split function), with the remaining 5 patients showing variable degrees of renal dysfunction, including 2 with severe dysfunction (split function <30%). No patient was noted to be hypertensive or have elevated creatinine levels or abnormal urinalysis results.

Larger prospective clinical and radiologic outcome studies are warranted to further assess time to healing, incidence of complications, residual function, and long-term outcomes after renal trauma to provide the physician with a more evidence-based approach to appropriate follow-up and counseling for the injured child. At present it is generally recommended that children with severe renal injuries (grades III, IV, and V) be followed with ultrasonography and DMSA renal scans at 3 to 6 months after injury as well as biannual to annual blood pressure monitoring and laboratory tests (urinalysis, BUN, and creatinine determinations) for the first several years after injury. Further imaging is also indicated to look for the onset of any urologic symptoms or development of hypertension.

## Operative Management of Renal Trauma

Although most cases of renal trauma in children may be successfully managed nonoperatively, the surgeon should be familiar with techniques of operative management as well. As discussed previously, operative management of renal trauma is generally reserved for hemodynamically unstable patients or patients with severe associated injuries. The patient is usually explored through a generous midline abdominal incision. Although traditionally it has been taught that the surgeon should first gain proximal control of the renal artery and vein before entering the Gerota fascia or the hematoma in order to reduce blood loss and decrease the nephrectomy rate,[118] this approach has recently been challenged. In both retrospective studies[119,120] and a prospective, randomized clinical trial[121] it was concluded that vascular control of the renal hilum before opening the Gerota fascia has no effect on the nephrectomy rate, transfusion requirements, or blood loss but does significantly prolong operative times by up to an hour or more. The nephrectomy rate appears to depend more on the degree of injury rather than on the type of renovascular control.[119]

No matter what the approach, the kidney is exposed and vascular control is obtained at the hilum. With exsanguinating hemorrhage, rapid mobilization of the kidney with digital control of the hilum may be necessary. The left renal vein can be ligated because collateral drainage is provided by the left adrenal and gonadal veins. However, trauma to the right renal vein requires repair. Segmental arteries may be ligated and partial nephrectomy performed if the area of infarction encompasses more than 15% of the kidney. If the patient is hemodynamically stable, the kidney itself is salvageable, and the period of warm ischemia after injury is acceptable (<4–6 hours), renal artery repair and revascularization may be attempted. Otherwise, a nephrectomy should be performed.

If it appears salvageable, the damaged kidney is debrided to viable tissue and intrarenal hematomas are evacuated. Hemostasis should be obtained with absorbable sutures placed in a figure-of-eight pattern. The open collecting system should be closed with fine, absorbable, monofilament sutures because woven sutures may cut through renal tissue. Internal stents may be required if the ureter or renal pelvis has been injured.

The renal capsule should be closed to approximate the renal margins. If the capsule is destroyed, the lacerated margins should be covered with omental pedicle grafts, retroperitoneal fat, or polyglycolic acid mesh. Approximation and covering of renal tissue aids in hemostasis and wound healing and prevents delayed bleeding and extravasation of urine.[92]

## Ureter

Ureteral injury is uncommon, accounting for less than 1% of all genitourinary trauma.[122] The rarity of ureteral injury may be attributed to its narrow diameter, mobility, and position in the retroperitoneum where it is well protected by the overlying peritoneal contents, psoas muscles, bony pelvis, and vertebrae. Not surprisingly, associated injuries, most commonly involving kidney, small bowel, colon, liver, and iliac vessels, occur in greater than 95% of patients with ureteral trauma.[123–125]

Anatomically, the ureter is divided into three portions—the proximal ureter extends from the ureteropelvic junction (UPJ) to the point where it crosses the sacroiliac joint; the middle ureter courses across the bony pelvis and iliac vessels; and the distal ureter extends from the iliac vessels to the bladder. The distribution of injuries is fairly equally divided—proximal ureter (37%); middle ureter (31%); distal ureter (32%).[123,124] Ureteral trauma is classified according to the AAST organ injury scaling system by the anatomic location of the injury and by the extent of mural damage (see Table 21-1).[65] The complexity of repair and number of associated injuries have been found to correlate with increasing AAST grade of ureteral injury.[123]

The overwhelming majority of ureteral injuries are due to penetrating trauma from gunshot wounds (94%) or stab wounds (2.5%), with blunt trauma accounting for only 3.5% of all ureteral injuries.[124] Blunt injury may occur by either direct or indirect mechanisms. Direct injuries may result from crush injuries or severe hyperextension or flexion injuries. Direct compression against a transverse process or vertebral body has been described,[126] and an association with traumatic paraplegia has been noted.[127] Patients with congenital ureteral obstruction are also predisposed to injury of the collecting system.[128] Surgical repair is unlikely to be successful if the underlying obstruction is not recognized and treated.

Indirect mechanisms of ureteral injury in children include falls or rapid deceleration. As noted by Boone and colleagues,[129] the UPJ is particularly prone to disruption secondary to these mechanisms. Howerton[130] reviewed 54 cases of ureteral avulsion within 4 cm of the UPJ and found that this type of injury was three times more common in children than in adults.

The clinical diagnosis of ureteral injury can be difficult because of the paucity of early signs and symptoms. For penetrating trauma, any missile tract in the vicinity of the ureter should raise suspicion for ureteral injury, and appropriate diagnostic testing or exploration should be undertaken depending on the clinical status of the patient. For blunt trauma, flank ecchymosis with significant deceleration or a hyperextension-flexion mechanism should alert the clinician to the possibility of ureteral injury. Overall, hematuria is noted in fewer than half of patients with ureteral injury and is thus not a very sensitive indicator of injury.[123–125] Furthermore, absence of hematuria does not exclude injury.

Imaging modalities for diagnosis of ureteral trauma include CT, retrograde pyelography, and IVP. In the setting of blunt trauma or in the hemodynamically stable patient with penetrating trauma, CT is the gold standard for evaluation. With the faster helical CT scanners currently in use, if an injury to the ureter is suspected, it is critical to obtain delayed images during the excretory phase (5 to 20 minutes) so that ureteral extravasation is not missed. Failure of opacification of the distal ureter on CT should raise suspicion for a ureteral injury,[64] and if insufficient detail is provided by CT, retrograde pyelography is indicated.

IVP is used more commonly for penetrating trauma, since emergent exploration may be required because of associated injuries; however, up to 75% of ureteral injuries are missed by IVP.[122,131] Single-shot IVP is often unreliable and nondiagnostic, whereas complete IVP is more accurate but more difficult to obtain in the emergent setting.[125] Abnormal

findings on IVP suggestive of ureteral injury include ureteric dilatation or deviation, incomplete visualization of the complete ureter, delayed or incomplete visualization of the kidney, and extravasation of contrast medium.[125]

Delayed diagnosis of ureteral injury occurs in approximately half of patients owing to the subtle nature of the clinical findings, frequent absence of hematuria, lack of sensitivity of radiologic imaging techniques, and high incidence of multisystem injury with concomitant patient instability.[122] Although intraoperative inspection of the retroperitoneum when a missile path is in the vicinity of the ureter may be the most sensitive indicator of injury, a comprehensive review of the literature reveals that 11.1% of ureteral injuries are missed at laparotomy despite preoperative or intraoperative imaging, or both, and intraoperative inspection.[132] Meta-analysis reveals a statistically increased rate of nephrectomy as well as prolonged hospital course when ureteral injury is missed at exploration.[128] Delayed signs of a missed ureteral injury that should prompt further investigation include prolonged ileus, continued high output from surgically or percutaneously placed drains, fever or sepsis, persistent flank or abdominal pain, urinary obstruction, elevated creatinine or BUN levels, and flank mass.[125] Delayed diagnosis results in significantly increased morbidity, including fistula, urinoma, abscess, sepsis, renal failure, and renal loss.[125]

A high index of suspicion for the presence of ureteral injury must be maintained by the clinician in order to avoid missing these highly morbid injuries.

Factors influencing optimal treatment of ureteral injuries include time to diagnosis, associated injuries, degree of injury, and hemodynamic stability of the patient. Many blunt and low-grade ureteral injuries (grades I and II) may be managed nonoperatively with observation and ureteral stenting. The treatment of more complex ureteral injuries is primarily surgical and dictated primarily by the location and mechanism of injury, amount of tissue loss, condition of the local tissues, and stability of the patient. The primary goal is renal preservation with maintenance of urinary drainage from the kidney.

A complex armamentarium of percutaneous and surgical techniques is available to the surgeon to address these injuries.[123–125,133] The most common surgical reconstructive techniques include primary ureteroureterostomy, transureteroureterostomy, and ureteral reimplantation by ureteroneocystotomy.[123] Basic surgical principles of ureteral repair include thorough assessment and staging of injury, adequate mobilization of the ureter taking care to preserve the adventitia, wide debridement to viable tissue, a spatulated tension-free watertight repair over a stent, and adequate drainage of the retroperitoneum.[124] Complex ureteral injury associated with a severely damaged or shattered kidney may be best managed by nephrectomy. In the absence of or with limited renal injury, attempts at primary ureteral repair should be attempted. Proximal ureteral injuries are often short and therefore amenable to debridement and ureteroureterostomy. With disruption of the UPJ, ureteropyelostomy or dismembered pyeloplasty are options for repair. If damage to the renal pelvis is extensive, it should be surgically debrided and closed with ureteral continuity restored by ureterocalicostomy. Middle ureteral injuries can usually be managed by primary ureteroureterostomy, transureteroureterostomy, or a Boari flap and reimplantation. Injuries to the distal ureter are often amenable to a simple ureteral reimplantation (ureteroneocystostomy) or psoas hitch.[123–125,133]

Unstable patients with multiple injuries are best managed by exteriorization of the transected ureter as an intubated ureterostomy or by simple ureteral ligation with intraoperative or postoperative percutaneous nephrostomy.[125] Definitive reconstruction of a long ureteral defect is performed on an elective basis once the patient is stable, and options for reconstruction may include ileal interposition and autotransplantation.[133]

Ureteral injuries in which the diagnosis is delayed or in which secondary leaks occur after primary repair are best managed by percutaneous nephrostomy and antegrade ureteral stenting with later elective surgical correction of stenosis or fistula if encountered. Infected urinomas or abscesses can usually be managed effectively with percutaneous drainage.[125]

# Bladder

## ANATOMY

Although the bladder in children is located in the extraperitoneal space of Retzius, it is considered an intra-abdominal organ until about the age of 6 years when, as the bony pelvis grows, the bladder assumes a pelvic position and is increasingly protected from injury. The anatomic attachments of the bladder influence the pattern of injury seen after some forms of trauma. The bladder is bound laterally by the internal obturator muscles and the umbilical ligaments. At its base the bladder is attached to the urogenital diaphragm. Denonvilliers fascia or the rectovesical fascia binds it posteriorly. Unlike the rest of the bladder, the dome is mobile and distensible.

## CAUSES

Injuries to the bladder are distinctly uncommon in children, accounting for about only 0.05% to 0.2% of all injuries.[134,135] Blunt trauma accounts for the vast majority of injuries to the bladder and usually results from a direct blow to the lower abdomen when the bladder is distended with urine or from a pelvic fracture in which there is shearing of the bladder from its fascial attachments or laceration from a bony spicule. The susceptibility of the bladder to injury is somewhat dependent on the amount of urine contained at the time of injury. Motor vehicle accidents are the most common cause of blunt trauma to the bladder, accounting for about 90% of cases, followed by falls and direct blows to the lower abdomen.[134] There have also been several case reports of bladder injury in children due to nonaccidental trauma.[135] Because of its relatively protected position within the pelvis, considerable blunt force is required to cause bladder injury. Not surprisingly, serious injuries to other intra-abdominal organs are seen in almost half of patients with bladder injuries.[134] Although 60% to 90% of bladder injuries are associated with pelvic fractures, only 2% to 11% of patients with pelvic fractures have concomitant bladder injuries.[134]

## CLASSIFICATION AND DEFINITIONS

Bladder injuries due to blunt trauma may be further classified as contusions and extraperitoneal and intraperitoneal ruptures. Extraperitoneal bladder ruptures occur in about 55% to 60% of cases, intraperitoneal ruptures occur in about

25% to 40% of cases, and a combination of the two occurs in about 10% of cases.[136,137] The AAST organ injury grading scale for bladder injuries is shown in Table 21-1.

Contusions are disruptions in the bladder muscular layer without loss of continuity of the bladder wall, whereas ruptures are complete disruptions of the bladder wall with extravasation of urine. Contusions typically resolve without intervention.

Extraperitoneal bladder ruptures are almost invariably associated with pelvic fractures.[134,137]

Nineteen percent of patients (mostly boys) with extraperitoneal bladder ruptures have a concomitant urethral injury, and 8% have an associated intraperitoneal injury.[138] In contrast to extraperitoneal ruptures, intraperitoneal ruptures are infrequently associated with pelvic fractures (Fig. 21-4). These injuries are often caused by compression (burst-type injury) from a suprapubic blow to a distended bladder or sudden, forceful deceleration. Intraperitoneal ruptures most commonly occur at the dome of the bladder, whereas extraperitoneal ruptures are usually caused by bony perforation or shearing forces.[139]

## DIAGNOSIS

The hallmark of bladder injury is gross hematuria, which is noted in 95% of cases.[134] Gross hematuria in association with suprapubic pain, inability to void, and pelvic fracture should prompt further investigation to exclude the presence of a bladder injury. Conventional CT and CT cystogram with multiplanar reformatted images are equally accurate for diagnosing bladder rupture.[57,58] Urinary ascites, intra-abdominal sepsis, ileus, abdominal distention, and unexplained abnormal serum electrolyte, BUN, and creatinine levels should alert the clinician to the possibility of a missed intraperitoneal bladder rupture.[134,140]

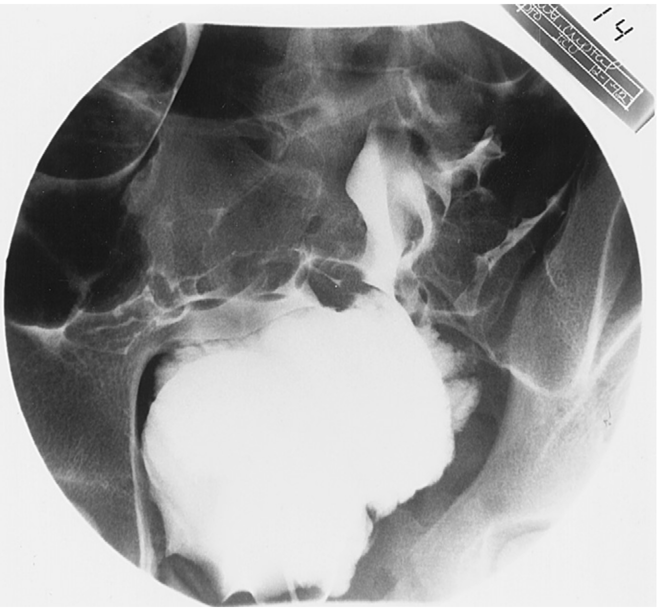

FIGURE 21-4 Voiding cystourethrogram demonstrating intraperitoneal rupture of the bladder. The patient also had bilateral fractures of the superior ischial and inferior pubic rami.

## MANAGEMENT

### Bladder Contusions

Most bladder contusions heal spontaneously without intervention. If the sacral innervation of the bladder is intact, patients with bladder contusions have excellent outcomes. Patients with a large pelvic hematoma that causes considerable bladder distortion may have difficulty voiding and may benefit from Foley catheter drainage.[134]

### Intraperitoneal Rupture

Intraperitoneal ruptures are frequently associated with other significant injuries, necessitating a thorough and deliberate evaluation of the patient. The weakest and most mobile part of the bladder, the dome, is the most common site of intraperitoneal rupture. This type of injury occurs more commonly in younger children. Intraperitoneal rupture is generally associated with a large rent in the dome of the bladder with leakage of urine into the peritoneal cavity.[134]

Intraperitoneal bladder ruptures are best managed by early operative repair through either an open or laparoscopic approach (in select patients).[141,142] For the open procedure the bladder should be approached through a lower midline abdominal incision to avoid lateral contained hematoma. If necessary the rent in the dome of the bladder can be widened to facilitate a thorough examination of the inner aspect of the bladder. Associated extraperitoneal tears can be closed from within by a single running layer of absorbable suture; however, the surgeon must ensure that the patency of the ureteral orifices is preserved. An intravenous injection of indigo carmine or methylene blue may help verify the location and integrity of the ureteral orifices. The dye should be seen exiting the ureteral orifices within 10 minutes. Lacerations extending into the bladder neck should be carefully repaired to reconstruct the sphincteric components and reduce the likelihood of later urinary incontinence. Intraperitoneal bladder injuries are repaired with absorbable suture in two layers.

After the bladder is repaired, a closed-suction drain is placed and brought out through a separate stab incision. Although in the past most surgeons would insert a large-bore suprapubic cystostomy tube instead of or in addition to a transurethral catheter for urinary drainage after repair of an intraperitoneal bladder rupture, more recent literature suggests that transurethral catheter drainage is not only adequate but also preferable. For any degree of bladder injury, transurethral catheters are equally effective, are associated with fewer complications, and may be removed sooner than suprapubic catheters.[143,144]

Urinary drainage is generally maintained for 7 to 10 days. Most surgeons will obtain a cystogram before removal of the urinary drainage catheter to evaluate the integrity of the repair. If no extravasation is documented, the urinary catheter and closed-suction drain can be removed.

### Extraperitoneal Rupture

The preferred management of extraperitoneal rupture is transurethral catheter drainage alone. This approach is safe and effective and obviates the need for bladder exploration, manipulation of the extraperitoneal hematoma, and converting a closed pelvic fracture into an open one. At times, the degree of extravasation of contrast medium may be alarming. However, because it is

dependent not only on the size of the tear but also on the amount of contrast medium instilled, the degree of extravasation alone may not indicate the severity or extent of the tear in the bladder.[138] In most instances, the tear heals completely and transurethral catheter drainage is successful even with extensive urinary extravasation.[138,139] Almost 90% of extraperitoneal bladder ruptures heal within 10 days and the remainder within 3 weeks.[138] Operative intervention is rarely required. Indications for operative management include failure of the transurethral catheter to provide adequate drainage due to persistent extravasation or clot formation, concomitant vaginal or rectal injury, bladder neck/avulsion injury, or internal fixation of a pelvic fracture to prevent infection of the orthopedic hardware.[134]

### Penetrating Injuries

Because of the high likelihood of associated injuries, which often take priority in management, patients with penetrating injuries to the bladder generally require exploratory laparotomy. The peritoneal cavity is opened in the midline, and injuries to the intra-abdominal viscera and major vasculature are addressed first. Attention is then directed to the bladder and the extent of injury is determined. All devitalized bladder tissue and debris from clothing or bony spicules are removed. The integrity of the ureters can be confirmed with intravenous injection of indigo carmine or methylene blue.[134] A diligent search should be made for extravasation, and if necessary the ureters should be intubated.

Bladder mobilization and extensive debridement is unnecessary and invites precipitous bleeding.[134] Large, nonexpanding hematomas should be left undisturbed. The bladder should be entered through the dome. Extraperitoneal defects should be closed intravesically with a single layer of running absorbable suture. A watertight closure is ideal but not essential. With adequate bladder drainage, even a tenuous closure can heal satisfactorily. Intraperitoneal defects should be closed in two layers with absorbable suture to achieve a watertight seal. With rectal or vaginal involvement, once repair is complete, viable tissue should be interposed to avoid overlapping suture lines and subsequent fistula formation.[134] Closed-suction drains are placed as previously described and transurethral catheter drainage is maintained for 7 to 10 days.

## Urethra

Although urethral trauma is a secondary consideration in children with potential life-threatening trauma, such injuries account for a disproportionate degree of long-term morbidity. Blunt trauma with disruption of the bony pelvis accounts for most posterior urethral injuries in children. About 5% to 10% of boys with a fractured pelvis will also have an injury to the posterior urethra, usually at the proximal bulbar urethra.[145] Of these cases, 10% to 20% will have an associated bladder rupture[146] and about 27 % will have associated intra-abdominal injuries.[147] Motor vehicle accidents account for 90% of posterior urethral injuries, and the remaining 10% result from falls, crush injuries, or sporting injuries. A lateral pelvic force without pelvic fracture rarely results in urethral disruption. Penetrating injuries involving the posterior urethra are exceedingly rare. Anterior urethral injuries are often encountered after straddle injuries—such as a fall astride a fence, kicks, or bicycle injuries. Penetrating trauma to the anterior urethra is rare but may be seen with gunshot or stab wounds.[147]

The diagnosis of urethral trauma is relatively straightforward. Symptoms of urethral injury may include the inability to void or the sensation of voiding without passing urine. Blood at the urinary meatus or gross hematuria after trauma strongly suggests urethral injury. Physical examination of the penis, scrotum, and perineum may reveal swelling and ecchymosis. The integrity of and boundaries of the Buck, Colles, and Scarpa fascias indicate the region injured. Digital rectal examination may reveal upward displacement of the prostate or a boggy mass. This, however, may be difficult to assess in young children, so urethral imaging is required to confirm the diagnosis.

If there is suspicion of a urethral injury, blind passage of a transurethral urinary catheter should not be attempted because there is a risk of creating a false passage with the catheter and converting a partial disruption into a complete one. Retrograde urethrography is the imaging modality of choice for diagnosis of urethral trauma. Findings of elongation, filling defect, or extravasation indicate urethral injury. If urethral integrity is demonstrated by retrograde urethrography, the catheter is then advanced and a cystogram is obtained to exclude concomitant bladder injury.

Table 21-1 outlines the classification of urethral injuries, which includes contusions, stretch injuries, partial disruptions, and complete disruptions. A filling defect caused by contusion and hematoma or an elongated urethra without extravasation on retrograde urethrography indicates grade I or grade II injury. Urethral extravasation with bladder continuity indicates partial disruption (grade III). Urethral extravasation with no admission of contrast agent into the proximal urethra or bladder suggests complete disruption (grade IV). Spasm of the periurethral musculature can mimic complete disruption. Figure 21-5 provides an example of injury to the bulbous urethra.

The long-term sequelae of urethral trauma can be devastating and may include impotence, retrograde ejaculation, incontinence, and urethral strictures. Some of these complications may be a direct consequence of the trauma itself or may be related to surgical attempts at repair.

**FIGURE 21-5** Extravasation of contrast from the bulbous urethra due to penoscrotal urethral disruption. The posterior membranous and prostatic urethra is intact.

A diagnosis of anterior urethral injury is suggested if the retrograde urethrogram reveals only minimal extravasation with good urethral continuity and if the patient is able to void. Grade I or grade II injury to the anterior urethra usually heals spontaneously without insertion of any indwelling urinary catheters, as long as the patient is able to void. Intermediate-grade anterior urethral injuries may be managed by an indwelling transurethral Foley catheter, whereas more complex injuries are best managed in the initial stages by placement of a suprapubic catheter. Delayed urethral strictures occur commonly and most are amenable to urethroplasty.

Penetrating injuries to the anterior urethra may be managed by exploration and primary repair or suprapubic urinary diversion. Husmann and colleagues[148] reviewed the management of 17 patients with partial transection of the anterior urethra due to low-velocity gunshot wounds and concluded that patients were best managed by aggressive wound debridement, corporeal repair, primary suture repair of the urethra, and placement of a suprapubic catheter. Strictures developed much less frequently with this approach (1 of 8 patients) compared with suprapubic diversion and transurethral catheter stenting (7 of 9 patients). If there is extensive hematoma at the site of injury, it may be more prudent to place a suprapubic catheter, allow the injury to heal, assess for stricture formation by contrast studies or urethroscopy, or both, after more than 3 months, followed by formal urethral reconstruction if indicated.[147]

In children, the majority of posterior urethral injuries may be managed nonoperatively. Grade I or grade II injuries, which may allow spontaneous voiding, are managed without surgery and without an indwelling urinary catheter. Patients who are unable to void are managed by insertion of a small, transurethral Foley catheter. Grade III injuries with minimal extravasation may also be managed by passing a small transurethral Foley catheter under fluoroscopic guidance immediately after the retrograde urethrogram is obtained. If the catheter does not pass easily, however, a suprapubic tube should be placed.

Options for repair of more complex posterior urethral injuries include primary surgical repair with anastomosis of the disrupted urethral ends, delayed primary repair, primary surgical catheter realignment, primary endoscopic realignment with imaging, or suprapubic cystostomy with delayed urethroplasty.

Primary surgical repair involves evacuation of the pelvic hematoma, mobilization of the prostate and urethra, and direct end-to-end anastomosis between the prostatic and membranous urethra. Problems with this approach include increased risk of uncontrolled bleeding from exploration of the injury site with release of the tamponade effect of the hematoma, increased rate of stricture formation, increased risk of impotence due to dissection of the periprostatic and periurethral tissues, and increased risk of incontinence due to damage to the intrinsic urethral sphincter mechanism by dissection, mobilization, and debridement of torn urethral ends.[147]

Primary surgical catheter realignment, despite not requiring direct suturing of the disrupted urethral ends, still requires an open procedure with entry into and evacuation of pelvic hematoma with all of the attendant risks of primary surgical repair. More recently innovative combined transurethral and transvesical endoscopic and interventional radiologic techniques have been introduced to achieve primary alignment without the risk of exploring the disrupted urethra.[147,149] Furthermore, because there is no manipulation of periprostatic tissues and no additional trauma to the cavernous nerves, there should be no additional risk of erectile dysfunction other than that caused by the injury itself.

Concerns about the impact of primary open surgical repair or catheter realignment on potency and urinary continence led to the introduction of an alternative treatment approach, namely suprapubic cystostomy with delayed urethroplasty. No attempt is made to explore the urethra; rather the urinary stream is simply diverted through a suprapubic cystostomy tube. A stricture is considered inevitable and is repaired several months later. Advantages of this approach include avoiding entry into a fresh pelvic hematoma with risk of blood loss and infection, speed and simplicity of suprapubic tube insertion, and decreased incidence of impotence and incontinence resulting from the avoidance of dissection of the prostate and urethra. Disadvantages include prolonged need for a suprapubic tube with risk of infection and stone formation as well as the nearly 100% risk for urethral strictures, which may be complex and difficult to repair even in the delayed setting. Tunc and colleagues[150] reviewed 77 cases of delayed repair of traumatic posterior urethral injuries and demonstrated adequate urethral continuity in 95%, postoperative incontinence in 9%, and postoperative erectile dysfunction in 16%. They concluded that delayed posterior urethroplasty is a successful treatment option with acceptable morbidity. Although suprapubic drainage with delayed urethroplasty is associated inevitably with stricture formation that may be difficult to repair even in the delayed setting, decreased rates of incontinence and impotence are a definite advantage.

Koraitim[151] reviewed and compared various techniques for repair of complex posterior urethral injuries, including primary repair (37 patients), which was associated with 49% stricture rate, 21% incontinence rate, and 56% impotence rate; immediate and early realignment (326 patients) which was associated with a 53% stricture rate, 5% incontinence rate, and 36% impotence rate; and suprapubic drainage with delayed repair (508 patients), which was associated with a 97% stricture rate, 4% incontinence rate, and 19% impotence rate. After extensive literature review regarding different approaches to management of complex posterior urethral injuries, Holevar and associates[136] in 2004 concluded that these injuries may be treated with either primary endoscopic realignment or suprapubic cystostomy with delayed urethroplasty with similar results. More recent studies in both children and adults, comparing early primary alignment with suprapubic cystostomy and delayed urethroplasty, favor early primary alignment because it may decrease the requirement for subsequent stricture therapy by as much as 50%, resulting not only in fewer strictures but also in strictures that are easier to treat.[152–154] Furthermore, it does not appear to increase the rate of incontinence and impotence.

Urethral trauma in girls is rare, since the urethra is very short and mobile with no significant attachments to the pubic bone.[147,155,156] The usual mechanism of injury involves pelvic fracture incurred during a motor vehicle accident. Straddle injury occasionally results in damage to the urethra. Female urethral injuries may be distal avulsion from the perineal attachment or proximal disruptions and lacerations. The latter type of injury is characteristically associated with other pelvic injuries, including vaginal and bladder neck lacerations.

Perry and Husmann[157] reviewed the evaluation of urethral injuries in girls with pelvic fractures. Blood at the vaginal introitus mandates a meticulous vaginal examination. The urinary meatus must also be carefully examined and its patency confirmed by passage of a catheter. However it is important to note that catheters can often be passed into the bladder even in the presence of a significant urethral injury. Development of vulval edema after removal of the catheter warrants prompt investigation. Because urethrography in young girls is difficult and unreliable, urethroscopy is the preferred diagnostic modality. Delays in diagnosis of urethral injury in girls occur frequently and have devastating consequences.[147,157] Such injury is misdiagnosed in about 50% of cases and can result in life-threatening sepsis and necrotizing fasciitis. Therefore one should have a low threshold for performing urethroscopy when urethral injury is suspected in a young girl.

Treatment is dictated by the extent and location of injury. Urethral injuries that extend into the bladder neck require meticulous repair with reapproximation of the bladder outlet and urethra. Such injuries are encountered about two thirds of the time. Associated vaginal injuries are repaired primarily. Urethral crush injuries that do not involve the bladder neck are managed by extended transurethral Foley catheterization (6 to 8 weeks) or, if necessary, suprapubic catheter drainage. Significant long-term complications associated with pediatric female urethral trauma are common and include urethral stenosis, urethrovaginal fistula, incontinence, and vaginal stenosis.[158] Clearly every effort must be made to promptly detect and aggressively manage this uncommon injury.

# External Genitalia

## GIRLS

Blunt genital trauma in girls is fairly common. The presenting symptoms are usually the presence of blood in the underpants or on the perineum shortly after injury.[159] Blunt genital trauma most commonly results from straddle injury. The most common types of injury in decreasing order of frequency are lacerations or contusions of the perineal body, vagina, labia, urethra, and rectum. Because of the extreme difficulty of performing a thorough genitourinary examination in an awake, uncomfortable, anxious, and embarrassed child, the majority of patients are best evaluated in the operating room under general anesthesia. Indeed, as many as 76% of patients will have more extensive injuries than can be appreciated in the emergency department.[159]

Management of female genital trauma is dictated by the type and extent of injury.[160] Vulvar hematomas may cause urinary retention and may benefit from placement of a urinary catheter and evacuation of large hematomas. Necrotic contused tissue should be debrided. Lacerations are primarily repaired after hemostasis is achieved. Absorbable sutures are used to preclude the need for removal. Vaginoscopy, urethroscopy, and proctoscopy may be necessary to evaluate the injury more thoroughly.

## BOYS

Penile injury resulting from blunt or penetrating trauma is rare in children. All penile injuries, other than very superficial injuries, should be evaluated with retrograde urethrography to exclude concomitant urethral injury. Urethral lacerations should be managed as described in the previous section. The findings of an expanding hematoma, palpable corporal defect, and excessive bleeding suggest cavernosal injuries. When possible these injuries should be repaired primarily. Urinary diversion with a suprapubic tube is occasionally necessary. The preferred method of management of gunshot wounds with a limited extent of injury is debridement of superficial wounds, repair of the cavernosal defects, and primary repair of the urethral injury.[47]

Injury resulting from zipper entrapment of the penis can be addressed in many cases in the emergency department but may require a general anesthetic for release of the penis.[161] Penile strangulation injuries due to constricting bands are managed by division of the constricting band in as atraumatic manner as possible. In children, hair tourniquets are common sources of constriction and may be difficult to remove. Severe strangulation injuries may result in necrosis of the distal penile skin, glans, cavernosum, or urethra. Conservative debridement and urinary diversion may be required.[47] Penile amputation injuries are rare and devastating injuries in children (Fig. 21-6), but reimplantation and reconstructive techniques have been described with variable functional and cosmetic outcomes.[162]

Scrotal injuries may result from penetrating trauma or blunt trauma, or both. High-resolution ultrasonography is useful in the evaluation of these injuries.[163] Ultrasonography of penetrating injuries can identify testicular rupture and extratesticular soft tissue abnormalities as well as the presence and location of foreign bodies.[164] This technique is also useful in distinguishing less serious injuries, such as scrotal hematomas, hydroceles, and hematoceles, from surgical emergencies, such as testicular rupture and infarction. Patients with

FIGURE 21-6 Penile amputation injury with associated intra-abdominal injury from lawn mower.

hematoceles should be considered for exploration to evacuate the blood from the tunica vaginalis testis because this approach reduces morbidity and hastens recovery. Testicular disruption is managed by debridement and primary closure even if 50% of the parenchyma is destroyed. This approach results in a testicular salvage rate of 30% to 39%.[165] Orchiectomy is reserved for the completely shattered testicle.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 22

# Musculoskeletal Trauma

Richard S. Davidson and B. David Horn

Musculoskeletal trauma is the most common medical emergency in children. The number of cases continues to increase in association with the popularity of motor vehicles, all-terrain vehicles, and power lawn mowers. In a child with multiple injuries, optimal treatment requires a cooperating team of medical professionals with diverse specialties who understand the priorities of each team member. As in all other pediatric specialties, it is important to remember that children are not "little adults." Priority management need not compromise complete patient management.

This chapter reviews the important differences between the musculoskeletal systems of children and adults, and it highlights the principles of evaluation and management in children with musculoskeletal injuries. The treatment of high-priority musculoskeletal injuries is specifically discussed, including open fractures, compartment syndrome, femoral neck fractures, mangled extremities, spine trauma, and suspected child abuse. For details on the management of specific musculoskeletal fractures and injuries of childhood, readers should refer to textbooks on children's fractures.[1–3]

## Musculoskeletal Systems of Children and Adults

Differences in the musculoskeletal anatomy and biomechanics of children and adults determine the unique patterns of musculoskeletal injury seen in childhood. Injuries to growing bones are a double-edged sword: They can have a remarkable capacity for healing and remodeling, but they are also subject to the problems of overgrowth and growth disturbance, which can have lifelong consequences.

### ANATOMY

The major anatomic distinctions of skeletally immature bones are the physis and the periosteum. Each long bone in a child consists of the epiphysis, physis, metaphysis, and diaphysis (Fig. 22-1). The epiphysis is the end of the bone beyond the physis, or growth plate, and contains the articular cartilage. The secondary center of ossification arises within the epiphysis and progressively enlarges as the cartilage ossifies during skeletal maturation. The physis, or growth plate, provides longitudinal growth of the bone by forming cartilage that is then converted into bone in the metaphysis. The diaphysis, or shaft, is surrounded by periosteum, which generates new bone and provides circumferential bone growth. In younger children, the periosteum also provides structural support to the bone. By adulthood, the growth plate closes, and there is limited potential for remodeling.

### BIOMECHANICS

Skeletally immature bones are more porous, less brittle, and better able to tolerate deformation than mature bones. The increased porosity of immature bones stops the progression of a fracture line but weakens the bone under a compressive force. As a result, a greater variety of fractures is seen in children than in adults. A child's bone may undergo plastic deformation, where it bends without fracture; it can buckle under compression, resulting in a buckle or torus fracture; it can fracture like a "green stick," with an incomplete crack on the tension side and a bend on the compression side; or it can fracture completely (Fig. 22-2).

The thick periosteum that surrounds the diaphysis of the bone can minimize or prevent displacement of diaphyseal fractures. The periosteum tears on the tension side of a fracture but often remains intact on the compression side. The intact periosteum can then function as a hinge or a spring, increasing deformity. Depending on the injury, the periosteum may simplify or complicate reduction of a fracture (Fig. 22-3).

In the complex of bone, ligaments, and cartilage in a child, the physis is the weakest part and therefore is the most likely site of failure. An angular force to a joint in a young child is most likely to cause a fracture along the growth plate, whereas in an adolescent or an adult, a ligamentous injury or dislocation would occur; so, it is not uncommon for growth plate fractures to be misdiagnosed as sprains. Frankel and Nordin[4]

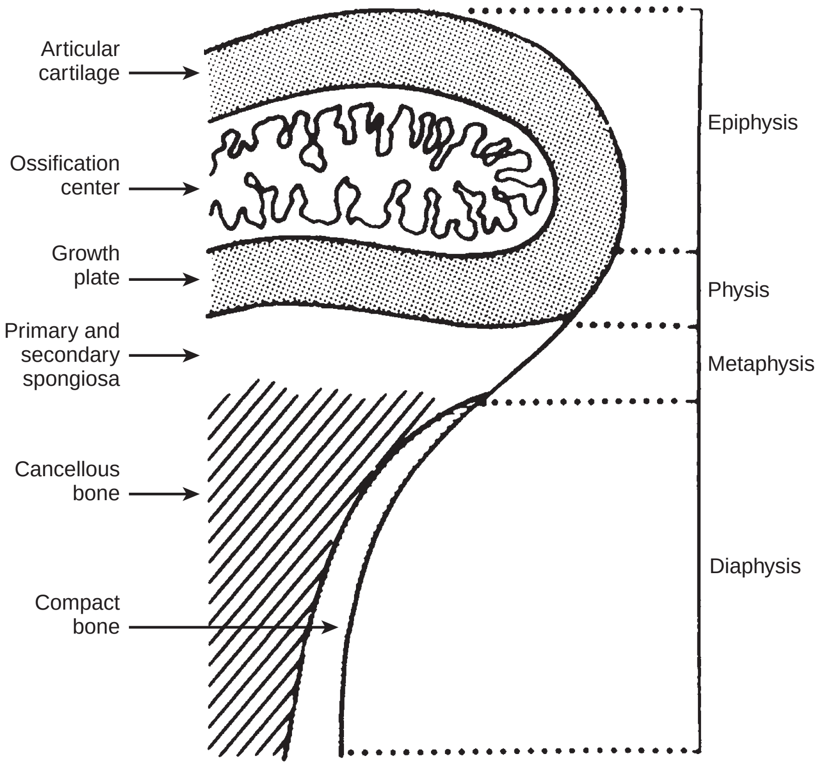


**FIGURE 22-1** Anatomy of a child's bone.

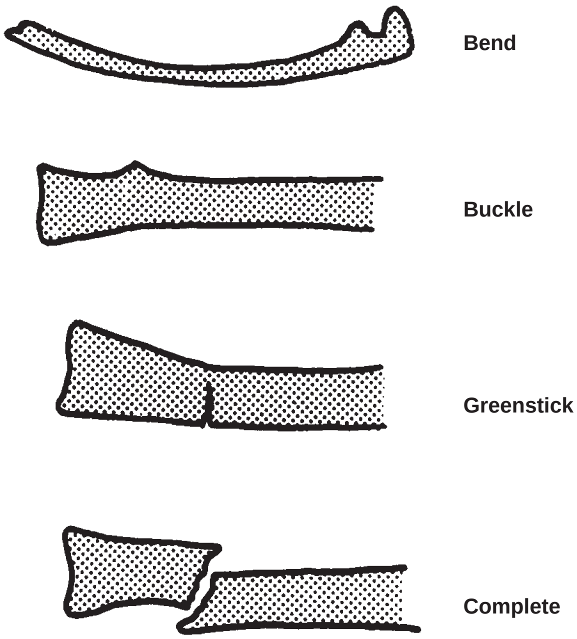


**FIGURE 22-2** Fracture types commonly seen in children. (From Rang M [ed]: Children's Fractures. Philadelphia, JB Lippincott, 1974.)

provide extensive information on the biomechanics of bone. In a fall on an outstretched hand, a young child is unlikely to sprain a wrist; more commonly, a child sustains a fracture through the growth plate of the distal radius. Similarly, instead of spraining an ankle, a child is more likely to sustain a physeal fracture of the distal fibula. Under low-energy forces, these injuries are unlikely to lead to growth disturbance.

The Salter-Harris classification system of fractures involving the physis can guide proper management (Fig. 22-4).[5] Type 1 fractures extend along the entire physis. Type 2 fractures involve part of the growth plate and part of the metaphysis; these fractures are seldom associated with growth arrest except when they occur in the distal femur and proximal tibia. Type 3 fractures involve part of the physis and pass across the epiphysis into the joint. Because of the possibility of incongruity of the joint, type 3 fractures often require open reduction and fixation. Type 4 fractures occur longitudinally, crossing the physis from the metaphysis into the epiphysis. This type of fracture is commonly associated with subsequent formation of a bony bar across the physis, which causes partial growth arrest with subsequent angulation. Open reduction and internal fixation are usually required for type 4 fractures, because joint incongruity and fusion across the physis are common. Type 5 fractures are diagnosed retrospectively, when all or part of the physis fails to grow. It is hypothesized that injury to the physis results from direct compression or local vascular insult. Growth disturbance may result in loss of longitudinal growth or angular deformities. Damage to the physis in high-energy injuries can lead to asymmetric growth in any of the fracture types.

## PHYSIOLOGY

Important physiologic differences between the musculoskeletal systems of children and adults are found in healing and remodeling. Growing bones are also at risk for the unique problems of overgrowth and growth disturbance.

Healing in children is rapid and age-dependent. A newborn may achieve clinically stable union of a fracture in 1 week, whereas a similar fracture in an adolescent may take

6 weeks to heal. In children, the rapid healing process partially results from the thick periosteum, which may form its own bone bridge. Except for displaced intra-articular fractures or fractures with gross soft tissue interposition, nonunion of fractures is rare in children.

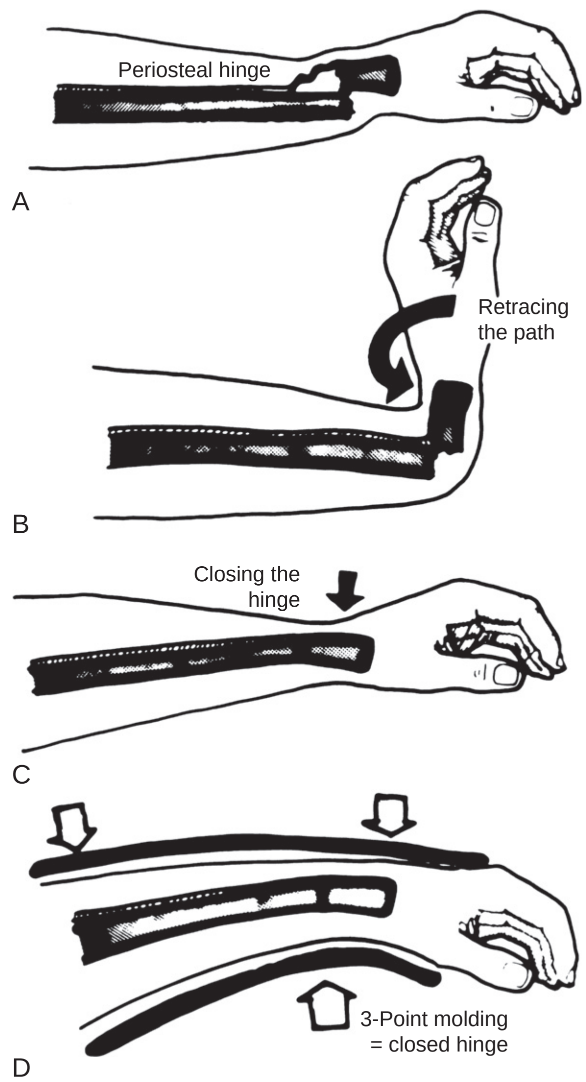


**FIGURE 22-3** **A,** In children, the intact periosteum of a fracture prevents reduction by traction. **B,** By retracing the path of injury, the fracture can be reduced. **C,** Closing the hinge. **D,** A cast with three-point molding holds the hinge closed and keeps the fracture reduced. (From Rang M [ed]: Children's Fractures. Philadelphia, JB Lippincott, 1974.)

The bones of children have great potential for remodeling, but limitations must be understood. Remodeling potential is better in younger patients, in deformities closer to the physes, and where angulation is in the plane of motion of the nearest joint. Remodeling does not effectively correct angulation perpendicular to joint motion or rotation. These deformities should be reduced before healing begins (Fig. 22-5).

Growth stimulation may follow fractures of long bones. This can be especially apparent in the lower extremity in children between 2 and 10 years of age. In this group, an average overgrowth of 1 cm can be expected in femur fractures.[6–8] Although discrepancies in leg length are unpredictable, it is often possible to reduce the ultimate inequality by allowing the fracture to heal with a 1-cm overlap in an otherwise anatomic alignment. Most of the growth stimulation occurs within the first year after injury; so, follow-up visits for 1 year are recommended, even after uneventful healing.

Damage to the physis can produce severe shortening, angular deformity, or both. Although this may be caused by the initial trauma, it can also result from failure to obtain anatomic reduction of a physeal fracture or from repeated or overzealous attempts at reduction (Fig. 22-6). Treatment depends on the amount of remaining skeletal growth and the projected difference in limb lengths and may involve timed ablation of the growth plate on the normal limb, shortening osteotomy of the normal limb, or lengthening of the short limb. Angular deformities can also be addressed, taking into consideration the patient's skeletal age and the severity of the deformity.

# Evaluation of Musculoskeletal Injuries

## CLINICAL ASSESSMENT

The initial assessment of children with multiple injuries may be difficult. Details of the incident may be missing, and the patient's history may be incomplete. The Advanced Trauma Life Support (ATLS) system of assessment involves a primary evaluation to identify and immediately address life-threatening injuries, followed by a secondary evaluation to find and treat other significant injuries. The injuries identified in the secondary evaluation must also be treated in a timely manner to prevent devastating lifelong consequences. Postponing the management of serious musculoskeletal injury for an extended period can be associated with a poor prognosis for return to normal function.

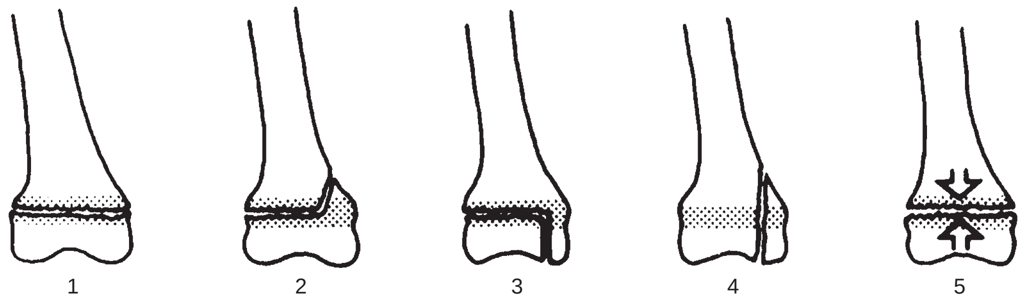


**FIGURE 22-4** Salter-Harris classification of epiphyseal fractures. Type 1 involves the entire physis. Type 2 involves part of the growth plate and part of the metaphysis. Type 3 involves part of the physis and passes across the epiphysis into the joint. Type 4 is longitudinal, crossing the physis from the metaphysis into the epiphysis. Type 5 is diagnosed retrospectively when the physis fails to grow. See text for clinical implications of each fracture type.

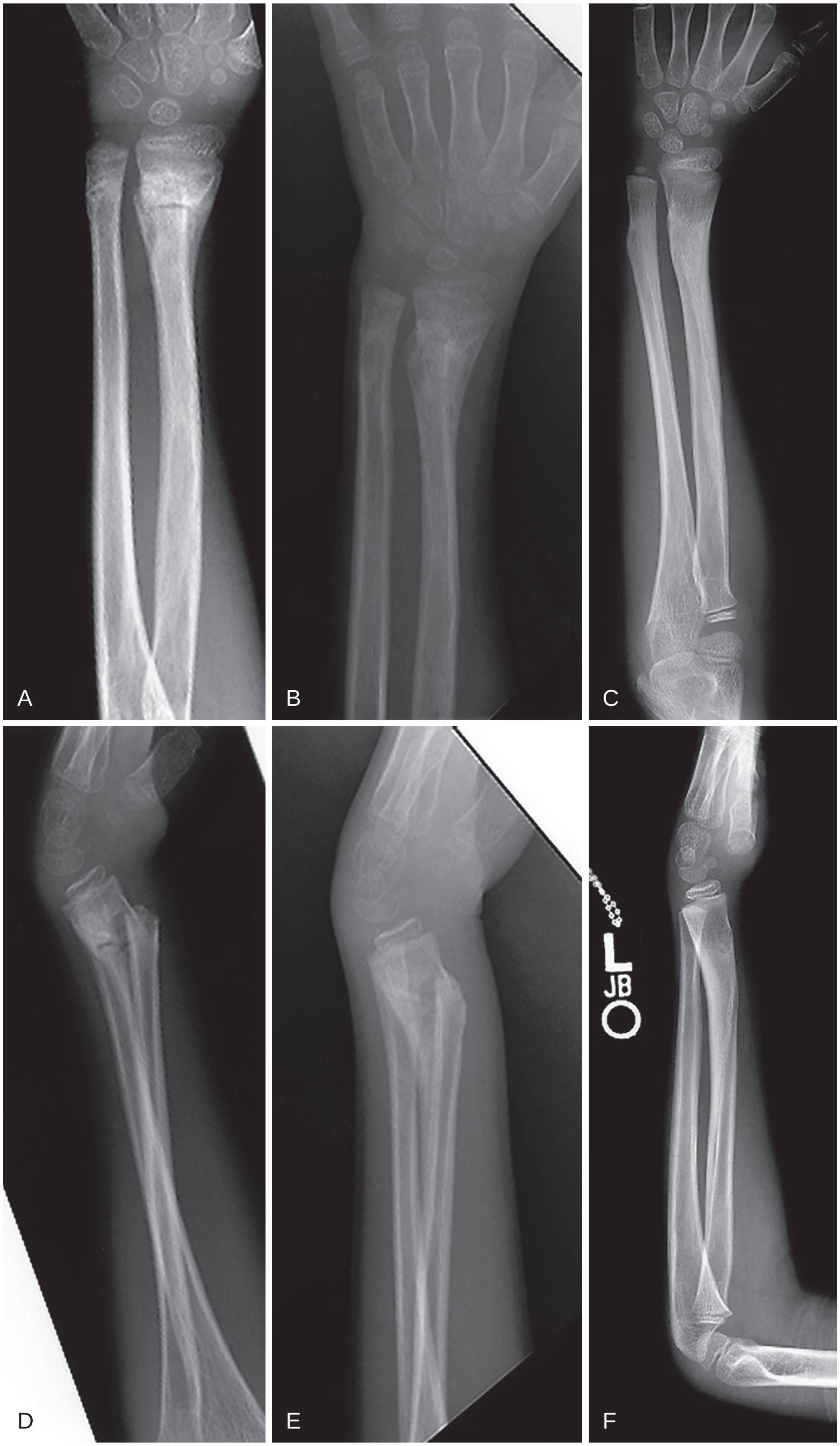


**FIGURE 22-5** Forearm radiographs of a 7-year-old boy demonstrating remodeling of a forearm fracture over a 9-month period. **A** to **C,** Anteroposterior plane. **D** to **F,** Lateral plane.


**FIGURE 22-6** Anteroposterior radiograph of the knees in a 13-year-old boy shows growth disturbance of the left distal femoral growth plate after a fracture (on right in photo).

The musculoskeletal examination begins with observation of the patient for sites of deformity, swelling, contusions, abnormal color, and open fractures. If a fracture is suspected, confirmatory diagnostic studies may be integrated into the complete physical examination. If such studies cannot be done, it must be assumed that a fracture exists, and the suspected site must be splinted until the fracture is confirmed or ruled out. Splinting may also reduce discomfort and limit further damage to soft tissue. A complete neurovascular examination is essential in any case of suspected limb or spine injury. When an uncooperative patient will not allow an adequate physical examination or, in the case of comatose patients or preverbal children, cannot provide a history, judicial use of special diagnostic studies can be critical.

## RADIOGRAPHIC ASSESSMENT

Plain radiography is the first and most widely used test to identify skeletal injury in children, but it can also be a major source of misdiagnosis in this age group. Cartilage, which makes up a large percentage of the child's skeleton, is radiolucent but can fracture. Ossification centers appear at different ages in different locations. The timing of their appearance and their location vary greatly and can suggest fractures. Confusion most frequently occurs in the elbow, knee, and cervical spine. Comparison of the injured and uninjured limbs can be useful. Plain radiographic soft tissue signs, such as the posterior fat pad sign in elbow injuries, are associated with a high likelihood of underlying fracture (Fig. 22-7).[9] A number of imaging studies are available for the assessment of pediatric musculoskeletal injuries and are injury and age specific. Radiographs may confirm fractures. Ultrasonography is a readily available, noninvasive imaging test that can be used to evaluate the unossified epiphysis, especially in injuries about the elbow.[10] Magnetic resonance imaging (MRI) may also be helpful, especially in evaluating the injured spine, but it may require general anesthesia in a young or uncooperative patient. Computed tomography (CT) scanning is useful in periarticular fractures in children approaching skeletal maturity. For example, ankle physeal fractures with articular extension in children with partially closed physes are best delineated with CT scan.[11] Arteriography may be required to assess vascular injury associated with a fracture. Rarely, proximal tibial physeal fractures and distal humerus fractures through the supracondylar region can be associated with disruption of the blood supply to the distal limb. These injuries require emergent treatment, and an intraoperative arteriogram may be of value in diagnosis and treatment (although in

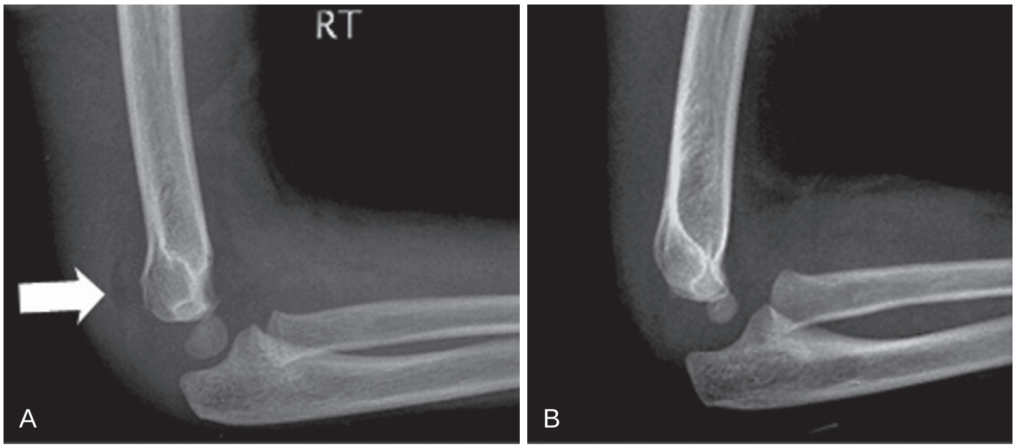


**FIGURE 22-7** Lateral elbow radiographs of a 2-year-old boy with a mildly displaced supracondylar humerus fracture and arrow showing a posterior fat pad sign (**A**) and a normal age-matched elbow (**B**).

most situations surgical treatment should not be delayed in order to obtain an arteriogram in the radiology suite).[12] Joint aspiration can identify blood and fat, which indicate an intra-articular fracture that would not be identified on radiographs. Finally, arthrography and arthroscopy may define intra-articular injury to the cartilage and ligaments.

# Management of Musculoskeletal Injuries

## IMMEDIATE TREATMENT

Priority treatment cannot interfere with complete treatment of an injured child. Proper timing and coordination of management with other disciplines are imperative. Traction or splinting often adequately stabilizes the musculoskeletal injury until other tests and treatments have been completed. Immobilization may also reduce the need for pain medications, which can mask the symptoms of other disorders, such as intra-abdominal injuries, and inhibit diagnosis.

Although there are many types of splints, ranging from plaster to traction bows, the basic principles of fracture management remain the same. The injured part should be splinted as it is found, and the joints above and below the injury should be immobilized without compromising the circulation of the soft tissues. Portable traction splints or custom-molded, well-padded plaster or fiberglass splints can be used in the initial management of fractures. Failure to immobilize the fracture can cause further soft tissue damage from sharp bone ends or the crushing of entrapped neurovascular elements.

## DEFINITIVE FRACTURE MANAGEMENT

Adequate stabilization of fracture fragments prevents further soft tissue injury, frequently decreases pain, and facilitates wound care and patient mobilization. Techniques of definitive stabilization in children include splinting, casting, skeletal traction, external fixation, pinning, flexible intramedullary nailing, and plating. The choice of fixation method depends on the child's age, the location of the fracture, the presence and extent of soft tissue injury, and the presence of multitrauma.

Metaphyseal undisplaced or impacted fractures are likely to heal faster than diaphyseal or displaced fractures. Fractures with devitalized bone or soft tissues take longer to heal. Radiographic evaluation in conjunction with clinical judgment and experience is needed when determining the healing time of fractures in children.

Fragments of bone must be held together until they are sufficiently strong to withstand the forces specific to the bone. A satisfactory position must be obtained, without harming adjacent tissue, before the fracture becomes fixed. Fractures in newborns and infants begin to heal within a few days, but fractures in adolescents can be moved freely for 10 to 14 days. Excessive cast padding, resolution of swelling, or a poorly applied cast may permit progressive malposition within the cast. Fractures should be followed with frequent radiographs until union is secure, to avoid displacement. Unstable fractures should be imaged before consolidation to evaluate for loss of alignment. This allows for easier repeat reduction.

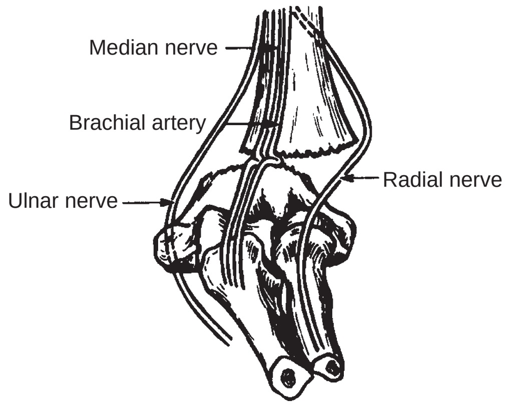


FIGURE 22-8 Supracondylar humerus fracture. Soft tissue and neurovascular structures may become entrapped between bone fragments in these types of fractures.

In children, the thick periosteum tears on the tension side of a fracture but often remains intact on the compression side. The intact periosteum can then function as a hinge, increasing the success of closed reduction of displaced fractures by three-point molding (see Fig. 22-3). Reduction must be performed gently. Forceful and repeated manipulation of physeal fractures can produce iatrogenic damage and growth disturbances. Entrapment of soft tissue occasionally prevents reduction of an otherwise stable fracture (Fig. 22-8) and requires open reduction and stabilization with internal or external fixation or immobilization in a cast.

In some cases, internal fixation with crossed pins, plates and screws, intramedullary nails, or external fixation with pins in metal outriggers or rods may be useful (Fig. 22-9). The benefits of each of these devices must be weighed against their risks, such as need for future operative removal and the possible disturbance to the growth plate, and should be individualized for each particular clinical scenario. Specific indications for internal and external fixation may include fractures with significant soft tissue injury, fractures in children with closed head injury, those associated with neurovascular injury, and fractures that fail nonoperative treatment. Comminuted and oblique fractures and those with complete tears of the periosteum may also prove to be too unstable for cast immobilization. In cases of intra-articular fractures, such as Salter-Harris types 3 and 4, open reduction and stable internal fixation are frequently necessary to avoid incongruity of the joint or growth disturbance. Fractures associated with neurovascular injury requiring repair should be stabilized first.

# High-Priority Musculoskeletal Injuries

Although many musculoskeletal injuries in children can be treated on an urgent rather than an emergent basis, the discussion of some high-priority musculoskeletal injuries in children is warranted. Even in nonurgent cases, it is important to remember that injuries to growing bones can have lifelong consequences.

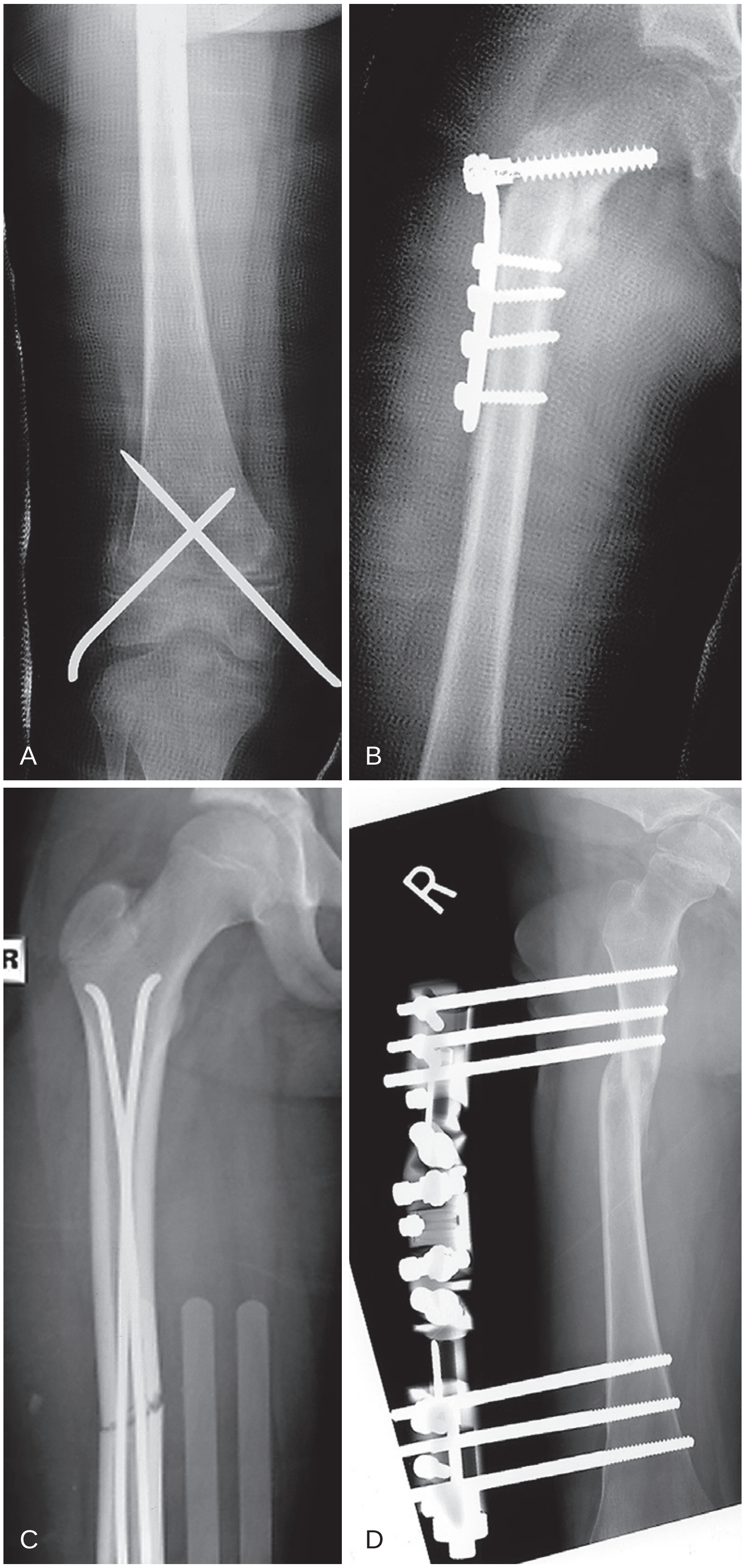


FIGURE 22-9 Anteroposterior radiographs of right femur fractures fixed with a variety of fixation methods. **A,** Salter-Harris type 2 fracture with crossed pins in a 9-year-old girl. **B,** Intertrochanteric fracture with screws and side plate in a 7-year-old boy. **C,** Transverse shaft fracture with elastic intramedullary nails in a 13-year-old boy. **D,** Subtrochanteric fracture with external fixator in an 8-year-old boy.

## OPEN FRACTURES AND TRAUMATIC ARTHROTOMIES

Open fractures frequently result from high-energy trauma and communicate with the outside environment, and so are at increased risk for infection.[13–14] The cornerstones of management include recognition, administration of appropriate antibiotics, stabilization of the fracture, and adequate irrigation and debridement of wounds. Open fractures may require multiple surgical procedures to achieve adequate soft tissue coverage and fracture healing.

When a laceration or abrasion is noted in proximity to a fracture, an open fracture must be suspected. Radiographic evidence of air shadows around the fracture may confirm the diagnosis. A sharp fragment of bone can tear through the skin, and the elastic properties of a child's bone can readily straighten the fracture fragments after the force is discontinued. The protruding point of bone can then draw back under the skin, taking debris and bacteria with it into the deep tissues. Minimal signs of injury do not necessarily mean a minimal chance of infection. Wounds should not be probed in the emergency department, where the risk of iatrogenic contamination is high and the likelihood of adequate debridement is low; if necessary, such procedures should be done in the operating room.

The Gustilo system classifies open fractures according to the size and extent of soft tissue damage.[13–15] Type I is an open fracture with a clean wound smaller than 1 cm. Type II is an open fracture with a laceration longer than 1 cm without extensive soft tissue damage, flaps, or avulsions. Type III is an open fracture with extensive soft tissue injury and is further divided into three subtypes: Type IIIA has adequate soft tissue coverage of a fractured bone despite extensive laceration of soft tissue, type IIIB involves extensive soft tissue injury with periosteal stripping that requires grafting or a flap for coverage, and type IIIC is an open fracture associated with arterial injury that requires repair. The risk of infection is related to the severity of the injury: 2% in type I open fractures, 2% to 10% in type II open fractures, and up to 50% in type III open fractures.[15] Wounds should initially be dressed with sterile gauze soaked with antiseptic. Hemorrhage should be controlled by direct pressure. Patients should receive tetanus prophylaxis and antibiotics at recognition of the injury. First-generation cephalosporins cover the gram-positive organisms found in type I and type II injuries. An aminoglycoside is added for type III injuries, and ampicillin or penicillin is added for farm injuries or other massively contaminated wounds to fight potential anaerobic infection.

Each wound must be adequately debrided and copiously irrigated with the patient under general anesthesia. Current evidence suggests that this should be accomplished as soon as the patient is stable, and within 24 hours after injury if possible.[16] Wounds may need to be re-evaluated after 2 or more days for additional debridement. Primary closure or delayed primary closure may be appropriate for some open fractures, whereas grafting or flap coverage is needed for larger soft tissue defects. The goal of debridement is removal of devitalized tissue to avoid the catastrophic consequences of an infection, which may include limb loss or chronic osteomyelitis. Adequate immobilization is necessary for soft tissue healing. For small lacerations, immobilization in a cast that has been windowed for wound inspection may suffice. For larger lacerations, external or internal fixation is often necessary to provide stable fixation with access to the wound.

Joint penetration by a foreign body can cause a diagnostic dilemma. Radiographs can be helpful if they reveal an "air arthrogram." Injection of sterile normal saline into the joint, or saline load test, can also be diagnostic.[17] If the saline load test results in the liquid exiting the wound or laceration, joint penetration has occurred and requires irrigation and debridement in the operating room.

## COMPARTMENT SYNDROME

Compartment syndrome occurs when pressure is elevated within a confined fascial space. This causes circulatory compromise and can progress to tissue necrosis. Closed fractures and crush injuries with associated edema may cause compartment syndrome. Forearm and leg compartments are most often involved. Ischemic injury starts when tissue pressure is 30 mm Hg less than mean arterial pressure.[18–19] The pressure within the compartments surrounding a fracture should be measured if compartment syndrome is suspected. Commercially available tissue pressure monitors or other measuring devices, including electronic arterial pressure monitoring devices, can be used.

The diagnosis of compartment syndrome in children can be difficult. Adults with compartment syndrome verbalize extreme pain and demonstrate pain with passive stretch of the muscles within the affected compartments, whereas children often have difficulty communicating their discomfort. The classical signs of compartment syndrome are the five Ps: pain, pallor, paresthesia, paralysis, and pulselessness. These signs are rather unreliable in children and may manifest late in the process. An increasing analgesia requirement is an important sign of compartment syndrome in children.[20]

With early recognition and timely management, full recovery can be achieved. All external compression is removed from the limb, compartment pressures are measured, and, if elevated, the compartments are surgically decompressed. In the forearm, volar and dorsal fasciotomies are required.[19] In the leg, all four compartments (anterior, lateral, deep posterior, and superficial posterior) must be released. This can be accomplished with either a one- or two-incision technique.[18] Without prompt intervention, the result is irreversible damage to soft tissues with loss of function, subsequent contractures, and deformity.[18–19]

## FEMORAL NECK FRACTURE

Although rare in children, fractures of the femoral neck and intertrochanteric region require attention (Fig. 22-10). These fractures frequently result from high-energy impact, including traffic accidents and falls from a height, and are associated with a high complication rate from avascular necrosis, coxa vara, nonunion, delayed union, and premature physeal closure.[21] The upper end of the femur lies within the joint capsule. After roughly 4 years of age, blood is supplied primarily by retinacular vessels that course from distal in the neck to proximal in the head. Delay in treatment of a fracture at the

**FIGURE 22-10** Anteroposterior pelvis radiograph of a 14-year-old boy shows a displaced left femoral neck fracture that required internal fixation.

neck is associated with increased risk of avascular necrosis of the head and destruction of the joint and can cause lifelong disability. Early decompression of the hip joint, reduction of the fracture, and internal fixation may minimize the complications.[21]

## MANGLED EXTREMITIES

Severely traumatized or mangled extremities in children must be assessed and treated through a multidisciplinary approach on a case-by-case basis. They may involve extensive injury to or segmental loss of skin, muscle, bone, and neurovascular structures. Some limbs may be unsalvageable owing to extensive damage, some can be reconstructed with a resulting dysfunctional limb, and others can be salvaged with a good outcome. The Mangled Extremity Severity Score rates injuries based on objective criteria at initial presentation, including skeletal and soft tissue injury, limb ischemia, shock, and patient age. Although originally developed in a primarily adult population,[22] it can be a useful adjunct to managing lower extremity trauma in children.[23]

Segmental bone loss is rare in children and does not necessitate amputation. If periosteum can be preserved, the potential to reform bone is extensive. Proper techniques of debridement and stabilization, along with adequate time for healing, may produce good results in children. External fixation techniques can allow for bone transport and osteogenesis to replace lost bone and axial deformity.

Power lawn mower injuries are uncommon, preventable injuries that cause significant morbidity in children.[24–26] Direct contact with the blade leads to laceration of tissue, amputation, or devitalizing shredding of the extremity. Such injury can result in damage to the vasculature and growth plate, joint stiffness, infection, or amputation. If salvage is undertaken, treatment follows that of open fractures.

In the case of amputation, preservation of bony length and retention of all viable soft tissue are important for the ultimate functional outcome. Amputation through the diaphysis of a child's bone frequently results in overgrowth of the bony stump through


**FIGURE 22-11** A pediatric backboard should have a torso mattress or an occiput recess to accommodate the child's relatively large head and avoid potentially dangerous cervical spine flexion.

the skin. This is especially true of the fibula, tibia, and humerus and can necessitate cutting back the bone every few years.

## SPINE TRAUMA

Injuries of the spine in children can be divided into those affecting the cervical spine and those in the thoracic and lumbar spine. Just as in other parts of the body, patterns of injury to the spine in children differ from those in adults. Radiographic imaging can be challenging. Principles of immobilization are different for children as well.

Cervical spine injuries in children differ from those in adults.[27–28] Children have greater ligamentous laxity and weaker neck musculature. In addition, they have large heads relative to body size; this effect is more pronounced in younger children. Cervical spine injuries in children tend to occur higher in the neck and can be primarily ligamentous or apophyseal without bony fracture.[29] When immobilizing a child on a backboard, the relatively large head should be considered; a child's backboard splint should have a recess for the occiput or a mattress for the torso to maintain the alignment of the cervical spine, avoiding flexion of the neck (Fig. 22-11).[30]

Radiographic evaluation of the pediatric cervical spine can be challenging. Pseudosubluxation, or the apparent forward displacement of C2 on C3 and, less commonly, C3 on C4, is a well-described plain radiographic finding in normal children younger than 8 years.[27,31] Other sources of difficulty in interpreting radiographs include incomplete ossification, epiphyseal variation, and elasticity of the disks and vertebral bodies relative to the neural structures, which allows extensive injury to the soft tissues without evidence of abnormality on plain radiographs or SCIWORA (spinal cord injury without radiographic abnormality). MRI is helpful in evaluating soft tissues in cases of possible cervical spine ligamentous injury in children.[27,32]

Injuries to the thoracic and lumbar spine are rare in children. The growth of vertebral bodies occurs through the apophyses or growth centers on the cranial and caudal ends of the bodies. With compression injury, adolescents are at risk for traumatic displacement of the vertebral apophysis and the attached disk into the spinal canal, especially in the lumbar region.[33] Symptoms are similar to those seen in central disk herniation, including muscle weakness and absent reflexes. This injury requires recognition and emergent surgical decompression.

Lap-belt injuries are flexion-distraction injuries that typically occur in the thoracolumbar region when children violently flex over the seat belt.[28,34] A fracture propagates from the posterior portions of the vertebra to the disks or vertebral body in the front (Fig. 22-12). In addition to the vertebral injury, children can sustain serious abdominal and aortic injuries, and these should be suspected when an abdominal contusion, or the telltale seat-belt sign, is evident in a trauma patient. Lap-belt injuries frequently require immobilization and possible internal fixation.[28]

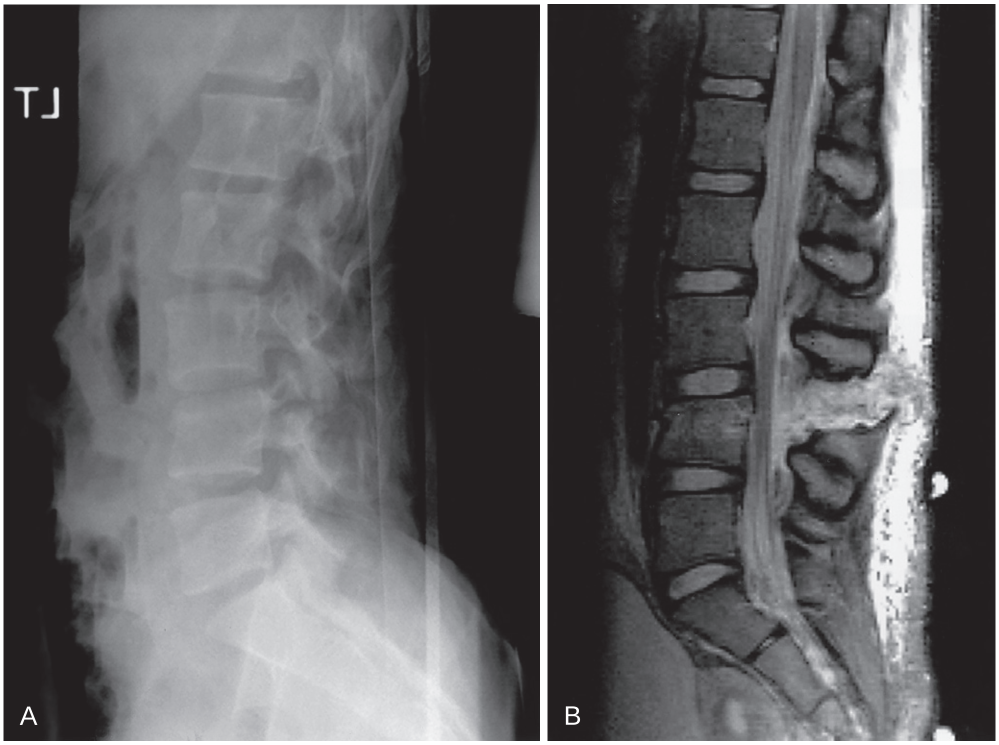


FIGURE 22-12 Lap-belt injury of L4 in a 15-year-old girl without neurologic injury. **A,** Lateral lumbar spine radiograph shows fracture of both the L4 body and the posterior spine. **B,** Sagittal magnetic resonance image of the lumbar spine shows the extensive bony and soft tissue injury.

## CHILD ABUSE

The maltreatment of children is a complex medical and social problem, and its recognition is key to management. Fractures before walking age in the absence of metabolic disease or child abuse are rare. Fractures are the second most common manifestation of child abuse after skin lesions.[35] Suspicion of abuse must be raised when there is a discrepancy between history and injury, when multiple fractures are present in different stages of healing, or when bruising, metaphyseal fractures, or long bone fractures appear in children younger than 1 year.[35]

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 23

# Hand, Soft Tissue, and Envenomation Injuries

Daniel B. Schmid and Michael L. Bentz

Evaluation of pediatric hand and soft tissue injuries requires a systematic approach that includes all relevant organ systems at the site of trauma.[1,2] A high index of suspicion is necessary to make an accurate diagnosis and exclude subtle problems, particularly in toddlers and infants who are unable to cooperate with a detailed examination. Injuries undergo triage according to their threat to life. After triage has taken place, the more peripheral and often more dramatic and distracting injuries can be better defined.[2] The history is important to define baseline function, previous injuries, right- or left-hand dominance, and the mechanism and timing of injury. The initial physical examination must define vascularity and perfusion because an ischemic or poorly perfused extremity necessitates emergent surgical intervention. Other findings can be handled in a less urgent fashion after an orderly assessment is complete. The patient should be examined in a well-lighted area with the parents present to exert a calming influence over a frightened child and thus increase the reliability of findings. This chapter focuses on the acute evaluation and management of hand, soft tissue, and envenomation injuries to provide a foundation for the accurate triage of injured children.[3,4]

## Hand and Soft Tissue Injuries

### EVALUATION

#### Vascularity

The goal of the initial examination is to determine the presence or extent of vascular injury, hypoperfusion, or ischemia. Symptoms of ischemia include pallor, paresthesia, paralysis, pain, and lack of pulse. The digits should be pink and warm if the patient has not had hypothermic exposure or proximal tourniquet application. Normal capillary refill time is 3 seconds and is most accurately tested by compressing the lateral aspect of the distal phalanx adjacent to the nail plate. A delayed refill time indicates impaired arterial inflow, whereas a rapid refill time suggests venous hypertension or insufficiency. The pulse should be palpated bilaterally at the radial, ulnar, and brachial arteries. Percutaneous Doppler ultrasonography can be used to qualitatively and quantitatively define inflow if the pulse cannot be detected or if it is asymmetric. An Allen test is important to define the relative contributions of the radial and ulnar arteries to the palmar arches of the hand. The ulnar artery is the dominant source of inflow to the hand and continues into a patent palmar arch in 85% of uninjured hands.[5,6] Significant bleeding noted during the initial evaluation is managed by firm manual compression or, if the time until definitive intervention is expected to be prolonged, by proximal tourniquet application. A hemostat or clamp should not be placed blindly into the wound because lack of blood flow may injure adjacent neural structures. Impaled or retained foreign objects should be left in situ until definitive management is possible because they may staunch the flow of blood from a vascular injury.

#### Peripheral Nerves

Peripheral nerves should be evaluated after vascular inflow has been assessed. Isolated nerve injuries cause predictable neurologic deficits that manifest as abnormalities in sensation or motor function depending on the location of injury.[7,8] Vascular injuries can also cause neurologic deficits, particularly in subacute wounds; therefore the evaluation of nerve and vascular injuries should generally occur in tandem. A clear concept of cross-sectional anatomy is helpful in visualizing potential at-risk structures.[8] Sensory examination requires a child to cooperate, but even in a young child anhidrosis (loss of sweating function) can be seen and indicates underlying nerve damage.[9,10] In the cooperative patient, evaluating the nerve function at the distal aspect of the hand can be used to screen for a more proximal nerve injury.

The median nerve is responsible for sensation to the three and one-half volar radial digits. The function of this nerve can be tested by a pinprick or, more objectively, by two-point tactile discrimination. Median nerve motor function can be tested by palpating the contraction of the abductor pollicis brevis and opponens pollicis muscles as the patient forms an "O" with the index finger and thumb (Fig. 23-1). The ulnar nerve supplies sensation to the one and one-half ulnar digits. Motor function of this nerve is most accurately tested by palpating the contraction against the force of the first dorsal interosseous muscle while the fingers are spread (Fig. 23-2). There is no radial nerve motor innervation of the intrinsic hand muscles,

FIGURE 23-1 The ability to form an "O" with the index finger and thumb, with palpable contraction of the thenar muscles, indicates an intact median nerve.

FIGURE 23-2 Digit spread with palpable contraction of the first dorsal interosseous muscle is consistent with an intact ulnar nerve.

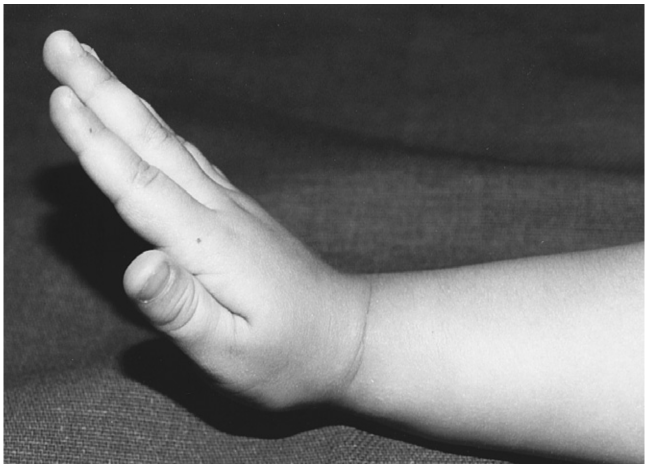

FIGURE 23-3 Digit and wrist extension demonstrates radial nerve integrity because no muscles in the hand are innervated by radial nerves.

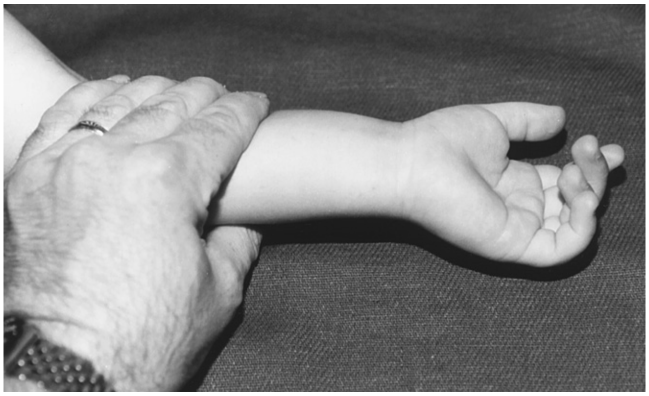

FIGURE 23-4 Forearm compression has failed to cause flexion of the index finger in this patient; this suggests flexor mechanism discontinuity to the index finger.

so the motor function of the radial nerve is best screened by wrist and digit extension (Fig. 23-3). The radial nerves provide sensation to the three and one-half dorsal radial digits of the hand to the level of the distal phalanges, although overlap is common. Serial examination can be helpful, and cooperation and a focused effort are essential for a reliable evaluation. Further, neurologic findings associated with compartment syndrome evolve over time and may not be obvious during the initial examination.[11,12]

## Skeleton, Tendons, and Ligaments

Although some skeletal injuries are obvious on routine examination, most require radiographic evaluation. Physical examination findings of fracture include deformity, crepitus, ecchymosis, pain, instability, and swelling. Anteroposterior, lateral, and oblique radiographs should be obtained for all but the most minor injuries to evaluate for fractures, dislocations, and foreign objects. Familiarity with the Salter-Harris classification of pediatric fractures is important because the specific fracture patterns offer prognostic information relevant to subsequent growth (see Chapter 22).[13,14] The presentation of fractures has been well documented.[15–19] Examination and radiographic appearance are combined to describe the fracture accurately. Open fractures have an associated full-thickness soft tissue injury, whereas closed fractures do not. Simple fractures result in two bone fragments, whereas comminuted fractures involve several fragments. Greenstick fractures involve one cortex and are particularly relevant in children because of their malleable bones. The description of a fracture should also include information regarding length (shortened, elongated, normal), angulation (volar, dorsal, radial, ulnar), rotation (present or absent), and displacement as a percentage of normal alignment.

Tendon injuries can be difficult to diagnose, particularly in young or uncooperative children. In such cases, surgical exploration is necessary to definitely confirm certain injuries. The posture of the hand at rest gives information regarding tendon integrity. In a relaxed position, the hand should form a gentle cascade; this position results from passive tension of the tendons. With compression of the distal forearm, all digits should adopt flexion posturing as a result of the tenodesis effect. A digit that remains extended out of the cascade suggests disruption of the flexor mechanism (Fig. 23-4). The flexor digitorum superficialis tendon to each of the four fingers is tested by holding the adjacent digits in a fixed position and

**FIGURE 23-5** Function of the flexor digitorum superficialis tendon is tested by demonstrating isolated metacarpophalangeal and proximal interphalangeal joint flexion. Flexor digitorum profundus tendon function is tested by holding the middle phalanx fixed and observing distal interphalangeal joint flexion.

allowing metacarpophalangeal joint flexion (Fig. 23-5). The flexor digitorum profundus and flexor pollicis longus tendons are evaluated by holding the middle phalanx and observing distal interphalangeal joint flexion.

Ligament injuries can be difficult to diagnose, particularly in the presence of associated soft tissue or skeletal injuries.[20] Abnormal joint stability is an indicator of disruption of the ligaments.[15] If the opposite side is uninjured, joint stability should be compared with that side as an indicator of preinjury status. Plain and stress radiographs of an avulsion fracture at the site of ligament insertion can confirm clinical findings.

### Soft Tissue

A thorough determination of soft tissue injuries is important for a knowledgeable evaluation of wound healing, but even more so for the evaluation of long-term function and outcome of primary or secondary reconstructive surgery.[21] The amount of soft tissue present in the area of a wound determines the feasibility of primary repair of vascular, neural, and osteoligamentous injuries, and an adequate amount is required for proper healing. The size (measured objectively), shape, location, and general configuration of each wound is recorded, and the mechanism of injury and preinjury status of the patient is established. Obvious foreign objects are removed, although projectiles impaled through an extremity are left in situ until they can be managed definitively. Exposed vital structures as well as associated fractures and tendon injuries are noted.

## EARLY TREATMENT

### Vascular Structures

Ischemia is one of the few surgical emergencies associated with upper limb trauma. Revascularization is a top priority after the correction of life-threatening injuries. Because irreversible changes start to occur after 4 hours of ischemia, expeditious surgical intervention is mandatory, especially if the ischemic tissue involves muscle. Primary vascular repair is the most effective procedure and is ideally accomplished by debridement, mobilization, and primary anastomosis of injured segments. Reversed vein grafts, which are frequently performed with foot, forearm, saphenous, or cephalic veins, should be used liberally if tension or lack of tissue prevents easy approximation of adjacent segments. In general, all arteries and veins proximal to the elbow should be repaired. Repair of arterial injuries below the elbow should also be considered to prevent cold intolerance; however, only about half of these repairs remain patent.[22,23] If necessary, the radial artery can be ligated primarily. Once repairs are complete, fasciotomy should be considered if ischemia has been prolonged, soft tissue damage is significant, or adequate postoperative monitoring is not available.[11] Serial examination should then be pursued in an effort to make an early diagnosis of recurrent ischemia or postsurgical thrombosis or bleeding. The role of anticoagulation therapy in this setting is controversial and is based on the surgeon's preference and experience.

### Peripheral Nerves

Injury to the peripheral nerves is not an emergency and can frequently be addressed when an adjacent vascular injury is being repaired. When a wound is clean, uninfected, and well vascularized, primary nerves should be repaired in an end-to-end fashion. Such repair can be facilitated through the mobilization of proximal and distal injured segments, which can reduce tension and augment blood flow. If mobilization of the injured segments cannot adequately repair the defect, interpositional nerve grafts, nerve conduits, or vein grafts can be used for definitive reconstruction.[8,24] In such cases, early secondary repair in the first 10 days after injury is optimal. To ensure that the injured area remains intact, the involved limb should be splinted to minimize further proximal migration of the transected nerve before surgery and to relieve anastomotic tension.

### Skeleton, Tendons, and Ligaments

When injuries to the skeleton, tendons, or ligaments are diagnosed, restoration of normal or acceptable anatomy followed by appropriate immobilization is indicated. In children, an injury that is suspected but not objectively defined is particularly common. Hand fractures may not be evident on radiographs for several weeks. In this situation, presumptive treatment should be carried out, which usually involves immobilization of the potentially injured area despite equivocal physical examination or radiographic findings. Immobilization is rarely contraindicated in children because it allows protection from further injury, improves pain control, and maintains local anatomy. Use of a splint (instead of a cast) is ideal because it allows swelling into a nonfixed space and limits the possibility of vascular compromise during the acute injury and postreduction periods.

Anatomic reduction of fractures and dislocations can be done at the time of injury or in the following week with good functional results.[25] In the acute setting, excellent anesthesia can be obtained by performing a hematoma block. This is accomplished by injecting 2 to 3 mL of lidocaine 1% without epinephrine into the fracture site. Reduction in the subacute setting most commonly requires a traditional digital block. It must be kept in mind, particularly in smaller children, that the limiting dose of plain lidocaine is 4 mg/kg of body weight. A description of the reduction maneuvers for specific types of fractures is beyond the scope of this chapter, but in general gentle manual traction or finger-trap distraction with

simultaneous rotation or derotation allows improvement in many types of fractures and dislocations. Postreduction radiographs should be obtained in most if not all patients before or after immobilization. The specific position of immobilization is less critical for children than for adults because children are less prone to stiffening and tightening of the ligaments. The "position of safety" can always be used at least initially for splinting: the wrist is placed in 30 to 45 degrees of extension, the metacarpophalangeal joints are placed in 70 degrees of flexion, and the interphalangeal joints are left straight. Serial physical and radiographic examinations are tailored to the specific injury and clinical course.

### Soft Tissue

After soft tissue and associated vital structure injuries are documented, irrigation of all significant wounds should be performed with normal saline solution, after which foreign objects are removed and tissue that is clearly devitalized is debrided.[26] These procedures may require a local anesthetic, which should be given only after a thorough neurologic examination has been completed. Simple lacerations and small surface area avulsions can be closed primarily using the same layered closure method used for deep or gaping wounds under tension. Suture choice depends on the location, size, and cause of the wound, as well as the patient's age. A smaller child who requires sedation for the primary wound repair will be hypersensitive to suture removal, when sedation is usually not available. In such cases, absorbable sutures reinforced with adhesive strips (Steri-strips) are ideal. Permanent sutures should be used in older or cooperative patients to minimize the inflammatory response and avoid early scarring. The potential for scarring depends on the location of the wound and the mechanism of injury. Scarring can be minimized through judicious wound closure.

Open wounds that cannot be closed primarily require more elaborate intervention. To bridge the gap between injury and wound closure, the wound must be managed and protected. Normal saline wet-to-wet dressings are a simple and effective way to provide limited debridement, allow the initiation of granulation, and prevent desiccation. Povidone-iodine dressings should be reserved for short-term use in infected wounds. Acetic acid solution (0.25%) is appropriate for wounds that have culture documentation of infection with *Pseudomonas* species. Subatmospheric pressure dressings are effective as temporary cover of a contaminated or extensive wound, as a bridge to more extensive soft tissue reconstruction, or for definitive closure of extremity wounds in the pediatric population.[27–29] Quantitative wound biopsies should be reserved for nonthermal burns.

If the skin defect is partial thickness only and no vital structures are exposed, split-thickness skin grafting or skin distraction is appropriate. Split-thickness skin grafts are used for larger wounds, less cosmetically significant wounds, or those in which the wound bed may not be optimal because of infection, inflammation, or ischemia. Full-thickness skin grafts contract less after revascularization and thus are ideal for cosmetically significant areas or where wound contraction is undesirable. Local skin flaps can also be used in such settings, offering a cosmetically favorable replacement of like tissue. These skin flaps can be random if they have no specific blood supply or axial if the blood is supplied by a specific vessel.[30] Regional muscle flaps can be used almost anywhere in the body, especially when highly vascularized tissue of significant bulk is required to cover exposed critical structures and fill dead space. Similar to axial pattern skin flaps, these muscle flaps are used on the basis of a known blood supply, which makes their dissection reliable and safe. Finally, when local tissue is not available or is inadequate to provide wound closure, microvascular free tissue transfer is indicated using specific donor "free flaps" to accomplish specific tasks.[31]

### Amputations

Traumatic amputations in children should be considered for replantation by a qualified microsurgical team, given the excellent results obtained when compared with adult series.[32–34] To optimize the chance of success, the amputated part should be wrapped in saline-moistened gauze, sealed in a plastic bag, and placed in a bag of ice and saline solution; the part must not contact the ice directly.

# Envenomation Injuries

## SNAKEBITES

More than 2700 species of snakes exist; 115 of these species are indigenous to the United States, and only 19 of the 115 species are poisonous.[35] In the United States approximately 8000 bites occur annually from poisonous snakes, half of which occur in children.[36,37] Pit vipers, which are named for the pit located between their eyes and nostrils, account for most bites. Pit vipers include rattlesnakes, copperheads, and cottonmouths (family Viperidae, subfamily Crotalinae).[38] Coral snakes (family Elapidae) represent the other poisonous family. Most bites occur during the summer months in the morning, late afternoon, or evening. Not all bites are associated with envenomation. Signs of envenomation include pain, edema, local tissue necrosis ecchymosis, nausea, vomiting, hypotension, disseminated intravascular coagulopathy, hemolysis, mental status changes, seizures, and death.[39] The severity of signs is proportional to the degree of envenomation. Early intervention includes reassurance and support, immobilization, limb elevation, venous tourniquet application, and rapid transfer to the nearest medical facility. Cryotherapy and wound incision and suction are no longer recommended because of potential damage to vital structures.[40–42] Tetanus immune globulin and toxoid should be given to patients who have had two or fewer immunizations.

The antivenin Fab AV is sheep immunoglobulin immunized with antigen from four snakes—three variety of rattlesnakes and a cottonmouth or water moccasin—that has been shown to be effective after envenomation by all North American rattlesnakes and was found to be safe in children in a small study of 12 subjects.[43–45] Antivenin is administered intravenously only after a skin test has been done to rule out the possibility of an anaphylactic reaction. Four to six vials (4-6 g) of Fab AV is given immediately, with redosing in 1 hour if the patient does not respond.[45] Initial dosing should be followed by aggressive intravenous hydration and close monitoring. A review of 93 patients receiving Fab AV noted immediate allergic reaction in approximately 5% of cases.[46] Because envenomation injuries and the use of antivenom require close monitoring, antivenom administration should not be delayed for skin testing.[47] Fasciotomy should be considered but is seldom required.[48] A review of 227 patients with rattlesnake bites of whom 211 were treated with antivenom showed favorable outcomes in nearly all

patients.[47] After initial treatment and baseline testing, patients should be closely observed for at least 12 hours in cases of crotalid envenomation and 24 hours for coral snake bites because of possible delayed-onset neurotoxicity.[49]

## OTHER BITE INJURIES

Gila monsters, which are found in the southwestern United States, and their relative the Mexican beaded lizard are active in late spring. These lizards inject venom as long as they cling to the victim. Wounds show edema, but tissue loss is less pronounced than that associated with envenomation by pit vipers; however, systemic signs can ultimately be similar. These injuries are managed by removing the animal from its victim, followed by local and systemic supportive care. Antivenin is not available. Radiographs should be obtained to exclude retained teeth.[50–52]

Black widow spiders are venomous New World spiders; the females are black with an hourglass-shaped red mark on the abdomen.[53–55] Local signs of a bite can be limited and are followed by systemic neuromuscular symptoms of diffuse rigidity and spasm that potentially lead to respiratory arrest approximately 1 hour later. Envenomations by black widow spiders are managed by local care, fluid and cardiovascular support, parenteral calcium gluconate, muscle relaxation, and antivenin.[3,51,55–58]

Scorpion stings in children have serious sequelae. Bark scorpions are the only toxic species in the United States; however, others are common in Mexico and equatorial countries. Local signs of envenomation are minimal, whereas systemic neuromuscular findings are present in the sympathetic and parasympathetic systems. Children are particularly susceptible to the severe cardiorespiratory and neuromuscular dysfunction associated with envenomation. Therapy of scorpion stings includes local wound care, topical ice, specific antivenin, and systemic support, including ventilation, control of tachyarrhythmias, and sedation. Treatment is similar to that for spider bites, although scorpion stings are generally less serious.[55,57,59–61]

Finally, human bite wounds can pose some of the most challenging definitive management problems among all bite-induced injuries.[62,63] Based on the quantitative and qualitative characteristics of oral flora, including the principal pathogen *Eikenella corrodens*, aggressive primary intervention is mandatory to achieve a satisfactory outcome in all these injuries. Thorough irrigation of penetrating bite wounds is mandatory as is broad-spectrum antibiotic coverage followed by frequent wound checks.[64]

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 24

# Central Nervous System Injuries

Andrew Jea and Thomas G. Luerssen

Injuries to the brain and spinal cord continue to be major contributors to mortality and morbidity from childhood trauma. Despite over 25 years of intensive clinical research, there is still not a specific medical therapy for traumatic neurologic injury. Nevertheless, there has been a steady and substantial advance in our understanding of the natural history of brain and spinal cord injuries, and accompanying changes in management that continue to be refined and have clearly resulted in improved outcomes.

We are now well into the era of evidence-based medicine, whereby recommendations for disease and injury management are supposed to be derived from critical analysis of scientific research. In the last decade, the management strategies for central nervous system (CNS) injuries have been subjected to this type of analysis, resulting in the publication and continuous updating of practice management guidelines.[1–4] The analysis of the clinical evidence and the development of these recommendations represented a substantial amount of work by many leading experts in the field. Unfortunately, these reviews also uncovered a remarkable lack of strong scientific evidence upon which to develop recommendations, especially in the pediatric age group, so that most of the available recommendations regarding the diagnosis and treatment of neurologic injuries can only be supported by the lowest degree of medical certainty. Nevertheless, these published practice parameters are useful summaries of the current understanding of the various treatments for brain and spinal cord injuries.

Even in the face of limited evidence, we are also learning that "quality improvement" strategies are beneficial in the management of injury. These strategies allow multidisciplinary agreement and reproducible diagnostic and treatment processes that have specific outcomes that can be measured and continuously improved. Thus although there may be variation between centers, approaches within a single center can be uniform and workable for that institution.

## Basic Strategy of the Therapy of Central Nervous System Injury

One of the most enduring concepts underlying the management of brain and spinal cord injury is that of primary and secondary injury.[5] The primary neurologic injury involves the immediate disruption of neuronal, axonal, supportive structures, and vascular tissues. The magnitude and location of the primary injury along with the variety of irreversible cellular processes that immediately ensue, which has been referred to as the delayed primary injury, are directly related to the mechanism of the injury. These immediate tissue disruptions are also considered to be self limited and are, by definition, essentially untreatable. Given all of this, one can easily see that the primary brain injury is still the major determinant of injury outcome.

The primary injury triggers a cascade of intracellular and extracellular biochemical changes, both in the region of the injury and systemically, many of which are deleterious and cause acceleration and augmentation of the initial injury. These reactive processes represent the onset of what has been termed the secondary injury. These secondary reactive processes can begin at almost any time after the injury and can persist for some time. The secondary injury results not only in new damage both in the region of the primary injury, but also in areas of previously uninjured brain or spinal cord. It can also cause deleterious effects in other organs and body systems.

Systemic reactions commonly seen after brain or spinal cord injury include alterations in blood pressure and respiration, usually manifested by hypotension and hypoxia. It has been clearly shown that even brief and mild episodes of either hypoxia or hypotension can have profoundly deleterious effects on the outcome of both brain and spinal cord injury.[6–8] Although it is well known that spinal cord–injured patients can be rendered hypotensive by an isolated injury, it is now also clear that isolated brain injury can cause systemic hypotension. Multiple injuries, occult organ injuries, or other causes of exsanguination that result in hypovolemia are not required for this hypotensive response to occur. Of the early systemic complications, it appears that hypotension is much more deleterious to the acutely injured brain than is hypoxia. This is probably also true for the acutely injured spinal cord. Finally, it is clear that these complications can occur very early, frequently, and, in many cases, so briefly that they can go undetected.[9,10]

There are also other common systemic responses, many of which occur shortly after an injury but can also cause further injury even days after the institution of therapy. Hyperthermia, either from fever or as the result of overly aggressive warming, is harmful to the injured brain.[11] Hyperglycemia, which is commonly seen in the stress response and which can be aggravated by fluid administration or attempted nutrition, is also thought to be deleterious to the acutely injured neurons.[12–14]

Tissue disruptions, commonly referred to as cerebral or spinal cord contusions, cause reactive changes in the tissues immediately surrounding the area of injury. A variety of tissue factors, such as those in the kallikrein-kinin system, are released, and these factors can cause disturbances of microcirculation and the blood–brain or blood–spinal cord barrier, which ultimately results in the complex entity that has been generally referred to as post-traumatic edema.[15] There are hypermetabolic responses related to neural-tissue injury that may outstrip the local or regional substrate supply.[16] Excitotoxic amino acids, such as glutamate and aspartate, are released from injured neurons.[17] Post-traumatic seizures, especially prolonged subclinical seizures, may contribute to this response in the injured brain.[18] Along with the reactive biochemical changes, expanding local hemorrhages can cause further compression of adjacent vessels and tissues, resulting in an ischemic penumbra around the acute injury.

Although the systemic and biochemical processes of the secondary injury are complex, it appears that the pathophysiologic end point of all of them is ischemic damage. Ischemic neuronal damage is almost universally seen in the neuropathologic examinations of patients who have suffered traumatic brain and spinal cord injuries.[19,20]

Even though numerous biochemical cascades have been identified and physiologically characterized, and many have been the targets of pharmaceutical intervention, no drug has yet been shown to be specifically effective for CNS injury treatment. Trials of high-dose steroids, calcium channel blockers, free radical scavengers, and glutamate antagonists have been generally negative, although small and specific subgroups of patients were identified in post hoc analyses, which may have benefited from one or another of these therapies. More concerning is that some groups of patients were apparently harmed by the administration of some of these agents.[21] Despite this lack of development of a specific therapy, there has been steady improvement in neurologic outcomes, more so in the arena of brain injury than in spinal cord injury. This trend in improved outcome is almost certainly because of the realization that many of the ischemic processes can be prevented by aggressively applying various systemic manipulations, beginning with the resuscitation phase of the injury and continuing through the acute therapy period.

The essential therapeutic strategies for brain and spinal cord injury are based on preventing ischemic injury by the aggressive support of intravascular volume and blood pressure at all times. The historical idea of restricting fluids to head-injured patients is no longer accepted or acceptable management. The early use of vasopressors for both brain and spinal cord injury is appropriate. Reduction of focal vascular compression by removing mass lesions and aggressively preventing and managing reactive brain or cord swelling to protect perfusion are beneficial. These three relatively simplistic concepts—support of systemic blood pressure, reduction of intracranial pressure to assure cerebral perfusion, and removal of compressive lesions and the prevention of deleterious complications—are still the mainstay of management for brain and spinal cord injuries.

# Immediate Issues: Resuscitation and Transport of Injured Children

Effective, supportive, and preventative therapy should begin as quickly after the injury as possible. Goals of the initial resuscitation are twofold: to prevent as much secondary injury as possible and any new primary injury prior to the undertaking of neurodiagnostic studies. One can accomplish the first goal by assuring oxygenated perfusion of the brain and spinal cord, by restoring and maintaining age-appropriate normal blood pressure, and maintaining normal ventilation. These factors are of primary importance and are more important than the administration of any drug. The exact means of accomplishing this goal—the type of resuscitation fluid or the means of assuring ventilation—is probably less important than accomplishing the goal itself. Most current studies indicate that isotonic or slightly hypertonic saline solutions are appropriate fluids for resuscitating and maintaining blood pressure for neurologically injured patients.[2,22,23]

Tissue oxygenation is important; so, adequate airway support and ventilation are required. Early intubation by experienced personnel and using appropriate analgesia and sedation certainly will accomplish this goal. However, the role of intubation of injured children (and adults) in the field is still controversial. This maneuver is associated with a relatively high complication rate and may not be warranted in many situations.[1,24,25]

For patients with possible spinal injuries, prevention of further injury begins with stabilizing the spine. This maneuver involves much more than applying a collar or securing a child to a rigid board. It is important that the normal anatomic alignment be maintained. Very young children have proportionately larger heads and therefore have a tendency for cervical flexion when lying supine.[26] A cervical collar alone does not completely immobilize a child's injured spine.[27] The spine should be immobilized in anatomic position, with the head in a normal relative position to the body. Young children will require some additional elevation of the body so that the head falls back to a truly neutral position. Once these parameters have been achieved, that is, stabilization of the spine in anatomic position and the establishment of support of systemic blood pressure and respiration, the injured child may be transported for definitive diagnosis and therapy of the injury.

# Traumatic Brain Injury

## EPIDEMIOLOGY

Despite the frequency of head injury in children, epidemiologic data in this area are relatively limited. A study in the United Kingdom indicated that 40% of all patients seen in emergency rooms for the treatment of head injuries were children.[28] It is important, however, to distinguish between

head injury and brain injury when discussing outcomes and therapy, although it is probably equally important to group these entities when discussing mechanisms and prevention. Accordingly, population-based studies indicate an average incidence of clinically important head injury in children at about 185 per 100,000, with the incidence generally dropping with increasing age.[29,30] Boys are injured at a rate approximately twice that of girls.

Overall, 85% of the brain injuries sustained in childhood are mild and non–life threatening.[31,32] On the other hand, well over half of all deaths resulting from blunt trauma in children are caused by a brain injury.[33,34]

The severity and mechanism of brain injury are determinants of outcome. The mechanism of injury also depends on age. The most common mechanism resulting in head injury in children is a fall, but the usual falls of childhood rarely cause severe injury. Inflicted injury is by far the leading cause of severe brain injuries in very young children. In older children, severe brain injury is most commonly seen in relation to motor vehicle accidents.

Many accidental brain injuries that occur in children are preventable. Proper use of occupant restraints in motor vehicles can prevent up to 90% of the serious injuries to young children.[35] The implementation of a mandatory child restraint law in Michigan reduced the number of motor vehicle–related injuries in children by 25%.[36] Wearing helmets for bicycle riding as well as for other recreational activities, such as skateboarding, skating, skiing, and horseback riding, should decrease the risk for brain injury,[37–39] although educational programs regarding helmet use have had only limited success so far.[40] Many falls are preventable. Vigilance regarding open windows and stairways, including the use of gates or bars substantially reduces the occurrence of these injuries.

## SPECTRUM OF TRAUMATIC BRAIN INJURY

There are many ways to undertake an overview of the major types of traumatic brain injuries. The authors have come to prefer one that includes a relationship of injury types, mechanism, and natural history. The simplest way to do this is by categorizing major injury types as either focal or diffuse. Accepting the caveat that many traumatic injuries are mixtures of focal and diffuse injury, one can still undertake individual management strategies based on the initial appearance of the type of brain injury.

### Focal or Diffuse Brain Injury?

Focal injuries include contusions, lacerations, traumatic hematomas, and localized damage resulting from expanding masses, shifts, and distortions of the brain. Diffuse injuries include the spectrum of diffuse axonal injury, which includes what is commonly called cerebral concussion, as well as other diffuse insults, such as global ischemia, systemic hypoxia, diffuse brain swelling, and diffuse vascular injury. Focal injuries are usually immediately apparent on the admitting computed tomography (CT) scans even when they appear to be clinically asymptomatic. In contrast, diffuse injuries may show much less striking changes on early neuroimaging studies, even though the patient may exhibit profound alterations in consciousness and neurologic function. Diffuse injuries may require a series of diagnostic studies to determine the type and magnitude of the injury. They are also more likely to require prolonged monitoring and management of intracranial pressure.

### Focal Brain Injury

Most focal brain injuries are associated with impact-related mechanisms. Because short falls are the most common cause of accidental head injuries in childhood, cranial impacts and resulting focal injuries are also common. Impact mechanisms also result in skull fractures, which are also commonly seen in the pediatric age group. In fact, about 20% of head-injured children who are admitted to the hospital have skull fractures.[41] Despite the frequency of skull fracture in childhood, the majority of children with this injury will not require any treatment. Therefore the clinical importance of most skull fractures is that the fracture serves as an indicator of both the mechanism and the severity of the head injury. Most studies of the importance of skull fractures have determined that finding a skull fracture in a head-injured patient is statistically associated with a higher likelihood of developing an expanding intracranial hematoma or harboring a significant brain injury.[41–45] Furthermore, complex skull fractures, or the occurrence of multiple fractures, are generally associated with higher-energy mechanisms and are therefore associated with more severe injuries to the brain.

As indicated previously, most focal brain injuries are immediately apparent on initial neuroimaging studies and, depending on the size and location, result in focal neurologic dysfunction. The most common focal injury resulting from nonpenetrating mechanisms is a cerebral contusion (Fig. 24-1). These are generally surface lesions related to cranial impacts or brain movement over irregular intracranial surfaces or along the edges of dura. The clinical presentation of cerebral contusions depends mostly upon the extent of the


FIGURE 24-1 A cerebral contusion underlying a linear skull fracture (not demonstrated). This was the result of a cranial impact, as demonstrated by the overlying soft tissue swelling and hemorrhage. The patient had no neurologic deficit.

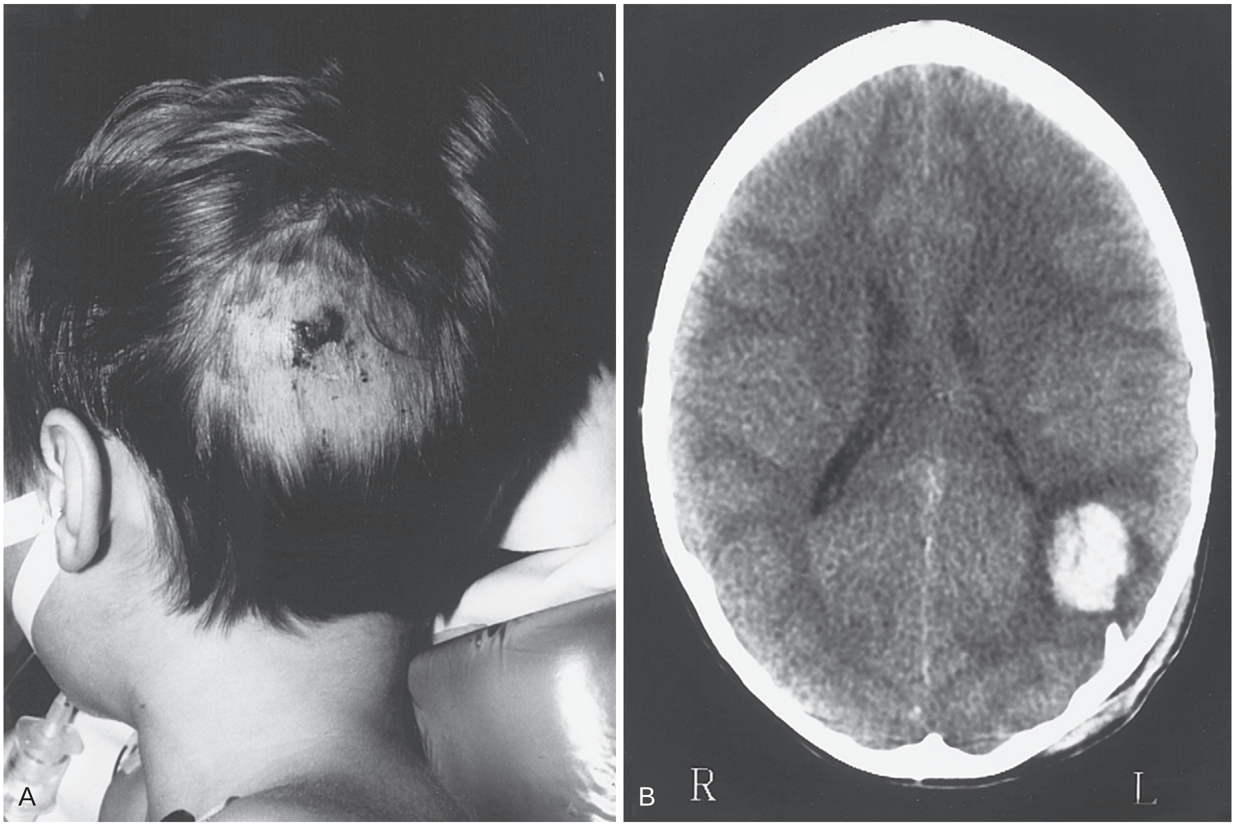


**FIGURE 24-2** The occult injury frequently seen with low-velocity cranial penetration in young children is demonstrated. The patient was struck in the left parietal region by a lawn dart, and loss of consciousness did not occur. The lawn dart fell out immediately. The injury was misinterpreted as a minor scalp laceration and was closed with butterfly bandages. Three days later, fever and headache developed. **A,** Appearance of the entry wound before surgical exploration. **B,** Computed tomography shows a compound fracture and intracerebral hematoma. During surgery, hair, dirt, and bone fragments were removed from the cerebral cortex.

initial injury, the amount of associated hemorrhage resulting in mass effect, and the location of the contusion in the brain. Even though cerebral contusions may develop localized swelling, isolated lesions are not generally life threatening. Many cerebral contusions are neurologically silent and only discovered on the initial CT scan, underlying a skull fracture or along the anterior cranial base. When these injuries are symptomatic, they usually cause focal neurologic deficit or seizures. The latter are thought to occur commonly in adults with acute cerebral contusions.[46] However, the incidence of seizures in children with cerebral contusions appears to be no greater than in children with either normal CT scans or epidural hematomas.[47]

Traumatic intracerebral hematomas are unusual lesions in the pediatric age group. The pathogenesis of these hemorrhages is unclear, but it seems to be related to the disruption of central arterial blood vessels. Accordingly, these lesions are associated with more severe mechanisms of injury and with more profound neurologic dysfunction. In many cases, these lesions are part of a larger picture of diffuse axonal injury that is discussed later. Traumatic intracerebral hematomas are distinguished from hemorrhagic contusions by their lack of contact with the surface of the brain.[48] They can be quite large and, because of the location, can leave a child with a profound neurologic deficit. Surgical evacuation can be considered if intracranial pressures are high, but, in the authors' experience, neurologic outcomes are not improved by the evacuation of these hematomas.

Children are prone to nonmissile penetrating injuries of the skull and brain. These injuries usually occur when a child falls onto or is struck by sharp objects, such as nails, pencils, sharp sticks, or lawn toys (Fig. 24-2). One of the major dangers of these injuries is that, unless the offending object remains embedded, the entry wound may be hidden or seem trivial.[49–51] The anterior penetrations of the skull base can be transorbital (through the orbital roof) or through the nose or mouth.

Penetrating injuries can result in focal contusions, intracerebral hemorrhages, and cerebral lacerations, but these lesions are usually silent because of their locations and small size. The deeper penetrations are more likely to be symptomatic, not only because the tissue injury is more extensive but also because of the potential for injuring major vessels. Many penetrating injuries become symptomatic in delayed fashion because of expansion of intracerebral hemorrhage, the recognition of cerebral spinal fluid (CSF) fistula, or by the appearance of symptoms indicating infection. Therefore a very high index of suspicion is required, and careful radiologic studies are called for whenever there is a possibility of subtle cranial penetration. Wood, glass, and residual bits of debris may be difficult to detect on routine imaging studies, including CT scans.[52]

Cranial penetrating injury is also strongly associated with direct cerebrovascular injury.[53] When there is evidence of deep cranial penetration or if there is substantial subarachnoid hemorrhage or focal intracerebral hemorrhage, one should

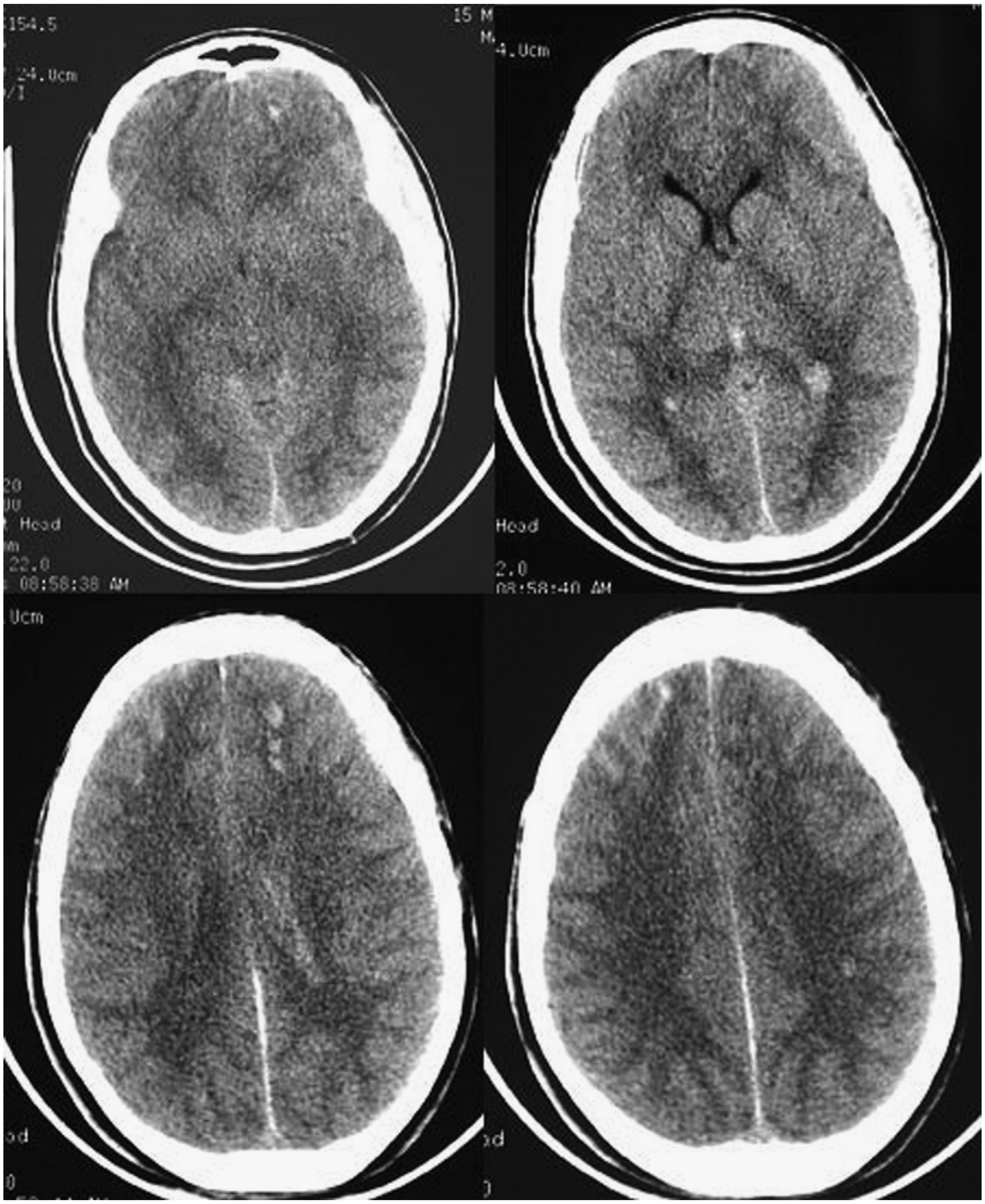

**FIGURE 24-3** The classical appearance of diffuse axonal injury on an admitting computed tomography (CT) scan. This includes subarachnoid and intraventricular hemorrhages, brain swelling, and small petechial hemorrhages throughout the brain.

consider magnetic resonance imaging (MRI) with the addition of magnetic resonance angiography or the increasingly useful modality of CT angiography.

## Diffuse Brain Injuries

The majority of brain injuries occurring in childhood are diffuse injuries that are characterized by general disturbances of neuronal function that begin immediately at the time of injury, while showing general preservation of brain structure on early CT scans. Diffuse injuries are a direct result of energy dissipation within the substance of the brain or as the result of systemic insults. All of these injuries exist on a continuum from extremely mild—and, apparently, completely reversible—to lethal. Frequently, the different types of diffuse brain injury occur together, or in sequence, and can act synergistically to affect the neurologic presentation and the outcome.

Diffuse primary brain injuries are generally the result of angular or translational accelerations (or decelerations), with the amount of tissue disruption being roughly proportional to the amount of energy dissipated in the brain substance.[54] As the amount of neuronal disruption increases, the depth and duration of neurologic dysfunction increases and the neurologic outcome worsens. The appearance of certain hemorrhages on the CT scans (specifically, subarachnoid hemorrhage), small but widespread intracerebral hemorrhages and intraventricular hemorrhage, are a typical finding (Fig. 24-3).[55] Finally, although the occurrence of traumatic surgical masses is not characteristic of the diffuse brain injuries, subdural hematomas occur commonly with

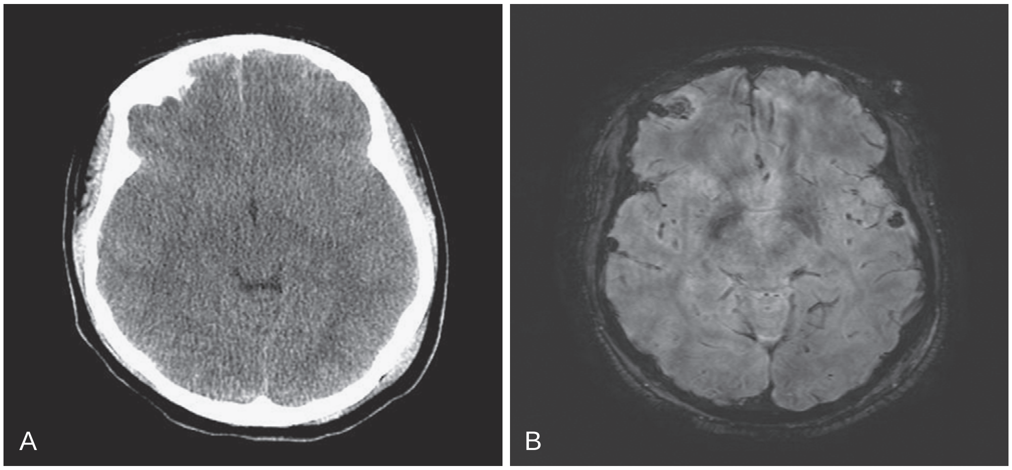


FIGURE 24-4 The importance of imaging in mild traumatic brain injury. Patients with apparently normal consciousness at presentation can suffer widespread cerebral damage when subjected to mechanisms that cause diffuse axonal injury. Cognitive disturbances and neurologic symptoms are common in these patients. **A,** Unenhanced computed tomography scan of conscious patient (GCS 15) showing subarachnoid hemorrhage. **B,** Susceptibility-weighted gradient echo magnetic resonance image (MRI) showing widespread parenchymal hemorrhages characteristic of diffuse axonal injury. (Courtesy Jill Hunter, MD.)

diffuse axonal injury, and some of these hemorrhages need early surgical evacuation. However, subdural hemorrhages are better viewed as another marker of the diffuse brain injury rather than as a mass that should be treated in isolation, such as an epidural hematoma or a hemorrhagic contusion.

Like all brain injuries, diffuse primary brain injuries occur within a spectrum of severity. At one end of the spectrum are the very mild, transient physiologic disturbances of neurologic function (which includes the syndromes commonly referred to as cerebral concussion), while at the other is the progressively more damaging and ultimately lethal entity that is now called diffuse axonal injury (DAI).

The modern view of cerebral concussion is based on the pioneering work of Ommaya and Gennarelli,[56,57] who define concussive brain injuries as a graded set of clinical syndromes with increasing disturbances in the level and content of consciousness. This definition allows specific post-traumatic disturbances commonly seen in children after so-called “mild” head injuries to be included, such as confusion without amnesia, confusion associated with amnesia of varying depths and duration, and the classical loss of consciousness with and without transient sensorimotor paralysis or disturbances of respiration or circulation.

As the amount of energy in the injury mechanism increases, tissue disruption occurs and results in DAI. It is now clear that the most common cause of prolonged coma from mechanical brain injury is DAI. Patients who have suffered DAI are unconscious from the time of injury and remain so for a prolonged period.[58] It is not uncommon to note pupillary changes, skewed gaze, and decerebrate posturing. This constellation of symptoms had historically been called a brainstem contusion in the era prior to MRI. Most comatose patients who appear to show brainstem dysfunction after closed head injury have really suffered DAI.

The appearance of DAI on CT scans depends upon the severity of the injury and the degree of associated hemorrhages. In some cases, the initial CT scan may appear to be normal. Subsequently, the characteristic lesions may be discovered on MRI, varying from some transient signal changes in the deep white structures to widespread hemorrhagic and nonhemorrhagic shears (Fig. 24-4). The characteristic CT scan appearance of DAI is multiple petechial hemorrhages in the deep white matter and central structures. However, the finding of intraventricular hemorrhage or focal subarachnoid hemorrhage specifically located in the prepontine cistern is also strongly suggestive of DAI.

## Gunshot Wounds

Children’s injuries from firearms are a major public health problem. Recent reports indicate that 10% of all childhood-injury deaths are related to firearms, a number exceeded only by deaths from motor vehicle accidents, drowning, and house fires.[59,60] From the standpoint of management and outcomes, there is little to differentiate gunshot injuries in children from those in adults. Poor outcomes are related to depth of coma, bilateral or transventricular injury, elevated intracranial pressure, and large intracerebral hemorrhages.[61] Aggressive treatment of all patients is recommended, except those with clearly nonsurvivable injuries,[62] although substantial neurologic and cognitive deficits can be expected.[63,64]

In childhood, injuries resulting from nonpowder firearms, such as BB and pellet guns, are more common than true gunshot wounds.[60] Adolescent males have the highest risk of this type of injury.[65] These injuries are generally less severe and therefore carry lower mortality rates. Surgical treatment is not usually required for BB gun injuries. Pellet rifle injuries, being higher velocity and larger caliber missile injuries, are more severe and are probably best treated as true gunshot wounds.

## Crush Injuries

Young children are susceptible to the unusual static-loading type crushing injury to the skull, which happens when a heavy object falls on a child or when the child is run over by a vehicle. These injuries are dramatic, both in the clinical presentation and in the radiographic findings (Fig. 24-5), but

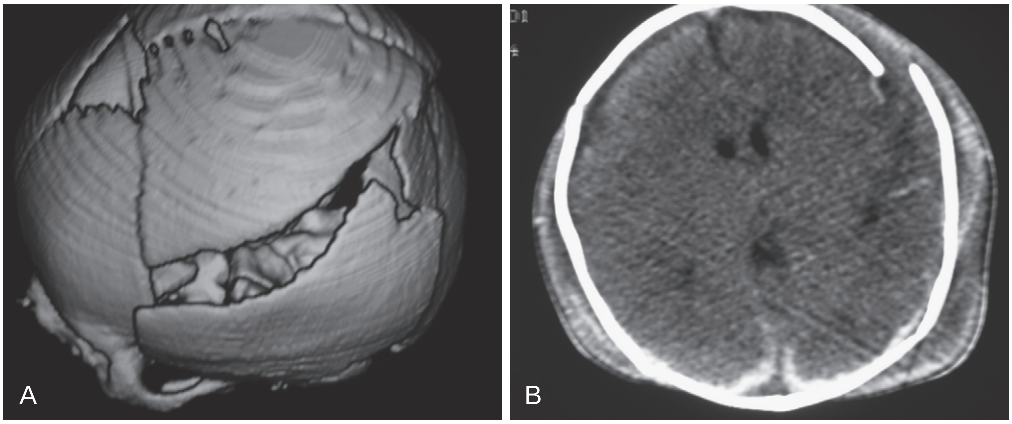


**FIGURE 24-5** A crushing type injury in an infant. **A,** This shows a cranial "burst" injury on CT three-dimensional reconstruction of the skull. **B,** Although there is intracranial hemorrhage and dural laceration, the structure of the brain is preserved and decompressed. The child required dural and cranial reconstruction but recovered with minimal deficits.

the neurologic outcomes can be quite good.[66] Multiple skull fractures, including complex basilar skull fractures and facial fractures, are typical. Cerebrospinal fluid leaks and cranial nerve palsies are commonly seen. However, despite the initial appearances of the injury, major cortical structures are often preserved. Therefore, if the child has survived the initial injury, aggressive multidisciplinary management can yield satisfactory long-term functional outcomes.

### Inflicted Injuries

The most common cause of severe and life-threatening brain injury in infants is inflicted injury. All physicians involved in the care of injured children should be familiar with the clinical presentations and the characteristic radiographic findings of inflicted injuries. This entity has been reviewed in detail.[67,68] Infants presenting with alteration of consciousness (with or without the new onset of seizures), retinal hemorrhages, and acute intracranial hemorrhages on the CT scan are likely to have suffered nonaccidental injuries, especially if the history of the injury is unknown or reported to be minor. The additional finding of new or healing skeletal fractures or other solid organ injuries are pathognomonic for this injury. All infants who are suspected to have been abused need a comprehensive multidisciplinary evaluation by physicians knowledgeable about the mechanisms and clinical spectrum of inflicted injury.

## INITIAL ASSESSMENT OF BRAIN-INJURED CHILDREN

The purpose of the initial assessment of a brain-injured patient is twofold. First, and most important, one establishes a working diagnosis of the type and severity of the injury that directs the selection of initial therapies as well as the planning and coordination of other diagnostic studies and the management of any associated systemic injuries. Second, it establishes a baseline to measure the effects, both positive and deleterious, of the therapies or interventions.

Historically, the main focus of a brain-injured patient's initial assessment was to determine the severity of the injury by scoring the level of consciousness. The most widely used scale for this purpose is the Glasgow Coma Scale Score (GCS),[69] which, as it was designed, correlates well with outcome. However, with improvements in transportation and field resuscitation of severely injured patients, which usually requires the prehospital administration of analgesics and sedation, a neurologic assessment to determine brain injury type and severity becomes less useful.[70] Furthermore, there is a small but important group of brain-injured patients who present with little or no impairment of consciousness and who subsequently deteriorate from mass lesions or brain swelling.[71–73]

It is now clear that neuroimaging is probably a better predictor of outcome from brain injury than is the clinical examination. Regardless of the apparent level of consciousness, the early radiographic identification of injury types and the institution of appropriate management or monitoring have substantially improved the overall outcome from traumatic brain injury. Furthermore, it is now clear that a head-injured patient who has a completely normal CT scan has an exceedingly low risk of either deterioration or poor outcome. In the authors' experience, the CT scan has become the most important element in diagnosing brain injury early, especially for young children.

The important CT scan findings not only involve the detection of potentially surgical mass lesions but also the search and detection of the constellation of findings typically seen with diffuse brain injury. These are subarachnoid, intraventricular, or intraparenchymal hemorrhage and what may be very subtle early signs of brain swelling, including compression of the perimesencephalic cisterns or shift or compression of the ventricular system. These findings should influence the expectations for outcome and the decisions for monitoring and therapy. Diffuse brain injury severity can be graded by the appearance of the admitting CT scan and can direct therapeutic decision making.[74]

Most current practice parameters regarding the evaluation of head-injured patients include recommendations for an early diagnostic CT scan.[1,2,22,75,76] Essentially, all potentially severely injured patients, that is, patients presenting with an alteration of consciousness, should undergo CT scanning as soon as they are physiologically stable and can be safely transported and maintained in the scanner. Older children with apparently trivial injuries can be observed clinically. However, as mentioned previously, the finding of a normal CT scan after

head injury can mitigate further clinical observation and allow return to home sooner. On the other hand, children with the following symptoms should undergo CT scanning as soon as possible: a history of more than a few seconds of unconsciousness; a seizure; clinical signs of cranial impact, skull fracture, cranial penetration, or CSF leak; and headache, persistent vomiting, lethargy, or irritability.[77,78] Finally, children who have been injured in accidents with high-energy mechanisms that result in apparently isolated chest, abdominal, or skeletal injuries should undergo a brain CT scan prior to anesthetic administration or the institution of narcotic analgesia or sedation that would preclude accurate ongoing neurologic examinations.

It should be clear from the previous discussion that plain skull radiography has only a limited and secondary role in the initial evaluation of head injury. CT scanning will detect most clinically important skull fractures. Conversely, skull radiographs provide only limited information about the type and location of any brain injury. MRI is more sensitive than CT scanning for detecting most brain pathology, and it has supplanted CT scanning as the study of choice for many neurologic disorders. Some centers are using “fast” MRI techniques to assess acute brain injury.[79] This may become more common, especially in view of the long-term effects of radiation in children.[80]

Finally, although acknowledging the expanding primary role of neuroimaging in the diagnosis and management of traumatic brain injury, a careful physical and neurologic examination is still extremely important. The entire head should be inspected for indications of impact, scalp injury, cranial deformities, and indications of cranial or orbital penetration. It is necessary to document cranial nerve function, especially pupillary size, shape, and reactivity, which will serve as a comparison for serial examinations. Evidence of anterior basilar skull fractures, manifested by periorbital ecchymoses, nasal hemorrhage, or CSF rhinorrhea, is a contraindication to the placement of nasogastric tubes until the integrity of the anterior cranial skull base can be determined. Retroauricular bruising, hemotympanum, otorrhagia, or CSF otorrhea are indicative of temporal bone fractures. In the circumstance of possible inflicted injury, dilated funduscopic examination by an ophthalmologist is recommended.[81] It is still necessary to document the level of consciousness and any apparent motor or sensory deficits and note the presence of confounders to the examination (such as intubation, medications, swelling, splints, etc.), in the initial evaluation of the head-injured patient.

## EARLY MANAGEMENT OF SEVERE BRAIN INJURY

The primary objective of resuscitating brain-injured patients is to preserve cerebral perfusion during transport and evaluation. The ongoing objective of therapy for severe brain injury is to optimize the perfusion of the injured and uninjured brain and create a milieu that minimizes the chance for secondary injury and maximizes the amount of neuronal recovery. One must do this while avoiding or reversing deleterious processes that would result in further neuronal injury or the expansion of hemorrhagic masses, including systemic complications that directly affect an injured brain, such as sepsis, acute lung injury, hyperglycemia, and coagulopathy.

There are a variety of treatment strategies that have been propounded for the treatment of traumatic brain injury. Most of these therapies involve systemic manipulations to achieve what is believed to be either a therapeutic or a protective response. All of the newer therapies have theoretical attractions, and their proponents report outcomes that appear to be better than historical controls. However, at least so far, when these therapies have been tested directly against what could be termed standard therapies, no benefits have been demonstrated. Given this, the treatment recommendations currently in place are essentially descriptions of how to apply the historically standard therapies of controlled ventilation, fluid management, sedation, and control of blood pressure and intracranial pressure (ICP).

To do this, one must understand intracranial dynamics and optimize cerebral perfusion by removing surgical masses and by managing the intracranial pressures, which can be done by safely manipulating, as much as possible, the cerebral blood volumes (arterial and venous), the cerebrospinal fluid volume, and the brain or skull volume.[82] For severely injured patients, and for some less severely injured patients, intracranial pressure monitoring guides the institution and manipulation of therapies. ICP monitoring provides the basis for making many of the important management decisions for brain-injured patients.[83,84]

The application of individual medical therapies is beyond the scope of this chapter. However, it is important to realize that each of the current therapies for elevated intracranial pressure has both general and specific effects, and each has complications associated with its use. The historically common administration of high-dose steroids to brain-injured patients is no longer considered to be beneficial and may, in fact, be harmful. Accordingly, the current guidelines do not recommend that *any* specific therapy—for instance, hyperventilation, osmotic diuretics, or other medications—be administered prophylactically or universally for brain-injured patients. It is also suggested that specific therapies be applied in a logical sequence, guided by ICP monitoring and by frequent reassessments of the responses to the therapy.

The basic level of therapy for severe traumatic brain injury includes controlled ventilation and maintaining normal oxygenation and $Pa_{CO_2}$ concentrations. Intubated patients should have adequate sedation and analgesia at all times. Intravascular volume should be supported at all times with blood and fluids, maintaining normal hematocrit and electrolyte concentration. Fluid restriction is not recommended. Hypotonic fluids should be avoided in order to avoid any trend toward hyponatremia. The head of the bed may be elevated to reduce intracranial venous pressure as long as normal central venous pressures are maintained by adequate volume replacement. For many severe diffuse brain injuries, this level of therapy may be all that is necessary.

Escalated therapies include the use of CSF drainage, usually by way of a ventricular catheter, osmotic therapy, and mild hyperventilation. Whenever escalation of therapy is considered, one must also escalate the physiologic monitoring for treatment effect and complications. Table 24-1 summarizes the authors' approach to escalating medical therapy for brain injury, based on current treatment guidelines. Others have different strategies, including the use of decompressive craniectomy early in the treatment cascade. As discussed at the outset of this chapter, the available evidence allows many

**TABLE 24-1**
**Medical Therapies for Traumatic Brain Injury**

| *Treatment* | *Monitoring* |
|---|---|
| **Evaluation and Resuscitation** | |
| Restoration of normal blood pressure | Systemic blood pressure and oxygenation |
| Intubation and ventilation | Neurologic examination |
| | End-tidal $CO_2$ |
| **Basic Level Therapy** | |
| Elevating head of bed | Systemic blood pressure and oxygenation |
| Keeping head in neutral position | Intracranial pressure |
| Sedation and muscular paralysis | Arterial $Po_2$, $Pco_2$, and pH |
| Mechanical ventilation to maintain $Paco_2$ at 35-40 mm Hg | Weight, urine output, pulse, and pulse pressure |
| Maintaining normal to slightly increased intravascular volume | Hemogram, serum electrolytes, glucose, and BUN |
| Normal fluid and electrolyte status (no fluid restriction) avoiding anemia, hyperglycemia | Monitoring and aggressively treating fever and sepsis |
| | CT scan |
| Body temperature normal to slightly hypothermic | |
| **Escalated Therapy** | |
| Ventricular CSF drainage | Ventricular catheter |
| Osmotic therapy including hypertonic saline | Central venous pressure |
| Moderate hyperventilation to maintain $Paco_2$ at 30-35 mm Hg | Serum osmolality and electrolytes |
| **Intensive Therapy of Refractory Intracranial Pressure** | |
| High-dose barbiturate therapy | Continuous or compressed spectral EEG |
| Decompressive craniectomy | Barbiturate levels |
| Optimized ventilation | Brain oximetry, monitors of cerebral blood flow |

BUN, blood urea nitrogen; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; $Paco_2$, partial pressure of arterial carbon dioxide; $Pco_2$, partial pressure of carbon dioxide; $Po_2$, partial pressure of oxygen.

different logical strategies for the management of traumatic brain injury, and each center should develop their own protocols and carefully measure the outcomes and complications.

Surgical decision making for severely injured patients is usually straightforward. Obviously, penetrating injuries, including compound skull fractures, require urgent surgical attention. The removal of large, surgically accessible mass lesions may be the first step in the overall therapeutic management of a severe brain injury. Some centers advocate decompressive craniectomy as an initial therapy. In many cases, such as closed depressed fractures, burst fractures, comminuted cranial, and craniofacial fractures, surgical correction can be performed when the patient is stable or improving from the neurologic injury.

Typically, major surgical therapy for brain injury involves the removal of traumatic intracranial hematomas. The overall incidence of surgical hematomas in childhood is substantially lower than in adults, and the distribution of hematoma types is different. Subdural hematomas are most common in infants but rarely reach a size that requires surgical removal. As discussed at the outset of this chapter, acute subdural hematomas in older children are generally more indicative of a severe diffuse injury (Fig. 24-6). Extradural hematomas are the more common surgical mass in children, especially older children who have suffered cranial impacts (Fig. 24-7). Small epidural hematomas over the cerebral convexity are likely to resolve without surgical removal, that is, those that occur in more limited "spaces" (like the temporal fossa) or the posterior fossa are more concerning, and even small epidurals in these locations may need removal. Large hemorrhagic contusions or traumatic intracerebral hematomas are very rare in the pediatric age group.[32] In summary, the decision to remove a traumatic intracranial hematoma is simply one part of an overall treatment strategy for the brain injury.


**FIGURE 24-6** Acute subdural hematoma. The hemorrhage overlying the hemisphere (left side of image) seems small. Note however, the extensive shift of the brain and the hemispheric swelling that are indicative of severe diffuse injury.

## Management of Minor Brain Injuries

The vast majority of children with head injury have trivial, minor, or minimal primary brain injuries. These children will most likely recover without any intervention. However, within this large group, there exists a small fraction of patients who

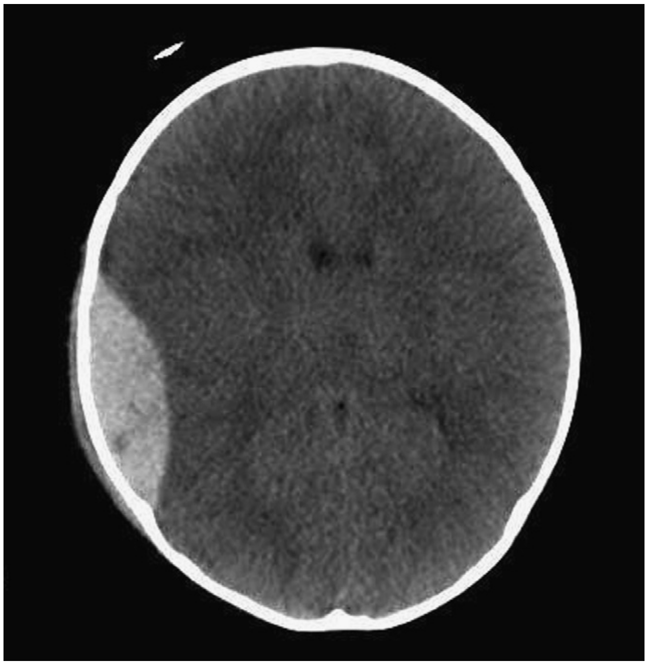

FIGURE 24-7 Acute extradural hematoma. Note the thickness of the hemorrhagic mass but also the lack of shift compared with what is demonstrated with a subdural hematoma shown in Figure 24-6. This lack of swelling and shift is an indication of an uninjured brain responding normally to the expanding mass. As long as this mass is removed prior to onset of coma, mortality and morbidity is essentially nil.

harbor enlarging hematomas or who are in the early stages of brain swelling. These patients face increased risk of delayed but rapid deterioration that will result in death or disability. The focus of evaluating of the apparently minor brain injury is twofold: (1) to identify patients at risk of neurologic deterioration or delayed complications and (2) to prevent either from occurring.[77] In many ways, the diagnosis and management of these patients is more challenging and important than managing severe injuries, because successful intervention results almost universally in good outcomes.[72,73]

There are published recommendations about this issue.[75,85] As with other types of brain injury, early neuroimaging is the lynchpin to accurately diagnose and recognize brain-injured patients at risk for deterioration.[44,86–88] Identification of cisternal compression, hemorrhagic shear, and contusion, or small traumatic hematomas indicates that the patient is at risk for deterioration regardless of their level of consciousness. These patients are candidates for frequent reassessments, including repeat neuroimaging, intracranial pressure monitoring, and even the early application of therapies to control the intracranial dynamics.[89,90] It appears that paying attention to intravenous fluid management is very important, because many children with trivial brain injuries seem to deteriorate in the face of even a mild hyponatremia.[91,92] Therefore maintenance fluids for these patients, as for most patients with brain injury, should be normal saline or its equivalent.[23] One should also pay close attention to maintaining normal intravascular volume and serum electrolyte status.

Identifying patients at risk for deterioration includes the appearance of certain abnormalities on CT scanning, but an even more important finding from the burgeoning literature about CT scanning and head injury is emerging: A completely normal CT scan in a mildly injured patient is associated with essentially no risk of life-threatening deterioration.[93,94] Given this additional information from a normal CT scan, a child with a history of an accidental minor head injury, who has neither a skull fracture nor a history of seizure and who is asymptomatic, may be released to competent caretakers and not be admitted for observation.

For adolescents who suffer cerebral concussion as a result of sporting activities, there are now published guidelines describing how to evaluate and manage these individuals, along with recommendations about when the athlete may return to sporting activities after a concussion.[95–98]

## EARLY COMPLICATIONS OF HEAD INJURY

Acute complications of head injury include those related to skull fractures, infectious processes related to cranial penetrations and CSF fistulas, and acute neurologic complications such as post-traumatic epilepsy. As with most aspects of head injury management, the key to optimizing the outcome is recognizing patients with injuries that put them at risk for these complications, followed by appropriate diagnostic studies, monitoring, and, when possible, intervention.

### Complications of Skull Fractures

Simple nondepressed or minimally depressed skull fractures will heal spontaneously. Widely diastatic or cranial burst fractures[99] in young children are indications of dural injury and are not likely to heal without surgical reconstruction. With modern neuroimaging, the early identification of these injuries allows elective early repair, thereby avoiding the complication usually referred to in the literature as "growing skull fracture."[100,101] The typical syndrome of an enlarging skull defect and progressive neurologic deterioration, both of which are related to a craniocerebral erosion and enlarging leptomeningeal cyst that appears during the course of months to years after the injury, is completely avoidable with early repair of the dura and skull. However, focal brain injury is commonly seen with severely depressed, diastatic, and cranial burst fractures, and these patients will have an increased incidence of seizures and focal neurologic deficits.

### Basilar Skull Fractures

For patients with presumed basilar fractures, the important clinical issue is that these are potentially compound fractures; therefore they place the patient at increased risk for infection. The obvious indication of CSF leaking from the nose or ear is present in only 10% to 20% of cases.[102,103] Therefore one must search for other signs of basilar fracture, which include bilateral orbital ecchymoses or swelling, signs of midface or orbital fracture, hemotympanum, otorrhagia, or the Battle sign, because these are easily missed on routine neuroimaging studies. These patients are at increased risk for developing meningitis, and this risk continues for several weeks after the injury. Given this, and considering that compounding of basilar fractures probably occurs more often than not without any evidence of CSF fistulas, it is necessary for parents and caretakers of children considered to have suffered basilar fractures to be counseled not only about the importance of recognizing CSF rhinorrhea or otorrhea, if it should occur at home,

but also about the urgent importance of seeking immediate medical attention for children who develop signs or symptoms even remotely suggestive of bacterial meningitis up to several weeks following the injury. Despite the increased risk of bacterial meningitis, the administration of prophylactic antibiotics has not been shown to be beneficial.[104–106] Some centers are administering pneumococcal vaccine to patients with presumed basilar skull fractures, although it is not yet clear that this reduces the occurrence of pneumococcal meningitis.

Basilar skull fractures are also associated with cranial neuropathies. The olfactory nerve is the most commonly injured of all cranial nerves, and patients with anterior basilar fractures are especially at risk of injuring them. Fractures that occur more posterior along the skull base, or that include the orbit and midface, place the optic nerves at risk. Visual loss may be acute or delayed, and ophthalmologic evaluation and follow-up are warranted. Basilar fractures involving the petrous bone can result in auditory, vestibular, and/or facial nerve injury. These patients may need otologic evaluation and audiometric studies.[107]

### Direct Cerebrovascular Injuries

Although traumatic intracranial aneurysms are exceedingly rare after closed head injury, greater than 20% of all post-traumatic aneurysms occur in the pediatric age group.[108] Penetrating injuries, especially stab wounds and deep penetrations, are associated with a high incidence of vascular injury. Suspicion of direct cerebrovascular injuries is raised when there is a large amount of subarachnoid hemorrhage or a focal intracerebral hemorrhage on the CT scan. CT angiography and/or magnetic resonance angiography can screen for injury, but in some cases, diagnostic angiography should be performed. If the studies are not conclusive, early repeat imaging is warranted.

### Post-traumatic Seizures

One of the most common complications of brain injury, even mild brain injury, is epilepsy. Most studies indicate that the incidence of post-traumatic seizures is substantially higher in children than in adults.[109,110] Risk factors associated with post-traumatic epilepsy include younger age and increasing injury severity.[47,111] However, it is not clear that the infants with inflicted injuries, who would have a very high incidence of early epilepsy, were excluded from these studies.[112] If one removes this particular group from the analysis, the incidence of post-traumatic epilepsy in children appears to be relatively low.

One must make a distinction between early and late post-traumatic seizures. Early seizures are generally defined as those that occur within the first week after injury. For pediatric patients, this definition would include the so-called impact-related seizure that occurs in up to 10% of mildly head-injured children.[47,113,114] These seizures are usually self limited, and the CT scan is normal. Treatment is not recommended, and the long-term outcome is good.[115,116] This particular syndrome is almost never seen in head-injured adults, in whom early epilepsy is strongly associated with structural brain injury or subdural hematoma.

For severely head-injured children, that is, children in coma or with structural injury on the admitting CT scan, there is limited and conflicting information regarding the clinical significance and the management of early and late post-traumatic epilepsy.[111,117,118] Current recommendations indicate that all severely injured patients who experience recurrent seizures should be treated with anticonvulsant medication. Phenytoin is still the most widely recommended drug for this purpose,[1,119] although newer agents are being introduced and studied.

### Postconcussion Syndromes

A syndrome of neurologic dysfunction that seems to be unique to young children has been called the pediatric concussion syndrome. Shortly after what would seem like a mild cranial impact injury, the child exhibits the acute onset of pallor, diaphoresis, and impaired responsiveness. CT scans are normal, and the syndrome appears to resolve as rapidly as it occurs. The underlying mechanism is unknown, although it has been suggested that it may be a variation of post-traumatic epilepsy.[120]

Other much more rarely occurring transient neurologic disturbances have been reported after mild head injury in childhood. This includes transient cortical blindness, speech arrest, ataxia, receptive dysphasia, and prolonged disorientation.[121,122] CT scans are, again, normal, and the symptoms resolve spontaneously. The etiology is not clear.

## OUTCOMES FROM TRAUMATIC BRAIN INJURY

There is substantial variability in the reporting of outcomes from childhood head injury. With the exception of infants suffering inflicted head injuries, the overall mortality from head injury in childhood is roughly half of that reported for similarly severe head injury in adults.[2] In larger series of patients, mortalities for head injury in childhood are generally less than 5% for all levels of injury severity and less than 20% for those children who are defined as having severe injuries based either on the GCS or other injury severity scoring systems.[32,117,123] Factors related to poor outcomes include high-energy mechanisms, structural injury, swelling and shift on admitting CT scans, persistent or resistant elevations in intracranial pressure, the presence of chest or abdominal injuries, and systemic complications.

Traumatic brain injury is the leading cause of acquired disability in childhood[124]; children who survive have neurologic and cognitive outcomes related to their age, severity of injury, and amount of permanent structural injury to the brain.[123,125–128] Children who have suffered severe brain injuries are likely to show persistent adverse effects on intellectual function, memory, attention, language, and behavior.[129] It is likely that these deficits have ongoing and perhaps compounding effects on learning and socialization. Given that, it is possible that the overall neurobehavioral outcomes for significant childhood head injury are worse for children than for similarly injured adults.

Outcomes from inflicted brain injuries deserve separate discussion. This particular injury is associated with the highest mortality and morbidity of childhood head injuries. Reported mortalities approach 40%.[130,131] Morbidity is also high, especially if the infant shows evidence of cerebral infarction or hypoxic-ischemic injury.

### POSTCONCUSSION SYNDROMES

Mild brain injury—a brain injury with a limited effect on consciousness and with preservation of brain structure—is by far the most common central nervous system injury in the pediatric age group. Greater than three quarters of all childhood head injuries are classified as mild.[32,132] Only recently have pediatric specialists begun paying attention to the long-term outcomes from cerebral concussion in children.[133] Although there is still variability in defining mild head injury and the spectrum of severity within that taxonomy,[134–136] there appears to be two general emerging concepts in the available literature. First, somatic complaints, such as headache, visual disturbances, light and noise intolerance and dizziness, emotional disturbances (such as depression, anxiety, or irritability), and cognitive impairments, including poor school performance, are common in mildly brain-injured children in the days and weeks immediately following the injury.[137] Second, as long as the child did not have any cognitive or behavioral disturbances before the brain injury, all of the early postconcussion symptoms described previously appear to resolve completely during weeks or months.[136]

## Spine and Spinal Cord Injury

Spinal cord injuries in children are rare, but the consequences of such injuries can be devastating. As with traumatic brain injury, modern neuroimaging has contributed considerably to the diagnosis and management of traumatic myelopathy. As discussed at the beginning of this chapter, the major therapeutic efforts for spinal cord injury are the same as for brain injury and aim to prevent new primary injury and ameliorate secondary injury. The first objective is accomplished by maintaining anatomic alignment of the vertebral column during the period of resuscitation and evaluation. The second objective is much more difficult[138] but begins with supporting blood pressure and oxygenation.

In general, the diagnostic and therapeutic algorithms for children with spinal and spinal cord injuries are similar to those used for adult patients. Guidelines for the management of spinal cord injury have been published recently and summarize current knowledge.[4] However, there are important differences in clinical presentations, anatomic and radiographic findings, and management for spinal injuries in children, especially very young children. This section will concentrate on those issues.

### EPIDEMIOLOGY

Less than 10% of spinal cord injuries[139–142] and approximately 1000 new spine[143] or spinal cord injuries[144] each year occur in children. Vertebral column injuries that do not involve the spinal cord are much more common. In a large recent series, only half of children with vertebral injuries had neurologic deficits.[145]

The mechanisms and pattern of injury are related both to age and gender. In very young children, the male to female ratio is roughly equal. In older children, the more "adult" distribution appears with a male to female ratio of about 4:1. Adolescent boys are most affected.[146] The most common causes of pediatric spine injury include falls, athletic activities, child abuse, diving accidents, and motor vehicle trauma.[146–151] Approximately one half of pediatric spinal injuries are the result of motor vehicle accidents.[152] One quarter of injuries are the result of diving accidents. Prevention efforts directed at those two mechanisms alone would dramatically reduce the rate of spinal injury in children. The remaining major mechanisms of injury—falls, child abuse, and sporting activities—each account for about 10% of reported injuries. Younger children are more likely to be injured as the result of a fall, while older children are more likely to be injured in diving accidents or sports.[153,154]

### ANATOMY

Younger children tend to have spinal column injuries in the cervical region, while older children tend to have a distribution of spinal injuries similar to that of adults.[155] Children are more likely to experience spinal cord injury without apparent vertebral fractures or dislocations. These characteristics are generally thought to be related to the anatomic properties of the juvenile spine and are independent of the mechanism of injury. The pediatric spine has several properties that essentially allow significant, self-reducing displacement of the vertebral column. These properties include increased elasticity of the joint capsules and ligaments, shallow- and horizontally-oriented facet joints, anterior wedging of the vertebral bodies, and poorly developed uncinate processes.[156,157] Furthermore, young children have disproportionately larger heads and weaker cervical musculature. All of these elements permit a wider range of flexion and extension and rostrocaudal distraction. The fulcrum of motion is higher in the juvenile spine, which explains the greater incidence of rostral injuries in children. This tendency decreases—and the incidence of more characteristic vertebral fracture and dislocation increases—with increasing age.[158] Finally, it is important to remember that 10% to 15% of spinal injuries in children involve "skip" injuries with vertebral or cord injuries at multiple levels.[145,159] Therefore, and depending on the injury mechanism, when a child is determined to have spinal cord injury or vertebral disruption, the entire spinal axis should be surveyed for other injuries.

Spine fractures in children represent 1% to 2% of all pediatric fractures.[160] Overall, injuries to the thoracic and lumbar spine are uncommon in children. When spine injury does occur, the thoracic region (T2-T10) is most commonly injured, followed by the lumbar region (L2-L5).[161] Trauma to the lower thoracic or lumbar spine in children is rarely associated with spinal cord injury,[160] most often occurring at the cervical spinal cord. Less than 20% of all spinal injuries in children occur below the cervical spine.[162] Pediatric cervical spine injuries are typically soft tissue, ligamentous injuries without associated bony fractures for the aforementioned reasons.

### EVALUATION OF SPINE AND SPINAL CORD INJURY

Because spinal cord injury is rare in children, it may be overlooked, especially in the very young and in the presence of multiple injuries. As discussed later, the presence of apparently normal plain radiographic studies will not completely

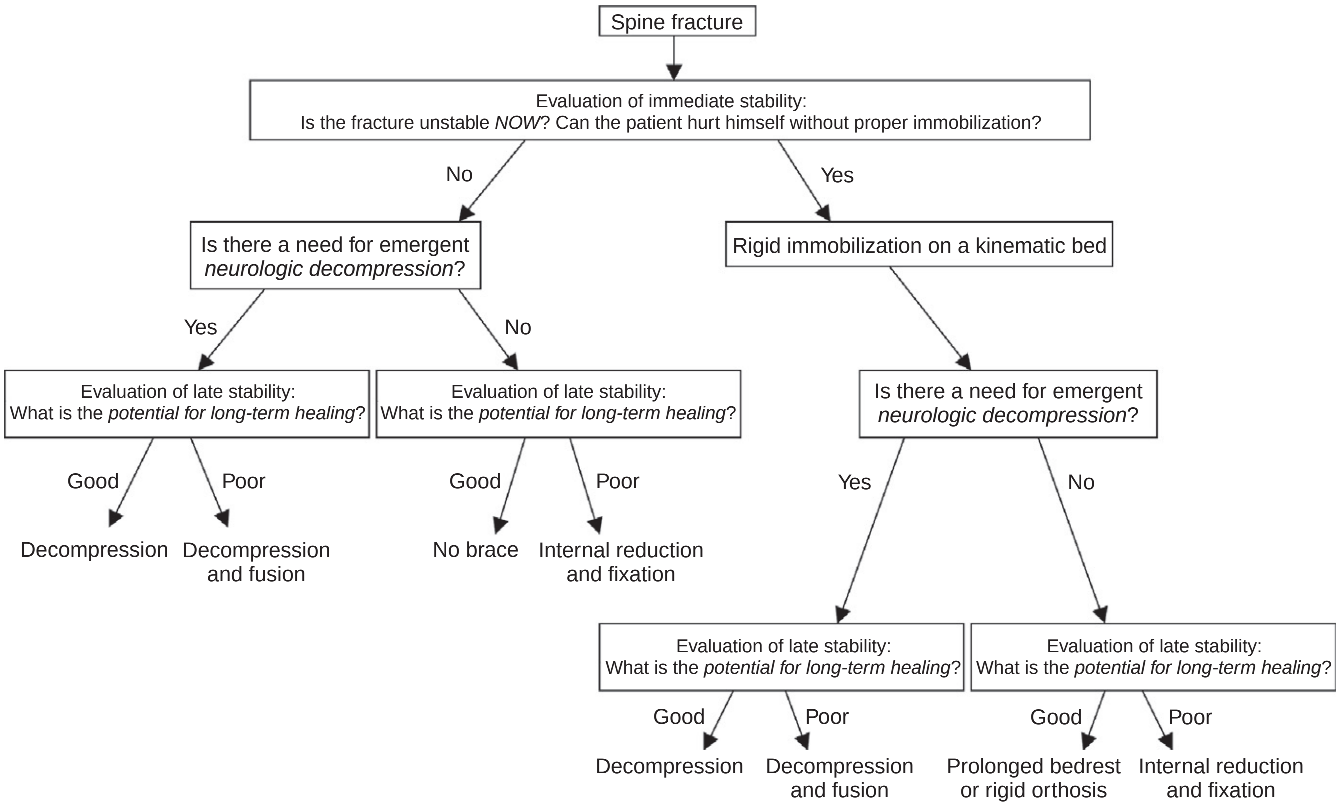


**FIGURE 24-8** A systematic approach to spine injuries. Indications for closed or open reduction and decompression and external or internal fixation borne out by answers to three fundamental questions: (1) Is the injury acutely stable or unstable; (2) is there a need for urgent neurologic decompression; and (3) what is the potential for healing with external orthosis?

rule out either vertebral instability or spinal cord injury. Therefore one must have an increased index of suspicion based on injury mechanism and the neurologic presentation. High-energy mechanisms, such as motor vehicle accidents and falls from heights, are more likely to cause spine or spinal cord injury. Until a complete assessment is possible, one should assume that an unconscious patient of any age has a spinal cord injury (Fig. 24-8).

## HISTORY

Neck or back pain after a major accident or fall from a significant height may increase suspicion for spine injury. A major accident may include significant vehicular damage, head-on high-speed collision, vehicular rollover, or death at the scene. Accidents that may be associated with spine injuries include those involving the lack of seatbelt use, prolonged extrication, airbag deployment, damage to the steering wheel or windshield, passenger ejection from the vehicle, or passenger space intrusion. Vehicular accidents involving motorcycles, bicycles, or pedestrians have a high association with spine injuries. Transient or persistent symptoms may include pain, weakness, numbness, and tingling. Children can present with torticollis as the result of atlantoaxial rotatory subluxation, which can occur from a minor injury or even a coughing spell. The children are usually neurologically normal. The plain radiographs can be deceiving, but the CT scan of the spine in the axial plane is diagnostic (Fig. 24-9).[163]

## PHYSICAL EXAMINATION

Examination should start with a general survey to look for tenderness, swelling, ecchymosis, or a palpable defect posteriorly along the spinous processes. A seatbelt mark across the abdomen or injury of abdominal organs should increase suspicion for any type of thoracic or lumbar fracture.[160] Injuries in the lower thoracic region to upper lumbar region (T11-L1) are notably associated with a significant increase in risk of gastrointestinal injury. Injuries in the lumbar and sacral regions (L2-sacrum) are noted to be associated with risks of orthopedic injuries and gastrointestinal injuries.[146] Any loss of sensation or motor function should be accurately documented. A child with spinal cord injury above the T6 level may present in spinal or neurogenic shock (hypotension and bradycardia), which represents a loss of descending sympathetic tone. This must be recognized early, because pure fluid resuscitation may not be effective and a vasopressor may be needed to restore adequate perfusion.[162]

## CLINICAL SPECTRUM OF SPINE AND SPINAL CORD INJURY

Spine injuries must be assessed in terms of immediate and late stability (Table 24-2). Immediate stability refers to the risk of new or further neurologic injury while bearing physiologic loads without immobilization. Late stability implies the potential to heal with proper immobilization based on a specific injury pattern.[164] Management decisions are based on the degree of stability (see Fig. 24-8).

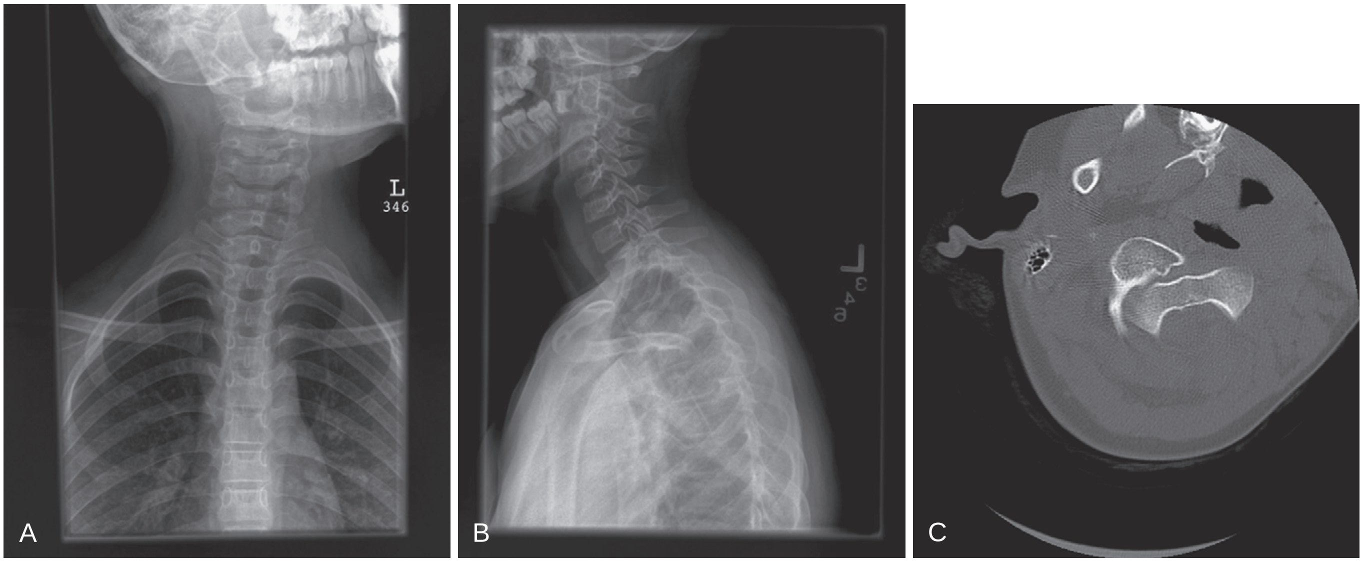


FIGURE 24-9 An example of C1-C2 rotatory subluxation. The patient is a 9-year-old girl with painful torticollis for 3 months after a motor vehicle accident. Anteroposterior (AP) (**A**) and lateral (**B**) cervical spine radiographs confirm torticollis; however, bony details and relationships are obscured at the craniocervical junction. **C,** Axial computed tomography (CT) shows the right C1 lateral mass dislocated and rotated clockwise relative to C2, which is diagnostic of C1-C2 rotatory subluxation.

**TABLE 24-2**
**Common Spine Injuries, Association with Spinal Cord Injury, and Stability**

| | | Stability | |
|---|---|---|---|
| *Fracture Type* | *Associated Spinal Cord Injury* | *Immediate* | *Late* |
| **Upper Cervical Spine** | | | |
| Atlanto-occipital dislocation | Common | Poor | Poor |
| Occipital condyle fracture (Montesano and Anderson type I or II unilateral) | Uncommon | Good | Good |
| Occipital condyle fracture (Montesano and Anderson type III or type I or II bilateral) | Uncommon (may be associated with cranial nerve deficit; XII most common) | Poor | Fair |
| C1-2 rotatory subluxation (Fields and Hawkins type I) | Uncommon | Good | Good |
| C1-2 rotatory subluxation (Fields and Hawkins type II or III) | Possible | Poor | Poor |
| C1 burst (Jefferson fracture) (sum C1/2 lateral mass overhang $<$ 14 mm) | Uncommon | Good | Good |
| C1 burst (sum C1/2 lateral mass overhang $>$ 14 mm) | Uncommon | Poor | Poor |
| Odontoid fracture (d'Alonso and Anderson type I or III) | Uncommon | Good | Good |
| Odontoid fracture (d'Alonso and Anderson type II) | Possible | Fair | Fair |
| C2 pars fracture (Effendi type I or II) | Uncommon | Good | Good |
| C2 pars fracture (Effendi type IIA or III) | Possible | Poor | Poor |
| **Subaxial Cervical Spine** | | | |
| Unilateral jumped facet | Uncommon | Good | Fair |
| Bilateral jumped facets | Common | Poor | Poor |
| Teardrop fracture (flexion-compression) | Common | Poor | Poor |
| **Thoracic and Lumbar Spine** | | | |
| Compression | Uncommon | Good | Good |
| Burst | Possible | Fair | Good |
| Fracture-distraction | Possible | Fair | Good |
| Fracture-rotation | Common | Poor | Poor |

The cardinal sign of a spinal cord injury is neurologic dysfunction below an anatomic spinal motor or sensory level. Complete or severe incomplete cord injuries with motor dysfunction are readily detectable in conscious patients. A spinal cord injury generally presents as symmetrical flaccid paralysis with sensory loss at the same anatomic level. There are strong indirect indicators of spinal cord injury in comatose patients or those with multiple injuries. Cervical spinal cord injuries can cause profound systemic hypotension, a syndrome known as neurogenic shock, which is caused by disruption of sympathetic pathways below the level of injury. Unlike the more common hypovolemic shock, neurogenic shock is suggested

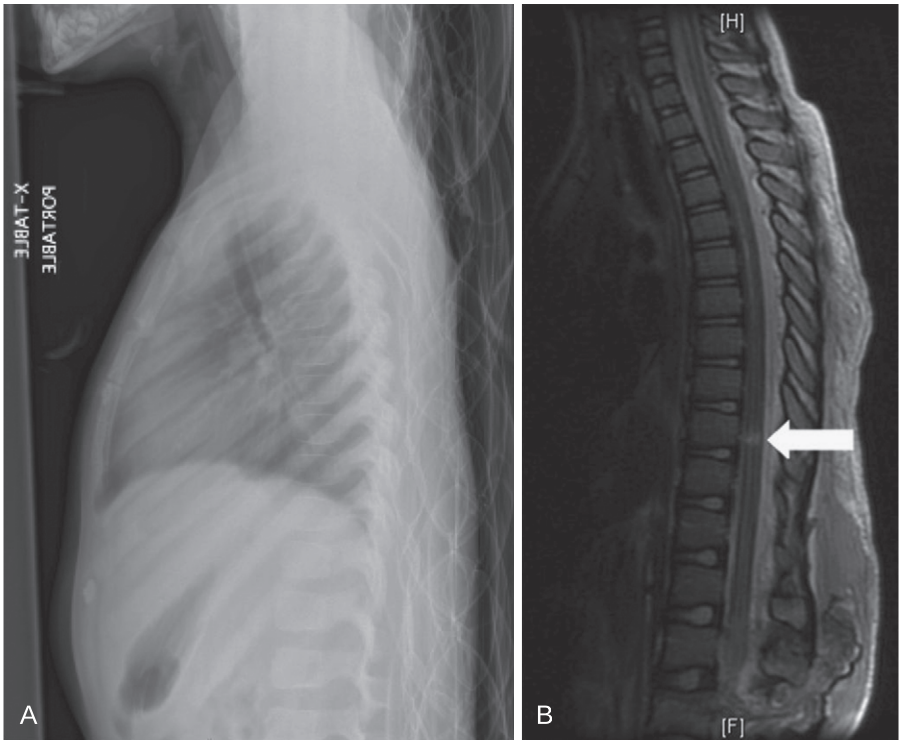


**FIGURE 24-10** An example of spinal cord injury without radiographic abnormality (SCIWORA). The patient is a 6-year-old girl who, on neurologic examination, is a T10 complete paraplegic after a motor vehicle accident. **A,** Normal-appearing plain radiograph of the thoracic spine. **B,** Further workup with magnetic resonance imaging (MRI) shows cord signal change *(white arrow)* at the T10 level on the sagittal T2-weighted sequence, indicating a spinal cord injury without evidence of abnormality on the plain radiograph at the T10 level.

by the finding of bradycardia in the face of hypotension. These patients are also vasodilated despite being hypothermic. Hypovolemic shock results in hypotension, tachycardia, and vasoconstriction. Other systemic findings suggesting spinal cord injury include paradoxic respiration, priapism, Horner syndrome, and inability to sweat.

Less severe injuries may present with transient neurologic dysfunction, dysesthesias, focal weakness or sensory loss, or a dissociation of motor and sensory dysfunction, such as Brown-Séquard or central cord syndromes. Any history of transient neurologic dysfunction involving the limbs or bladder, regardless of duration and apparent complete recovery, must be taken as strong evidence for spinal cord injury.

### Spinal Cord Injury Without Radiographic Abnormality

Pang and Wilberger defined spinal cord injury without radiographic abnormality (SCIWORA) in 1982 to describe patients who exhibit objective findings of traumatic myelopathy with no evidence of fracture or ligamentous instability on routine screening plain radiography or CT scanning.[165] SCIWORA is essentially an injury of children, especially younger children, and is likely directly related to the biomechanical properties of the juvenile spine outlined previously. As with vertebral injury, there is a tendency toward more rostral injury with younger age. Younger children suffering SCIWORA are more likely to have severe or complete spinal cord injuries than older children. Severe spinal cord injury in older children is more often associated with a vertebral injury than with SCIWORA.[145,166,167]

The diagnosis of this syndrome is complicated by the frequent occurrence of delayed neurologic deficits. Many children with this injury will develop neurologic deficits hours to days after the reported injury and in the absence of any further injury. The mechanism of this delayed deterioration is unknown, but Pang has speculated that there is repeated injury to an already mildly injured spinal cord either because of the innate normal flexibility of the spine or because of subtle ligamentous injury with increased segmental movement at the injury site.[168] This argument is supported by the observation that recurrent SCIWORA may occur in about 20% of children who are not immobilized and that immobilization of the cervical spine markedly reduces the incidence of this phenomenon.[169]

Finally, this syndrome was initially described before the widespread use of MRI for spinal disease diagnosis. Although it is still true that these children do not have evidence of bony injury or overt instability on plain spine radiographs or CT scans, most (but not all) patients will have evidence of spinal cord and/or ligamentous or other soft tissue injury on MRI (Fig. 24-10).[170–172] Therefore it is essential that all physicians who provide early evaluations of injured children be aware of this disorder and continue to consider the possibility of spine or spinal cord injury, even when the initial radiographic studies may be reported as normal.

## INITIAL MANAGEMENT OF SPINE AND SPINAL CORD INJURY

### Spine Stabilization

The mainstay of management of spine injury is immobilization of the entire spinal axis in the field. An appropriately sized cervical collar should be used; in the absence of an appropriately sized collar, blocks and tape are effective for immobilizing the head on the backboard.[162] In young children less than the age of 8 years, the disproportionately large head places them in flexion when placed on a neutral board. Proper immobilization requires either a special board with a recess for the occiput, allowing the head to rest in-line with the body, or placement of a thin mattress under the torso relative to the head.[162]

## Imaging

Currently, no national guidelines exist for the clearance of the pediatric spine, particularly the cervical spine, after trauma. In addition, no institution-specific spine clearance protocol has been shown to be superior versus another. A meta-analysis conducted and published in 2002 found insufficient evidence to support a standardized, diagnostic protocol.[173]

Radiologically, the integrity of the pediatric spine (especially the cervical spine), may be difficult and time consuming to assess. However, an accurate and timely evaluation is important in pediatric trauma. Younger children present an additional challenge, because they are developmentally unable to communicate crucial symptoms or are unable to cooperate with a detailed neurologic examination.

Most institutional spine clearance protocols require pediatric trauma victims to undergo lateral and anteroposterior (AP) plain radiography of cervical spine, with the addition of an odontoid image for children older than 3 years.[174] An improper radiographic evaluation has been shown to be the leading cause of missed injury and subsequent neurologic deterioration in large series of trauma patients.[175–178]

Performing CT of the cervical spine has recently led to a more efficient evaluation of the cervical spine in adult trauma victims.[179–181] Little is known about the use of CT for evaluating the cervical spine in pediatric victims of acute trauma. However, the number of repeat radiographs required to ascertain that the pediatric cervical spine is free of injury after suspected head trauma has been shown to be significantly decreased when initial CT of the cervical spine is performed at the time of head CT.[182] Including cervical spine CT in trauma protocols for children undergoing workup for traumatic brain injuries may lead to more effective clearance of the pediatric cervical spine; likewise, reconstructing thoracic and lumbosacral spine CTs from chest and abdomen and pelvis CTs in patients undergoing workup for multisystem blunt trauma may effectively clear the pediatric thoracic and lumbosacral spines (Fig. 24-11).

***Plain Radiographs*** In general, plain radiographs are able to detect most osseous injuries of the cervical, thoracic, and lumbosacral spine in children and give an adequate global view of the spine.[162] Flexion/extension radiographs of the cervical spine are important to rule out subluxation in any patient with reported transient neurologic symptoms. Paraspinous muscles will often "splint" the cervical spine, rendering any subluxation undetectable in the acute setting; follow-up radiographs should be performed in 5 to 7 days after muscle spasm subsides.[165]

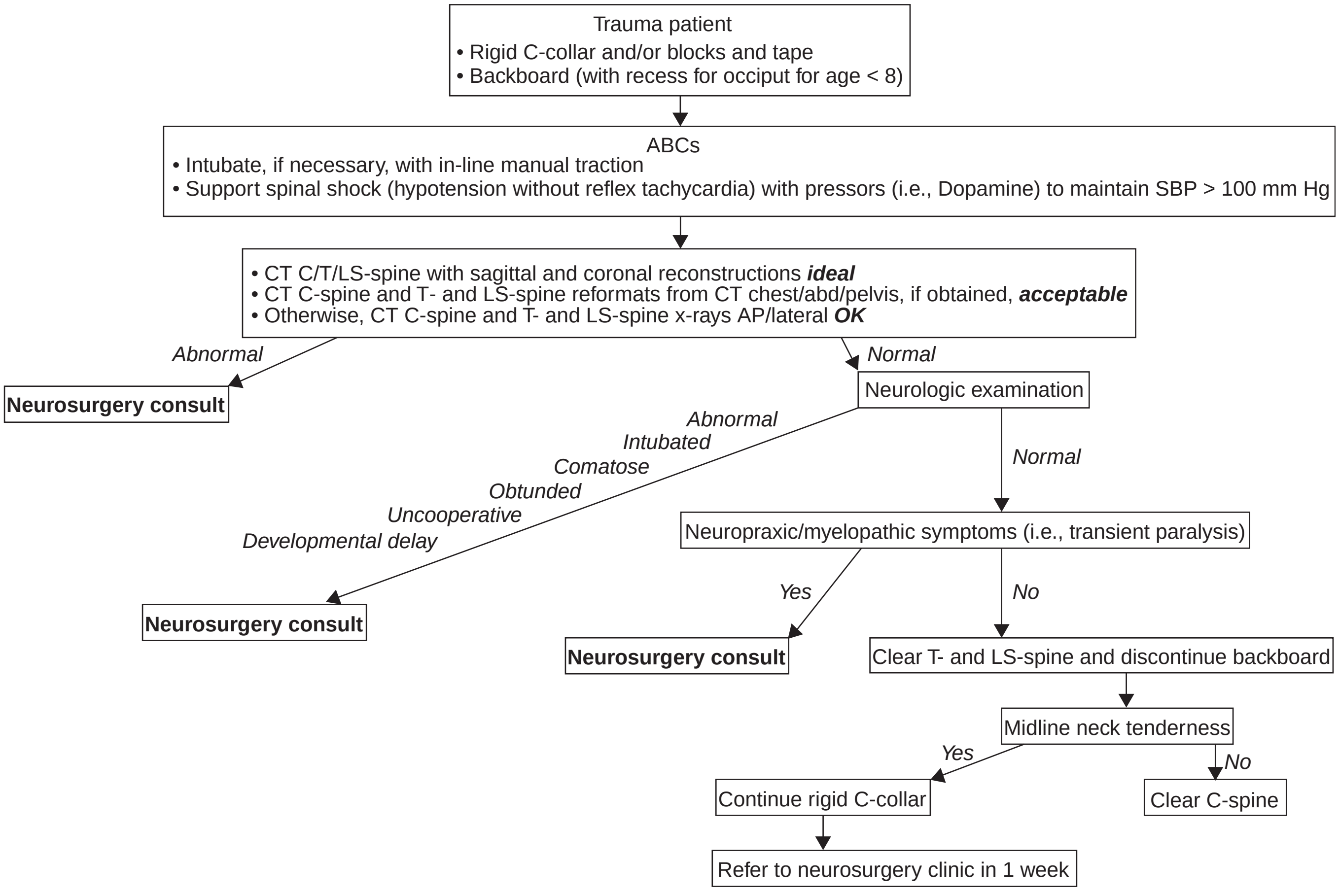


**FIGURE 24-11** A proposed computed tomography (CT)-based algorithm for the evaluation and treatment of pediatric spine trauma. Establishment of CT-based protocols to clear the pediatric spine of suspected injury has been shown to decrease the time required to accomplish clearance[178–181,201] and reduce the number of missed injuries.[174,175,178,181,202] ABC, airway, breathing, circulation; abd, abdomen; AP, anteroposterior; C-collar, cervical collar; C-spine, cervical spine; CT, computed tomography; LS-spine, lumbosacral spine; SBP, systolic blood pressure; T-spine, thoracic spine.

***Computed Tomography*** Computed tomography may suggest soft tissue, ligamentous injury, which most often occurs in the pediatric cervical spine. When using atlanto-occipital dislocation as a model for purely ligamentous injury, seen almost exclusively in the pediatric population, lateral cervical spine plain radiographs helped to make the diagnosis in 57% of patients; CT helped make 84% of diagnoses.[173] Another example of purely soft tissue injury in the pediatric population is atlantoaxial rotatory subluxation. Radiographic sensitivity during diagnosis was only 33%, whereas CT sensitivity reached 93% to 95%.[183]

Patients undergoing cervical spine and brain CT simultaneously had statistically significant less repeat or excessive radiographs than patients undergoing brain CT with cervical spine radiographs.[182] Children who underwent initial cervical spine CT did receive approximately 4 to 8 mSv of radiation; however, statistically significant increased risk of fatal cancer from low-dose radiation is in the range of 50 to 100 mSv.[184]

High-quality CT scans, perhaps, are most useful in identifying an occult and, possibly, surgically correctable vertebral fracture or dislocation.[166]

***Magnetic Resonance Imaging*** In the last decade, MRI has become the modality of choice for pediatric patients with apparent spinal cord injury but negative radiographic studies. MRI seems to be very sensitive at detecting ligamentous disruption and instability not seen on plain radiographs or CT.[185] MRI demonstrates the extent of actual damage to the spinal cord, ranging from mild hemorrhage and/or edema to cord transection.[186]

Magnetic resonance imaging findings are prognostic of patient outcome. A normal-appearing MRI suggests excellent recovery of function; major hemorrhage or cord transection on MRI is associated with permanent cord injury.

Magnetic resonance imaging is also useful in ruling out surgical lesions (i.e., those causing persistent cord compression, such as epidural hematoma or traumatic disc herniation).[187–189]

## EARLY MANAGEMENT OF SPINAL CORD INJURY

As with traumatic brain injury, it is extremely important to aggressively support systemic perfusion and oxygenation. Because children tend to have more rostral cervical cord injuries, impaired respiratory function is likely to be a concern. Furthermore, gastric dilatation commonly accompanies acute spinal injuries and can add a substantial mechanical barrier to effective respiration; therefore early nasogastric decompression of the stomach should be considered. For midlevel and higher cervical injuries, elective intubation may be needed to support respiration until a comprehensive assessment of the injury is completed. Because endotracheal intubation in a spinal-injured child is technically challenging, it should be performed by an expert who should not manipulate the relative position of the head and neck.

By restoring and supporting systemic blood pressure, one can maintain perfusion of the injured spinal cord. Patients with severe cord injuries, especially in the cervical cord, are most at risk for systemic hypotension. Although a patient can undergo initial resuscitation with intravascular volume loading, neurogenic hypotension should be treated with vasopressors. The resuscitation and maintenance of normal blood pressure in a patient with a spinal cord injury is complicated and may be aided by invasive monitoring of central venous pressure.

The pharmacotherapy of spinal cord injury has been the subject of active research and scientific controversy. The second National Spinal Cord Injury Study (NASCIS-II)[190] recommended that all patients with acute spinal cord injuries be administered high-dose methylprednisolone. Although the recommendations did not officially extend to pediatric patients, most centers applied these treatment recommendations to all age groups. Despite a subsequent study[191] that appeared to confirm the initial findings, the methodology and conclusions of these studies have been seriously questioned.[4,192] Current evidence suggests that administering high-dose steroids to spinal cord–injured patients, including children, is a listed treatment option, albeit one in which the harmful side effects may not justify clinical benefit.[4]

Early surgical therapy is rarely needed. Most pediatric fractures and dislocations can be reduced and maintained in anatomic alignment with a variety of orthotic devices, including a halo brace. Early surgical reduction and fusion is considered only for cases where there is clear neurologic deterioration occurring in the face of irreducible subluxation or compression from bone fragments, extruded disk material, or enlarging hematoma. These issues are unusual in young children. Adolescents suffer injuries similar to adults and can be treated using the surgical recommendations available for adult patients.[4] There is limited scientific information about the advisability and outcomes of operative management of spinal injury in young children, although recent reports indicate that surgical instrumentation is becoming more common.[193,194] Anatomic reduction of deformity, stabilization of clearly unstable injuries, and decompression of neural elements are indications cited for surgical treatment of spinal injury in children. Most of these goals can be accomplished nonoperatively. Current recommendations indicate that most vertebral injuries in young children should be initially treated nonoperatively, reserving surgical management for persistent or progressive deformity or ligamentous instability (see Fig. 24-8).[4]

## COMPLICATIONS

Children are subject to all of the complications associated with spine injury, which include skin breakdown, infections, deep venous thrombosis, autonomic dysreflexia, contractures, spasticity, neurogenic bladder and bowel, and progressive spine deformity.[195] However, the single major acute complication of spinal cord injury in children is respiratory; the most common cause of death in the acute phase of injury is respiratory failure.[196] Aggressive pulmonary care is essential, and ventilatory support may be necessary until accessory muscles of respiration can strengthen. Many of the other complications can be avoided or minimized by the early intervention of physiatrists and other rehabilitation specialists.

The incidence of venous thromboembolism in spinal-injured children has been reported, probably incorrectly, to be roughly similar to the incidence reported in adults.[195] However, series involving only pediatric patients indicate that this complication is extremely rare.[197] Therefore specific

recommendations for prophylaxis of this possible complication vary widely. For adults, and presumably, for older children and adolescents, thromboprophylaxis for up to 12 weeks after the injury is recommended, using low-molecular-weight or low-dose heparin in combination with rotating beds, pneumatic compression stockings, or electrical stimulation.[4,195]

## OUTCOMES

The mortality of spinal cord injury in childhood has been reported at 28%, which is significantly higher than the mortality rate for this injury reported for adults (approximately 15% at 10 years postinjury).[168,198] The majority of these deaths appeared to occur at the scene and would not be affected by current management strategies. For survivors of spine injury, outcomes are related to the level and severity of injury. Complete injuries remain complete, and although limited functional improvement may be seen over time, full recovery is not expected.[145,159,166,167] Children with incomplete spinal cord injuries have a good chance of showing significant functional improvement and even complete recovery.

The cost of long-term care for these injuries is staggering. The lifetime cost of care for a child with a spinal cord injury extends into the millions of dollars.[154,199,200] This cost must be added to the loss of productivity that accompanies these devastating injuries. The adult employment rate for individuals suffering childhood spinal cord injury is about 50%.[195] Factors associated with successful employment are younger age at injury, less severe neurologic impairment, better education, longer duration of living with the sequelae of the injury, and ability to drive independently.

### *Acknowledgments*

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*The complete reference list is available online at www.expertconsult.com.*

# CHAPTER 25

# Vascular Injury

Joseph J. Tepas III and Danielle S. Walsh

In the century since Alexis Carrel was awarded the Nobel Prize for his work in devising the surgical technique of vascular transplantation and repair, management of the patient with multisystem injury has emerged as a constantly improving process of recognition, rescue, resuscitation, and repair. Recent combat casualty experience in Iraq and Afghanistan has validated the role of damage control surgery and has stimulated the emergence of increasingly sophisticated systems of care for the severely injured. Although this experience has been forged in the treatment of massive open wounds usually caused by explosive devices, the principles that have been developed are beginning to permeate the process of civilian trauma care. The treatment of vascular injury in particular has been advanced through the use of temporary vascular shunts, permitting the transfer of life- and limb-threatening injuries to centers able to perform reconstruction.[1] Sadly there are also a significant number of pediatric casualties about whom little is known because they were simply the collateral damage of civil war. Reports by pediatric specialists deployed to these theaters validate the incidence and intensity of these injuries and indicate that the same management approaches used in the adults have been equally effective in rescuing children. Also noted has been a significantly better outcome for those children managed by pediatric specialists. In short the war experience has taught us that the basic principles of management of vascular injuries are similar for children and adults.[2]

The pediatric surgeon must approach every injured child with an organized process of assessment based on thorough review of the mechanism of injury, a careful physical examination, and an appropriate strategy for imaging and intervention. The predictive accuracy of clinical examination and better definition of indications and techniques for arteriography have led to more timely operative intervention after effective resuscitation, assessment of associated injuries, and anticipation of reperfusion injury.[3,4] The emergence of endovascular technology has begun moving the acute management of some vascular injuries from the operating room to the angiography suite. At the heart of vascular injury management, however, remains restoration of peripheral perfusion and the technical repair of damaged blood vessels. Although these basic surgical skills are similar for patients of all ages, infants and children have unique characteristics, which can present significant challenges.[5–9]

## Epidemiology

As in the adult population, vascular trauma can be classified into torso injuries that involve major truncal vessels and extremity injuries that disrupt peripheral perfusion. Although blunt injury predominates in pediatric trauma overall, our young patients increasingly mirror the adult population as is evidenced by penetrating injury overtaking blunt injury as the cause of most vascular injury.[10,11] Fortunately the incidence of both remains relatively low, although the mortality rates are significant. Archival data in the National Pediatric Trauma Registry (NPTR), demonstrated an incidence of vascular trauma of only 1.3% of registry cases in a 13-year span. However the 13% crude mortality rate for this group was significantly higher than the 2.9% rate for the entire registry, demonstrating the lethality of these injuries. Table 25-1 lists mechanisms of injury and mortality in 1368 children with at least one vascular injury recorded in the registry. Table 25-2 further characterizes these injuries by variability of outcome with body region affected. Penetrating injury accounted for slightly more than half of reported cases and was more likely to require intervention. Blunt traumatic disruption of torso vessels, in contrast, was more likely to be fatal. Two institutional trauma databases from the Medical College of Wisconsin and the University of Miami similarly found a higher incidence of penetrating wounds at 68% and 53%, respectively, in children with vascular injury.[11,12]

A report by Allison and colleagues[13] reviewed management and outcome of 75 truncal vascular injuries encountered in 57 of 10,992 patients 17 years or younger treated at their regional pediatric trauma center between 1997 and 2006. The low incidence (0.7%) and high lethality associated with presenting hemodynamic instability is in accord with the NPTR experience as well as the experience at our University of Florida, Jacksonville regional trauma center with 38 of 3996 (1%) children younger than 14 years treated between 1995 and 2009. Our experience included a 47% incidence of penetrating extremity vascular injury; all these patients survived. Of epidemiologic significance in all these reports is that boys are more likely than girls to sustain vascular injuries of all types, by a margin of 2 or 3:1.[14,15]

**TABLE 25-1**
**Injury Mechanism in 1367 Children in the National Pediatric Trauma Registry II and III**

| | *Proportion* | *Mortality* |
|---|---|---|
| Penetrating | 52% | 10% |
| Blunt | 47% | 17% |
| Crush | 1% | 8% |

# Evaluation

General principles of assessment of acute vascular disruption are based on clinical evaluation. Regardless of cause, suspicion of vascular injury should prompt an organized clinical assessment based first on the patient's history. During initial clinical evaluation two immediate questions must be answered. First, is there evidence of disruption of integrity of the circulatory system, and second, is perfusion adequate? Despite the implied causal relationship of these two points, each can be deranged without immediate effect on the other. Prolonged spasm after injury, a common characteristic of childhood vascular trauma, may cause peripheral ischemia in an otherwise anatomically intact vascular tree. Conversely, effective collateral circulation, enhanced by the absence of obliterative vascular disease, may sustain distal circulation despite deranged proximal flow. Thus not every disruption of vascular flow produces immediate peripheral ischemia, and evidence of acute ischemia may not necessarily portend operative vascular injury. Regardless of circumstances, confirmation of restoration of cellular perfusion is the immediate priority in assessing any child with vascular injury.[8]

Children usually do not suffer from atherosclerotic vascular disease. Their vessels are more elastic and usually respond to application of force by stretch and transient deformity rather than rupture. The immediate result of this is an increased potential for intimal tears, which cause flow disruption in an otherwise anatomically intact vessel. The effect of this decreased flow may be acute ischemia or marginal insufficiency that stimulates increased collateralization. Although the former should be easily discernable on clinical examination, the latter can be subtle and clinically silent. The relevance of this is rooted in the mandate that functional and anatomic integrity of the circulation be clinically confirmed and documented in every injured child. Of equal importance is the understanding that unexplainable absence of palpable pulses, especially in the lower extremities, may be the result of preexisting rather than acute injury. If perfusion pressure is suddenly lowered because of other acute injuries, collateral circulation may become inadequate and symptoms of progressive ischemia may emerge.

Frykberg and associates demonstrated the predictive accuracy of "hard signs" of injury and recommended immediate operative intervention for any patient with active bleeding, an expanding hematoma, pulse deficit, or a bruit/thrill.[16] Nonexpanding hematoma, hypotension, peripheral nerve deficit, or a history of bleeding from the wound were considered "soft" signs, which required only clinical observation. Long-term follow-up of this population has confirmed the predictive accuracy of this approach and has validated the authors' initial recommendation that routine arteriography was not necessary for management of proximity injury.[4,17] Reichard and colleagues analyzed the predictive accuracy of clinical signs in their review of 75 children with vascular injury treated at the pediatric trauma service of Cook County Hospital.[18] Part of their report includes comparison to an additional 12 children managed by an "adult" protocol that required traditional arteriography. None of the studies performed for proximity injury alone was abnormal. All 10 children with vascular injury had hard signs. Four of 77 children with no vascular injury also manifested at least one hard sign, yielding a sensitivity of physical examination of 100% and a specificity of 95%. It is of note that these data validate similar recommendations published by Meagher and colleagues in 1979 and emphasize that arteriography for acute injury should be considered only if the risk of performance is outweighed by a threat of ischemia that cannot be defined by history and clinical signs.[16,19–21] Numerous investigators have validated the predictive accuracy of thorough clinical examination and in the process have refined indications for further imaging, particularly arteriography.[3,16] Although the emergence of multidetector computed tomography (CT) and magnetic resonance angiography (MRA)-based angiography has minimized the trauma of arterial vascular access, the additional radiation of CT, the lesser availability of MRA, and the risk of contrast toxicity still mandate a studied decision as to the appropriateness of these imaging studies.[22] Although CT and MRA do not require direct arterial puncture or manipulation of foreign bodies against arterial intima, they do require relatively large boluses of contrast medium and in the case of CT significant radiation exposure. The risk of inappropriate angiography has simply changed in characteristic rather than in magnitude or incidence.

Lineen and colleagues published their review of 78 pediatric patients with suspected vascular injury undergoing CT angiography for 41 penetrating and 37 blunt mechanisms.[12,23] Eleven injuries were identified from the penetrating trauma group, with 100% sensitivity and 93% specificity. Two normal veins were read as abnormal adjacent to missile tracts: one patient had ultrasonography to confirm the integrity of the adjacent vein and the other was observed because the physical

**TABLE 25-2**
**Vascular Injuries (1628) in 1368 Children in the National Pediatric Trauma Registry II and III**

| *Region* | *ICD-9-CM* | *Total* | *Lived* | *Died (%)* | *Operated (%)* |
|---|---|---|---|---|---|
| Neck | 900-901 | 249 | 196 | 53 (21) | 41 |
| Chest | 901-902 | 161 | 98 | 63 (39) | 70 |
| Abdomen/pelvis | 902-903 | 374 | 248 | 126 (34) | 50 |
| Upper Extremity | 903-904 | 497 | 494 | 3 (1) | 21 |
| Lower Extremity | 904-905 | 326 | 318 | 8 (3) | 36 |

examination was normal. Eight injures from blunt trauma were noted with 88% sensitivity and 100% specificity. One injury was listed as "indeterminate" but was confirmed on conventional arteriography as a subclavian artery injury. The authors therefore propose that CT angiography be used as the study of choice when the soft signs of vascular trauma are present on physical examination.

A recent report by Hsu and colleagues defined the clear benefit of CT angiography in assessment of pediatric extremity injuries both acutely and as an essential planning "road map" before definitive reconstruction.[24] In addition to avoiding problems with direct vessel injury, these authors cite the speed and accessibility of CT scanners and the ability of CT to define three-dimensional spatial anatomy as major advantages in assessing the injured child. Three-dimensional reconstructions precisely define level of injury and efficiency of collateral circulation (Fig. 25-1). However they may require a higher volume of contrast medium.

Duplex Doppler and B-mode ultrasonography are emerging, noninvasive, portable technologies that supplement clinical imaging with determination of flow and flow velocity. Their role in the diagnosis of acute injury, however, has not been well established. Because both CT and magnetic resonance imaging (MRI) are limited in accurate identification of spasm, Doppler flow studies can be extremely useful for both diagnosis and follow-up. Transesophageal echocardiography may also provide useful data in the evaluation of thoracic truncal injuries in particular.[25] "One-shot" emergency department arteriography, despite reports of safety and efficacy, has essentially been replaced by CT angiography.[26]

**FIGURE 25-1** Computed tomographic angiogram from a 5-year-old hit by a car. He underwent repair of transposition of the great vessels as an infant and was noted to have a pulseless right foot. Evaluation demonstrated a clinically silent femoral artery disruption.

## Traumatic Injuries

Traumatic injuries can be divided into those involving the torso (neck and trunk) and those involving the extremities (upper or lower). Each area presents unique challenges to accurate diagnosis and timely management.

### TORSO INJURIES

Torso injuries in the cervical region appear to be rare in childhood, although they are more common in metropolitan areas with a higher incidence of pediatric penetrating trauma from missile and stab wounds.[12,23] Cox and associates' review of the operative management of 36 children with vascular injury included 9 children with 11 carotid or jugular injuries.[13,27] Eight of these injuries were penetrating neck wounds. Mortality occurred in 2 of the 3 hemodynamically unstable children. Their updated publication of 2009 identified 14 patients with 20 head and neck vascular injuries, of which 53% were of a penetrating mechanism. Of the 8 children managed in our unit, 5 were victims of penetrating trauma, including all 3 fatalities, each of whom presented with nonsurvivable injuries. Rozycki and colleagues evaluated their proposed algorithm for diagnosis of blunt cervical vascular injury by reviewing injuries associated with a cervicothoracic seat belt sign in 797 motor vehicle accident victims treated over 17 months by the Grady Memorial Hospital Trauma Service.[28] The 3% of patients with carotid injury were all adults. No injuries were missed, and no injuries were noted in children. With the gradual increase in child restraint law compliance, this potential association between seatbelt marks and significant vascular injury will require continued close follow-up.

Thoracic and abdominal torso vascular injuries are also relatively rare in childhood. This is probably the result of the greater elasticity of young and healthy vessels. Although children are not immune to thoracic vascular disruption, most series that include pediatric patients demonstrate a low incidence compared with adults. The report by Cox and colleagues included abdominal vascular injuries in 39 children and thoracic vascular trauma in 13 patients.[27] Fifty-four percent of the abdominal injuries and 46% of the thoracic injuries stemmed from blunt trauma. A higher percentage of the injuries specific to the aorta were by blunt mechanism, whereas nonaortic injures—such as great vessel, mammary, and pulmonary vein injuries—were from traumatic missiles. In general, clinical reports of aortic injuries seen in children suggest a natural history no different from that of adults. Mortality is extremely high, especially for children with a presenting systolic blood pressure below 90 mm Hg and those with associated severe traumatic brain injuries.[13] Eddy and colleagues reviewed the King County Coroner's records over a 12-year period (1975–1987), and found 13 cases of aortic disruption in children.[29] Only 3 of these children reached a hospital alive, and just 1 child survived. Experience in the NPTR is somewhat more heartening in that 26 of 54 children with aortic ruptures (48%) survived to hospital discharge. This representative sample from multiple contributing hospitals in North America is similar to that reported from a single institution by Cox and colleagues, suggesting that outcome from this catastrophic injury may be better than what has been

consistently reported for adults.[27] Major thoracic venous injuries are even less common and are usually associated with major pulmonary disruption.

Because of the preponderance of blunt mechanisms of injury in the pediatric population, especially as the result of vehicular-related mishaps, abdominal vascular injuries can and do occur.[30] Arterial disruption is far less common than venous disruption. Hypotension progressing to frank shock is the most common associated finding, making the decision to explore the abdomen relatively straightforward, although usually there is the expectation of solid viscus derangement as the most likely cause. Fayiga and colleagues reviewed 18 years of experience in operative management of pediatric blunt vascular injury.[31]

Twenty-one major abdominal venous injuries were present in 17 patients and were lethal in 11 of them (65%). None of the abdominal venous injuries was recognized before laparotomy. As in numerous other series, survival was directly related to the presence of hemodynamic stability. Most complications were related to nonvascular injuries. The majority of vascular injuries were repaired directly, which parallels the experience from a similar series of 16 abdominal vascular injuries reported by Cox and colleagues.[27] Interposition grafts were required to repair only one aortic disruption and one superior mesenteric artery transection.

## EXTREMITY INJURIES

Vascular extremity injuries are uncommon in children. Most are associated with fractures, although the rising tide of violent crime is also driving an increase in penetrating mechanisms. As in the adult, careful and expeditious clinical examination is the critical starting point. Evidence of diminished peripheral flow may be the result of spasm (discussed in detail further on) with or without associated vascular disruption. In the absence of hard signs of disruption, imaging assessment using ultrasonography or CT angiography may be required to define the cause of distal ischemia. The use of stents for angiographically identified injuries is becoming more common in the adult population. However it is still rare and controversial in children.[32,33] Migration and stent impact on subsequent growth are still undefined, making formal operative repair the recommended option for vascular disruption. Chang's[33] report of use of a stent to treat an axillary arterial and venous stab wound includes follow-up that documents critical stenosis mitigated by adequate collateralization. The authors make a strong case, however, that this approach avoided dissection of a huge hematoma in an anatomic space that is difficult to approach safely. Future elective reconstruction, if required, will be much less difficult and dangerous than operative repair during the acute phase of injury. This experience implies a reasonable role for at least a temporizing if not definitive therapy for some vascular injuries.

Interposition of reversed contralateral saphenous vein remains the treatment of choice for all disrupted segments. Synthetic material should be considered only as a last resort when an autologous vessel cannot be harvested and fabricated into a patch or conduit.[7] Veins should be repaired before arteries. Anastomoses are constructed using monofilament simple sutures.[8] As the repair is being completed, the distal clamp is first released to confirm adequate backflow. The proximal clamp is then released to flush any residual air or clot before the final sutures are tied. Vasospasm if significant can usually be reduced by gentle mechanical dilation, using coronary artery dilators, topical 2% lidocaine, or papaverine. Investigators emphasize that the high proclivity for prolonged vasospasm can make arterial anastomosis in childhood especially challenging.[31] LaQuaglia and associates described experience in nine children with iatrogenic arterial injuries repaired using microsurgical technique using 9-0 to 11-0 nylon suture.[34] As microsurgical technique continues to evolve and better suture materials become available, this approach will become an increasingly valuable adjunct to the management of major injuries to tiny vessels. If ischemia time has been prolonged longer than 6 hours, the possibility of evolving compartment syndrome should spark consideration for fasciotomy.[35] Children who have undergone repair of injuries should undergo anticoagulation for 48 hours postoperatively. Some authors use heparin, whereas others simply use dextran solutions for 2 to 3 days postoperatively.

Although lower extremity vascular injuries are most commonly associated with fractures and soft tissue avulsions, the rising incidence of violence in our urban youth is increasing the frequency of disruption of groin and femoral vessels.[12] Popliteal injuries are often the result of sport and cycling mishaps associated with a skeletal fracture and warrant particular attention. Initial assessment must confirm the presence of palpable distal pulses and adequate capillary perfusion. Immediate reduction of displaced fracture fragments or subluxed joints will often result in restoration of palpable distal pulses. Reed and colleagues reported their experience with seven children with popliteal arterial injury who underwent immediate operative repair. Four had blunt trauma and three had penetrating injuries.[36] Associated morbidity included three fractures, four severe soft tissue wounds, and one nerve injury. All patients underwent angiography; three cases were intraoperative. Treatment included two primary repairs and four vein graft bypasses. One child required fasciotomy; there were no deaths, amputations, or reoperations. At the time of their report, follow-up ranged between 10 and 42 months. All patients had normal Doppler pressures or distal pulses, or both. These data illustrate the relationship between prompt, aggressive treatment and successful outcome. The potential for development of delayed pseudoaneurysm, which usually requires excision with vein grafting, mandates that every child with an extremity vascular injury be followed for at least 5 years.

Upper extremity vascular injury is most often associated with supracondylar fractures or penetrating trauma. Supracondylar fractures may disrupt brachial arterial flow by direct injury or by compression with or without prolonged spasm.[37] As with the lower extremity, definitive management begins with assessment of adequacy of perfusion and confirmation of integrity of the vessel. Of interest is a recent report that describes the use of the ipsilateral basilic vein as an ideal interposition graft for reconstruction of vessels in which segmental loss has occurred.[38] Axillary stretch injuries, especially when associated with high energy such as vehicular ejection, may disrupt arterial or venous structures, producing a hematoma that is not as precisely definable as those seen with more distal injuries. In addition to signs of obvious blood loss, diffuse edema of the axilla or shoulder region and diminution of peripheral pulses should prompt angiographic confirmation of both the existence and anatomic configuration of the

injury. Salvage from damage of upper extremity injuries is generally good, with return of functionality related to the nature of the associated musculoskeletal and neurologic disruption. The incidence of compartment syndrome as a result of prolonged ischemia in the upper extremity is reported to be significantly lower than that for lower extremity injuries. However careful follow-up for adequacy of perfusion and avoidance of potential postischemia muscular contracture must be part of long-term management.

### Mangled Extremity

The vast majority of extremity vascular injuries seen in children are associated with axial skeletal disruption. In its most severe form, this combination of bone and soft tissue destruction can result in what has been called the "mangled extremity." It is usually characterized by major soft tissue avulsion that can be associated with significant tissue loss. Initial assessment must consider tissue viability, anticipated limb function, and the need for amputation of a potential source of massive tissue necrosis and sepsis. The Mangled Extremity Severity Score (MESS) has been proposed as an accurate system of evaluation and prediction of limb salvage (Table 25-3). Although originally devised for adults, Fagelman and colleagues demonstrated a predictive accuracy of 93% when it was retrospectively applied to 36 injured children.[39]

Vascular disruption associated with fractures must be immediately addressed so that subsequent axial skeletal repair will produce a viable extremity. Restoration of flow may be achieved by temporary bypass until fracture fixation is achieved. When possible, venous repair should precede arterial repair. Devitalized tissue must be debrided and fasciotomy considered. Nerve function must be evaluated and documented before debating amputation. Although it is true that children do recover amazingly well from what initially appear to be devastating injuries, being permanently disabled by an insensate, immobile extremity is a poor alternative to an active life with a functional and properly fitted prosthesis. The decision to amputate is therefore based on assessment of limb viability and prediction of limb functionality. The Mangled Extremity Severity Score serves as a reasonable guideline, although the ultimate decision rests with the surgeon, the child's parents, and when possible the child.

**TABLE 25-3**
**Mangled Extremity Severity Score (MESS)**

| | |
|---|---|
| Skeletal/soft tissue injury | |
| Low energy (stab, simple fracture, pistol or gunshot wound) | 1 |
| Medium energy (open or multiple fractures, dislocation) | 2 |
| High energy (high-speed crash or rifle gunshot wound) | 3 |
| Very high energy (high-speed injury, gross contamination) | 4 |
| Limb ischemia | |
| Reduced/absent pulse, normal perfusion | 1* |
| Pulseless, paraesthesias, poor capillary refill | 2* |
| Cool, insensate, paralyzed, numb | 3* |
| Shock | |
| Systolic BP always >90 mm Hg | 1 |
| Transient hypotension | 2 |
| Persistent hypotension | 3 |
| Age (yr) | |
| <30 | 1 |
| 30-50 | 2 |
| >50 | 3 |

*Score doubled for ischemia >6 hours.
MESS >7 = 100% prediction for amputation
BP, blood pressure.

## Iatrogenic Injury

With continued evolution of increasingly sophisticated methods of imaging for infants and children, the potential for damage to the vascular integrity of a small child or tiny infant remains ever present. There have been numerous reports over the past decade describing this particular problem.[40–43] Many have been case reports of complications from some usually innocuous maneuver of routine care. Demircin and associates, for example, reported an infant with brachial arterial pseudoaneurysm resulting from inadvertent puncture during antecubital venipuncture.[10] The lesion was repaired by direct suture under proximal compression. Gamba and colleagues reviewed their experience with iatrogenic vascular lesions in low-birth-weight neonates. Of 335 infants encountered between 1987 and 1994, 9 (2.6%) were diagnosed with vascular injury.[44] Mean birth weight was 880 g (range 590-1450 g), although mean weight at diagnosis was 1825 g (range 1230-2730 g). Injuries were associated with venipuncture in seven of the nine cases and included six femoral arteriovenous fistulas, two of which were bilateral. One carotid lesion and five femoral arteriovenous fistulas were repaired using microvascular technique. Outcome as determined by follow-up clinical examination and Doppler flow was excellent, leading the authors to emphasize the role of aggressive medical and microsurgical management of these injuries. In 1981 O'Neill and colleagues reviewed their experience with surgical management of 41 infants with major thromboembolic problems associated with umbilical artery catheters.[45] Although the majority of complications were related to emboli distal to the femoral artery, 8 infants required emergency operative intervention for acute aortic obstruction. Four of these operations were transverse aortic thrombectomies; three patients recovered completely. As principles of umbilical artery catheter management have become better established, these problems appear to have become less frequent.

In their analysis of the predictive accuracy of clinical findings in pediatric vascular injury, Reichard and colleagues extolled the accuracy of the ankle-brachial index (ABI) as indicative of inadequate peripheral perfusion.[18] Their data suggest that an ABI less than 0.99 indicates clinically critical vascular injury and reinforce recent reports of intensive care nursery discharge data that suggest the true incidence of vascular injury is far more common than previously thought. In fact, findings reported by Seibert and colleagues suggest that assessment of the peripheral pulses and measurement of the ABI should be part of a routine postdischarge assessment of any infant treated with umbilical artery catheterization.[46]

The increasing use of complex endovascular diagnostic and therapeutic procedures in pediatric patients is also associated with a low but consistent incidence of unplanned iatrogenic damage to vascular structures.[9,42,47] However, with refinement of technique and improving technology, this also appears to be decreasing.[9,48] Morbidity from these iatrogenic

injuries occurs primarily in the neonatal period when small vessel diameter and vasospastic tendencies predispose to ischemia. Long-term consequences of such injuries include soft tissue loss, amputation, limb growth discrepancies, and the ultimate need for surgical reconstruction of these deformities. As CT and MRI-based angiography becomes more common and diagnostic, incidence of injuries directly related to vascular access for traditional angiography may be minimized.

Lin and associates analyzed 1674 diagnostic or therapeutic catheterizations performed in 1431 infants over a 15-year period.[49] Thirty-six procedures were required in 34 children. The authors stratified complications into nonischemic, acute femoral ischemia, and chronic femoral ischemia. Nonischemic lesions included pseudoaneurysms (n = 4), arteriovenous fistulas (n = 5), and groin hematoma (n = 5), and all underwent direct suture repair. Acute femoral ischemic lesions were most common and required a variety of procedures from thrombectomy to patch repair. Seven children presented with chronic femoral ischemia, defined as having evidence of flow disruption more than 30 days after the procedure, at an average of 193 days (range 31-842 days) after the index intervention. All seven children were symptomatic with claudication, leg length discrepancy, or gait disturbance. Operative repair consisted of revascularization using reversed saphenous vein for iliofemoral bypass in five children and femorofemoral bypass in one child. One child required patch only angioplasty. Risk factors for ischemia included age younger than 3 years, need for therapeutic or multiple catheterizations, and catheter size larger than 6 French. The value of this study lies not only in its identification of potentially predictive factors but also in its documentation of the relatively short time interval required for chronic ischemia to become symptomatic.

Children at risk of vascular injury with any abnormal clinical finding must be followed at least 5 years and preferably through at least the start of adolescence. The evolution of limb length discrepancy as a result of disruption of a major vascular structure may not become manifest until years after the precipitating event.[50] Recent reports have suggested that operative revascularization of iatrogenic injury before adolescence will correct some limb length discrepancy; however, these reports have been relatively small series and do not represent consensus.

The femoral artery remains the most common site of iatrogenic injury. As noted previously in the discussion of traumatic injury, efficient collateralization of the pelvis and gluteal region may result in these lesions remaining clinically silent throughout most of childhood. Mourot and colleagues reported their experience with ischemia after femoral arterial line placement in the pediatric burn population.[51] In a group of 234 children who underwent 745 femoral artery catheterizations, 8 patients developed loss of distal pulses, indicating occlusion or spasm of the femoral artery. Five children responded to nonsurgical treatment consisting of catheter removal and systemic heparinization. The other 3 patients required surgical thrombectomy.[51] The authors point out the importance of timely removal of foreign bodies from vessels in ischemic limbs with both vasospasm and occlusion for prevention of tissue loss.

Extracorporeal membrane oxygenation (ECMO) represents another area in which iatrogenic vascular injury may result in long-term consequences. Many authors advocate preferential use of venovenous ECMO over venoarterial ECMO because of uncertainty over the potential long-term consequences of neonatal carotid artery injury.[52] For patients requiring carotid artery cannulation, scientific inquiry continues to ensue over whether carotid artery reconstruction should be performed at decannulation, particularly in the neonatal population. Sarioglu and associates reported their experience in 61 infants with carotid artery cannulation for ECMO. End-to-end carotid artery repair was performed in 32 patients and simple ligation in 29 patients.[53] Early patency rate as evidenced by MRI and ultrasonography was 97%, although 12% appeared stenotic. These authors recommend routine carotid artery repair when technically feasible. Longer term patency after carotid artery reconstruction following ECMO for congenital diaphragmatic hernia was assessed by Buesing and associates in 18 infants.[54] All underwent three-dimensional MRA 2 years after the procedure and the common carotid artery was occluded or highly stenotic in 72% of the patients. All had patent internal carotid arteries and evidence of both intracranial and extracranial collateral vessel development. They also noted that unsuccessful repair of the artery was not predictive of a poor neurologic outcome. They concluded that the benefits of surgical repair are "doubtful" but that longer term assessment is still required. A recent report from Duncan and associates points out two cases of aneurysms at the site of carotid artery repair after ECMO, highlighting a potential complication of repair.[55]

## Vasospasm

As is the case with management of traumatic injury, the high proclivity for spasm and the need to differentiate prolonged spasm from arterial disruption remains one of the most challenging components of initial assessment. Prolonged spasm is felt to be the result of intimal injury, which causes derangement of nitric oxide production and disrupts control of arterial wall tension.[56,57] When endothelial-medial contact is lost, as can be caused by shearing friction from an oversized or overzealously placed catheter, underlying vascular smooth muscle is incapable of relaxation.[58] Angiographic confirmation of spasm requires the additional risk of the very mechanism suspected of causing the problem. CT or MRA may be the solution to this clinical conundrum, although dose and concentration of contrast medium must be carefully considered in comparing risk to benefit.

The role of spasm in causing gangrene is controversial despite case reports suggesting cause and effect.[59] From a clinical perspective once spasm has been confirmed to be the sole cause of diminished peripheral perfusion, management must focus on confirmation of evidence of tissue viability and absence of signs of evolving compartment syndrome or peripheral ischemia. Assuming that the basic cause of acute spasm is at least partly related to intimal injury, risk of thrombosis must be a primary consideration. Over the past few years, routine anticoagulation therapy has been supplemented by thrombolytic agents, especially urokinase.[60] Recommended doses of urokinase vary and tend to be empirical. Up to 6000 U/kg/hr have been used in infants with good success and no complications. Most recently, a report by Zenz and colleagues on the use of tissue plasminogen activator suggested that more rapid restoration of flow could be

achieved with this drug.[61,62] Some patients may still require operative intervention for thrombectomy after a period of time in a low-flow state.

## Digital Ischemia Syndrome

Intravenous catheter-related, ipsilateral digital ischemia may suddenly develop in acutely ill infants or small children with acute infectious disease. It is usually associated with dehydration and hypovolemia. In a review of 104 cases, Villavicencio and González Cerna reported primary involvement of the hand in 68.2% of patients and the foot in the remainder.[63] The age of the patients ranged from 29 days to 36 months; the mean age was 14 months. The infectious process was of respiratory origin in 27.8% of cases, localized to the gastrointestinal tract in 60.5%, and other areas in 11.5%. The most frequently cultured microorganisms were *Escherichia coli, Salmonella, Shigella, Streptococcus, Staphylococcus, Klebsiella*, and *Pseudomonas* species. Digital cyanosis usually occurs shortly after vessel cannulation and is probably the result of vasospasm provoked by the presence of an indwelling catheter. As described earlier, damaged endothelium may stimulate vasoconstriction. Immobilization causes constriction of the limbs and impairs the muscle action that is necessary to assist venous return. Persistence of these conditions increases extravascular pressure and gradually produces microcirculatory failure, leading to necrosis, which begins at the most distal areas of the digits.

Effective treatment requires prompt recognition of persistent cyanosis, correction of the underlying systemic disorder, and immediate removal of the catheter. Anticoagulation therapy should be initiated immediately. Application of nitroglycerin paste has been shown to improve local microcirculation and limit the extent of ischemic necrosis.[64,65] Lesions should be gently washed daily in warm water, and the involved limb should be actively and passively exercised through the full range of motion. Direct heating should be avoided because ischemic tissue burns at lower temperatures. Small pieces of cotton should be placed between fingers or toes; all lesions should be covered with sterile, dry dressings. Areas of dry gangrene do not require surgical removal. If there is concern whether infection is trapped under eschar, the area can be gently elevated at its corners to allow adequate drainage. As is the case with arterial lesions, amputation should not be considered until clear demarcation has occurred.

## Conclusion

In summary, although the epidemiology of vascular injury in the pediatric population is considerably different from that encountered in adults, treatment imperatives remain the same. Traumatic injury presents a unique set of characteristics that reflect the epidemiology of pediatric trauma. All vascular injuries, if carefully managed, can exploit the intrinsically healthy status of the child's vascular system and yield optimal results. Iatrogenic injury is the price of miniaturization. It is a recognized tradeoff for the dramatic advances that now make possible many lifesaving procedures. Attention to detail in those most at risk may not eliminate the problem but will at least reduce incidence and raise awareness. Accurate diagnosis, timely revascularization, and aggressive management of reperfusion are essential for complete recovery and normal long-term growth. The key to success is a high index of suspicion, recognition of the unique characteristics listed earlier, and operative intervention using the high level of precision that is the cornerstone of success in the surgical care of children.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 26

# Burns

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The cornerstone of burn management stems from decades-long advances in the understanding of major burn sequelae. In 1944, Lund and Browder introduced a diagram to assess burned areas, allowing a quantifiable assessment of percentage of total body surface area (TBSA) burned.[1] While treating victims of the Coconut Grove fire in Boston in 1946, Oliver Cope and Francis Moore were able to quantitate the appropriate amount of fluid required to maintain the central electrolyte composition after "burn shock."[2] From there, the development of the Parkland formula transformed our approach to fluid resuscitation. In the 1960s, the discovery of efficacious topical antimicrobial agents, such as 0.5% silver nitrate,[3] mafenide acetate (Sulfamylon),[4] and silver sulfadiazine (Silvadene),[5] likewise revolutionized burn wound care, and when used adjunctively with early debridement and grafting, the rates of wound infection and graft failure decreased dramatically. In recent years, continued progress has been made in several areas of burn care. Early surgical excision of eschar and grafting has significantly lowered the incidence of burn wound sepsis and shortened length of hospital stay. The nutritional support with early enteral feeding has been found to blunt the hypermetabolic response that contributes to derangements in gut function and immunomodulation seen with severe burns. Treatment with anabolic agents restores net positive nitrogen balance during prolonged postburn hypermetabolic period. Acute recognition of inhalation injury and effective treatment have also improved overall burn patient outcome. These examples of significant recent advances made in burn care have led to a further decline in burn-related deaths.[6] Today, the overall increase in survival of major burn victims is most evident in the pediatric burn population, where mortality rate is 50% for 98% TBSA burns in children 14 years old and younger and 75% TBSA burns in other age groups.[7]

Hence, burn injuries that were once considered to be uniformly fatal are now survivable, in part because of vigorous efforts to promote evidence-based care of the burned patient. Despite implementation of aggressive prevention measures and legislation, nearly one million people sustain a total of 2 million burn injuries yearly in the United States alone, and one half of these require medical treatment. Approximately 60% of the 40,000 admissions for burn injury are now admitted to hospitals with specialized burn centers.[8] The majority of burns are minor and represent less than 10% TBSA, and although the mortality rate for all burns is 3.7%, mortality increases dramatically with larger TBSA burns (42% to 81% for 60% to greater than 90% TBSA). Although mortality from burn injury increases with advancing age and burn size, the presence of an inhalation injury in patients with a TBSA of less than 20% significantly increases the likelihood of death by 25 times (National Burn Repository 2010). Unfortunately, those at the extremes of age continue to have worse outcomes, likely related to their unique physiology. Burns in children, particularly those less than 5 years of age, represent 17% of total reported burn cases and constitute a large at-risk population in which burn injuries are responsible for nearly 2,500 deaths per year. The percentage of admissions accounting for child abuse–related burn injuries varies, but is estimated to be anywhere from 1% to 25%, with infants and toddlers comprising the majority of these cases.[9]

Accounting for more than 70% of reported instances, the most common etiologies of burn injuries are fire/flame and scalds. Scald burns remain the most common cause of burn injury in children younger than 5 years of age. The majority of scald burns in infants and toddlers are from hot foods and liquids. Hot grease spills are notorious for causing deep burns. Hot tap water burns frequently result in larger TBSA injuries in children and can easily be averted by installing faucet valves that prevent water from leaving the tap if its temperature is greater than 120° F (48.8° C). Children also frequently suffer contact burns to their hands and faces from curling irons, ovens, steam irons, and fireworks. In the adolescent age group, flame burns are more common, often occurring as a result of experimentation with fire and volatile agents. Particular consideration must be given to burn injuries secondary to child abuse, which also represents a significant cause of burns in children. Burns with a bilaterally symmetrical or stocking-glove distribution in conjunction with a delay in seeking medical attention should raise the suspicion of child abuse (Fig. 26-1).

## Pathophysiology

As the largest organ in the body, the skin guards against harmful environmental insults, prevents entry of microorganisms, maintains fluid and electrolyte homeostasis, and is critical for thermoregulation. Other important functions include

FIGURE 26-1 Scald burn from child abuse of an infant. Bilateral stocking-glove distribution with well-demarcated margins is consistent with a burn injury from abuse.

vitamin D metabolism and processing neurosensory inputs. The total surface area of skin ranges from 0.2 to 0.3 $m^2$ in an average newborn to 1.5 to 2.0 $m^2$ in an adult, making up nearly 15% of total body weight. The epidermis is composed primarily of epithelial cells, the most abundant of which are keratinocytes. Cells are generated at the stratum basale, from which they divide and migrate upwards through the strata spinosum, granulosum, lucidum, and finally, the stratum corneum. As they move through layers, the keratinocytes begin to flatten out, their nucleus degenerates, and they secrete a matrix made of lipids, cholesterol, and ceramides, which increases cohesion between the cells and is responsible for the barrier characteristic of skin. Once at the stratum corneum, the keratinocytes become corneocytes-anucleate cells that are filled with keratin, and the complete transformation is termed keratinization. Eventually, the corneocytes lose their cohesion and slough off. This entire process of epidermal maturation from the basal layer to desquamation generally takes 2 to 4 weeks.

The basement membrane at the dermoepidermal junction is composed of mucopolysaccharides rich in fibronectin, and the basement membrane functions as a barrier to the passage of macromolecules. The dermis, consisting of fibroblasts that produce collagen and elastin, is subdivided into a superficial papillary dermis and a deep reticular dermis. The papillary dermis is rather functionally active, and because it is this layer that is lost in deeper partial-thickness burns, such injuries tend to heal much more slowly than superficial partial-thickness burns.[10] A plexus of nerves and blood vessels separates the papillary and reticular dermis, and the reticular dermis and hypodermis (subcutaneous tissue) contain skin appendages, such as hair follicles, sweat glands, and sebaceous glands. Therefore burns involving the depth of deep dermis are generally insensate to touch and painful stimuli.

Thermal injury produces coagulation necrosis of the epidermis and a varying depth of injury to the underlying tissue. The extent of burn injury depends on the temperature, duration of exposure, skin thickness, tissue conductance, and specific heat of the causative agent. For example, the specific heat of lipid is higher than that of water, and therefore grease burns often result in much deeper burns than a scald burn from water with the same temperature and duration of exposure. Thermal energy is easily transferred from high-energy molecules to those of lower energy during contact through the process of heat conduction. The skin generally provides a barrier to the transfer of energy to the deeper tissues, and hence, much of the burn injury is confined to this layer. However, local tissue responses to the zone of the burn injury can lead to progression of the burn injury, with the result being a much deeper burn of the surrounding tissue than initially observed.

Classified according to the depth of injury, burns are described as superficial, superficial partial-thickness, deep partial-thickness, full-thickness, and subdermal (Fig. 26-2). Superficial (*first-degree*) burns, like sunburns, affect only the epidermis and are characterized by erythema, pain, and desquamation that resolve without scarring within 7 to 10 days. Superficial partial-thickness (*second-degree*) burns extend through the epidermis into the papillary dermis and are characterized by blisters, erythema, and edema. These burns blanch with pressure and have a brisk capillary refill. Deep partial-thickness (*second-degree*) burns involve the reticular dermis and exhibit a more sluggish capillary refill. The wound is very moist and edematous with diminished to complete loss of sensation. The tissue injury of full-thickness (*third-degree*) burns extends into the subcutaneous tissue and can have a leathery appearance, whereas that of subdermal (*fourth-degree*) burns extends into the fascia, muscles, and bone.

The early response to a burn can be described as local and systemic. The local phase response is characterized by three zones: coagulation, stasis, and hyperemia (Fig. 26-3). Representing the product of maximal insult, the zone of coagulation is identified by surface tissue necrosis as cells are irreversibly damaged secondary to denaturation and coagulation of constituent proteins and loss of plasma membrane integrity. The area immediately surrounding the necrotic area is called the zone of stasis. In this zone, most cells are initially viable, but tissue perfusion becomes progressively compromised because of the local release of inflammatory mediators, such

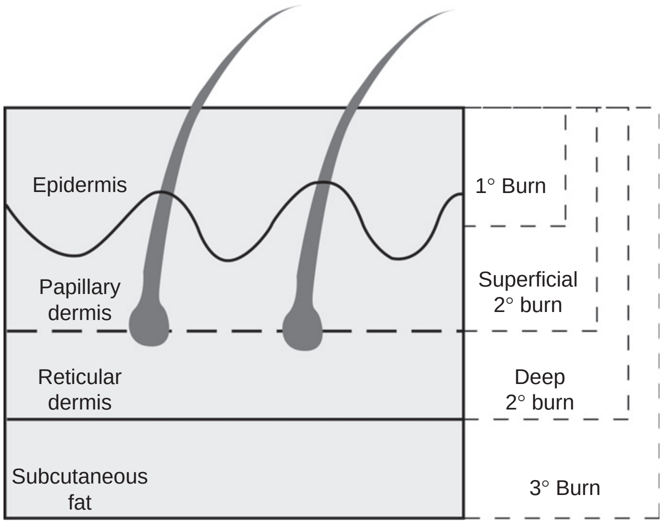


FIGURE 26-2 Depths of burn. First-degree burns are confined to the epidermis. Superficial second-degree burns involve the papillary dermis, and deep second-degree burns involve reticular dermis. Third-degree burns are full-thickness through the epidermis and dermis.

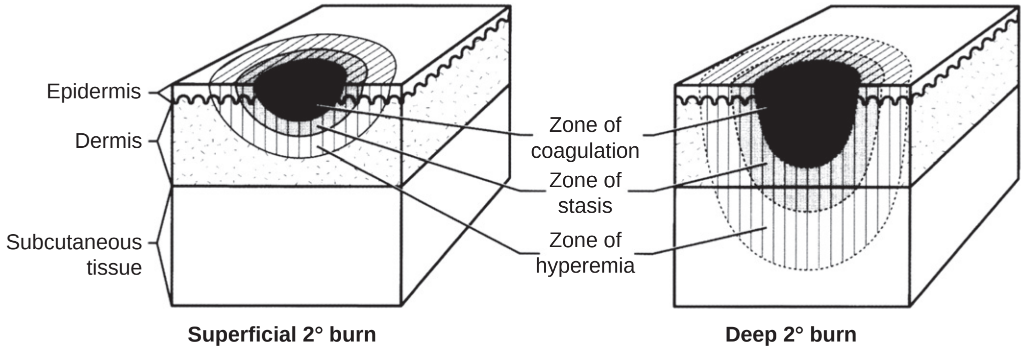


FIGURE 26-3 Three zones of burn injury: coagulation, stasis, and hyperemia.

as thromboxane $A_2$, arachidonic acid, histamine, oxidants, and cytokines. Their influence on the microcirculation results in the formation of platelet thrombus, neutrophil adherence, fibrin deposition, and vasoconstriction, all of which lead to cell necrosis and progression of the burn injury. However, adequate wound care and resuscitation may reverse this process and prevent extensive cell necrosis.

Thromboxane $A_2$ inhibitors, antioxidants (vitamins C and E), and bradykinin inhibitors can significantly improve dermal blood flow and thereby limit the expansion of the zone of stasis. Recently, activated protein C, a physiologic anticoagulant with antithrombotic and anti-inflammatory properties, was shown to improve perfusion in the zone of stasis and decrease the area of necrosis in animal models.[11] Similarly, statins are known to have multiple effects, such as decreasing oxidative stress while up-regulating endothelial nitric oxide synthesis, prostacyclins, and tissue-type plasminogen activator. In another animal model study, the administration of simvastatin was shown to increase blood flow and decrease intravascular coagulation, which resulted in salvage of the zone of stasis.[12] Finally, the zone of hyperemia lies peripheral to the zone of stasis and is characterized by vasodilatation with subsequent increased blood flow and edema resulting from the inflammatory response. Tissue within this zone frequently recovers unless affected by severe sepsis or prolonged hypoperfusion.[13]

The mechanisms involved in the response to burns are rather complicated but interconnected. The initial tissue loss sets off a chain of reactive processes, beginning with activation of toxic inflammatory mediators, such as oxidants and proteases, that not only further damages tissue and capillary endothelial cells but also potentiates further tissue necrosis. Both complement and neutrophil activation results in the production of cytotoxic reactive oxygen species and histamine, which mediates progressive vascular permeability.[14] Disruption of collagen cross-linking and loss of cell membrane integrity compromises osmotic and hydrostatic pressure gradients, resulting in local edema and exacerbation of marked fluid shifts.[10] Thus burn wound progression is compounded by the presence of edema, infection, and hypoperfusion.

The burn-induced inflammatory response is not limited to the local burn wound. A massive systemic release of thromboxane $A_2$, along with other inflammatory mediators (bradykinin, leukotrienes, catecholamines, activated complement, and vasoactive amines) induces a significant physiologic burden on multiple organ systems, particularly the cardiopulmonary, renal, and gastrointestinal systems. Decreased plasma volume resulting from increased capillary permeability with a subsequent plasma leak into the interstitial space can lead to depressed cardiac function. As a result of low cardiac output, renal blood flow can decrease, leading to a diminished glomerular filtration rate. Activation of other stress-induced hormones and mediators, such as angiotensin, aldosterone, and vasopressin, can further compromise renal blood flow, resulting in oliguria. If not promptly recognized and treated, this condition can progress to acute tubular necrosis and renal failure, which contributes to poor outcomes in burn patients.

Burn injury can also affect remote organ systems, such as the gastrointestinal tract. Splanchnic vasoconstriction can cause transient mesenteric ischemia and a rapid onset of atrophy of the small bowel mucosa resulting from increased epithelial apoptosis and decreased epithelial proliferation. Moreover, studies have found that intestinal permeability to macromolecules increases after burns, lending an explanation to how bacterial translocation and subsequent endotoxemia ensue. Burn injury also causes a global depression of immune function. Macrophage production and cytotoxic T-lymphocyte activity are decreased, and neutrophils become impaired in terms of diapedesis, chemotaxis, and phagocytosis. Taken together, these impairments in function contribute to an increased risk for infectious complications after burns.

# Acute Management

## INITIAL EVALUATION

The burn patient must be immediately removed from the source of burn injury and potential life-threatening injuries quickly assessed and addressed independent of the cutaneous burns, as in the case of a multiple-trauma victim. Burning clothing articles and metal jewelry are quickly removed. Immediate cooling, such as pouring cold water on the burn wound, can minimize the depth of burn injury but must be used with extreme caution in a small TBSA burn because doing so can result in systemic hypothermia. In the case of chemical burns, victims should be promptly removed from the continued exposure to the causative chemical agent(s) and the wounds irrigated with copious amounts of water, taking caution not to spread chemical on burn wounds to adjacent uninvolved skin areas. Attempts to neutralize chemicals

are contraindicated, because this process may produce additional heat and further add insult to the initial burn injury.

As with any trauma patient, burn patients are quickly assessed through primary and secondary surveys. Airway, breathing, and circulation status are assessed, and any potential life-threatening conditions should be promptly identified and managed as deemed appropriate. Respiratory symptoms, such as wheezing, tachypnea, or hoarseness, may signify an impending major airway problem. Therefore the airway should be rapidly secured with 100% oxygen support. Oxygen saturation is monitored using pulse oximetry, and chest expansion is observed to ensure adequate and equal air entry. Circumferential full-thickness burns to the chest can significantly impair respiratory function by constricting the chest wall and preventing adequate chest expansion. If necessary, escharotomy should be performed to allow for better chest expansion and subsequent ventilation. Blood pressure may be difficult to obtain in burned patients with charred extremities, and an arterial line may be necessary. One review of femoral artery catheterization in pediatric burn patients found that the complication rate was quite minimal and provided a more accurate measure of hemodynamics.[15] Nonetheless, a change in the pulse rate is a sensitive indicator for intravascular volume status, and therefore the presence of tachycardia should prompt aggressive fluid resuscitation.

The management of the burn patient depends on the depth of the injury. For superficial or first-degree burns, the treatment is focused on symptomatic relief and consists of a topical ointment containing *Aloe vera* along with a nonsteroidal anti-inflammatory agent. Superficial and deep partial thickness burns are also known as second-degree burns. The former heals spontaneously with re-epithelialization occurring within 10 to 14 days. Slight skin pigment discoloration is usually the only significant sequela. Deep partial thickness wounds, on the other hand, heal slowly over several weeks, usually with significant scarring, and generally require surgical debridement and skin grafting for a more rapid recovery and shorter hospitalization. Third-degree burns are synonymous with full-thickness injuries, and because there are no residual epidermal or dermal appendages, these burn wounds heal by re-epithelialization from the burn wound edges. As can be expected, this process is slow, requiring a prolonged hospitalization with an increased risk of burn wound infection. Fourth-degree burns, typically resulting from a profound thermal or electrical injury, involve organs beneath the layers of the skin, such as muscle and bone. The treatment for both third- and fourth-degree burns is similar in that they respond best to early debridement and grafting.

Accurate and rapid determination of burn depth is vital to the proper management of the injury. In particular, the distinction between superficial and deep dermal burns is critical because this can dictate whether the burn can be managed with or without excision and grafting. Early excision and grafting provides better results than nonoperative therapy even for so-called indeterminate burns. Because overall estimates report that clinical depth assessment is accurate in about two thirds of cases, more precise and objective methods to determine burn depth have been investigated.[16,17] One particular study examined the use of laser Doppler imaging in 48 children with burn injury and found that it could accurately predict whether a wound would need grafting or would re-epithelialize in less than 21 days.[18] A similar study reported that wounds healing within 14 days had a significantly higher perfusion on Doppler evaluation than late-healing wounds.[19] Thus laser Doppler flowmetry can be helpful in accurately predicting burn depth and wound healing capacity. Other less frequently used techniques include a punch biopsy with histologic confirmation, fluorescein fluorescence, indocyanine green video angiography, and high-frequency ultrasonography. Reflection-optical multispectral imaging and fiberoptic confocal imaging are two novel, noninvasive techniques that rely on the illumination characteristic of the tissue to determine the depth of the burn, and they may very well become the newest innovation in the field of diagnostics.[16] Ultimately, burn wound biopsy would seem to be the most precise diagnostic tool. However, this is not clinically useful, since it is invasive and can only provide static information of burn wound. It also requires an experienced pathologist to interpret histologic findings. Despite recent diagnostic advances, clinical observation still remains the standard and the most reliable method of determining the burn depth.

The size of the burn is generally assessed by the "rule of nines" in adolescents and adults. The upper extremities and head each represent 9% of the TBSA, and the lower extremities and the anterior and posterior trunks are 18% each. The perineum, genitalia, and neck each measure 1% of the TBSA. A quick rough estimate of the burn size can also be assessed by the use of the patient's palm, which represents 1% TBSA. However, the general use of this rule can be misleading in children, because of different body proportions. Children have a relatively larger portion of their body surface area (BSA) in the head and neck and a smaller surface area in the lower extremities. For instance, an infant's head constitutes 19% of TBSA compared with 9% in an adult. Thus the modified rule of nines takes into account the anthropomorphic differences of infancy and childhood, making it a more accurate assessment of pediatric burn size (Fig. 26-4). Table 26-1 also shows the chart used to estimate the percentage of TBSA burned based on age of patients and area of burns.

Full-thickness circumferential burns to the extremities produce a constricting eschar, which potentially can result in vascular compromise to the distal tissues including nerves. Accumulation of tissue edema beneath the nonelastic eschar impedes venous outflow, first resulting in a compartment syndrome and eventually affecting arterial flow. When distal pulses are absent by palpation or Doppler exam, which is not as a result of global hypoperfusion, escharotomies should be performed to avoid vascular compromise of the limb tissues. With the use of either the scalpel or electrocautery, escharotomies can be performed at bedside along the lateral and medial aspects of the involved extremities (Fig. 26-5). When the hands are involved, incisions are carried down onto the thenar and hypothenar eminences and along the dorsolateral aspects of the digits, taking care to avoid injury to the neurovascular bundle. Because burn wounds requiring escharotomies are typically full-thickness injuries, minimal bleeding is encountered. With prolonged vascular compromise, reperfusion after an escharotomy may cause reactive hyperemia and further edema formation in the muscle compartments. Ischemia-reperfusion injury also releases free oxygen radicals resulting in transient hypotension. If increased compartment pressures are noted, fasciotomy should be performed immediately to avoid permanent ischemic injuries to nerves and soft tissues.

Intravenous (IV) access should be established immediately to infuse lactated Ringer solution according to the

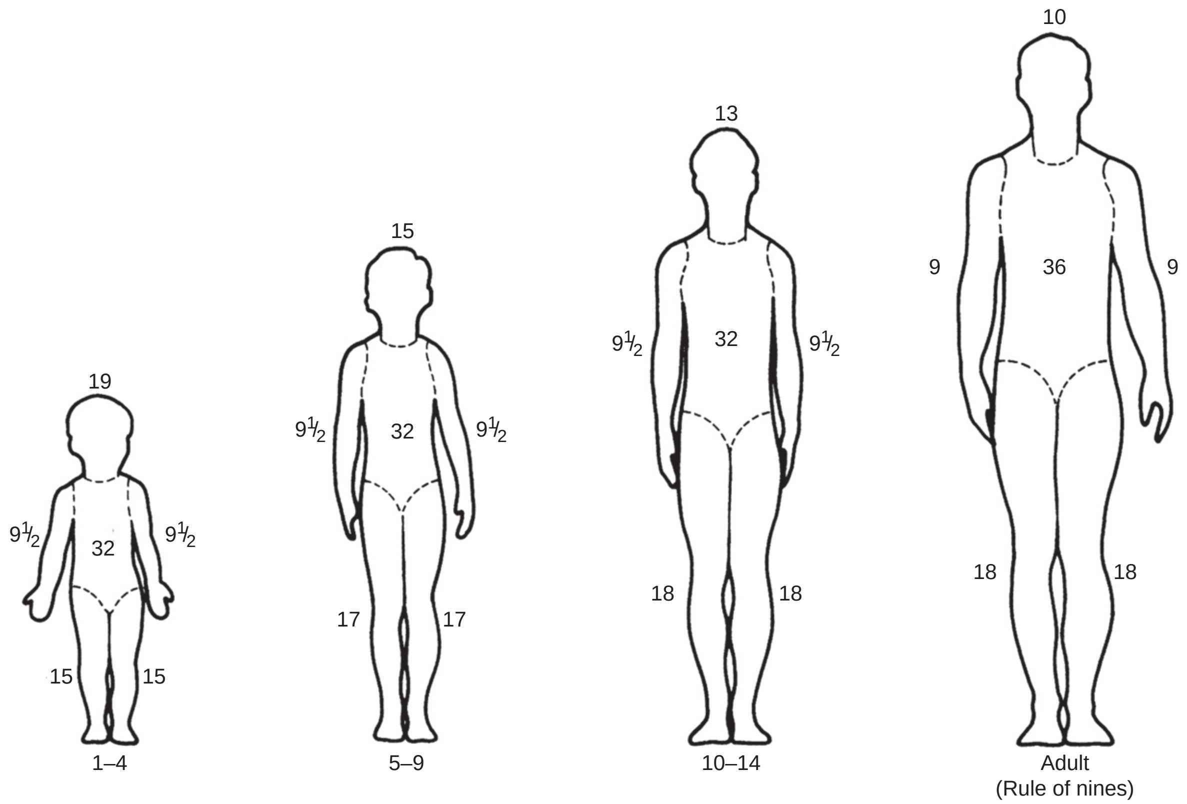


**FIGURE 26-4** Modified "rule of nines" for pediatric burn patients. (Adapted from Lee J, Herndon DN: The pediatric burned patient. In Herndon DN [ed]: Total Burn Care, ed 3. Philadelphia, Saunders, 2007, p 487.)

**TABLE 26-1**

**Burn Size Estimates Based on Area of Burn and Age Groups (Value = % Total Body Surface Area)**

| *Area* | *<1 Year* | *1-4 Years* | *5-9 Years* | *10-14 Years* | *15 Years* | *Adult* |
|---|---|---|---|---|---|---|
| Head | 19 | 17 | 13 | 11 | 9 | 7 |
| Neck | 2 | 2 | 2 | 2 | 2 | 2 |
| Anterior trunk | 13 | 13 | 13 | 13 | 13 | 13 |
| Posterior trunk | 13 | 13 | 13 | 13 | 13 | 13 |
| Buttock | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Genitalia | 1 | 1 | 1 | 1 | 1 | 1 |
| Upper arm | 4 | 4 | 4 | 4 | 4 | 4 |
| Lower arm | 3 | 3 | 3 | 3 | 3 | 3 |
| Hand | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Thigh | 5.5 | 6.5 | 8 | 8.5 | 9 | 9.5 |
| Leg | 5 | 5 | 5.5 | 6 | 6.5 | 7 |
| Foot | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |

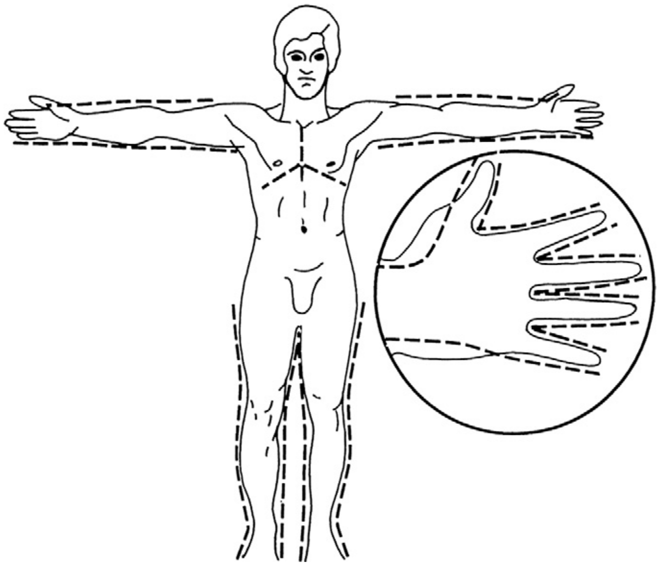

**FIGURE 26-5** Escharotomies. The incisions are made on the medial and lateral aspects of the extremity. Hand escharotomies are performed on the medial and lateral digits and on the dorsum of the hand. (With permission from Eichelberger MR [ed]: Pediatric Trauma: Prevention, Acute Care, Rehabilitation, St Louis, Mosby, 1993, p 569.)

resuscitation guideline. Peripheral IV access is preferred, but femoral venous access is an ideal alternative in patients with massive burns, particularly those involving the extremities. When vascular access becomes problematic in small children with burned extremities, the intraosseous route is another alternative option in children less than 6 years of age. However, proper technique must be used to avoid potential injury to the bone growth plate. A nasogastric tube is placed in all patients with major burns in anticipation of a gastric ileus and potential vomiting. In addition, almost immediate implementation of enteral nutrition by either a gastric or transpyloric feeding tube can mitigate burn-induced small bowel ileus. A urinary catheter should likewise be inserted to accurately monitor urine output as a measure of end-organ perfusion. Initial laboratory tests should include complete blood count, type and

**TABLE 26-2**
**Calculation Formulas for Body Surface Area**

| | |
|---|---|
| Dubois formula | BSA ($m^2$) = height (cm)$^{0.725}$ × weight (kg)$^{0.425}$ × 0.007184 |
| Jacobson formula | BSA ($m^2$) = [height (cm) + weight (kg) − 60]/100 |

BSA, body surface area.

crossmatch for packed red blood cell, chemistry, urinalysis, coagulation profile, and chest radiograph. If inhalation injury is suspected, arterial blood gas with carboxyhemoglobin level should also be determined to guide respiratory therapy.

## FLUID RESUSCITATION

Appropriate fluid resuscitation should begin promptly upon securing IV access. Peripheral IV access is sufficient in the majority of small to moderate size burns. Saphenous vein cut-downs are useful in cases of difficult access in larger patients. In children, percutaneous femoral central venous access may be easier and more reliable when confronted with a difficult peripheral IV access situation. Many guidelines exist regarding fluid resuscitation, with the administration of varying concentrations of colloid and crystalloid solutions.[20] The Parkland formula (4 mL of lactated Ringer solution per kg of body weight per percentage of TBSA burned) is most widely used, but children's fluid resuscitation guideline should be based on BSA. Children have a greater BSA in relation to weight, and as a result, weight-based formulas can under-resuscitate children with minor burns and may grossly over-resuscitate with extensive burns. Nonetheless, fluid loss is also proportionally greater in children, and consequently, they may require more fluid per kilogram. TBSA can be assessed using standard nomograms based on height and weight or calculated using formulas (Table 26-2). The Galveston formula (Shriners Hospital for Children) uses 5000 mL/m$^2$ BSA burn plus 2000 mL/m$^2$ BSA of lactated Ringer solution given during the first 24 hours after burn, with half the volume administered during the first 8 hours and the remaining half during the following 16 hours (Table 26-3).

Regardless of which guidelines are used, the primary goal of fluid resuscitation is to achieve adequate organ tissue perfusion. Fluid administration should be titrated to maintain a urine output of greater than 1 mL/kg/hr. Approximately 50% of administered fluid is sequestered in nonburned tissues in 50% TBSA burns because of increased capillary permeability that occurs particularly in the first 6 to 8 hours after injury. During this period, large molecules leak into the interstitial space to increase extravascular colloid osmotic pressure. Therefore to maintain intravascular osmotic pressure, albumin is added 12 hours after the injury. Closely mirroring a similar study in adults, one retrospective study of fluid resuscitation in pediatric burn patients noted that patients requiring albumin supplementation took significantly longer to resuscitate (30.5 vs. 22.0 hr) and received significantly more fluid than patients receiving crystalloid only (9.7 vs. 6.2 mL/kg/%TBSA). Although their outcomes were the same, the nature of their injuries was more significant, however, given the greater percentage TBSA full-thickness burn and presence of inhalation injury.[21] After the first 24 hours, 3750 mL/m$^2$ BSA burned is given to replace evaporative fluid loss plus 1500 mL/m$^2$ BSA per 24 hours for maintenance requirement (Galveston formula). Dextrose containing solution, such as 5% dextrose with {1/4} to {1/2} normal saline is used as the primary solution. Children less than 2 years of age are susceptible to hypoglycemia because of limited glycogen stores, and therefore lactated Ringer solution with 5% dextrose is usually given during the first 24 hours after burns.

**TABLE 26-3**
**Acute Burn Fluid Resuscitation Guidelines**

| *Formula* | *First 24 Hours* | *Thereafter* |
|---|---|---|
| Parkland | Lactated Ringer solution; 4 mL/kg/% TBSA burn: 50% total volume during the first 8 hr after injury and the remaining during the subsequent 16 hr | 5% dextrose with $Na^+$, $K^+$ and albumin to maintain normal serum electrolytes and colloid oncotic pressure |
| Brooke | Lactated Ringer solution (with colloid 0.5 mL/kg/% TBSA burn); 2 mL/kg/% TBSA burn; 50% total volume during the first 8 hr after injury and the remaining during the subsequent 16 hr | Titrate to maintain urine output 0.5-1.0 mL/kg/hr |
| Shriners-Galveston | Lactated Ringer solution (12.5 g albumin/L added 12 hr after injury); 5000 mL/m$^2$ BSA burn + 2000 mL/m$^2$ TBSA; 50% total volume during the first 8 hr after injury and the remaining during the subsequent 16 hr | 3750 mL/m$^2$ BSA burn + 1500 mL/m$^2$ TBSA; substitute IV fluid volume with enteral formula |

IV, intravenous; TBSA, total body surface area.

Over-resuscitation during the first 24 hours postburn has been shown to be associated with an increased incidence of pneumonia, bloodstream infection, acute respiratory distress syndrome, multiple-organ failure, and death. "Permissive hypovolemia" during burn fluid resuscitation has been shown to improve multiple-organ dysfunction, further suggesting that this is a safe and beneficial approach during the acute burn resuscitation. One recent study reiterated the findings of a prospective clinical study, which reported that the use of high-dose ascorbic acid is associated with a decrease in fluid requirements and an increase in urine output during resuscitation after thermal injury without an increased risk of renal failure.[22] Some interest lies in the use of hypertonic saline as a resuscitative fluid in burn-induced shock and has been shown to be beneficial in treating burn-induced shock.[23] It theoretically should maintain intravascular volume more effectively by removing fluid from the interstitial space by osmosis, resulting in a decrease in generalized tissue edema. However, it is not widely used because of its potential risk for hypernatremia, hyperosmolarity, renal failure, and alkalosis. Importantly, no prospective randomized controlled studies have yet to confirm these end points.[24] Some favor the use of a modified hypertonic solution by adding one ampule of sodium bicarbonate to each liter of lactated Ringer solution during the first 24 hours of resuscitation.

Children often do not exhibit clinical signs of hypovolemia until more than 25% of the circulating volume is depleted and complete cardiovascular collapse is imminent. Thus

**TABLE 26-4**
**American Burn Association Criteria for Major Burn Injury**

| |
|---|
| Second- and third-degree burns > 10% TBSA in patients < 10 or > 50 years of age |
| Second- and third-degree burns > 20% TBSA in other age group |
| Third-degree burns > 5% TBSA in any age group |
| Burns involving the face, hands, feet, genitalia, perineum, and skin overlying major joints |
| Significant chemical burns |
| Significant electrical burns including lightning injury |
| Inhalation injury |
| Burns with significant concomitant trauma |
| Burns with significant preexisting medical disorders |
| Burn injury in patients requiring special social, emotional, and rehabilitative support (including suspected child abuse and neglect) |

symptoms of hypovolemia, such as hypotension and oliguria, can be late signs of shock in such children. Tachycardia typically indicates an early sign of hypovolemia, but caution should be used not to overinterpret, because reflex tachycardia caused by postinjury catecholamine response is also common. A lethargic child with decreased capillary refill and cool, clammy extremities requires prompt attention. Measurement of arterial blood pH and base deficit values can also reflect adequacy of fluid resuscitation. Hyponatremia is also a frequent complication in pediatric burn patients after aggressive fluid resuscitation. Although rare, a serious complication, such as central pontine myelinolysis, can occur with rapid correction of hypernatremia.[25] Frequent monitoring of serum chemistry with appropriate correction is required to avoid severe electrolyte imbalance.

After initial first aid and start of appropriate fluid resuscitation, it must be determined whether a burn victim should be transferred to a tertiary burn center. Burn units with experienced multidisciplinary team members are best prepared and experienced to handle major burn patients. In addition to physicians and nurses, respiratory and rehabilitation therapists also play critical roles in the management of acute burn patients. As defined by the American Burn Association, any patients who sustain *major burn injury* should be transferred appropriately to a nearby burn center for further care (Table 26-4).

## INHALATION INJURY

Inhalation injury remains the major contributor to mortality in burn patients. The mortality rate of children with isolated cutaneous burns is 1% to 2%, but this can significantly increase to 16% in the presence of inhalation injury.[26] The initial assessment of patients with combined thermal and other traumatic injuries should, as always, center on airway, breathing, and circulation per advanced trauma life support (ATLS) guidelines. The treatment of inhalation injury begins at the scene of the burn accident. The administration of 100% oxygen rapidly decreases the half-life of carbon monoxide. If the respiratory distress is significant, intubation or a surgical airway may be required. Although hypoxemia is usually evident, the initial chest radiograph and arterial blood gas may be normal, but the inhalational injury can evolve for hours.

The diagnosis of an inhalation injury is usually made on the clinical history and physical findings at the initial evaluation. For instance, victims trapped in a house fire with excessive smoke and fumes are likely to have sustained a severe inhalation injury. Common signs include cough, stridor, singed nasal hair, carbonaceous sputum, and a hyperemic oropharynx. Although the immediate injury results in hyperemia, ulceration, and edema, these symptoms may not be obvious until the airway becomes significantly obstructed, in which case the time lapse can exceed 18 hours. Hoarseness and stridor should alert the surgeon to significant airway obstruction, and the airway should immediately be secured with endotracheal intubation. Patients who present with disorientation and obtundation are likely to have an elevated carbon monoxide level (carboxyhemoglobin > 10%). Cyanide toxicity as a result of the combustion of common household items may also contribute to unexplained metabolic collapse. Fiberoptic bronchoscopy remains the gold standard test to confirm a diagnosis of an inhalation injury by demonstrating inflammatory changes in the tracheal mucosa, such as edema, hyperemia, mucosal ulceration, and sloughing. A ventilation/perfusion scan can also identify regions of inhalation injury by assessing respiratory exchange and excretion of xenon gas by the lungs.[27] Together, these complementary diagnostic tools are more than 90% accurate in the diagnosis of inhalation injury.

Smoke inhalation injury can be divided into three different types of injury: thermal (usually restricted to the upper airway), chemical irritation of the respiratory tract, and systemic toxicity resulting from inhalation of fumes, gases, and mists. Although the supraglottic region can be injured by both thermal and chemical insults because of highly efficient heat exchange, tracheobronchial and lung parenchymal injuries rarely occur as a result of direct thermal damage, because the heat disperses so rapidly in the larynx. The heat destroys the epithelial layer, denatures proteins, and activates the complement cascade, leading to the release of histamine and the formation of xanthine oxidase to release reactive oxygen species (ROS) such as superoxide. At the same time, nitric oxide (NO) and reactive nitrogen species (RNS) formation by endothelial cells is propagated by histamine stimulation. Both ROS and RNS cause increased permeability to proteins, resulting in edema formation. In addition, interleukin-8 (IL-8) is also released after injury, leading to the recruitment of polymorphonuclear cells, which further amplify the inflammatory process.[28] Using an ovine model with combined thermal and inhalation injuries, one group found that infusion of 7-nitroindazole, a selective neuronal nitric oxide synthase inhibitor, blocks the inflammatory cascade, as demonstrated by a 40% and 30% respective decrease in IL-8 and myeloperoxidase activity in lung tissue concentrations compared with the injured control group. The treated group also saw a reduction in bronchial injury, peak pulmonary pressures, and shunting.[29] Thus 7-nitroindazole may represent an effective therapy in the management of inhalation injuries.

Hypoxia, increased airway resistance, decreased pulmonary compliance, increased alveolar epithelial permeability, and increased pulmonary vascular resistance may be triggered by the release of vasoactive substances (thromboxanes $A_2$, $C_{3a}$, and $C_{5a}$) from the damaged epithelium.[30] Neutrophil activation plays a critical role in this process, whereby pulmonary function has been shown to improve with the use of a ligand binding to E-selectins (inhibiting neutrophil adhesion) and

anti–IL-8 (inhibiting neutrophil chemotaxis). Sloughing of the respiratory cilia impairs the physiologic cleaning process of the airway, resulting in an increased risk of bacterial infections and pneumonia. This may be further complicated by increased bronchial secretions and mucous plugging, which may predispose to distal airway obstruction and atelectasis, thereby impairing pulmonary gas exchange. These exudates, consisting of lymph proteins, coalesce to form fibrin casts that can create a "ball-valve" effect in localized areas of lung, eventually causing barotrauma.

To reduce respiratory complications such as pneumonia, protocols have been instituted in an effort to improve the clearance of tracheobronchial secretions and decrease bronchospasm (Table 26-5). Aggressive pulmonary toilet with physiotherapy and frequent suctioning is an important adjunct. The patient is frequently turned side to side along with chest physiotherapy every 2 hours. In the critically ill patient, high-frequency percussive ventilation has been shown to reduce development of pneumonia through clearance of bronchial secretions. When physiologically stable, the patient is transferred out of bed to a chair, with progressive ambulation to prevent compressive atelectasis. Humidified air is delivered at high flow, while bronchodilators and racemic epinephrine are used to treat bronchospasm. The use of nebulized heparin has been shown to reduce tracheobronchial cast formation, improve minute ventilation, and lower peak inspiratory pressures after smoke inhalation. Inhalation treatments, such as 20% acetylcysteine nebulized solution (3 mL q4h) plus nebulized heparin (5,000 to 10,000 units with 3 mL normal saline q4h), are effective in improving the clearance of tracheobronchial secretion and minimizing bronchospasm, thereby significantly improving reintubation rates and decreasing mortality.[31,32]

The presence of inhalation injury generally requires an increased amount of fluid resuscitation, up to 2 mL/kg/% TBSA burn more than would be required for an equal-size burn without an inhalation injury. In fact, pulmonary edema that is associated with inhalation injury is not prevented by fluid restriction, but rather, inadequate resuscitation may increase the severity of pulmonary injury by sequestration of polymorphonuclear cells.[33] Corticosteroids have not been shown to be of any benefit in inhalation injury. Prophylactic IV antibiotics are not indicated unless there is clinical suspicion of pneumonia. Early pneumonia is usually the result of gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus*, whereas gram-negative organisms, such as *Pseudomonas* and *Acinetobacter,* are responsible for later-onset infection. Antibiotic therapy should be guided by sensitivities and susceptibilities of serial cultures from sputum, tracheal aspirates, or bronchoalveolar lavages.

**TABLE 26-5**
**Inhalation Injury Treatment Protocol**

| *Treatment* | *Interval and Dosages* |
|---|---|
| Suction and lavage | q2h |
| Bronchodilators (Albuterol) | q2h |
| Nebulized heparin | 5000-10,000 units with 3 mL NS q4h |
| Nebulized acetylcysteine | 20%, 3 mL q4h |
| Hypertonic saline | Induce effective coughing |
| Racemic epinephrine | Reduce mucosal edema |

NS, normal saline.

# Burn Wound Care

The proper wound care is generally dictated by the accurate assessment of the burn depth and size. First-degree burns require no particular dressing, but the involved areas should be kept out of direct sunlight. They are generally treated with topical ointments for symptomatic pain relief. Superficial second-degree burns are treated with daily dressing changes with topical antimicrobial agents. They can also be treated with application of petroleum gauze or a synthetic dressing to allow for rapid re-epithelialization. Deep second- and third-degree burn wounds eventually require excision of the eschar with skin grafting. Table 26-6 describes various available antimicrobial, synthetic, and biologic dressing products for burn wound care.

## TOPICAL ANTIMICROBIALS

Various topical antimicrobial agents have been used for management of burn wounds. None of these agents effectively prevent colonization of organisms that are commonly harbored in the eschar, but instead promote bacteriostasis to limit bacterial burden to less than $10^2$ to $10^5$ colonies/g of tissue. Routine punch quantitative wound biopsy of burned areas can alert to impending burn wound sepsis and risk of failure of skin graft from infection. The National Burn Repository estimates that 4.4% of deaths after burn injury are attributable to burn wound sepsis. With evidence of multidrug-resistant organisms (MDROs), one study evaluated 47 MDROs and 27 non-MDRO controls versus 11 different topical agents, in which the topical agents were effective against 88% of the non-MDROs but only 80% of MDROs. Mafenide acetate, silver sulfadiazine, and silver nitrate were effective against both gram-negative and gram-positive bacteria, regardless of drug resistance status. Nonetheless, the results reinforce the concern that bacteria are becoming more resistant to antimicrobial regimens.[34]

Silver sulfadiazine (Silvadene; Monarch Pharmaceuticals, Bristol, Tenn.) is the most commonly used topical agent for burn wound dressings. Although it does not penetrate eschar, Silvadene has a broad spectrum of efficacy and mitigates the pain associated with second-degree burns. However, it frequently adheres to the wound surface, thereby traumatizing newly generated epithelial surfaces and delaying healing. Silvadene on fine mesh gauze can be used separately or in combination with other antimicrobial agents, such as nystatin. The combination of Silvadene with nystatin has significantly reduced the incidence of *Candida* infection in burned patients.[35] The most common side effect of Silvadene is leukopenia, which is likely related to margination of white blood cells and is only transient.[36] However, when the leukocyte count falls below 3000 cells/mm$^3$, changing to another topical antimicrobial agent is warranted.

Mafenide acetate (Sulfamylon; UDC Laboratories, Rockford, Ill.) is more effective in penetrating eschar, and therefore is frequently used in third-degree burns. Fine mesh gauze impregnated with Sulfamylon (10% water-soluble cream) is applied directly onto the burn wound. Sulfamylon has a much broader spectrum of antimicrobial efficacy, including against *Pseudomonas* and *Enterococcus*. It is also available in 5% solution to soak burn wounds, eliminating a need to perform

**TABLE 26-6**
**Burn Wound Dressings**

| *Dressings* | *Advantages* | *Disadvantages* |
|---|---|---|
| **Antimicrobial Salves** | | |
| Silver sulfadiazine (Silvadene) | Painless; broad spectrum; rare sensitivity | Leukopenia; some gram-negative resistance; does not penetrate eschar; inhibition of epithelialization |
| Mafenide acetate (Sulfamylon) | Broad-spectrum; penetrates eschar; effective against *Pseudomonas* | Painful; metabolic acidosis (carbonic anhydrase inhibitor); inhibition of epithelialization |
| Bacitracin/neomycin/polymyxin B | Ease of application, painless, useful on face | Limited antimicrobial property |
| Nystatin | Effective in inhibiting fungal growth; use in combination with Silvadene, Bacitracin | Cannot use in combination with mafenide acetate |
| Mupirocin (Bactroban) | Effective against *Staphylococcus,* including MRSA | Cost; poor eschar penetration |
| **Antimicrobial Soaks** | | |
| 0.5% Silver nitrate | Painless; broad-spectrum; rare sensitivity | No eschar penetration; discolor contacted areas; electrolyte imbalance; methemoglobinemia |
| Povidone-iodine | Broad-spectrum antimicrobial | Painful; potential systemic absorption; hypersensitivity |
| 5% Mafenide acetate | Broad-spectrum antimicrobial | Painful; no fungal coverage; metabolic acidosis |
| 0.025% Sodium hypochlorite (Dakin solution) | Effective against most organisms | Mildly inhibits epithelialization |
| 0.25% Acetic acid | Effective against most organisms | Mildly inhibits epithelialization |
| **Silver-Impregnated** | | |
| Aquacel, Acticoat | Broad-spectrum antimicrobial; no dressing changes | Cost |
| **Synthetic Dressings** | | |
| Biobrane | Provides wound barrier; minimizes pain; useful for outpatient burns, hands (gloves) | Exudate accumulation risks invasive wound infection; no antimicrobial property |
| Opsite, Tegaderm | Provides moisture barrier; minimizes pain; useful for outpatient burns; inexpensive | Exudate accumulation risks invasive wound infection; no antimicrobial property |
| Transcyte | Provides wound barrier; accelerates wound healing | Exudate accumulation risks invasive wound infection; no antimicrobial property |
| Integra, Alloderm | Complete wound closure, including dermal substitute | No antimicrobial property; expensive; requires training, experience |
| **Biologic Dressings** | | |
| Allograft (cadaver skin), Xenograft (pig skin) | Temporary biologic dressings | Requires access to skin bank; cost |
| Amniotic membrane | Minimizes dressing changes | Minimal experience; not widely used |

frequent dressing changes. Sulfamylon is a potent carbonic anhydrase inhibitor and can therefore cause metabolic acidosis. This side effect can usually be avoided by limiting its use to only 20% TBSA at any given time and rotating application sites every several hours with another topical antimicrobial agent. In addition, the application of Sulfamylon can be painful, which limits its practical use in an outpatient setting, especially with children.

Other agents, such as 0.5% silver nitrate and 0.025% sodium hypochlorite (Dakin solution), are also available as soak solutions. These soak solutions are generally poured onto gauze dressings, which minimizes dressing changes and the potential loss of grafts or healing keratinocytes. Silver nitrate is painless on application and has broad coverage, but its side effects include electrolyte imbalance (hyponatremia, hypochloremia) and dark gray or black stains. Dakin (0.025%) solution is effective against most microbes, including *Pseudomonas*. However, it requires frequent dosing because of inactivation of hypochlorite when coming in contact with protein and can also retard healing cells.[37] Petroleum-based antimicrobial ointments, such polymyxin B, bacitracin, and polysporin, are painless and transparent, allowing easier monitoring of applied burn wounds. These agents are mostly only effective against gram-positive organisms, and their use is limited to facial burns, small areas of partial-thickness burns, and healing donor sites. As with Silvadene, petroleum-based agents can also be used in combination with nystatin to suppress skin *Candida* colonization.

Commercially available dressings containing biologically active silver ions (Aquacel, ConvaTec, Skillman, NJ; Acticoat, Smith & Nephew, Auckland, NZ) hold promise for retaining the effectiveness of silver nitrate but without its side effects. Allowing it to adhere to the wound within 24 hours, the hydrocolloid properties of the Aquacel dressing make it absorbent and non-traumatic to the delicate tissues of the healing wound. Since it can be left without dressing changes for up to 2 weeks, it may be useful in the outpatient management of a burn injury. Similarly, Acticoat has been shown to have improved bacterial clearance, which is related to a sustained release of silver that allows for less frequent dressing changes.[38]

## BURN WOUND DRESSINGS

Superficial second-degree burns can be managed using various methods. A topical antimicrobial dressing using Silvadene is most commonly used, but synthetic dressings, such as Biobrane (UDL Laboratories, Rockford, Ill.) and Opsite (Smith & Nephew), offer unique advantages of eliminating frequent

painful dressing changes and potential tissue fluid loss. The general principle of these synthetic products is to provide sterile coverage of superficial partial-thickness burn wounds to allow rapid spontaneous re-epithelialization of the involved areas. Biobrane is a bilaminate thin membrane composed of thin semipermeable silicone bonded to a layer of nylon fabric mesh that is coated with a monomolecular layer of type I collagen of porcine origin. This dressing provides a hydrophilic coating for fibrin ingrowth that promotes wound adherence. Its porosity allows for drainage of exudates while remaining permeable to topical antibiotics, and it simultaneously acts as a barrier to the ingress of bacteria and evaporation to prevent dessication.[39] It is supplied in simple sheets or preshaped gloves (Fig. 26-6). After it is placed onto clean fresh superficial second-degree burn wounds using Steri-strips and bandages, the Biobrane dressing dries up and becomes well adhered to burn wounds within 24 to 48 hours. Once adherent, the covered areas are kept open to air and examined closely for the first few days to detect any signs and symptoms of infection. As the epithelialization occurs beneath the Biobrane sheet, it is easily peeled off the wound. When serous fluid accumulates beneath the Biobrane, a sterile needle aspiration can preserve its use. However, once foul-smelling exudate is detected, it should be removed and topical antimicrobial dressings applied. When used as directed, Biobrane has been found to reduce pain levels, fluid loss, healing time, instances of hypothermia, and hospital stay when compared with traditional dressings.[39,40]

Alternatively, Opsite or Tegaderm (3M Pharmaceuticals, St. Paul, Minn.) can also be used to cover superficial partial-thickness burns. Commonly used as postoperative dressings, it is easy to apply and provides an impervious barrier to the environment. It is also relatively inexpensive, and its transparent nature allows for easier monitoring of burn wounds. Despite lacking any special biologic factors (i.e., collagen, growth factors) to enhance wound healing, it promotes spontaneous re-epithelialization process. Biobrane and Opsite are preferred to topical antimicrobial dressings when dealing with small superficial second-degree burn wounds, especially in the outpatient settings to alleviate pain associated with dressing changes. TransCyte (Advanced BioHealing, Westport, Conn.), composed of human fibroblasts that are then cultured on the nylon mesh of Biobrane, is also an alternative option.

**FIGURE 26-6** Biobrane glove for superficial second-degree burn. Biobrane is an ideal synthetic wound coverage for superficial second-degree burns, promoting rapid re-epithelialization without painful dressing changes.

Synthetic and biologic dressings are also available to provide coverage for full-thickness burn wounds. Integra (Integra LifeSciences, Plainsboro, NJ) consists of an inner layer made of a porous matrix of bovine collagen and the glycosaminoglycan chrondroitin-6-sulfate, which facilitates fibrovascular growth. The outer layer is composed of polysiloxane polymer with vapor transmission characteristics similar to normal epithelium. In the treatment of full-thickness burn wounds, Integra serves as a matrix for the infiltration of fibroblasts, macrophages, lymphocytes, and capillaries derived from the wound bed, and it promotes rapid neodermis formation. After the collagen matrix engrafts into the wound in approximately 2 weeks, the outer silicone layer is replaced with epidermal autografts. Epidermal donor sites heal rapidly without significant morbidity.

Although synthetic dermal substitutes have a tremendous potential for minimizing scar contractures with improvement in cosmetic and functional outcome, they are also susceptible to wound infection and must be monitored carefully. The use of Integra for children with large TBSA burns was evaluated for short- and long-term follow-up.[41] Burned children treated with Integra demonstrated significantly decreased resting energy expenditure as well as increased bone mineral content and density, along with improved scarring at 24 months after burn injury, thus validating the use of this dermal substitute in the management of pediatric burned patients.[41] Moreover, some advocate that Integra can be successfully used in extensive postburn scar revisions in younger patients.[42] Recently, the use of Integra with negative-pressure therapy and a vacuum-assisted closure system has been shown to shorten the time between the application of Integra and skin grafting by fixing the dermal substitute to the wound bed and promoting neovascularization.[43] In addition, this method simplifies wound care, evacuates fluid, and provides a sterile covering.

Biologic dressings, such as xenografts from swine and allografts from cadaver donors, can also be used to cover full-thickness burn wounds as a temporary dressing. Alloderm (LifeCell, Branchburg, NJ) is a dermal substitute procured from decellularized cadaveric dermis. This synthetic dermal substitute also has a potential for minimizing scar contractures, particularly at joints, and improving cosmesis and functional outcomes. Particularly useful when dealing with large TBSA burns, biologic dressings can provide the immunologic and barrier functions of normal skin. The areas of xenograft and allograft are eventually rejected by the immune system and sloughed off, leaving healthy recipient beds for subsequent autografts. Although extremely rare, the transmission of viral diseases from the allograft is of potential concern.

Finally, human amnion has been used as a dressing for burns, because it not particularly antigenic. It contains substantial amounts of many growth factors that stimulate epithelial proliferation, but it also minimizes evaporative fluid losses and reduces bacterial counts in the burn wound.[44] Several preservation methods are currently described, including cryopreservation, glycerol preservation, lyophilization, and $\gamma$-irradiation. Its use has been limited to dressing partial-thickness burns in specialized areas such as the face. One study compared the use of amnion and traditional topical treatment in pediatric patients with facial burns. Although patients in the amnion group had significantly fewer dressing changes, the overall time to healing, length of stay, and hypertrophic scarring were not different between the two treatment groups. Importantly, the use of amnion was not associated with an increased

risk of infection, which suggested that it is a safe alternative dressing for superficial partial-thickness burns.[45]

## EXCISION AND GRAFTING

Early excision with skin grafting has been shown to decrease operative blood loss, length of hospital stay and ultimately improve overall survival of burn patients.[46,47] Similar to earlier clinical reports in patients, two separate murine studies found that early excision of full-thickness burns can reduce proinflammatory cytokines, such as IL-6 and tumor necrosis factor-α (TNF-α), in rats with 30% TBSA burn injuries, allowing for abrogation of the systemic inflammatory response.[48,49] Adequate surgical debridement does rely on experience and judgment to determine which tissues are devitalized and should be excised as opposed to those that are still viable. Moreover, aggressive debridement can result in poor functional and cosmetic results, whereas inadequate debridement will often result in infection and poor healing. One group has recommended intraoperative staining of the burn wound with methylene blue to demarcate normal epithelium from granulation tissue and eschar, which can aid in excision. There were no reports of adverse reactions, alterations in skin graft take, or wound healing problems with topical application of methylene blue, though no objective measures of these findings were provided.[50]

Excision and grafting may be staged, with the goal of removing all eschar as early as possible, to not only blunt the inflammatory cascade but also to prevent wound colonization. However, since burn depth from scald burns is more difficult to assess, a more conservative approach is taken with delayed excision. Typically, tangential excision of the full-thickness burn wound is performed 1 to 3 days after burn injury, when relative hemodynamic stability has been achieved. The eschar is sequentially shaved off using a powered dermatome (Zimmer) and/or knife blades (Watson, Weck) until a viable tissue plane is achieved, which is usually characterized by punctate bleeding (Fig. 26-7). Particularly in burns greater than 30% TBSA, early excision of the eschar (usually < 24 hours after burns) generally decreases operative blood loss resulting from vasoconstrictive substances, such as thromboxane and catecholamines, in the burn wounds. Once the burn wounds become hyperemic 48 hours after burns, bleeding at the time of excision of the eschar can be excessive. Tourniquet and subcutaneous injections of an epinephrine-containing solution can lessen the blood loss, but these techniques can potentially hinder the surgeon's ability to differentiate viable from nonviable tissues. Topical hemostatic agents, such as thrombin, can also be used, but they are expensive and not very effective in preventing excessive bleeding from open wounds. In patients with deep full-thickness burns, electrocautery is useful to rapidly excise eschar with minimal blood loss. The use of Versajet hydrosurgery (Smith & Nephew), which utilizes a high-powered stream of sterile saline for tissue excision, is becoming increasingly popular. Because it is capable of small-scale incremental debridement, the Versajet preserves more dermis than traditional tangential excision techniques and allows for more precise contouring. It has been shown to reduce bleeding and healing times, with improved adherence of biologic dressings.[51] It has the advantage of dermal preservation, which is necessary to minimize hypertrophic scarring and contracture formation, and a significant reduction in bleeding associated with traditional excision. It has been suggested that large TBSA pediatric burn patients receiving blood products have increased morbidity because of being immunocompromised and succumbing to subsequent infections.[52] Thus limiting blood loss and transfusions are critical.

FIGURE 26-7 Tangential excision of eschar. Eschar is excised to the depth of viable, bleeding tissue plane. (With permission from Herndon DN [ed]: Total Burn Care, ed 2. Philadelphia, WB Saunders, 2002, plate 2.)

Ideally, the excised burn wound is covered with autograft from donor sites, such as the upper leg, back, or abdomen. For burns less than 20% to 30% TBSA, debrided wounds can be covered at one operation with split-thickness autografts if the wound bed is amenable. It is preferable to use sheets of autografts for better long-term aesthetic outcome, but narrowly meshed autografts (1:1 or 2:1) have the advantage of allowing better drainage of fluid at the grafted sites. However, this also means that they require larger donor areas than more widely meshed grafts. With massive burns, the closure of burn wounds is achieved by a combination of widely meshed autografts (4:1 to 6:1) with an allograft (2:1) overlay (Fig. 26-8). Alternatively, it may be necessary to use only temporary biologic dressings, cadaveric allograft, or a dermal replacement until autologous donor sites are available. Once split-thickness autografts are harvested, the donor sites are dressed with a petroleum-based gauze, such as Xeroform or Scarlet-red (Covidien, Mansfield, Mass.). OpSite can be used to cover donor sites. Repeat grafting is required for large burns, with sequential harvesting of split-thickness autograft from limited

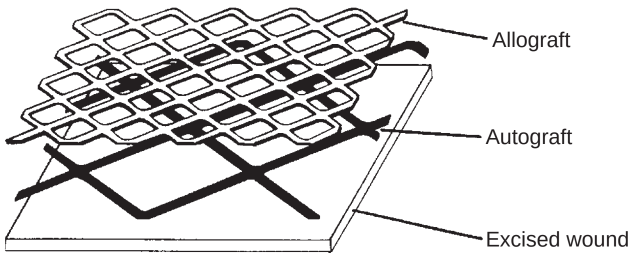


FIGURE 26-8 Schematic diagram of wound covering with 4:1 meshed autograft with 2:1 meshed allograft overlay. (With permission from Eichelberger MR [ed]: Pediatric Trauma: Prevention, Acute Care, Rehabilitation, St Louis, Mosby, 1993, p 581.)

donor sites, until the entire burn wound is covered. As meshed autografts heal, the allografts slough. However, the formation of significant scar remains the major disadvantage of this technique. Therefore the use of widely meshed graft is avoided on the face and hands. Full-thickness grafts that include both dermal and epidermal components provide the best outcome for wound coverage, with less contractures and better pigment match. However, its use is generally limited to small areas because of the lack of abundant full-thickness donor skin.

The limitation of donor sites in patients with burns over massive areas is partially addressed with the use of recombinant human growth hormone (rHGH). Administration of rHGH has resulted in accelerated donor-site healing, allowing more frequent donor-site harvest in a given period of time.[53] The use of rHGH decreased donor-site healing time by an average of 2 days, which ultimately shortened the overall length of hospitalization from 0.8 to 0.54 days per percentage of TBSA burned.[53] These effects from rHGH are thought to result from stimulation of insulin-like growth factor (IGF)-1 release and induction of IGF-1 receptors in the burn wound.[54] Given alone, insulin has been shown to decrease donor-site wound protein synthesis, accelerating healing time from 6.5 to 4.7 days.[55] The decrease in donor-site healing by 1 day between each harvest can significantly impact overall length of hospital stay in patients with massive burns who require multiple grafting procedures. The administration of rHGH in burned children was associated with a 23% reduction in total cost of hospital care for a typical 80% TBSA burn.[53]

The use of cultured keratinocytes from the patient's own skin has continued to generate considerable interest as a potential solution for massively burned patients with limited donor sites. Cultured epithelial autografts (CEA) can theoretically be used to provide complete coverage, but it is wrought with problems in its practical application. Although cultured keratinocytes grow slowly, they are particularly fragile and very susceptible to shear trauma. In noncritically ill patients who are otherwise not sedated, strict bedrest may be necessary to prevent loss of the graft, which consequently delays mobilization and rehabilitation. Thus the successful take rate of CEAs is only 50% to 70%. In one burn center's experience, they recommended CEA in the following subpopulation: large full-thickness burns (>50% TBSA), moderate burns (30% to 50% TBSA) with limited donor-site availability, and burns in which the donor site presents a significant functional or cosmetic issue. They also noted an estimated graft take rate of 72.7% at discharge, but that children had a higher contracture rate than their adult counterparts (90% vs. 57%).[56] It has been reported that there is a significantly longer hospitalization with these grafts in patients with burns of more than 80% TBSA. However, this technology continues to hold promise in treating massive burns.

## Hypermetabolic Response

Burn patients demonstrate dramatic increases in metabolic rate. The hypermetabolic response, which is generally greater with increasing burn size, reaches a plateau at 40% in a TBSA burn.[57] The hypermetabolic response to burn injury is characterized by catabolic metabolism, hyperdynamic circulation, insulin resistance, delayed wound healing, and increased risk of infection.[58] These physiologic changes of increased energy expenditure, oxygen consumption, proteolysis, lipolysis, and nitrogen losses are induced by up-regulation of catabolic agents, such as cortisol, catecholamine, and glucagons, which act synergistically to increase the production of glucose, a principal fuel during acute inflammation. Cortisol stimulates gluconeogenesis, proteolysis, and sensitizes adipocytes to lipolytic hormones. Catecholamines stimulate the rate of glucose production through hepatic gluconeogenesis and glycogenolysis, as well as promoting lipolysis and peripheral insulin resistance. Thus serum insulin levels are elevated, but the cells themselves become insulin resistant.[59] The increase in glucagon, which is stimulated by catecholamines, further promotes gluconeogenesis. Recent trials have demonstrated that intensive insulin therapy aimed at maintaining a daily average glucose of 140 mg/dL improves postburn outcomes.[60,61] Patients with intensive insulin treatment have demonstrated improved immune function and decreased sepsis, along with an attenuation of the inflammatory and acute phase response. As such, tight glucose control is thought to be critical in improving the overall recovery of burn patients.

Significant protein catabolism occurs in severe burns. Cortisol is catabolic and is partially responsible for the loss of tissue protein and negative nitrogen balance. In addition, burn injury is associated with decreased levels of anabolic hormones, such as growth hormone and IGF-1, which contribute significantly to net protein loss. The synthesis of protein (essential for the production of collagen for wound healing) and antibodies and leukocytes participating in the immune response, requires a net positive nitrogen balance. Excess catecholamines in postburn patients also contribute to persistent tachycardia and lipolysis. The consequences of these physiologic insults are cardiac failure and fatty infiltration of the liver. The use of a beta blocker, propranolol, has been shown to lower resting heart rate and left ventricular work and decrease peripheral lipolysis without adversely affecting cardiac output or the ability to respond to cold stress.[62,63] Propranolol also increases lean body mass and decreases skeletal muscle wasting. Herndon and colleagues[57] demonstrated that beta blockade using propranolol during hospitalization attenuated hypermetabolic response and reversed muscle-protein catabolism in burned children. Propranolol was given at a standard starting dose (1.98 mg/kg/day) and then titrated to achieve a decrease in the heart rate of approximately 20% from a baseline values. At 2 weeks of treatment, resting energy expenditure and oxygen consumption had increased in the control group. In contrast, patients in the propranolol group had significant decreases in these variables. Concurrent with the decline in energy expenditure, beta blockade also improved the kinetics of skeletal-muscle protein. The muscle protein net balance improved by 82% compared with pretreatment baseline values, whereas it decreased only by 27% in untreated controls.[57] Furthermore, the administration of propranolol to burned children receiving simultaneous human growth hormone has salutary cardiovascular effects, a decrease in the recent release of free fatty acids from adipose tissue, and an increase in efficiency of the liver's handling of secreted free fatty acids and very-low-density lipoproteins. Administration of propranolol has been shown to decrease peripheral lipolysis and fat deposition in the liver of burn patients.[57] A recent report also suggested that administration of propranolol (4 mg/kg/q24h) markedly decreases the amount of insulin necessary to decrease elevated glucose level postburn.[64] The mechanism

by which propranolol exerts its effects is still unknown, but it appears to be secondary to increased protein synthesis despite persistent protein breakdown.

Growth hormone and IGF-1 levels are shown to decrease after burn injury. Pharmacologic agents have been used to attenuate catabolism and to stimulate growth despite a burn injury.[65] Growth hormone, insulin, IGF-1/IGF-binding protein-3, testosterone, and oxandrolone improve nitrogen balance and promote wound healing.[66–68] Exogenous administration of rHGH, which increases protein synthesis, has been shown to improve nitrogen balance, preserve lean muscle mass, and increase the rate of wound healing.[69] The anabolic action of growth hormone appears to be mediated by an increase in protein synthesis, whereas IGF-1 decreases protein degradation. Growth hormone also enhances wound healing by stimulating hepatic and local production of IGF-1 to increase circulating and wound-site levels.[70] Plasma growth hormone levels, which are decreased following severe burns, can be restored by administration of rHGH (0.2 mg/kg/day) in massively burned children to accelerate skin graft donor-site wound healing and shorten hospital stay by more than 25%.[71] rHGH in severely burned children has shown to be safe and efficacious. In one randomized prospective trial in pediatric burn patients, rHGH administration led to elevations in serum growth hormone, IGF-I, and IGFBP-3, whereas the percent body fat content significantly decreased when compared with the control group. Long-term administration of 0.1 and 0.2 mg/kg/day rHGH also significantly improved scarring at 12 months postburn.[72] However, it has previously been shown that rHGH is associated with hyperglycemia, along with increased free fatty acids and triglycerides, which limits its clinical applicability. A prospective randomized control trial showed efficacy in rHGH and propranolol treatment in attenuating hypermetabolism and inflammation in severely burned children.[73] In this study, patients receiving rHGH (0.2 mg/kg/day) and propranolol (to decrease heart rate by 15%) for more than 15 days demonstrated significantly decreased percent predicted resting energy expenditure, C-reactive protein, cortisone, aspartate aminotransferase, alanine aminotransferase, free fatty acid, IL-6, IL-8, and macrophage inflammatory protein-1 when compared with controls. Other markers, such as serum IGF-1, IGF-binding protein-3, growth hormone, prealbumin, and IL-7 increased in rHGH/propranolol-treated burned patients.[73] These findings further validate the beneficial role of combination treatment with rHGH and a beta blocker in pediatric burn patients.

In severely burned patients, muscle anabolism can result from administration of submaximum dosages of insulin by stimulating muscle protein synthesis. Insulin administration has also been demonstrated to improve skin graft donor-site healing and wound matrix formation.[74] Testosterone production is greatly decreased after severe burn injury, which may last for months in postpubertal males. Increased protein synthesis with testosterone administration is accompanied by a more efficient use of intracellular amino acids derived from protein breakdown and an increase in inward transport of amino acids. An increase in net protein synthesis is attainable in adults with large burns by restoring testosterone concentrations to the physiologic range.[66] An analog of testosterone with less androgenic effect, oxandrolone (Upsher-Smith Laboratories, Minneapolis, Minn.), has been used in acute and rehabilitating adult burn patients, with promising results regarding weight gained. Oxandrolone, an oral synthetic derivative of testosterone with a lower androgenic/anabolic ratio, has been safely used to improve lean body mass and weight gain in severely burned adults and children. A large prospective double-blind randomized study involving 235 severely burned children (TBSA > 40%) showed that oxandrolone treatment significantly increased lean body mass along with serum total protein, prealbumin levels, and mean muscle strength. Interestingly, the oxandrolone-treated group also had a shorter hospital stay.[75] Similar results were reported in adult burn patient population.[76]

## Nutrition

The metabolic rate of patients with burns increases from 1.5 times the normal rate in a patient with 25% TBSA burns to 2 times the normal rate in 40% TBSA burns.[77] Children are particularly vulnerable for protein-calorie malnutrition because of their proportionally lower body fat and smaller muscle mass, in addition to increased metabolic demands. This malnutrition is associated with dysfunction of various organ systems, including the immune system, and delayed wound healing. To ensure that patients remain caught up nutritionally, enteral feeding should be initiated early after a burn injury, especially since early enteral feedings have been shown to decrease the level of catabolic hormones, improve nitrogen balance, maintain gut mucosal integrity, and decrease the incidence of sepsis and overall hospitalization. Feeding tubes are generally placed under fluoroscopy immediately after the initial evaluation of burns, and enteral nutrition is started within hours after burns. Early enteral feedings have been shown to decrease the level of catabolic hormones, improve nitrogen balance, maintain gut mucosal integrity, and decrease overall hospital stay.[78] Although hyperalimentation can deliver sufficient calories, its use in burn patients has been associated with deleterious effects on immune function, small bowel mucosal atrophy with increased incidence of bacterial translocation, and decrease in survival.[79] Enteral nutrition through a feeding tube placed into the stomach or duodenum is always preferred to parental nutrition, and is associated with decreased metabolic rate and decreased sepsis in burn patients.

Several formulas are used to calculate caloric requirement in burn patients. Both Curreri (25 kcal/kg plus 40 kcal/% TBSA burned) and modified Harris-Benedict (calculated or measured resting metabolic rate times injury factor) formulas use the principle of providing maintenance caloric needs plus the additional caloric needs related to the burn size. Similar to fluid resuscitation guidelines, a caloric requirement guideline based on total and burned BSA is more appropriate for pediatric burn patients (Table 26-7).[80] The exact nutrient requirements of burn patients are not clear, but it is generally

**TABLE 26-7**
**Caloric Requirements for Burned Children (Shriners Hospital for Children-Galveston)**

| *Age Group* | *Daily Caloric Requirements* |
|---|---|
| Infant and toddler | 2100 kcal/m$^2$ total + 1000 kcal/m$^2$ burn |
| Child | 1800 kcal/m$^2$ total + 1300 kcal/m$^2$ burn |
| Adolescent | 1500 kcal/m$^2$ total + 1500 kcal/m$^2$ burn |

accepted that maintenance of energy requirement and replacement of protein losses are vital. The recommended enteral tube feedings should have 20% to 40% of the calories as protein, 10% to 20% as fat, and 40% to 70% as carbohydrates. Milk is one of the least expensive and best tolerated forms of nutrition, but, to avoid dilutional hyponatremia, sodium supplementation may be needed when milk is used in large quantity. There are also numerous commercially available enteral formulas, such as Vivonex (Nestlé-Nutrition, Vevey, Switzerland) or Pediasure (Abbott Laboratories, Abbott Park, Ill.). One study compared outcomes with the use of Vivonex and milk in 944 pediatric burn patients and found that patients receiving Vivonex had shorter stays in the intensive care unit, a lower incidence of sepsis, and lived significantly longer until death than those receiving milk. Although there was no difference in mortality between the two groups, autopsies demonstrated decreased hepatic steatosis.[81] One report evaluated the efficacy of an anti-inflammatory, pulmonary enteral formula in the treatment of pediatric burn patients with respiratory failure.[82] Based on evidence that the inclusion of dietary lipids (e.g., omega-3 fatty acid, eicosapentaenoic acid) is known to modulate the inflammatory response, and the addition of antioxidants may improve cardiopulmonary function and respiratory gas exchange, this study evaluated the role of a specialized pulmonary enteral formula (SPEF) containing anti-inflammatory and antioxidant-enhanced components in pediatric burn patients. The use of SPEF was shown to be safe in pediatric patients and resulted in an improvement in oxygenation and pulmonary compliance in burned patients with acute respiratory distress syndrome.[82]

# Pharmacotherapy

## ANALGESIA

Burn wound treatment and rehabilitation therapy produce pain for patients of all age groups. Infants and children do not express their pain in the same way that adults do and may display pain through behaviors of fear, anxiety, agitation, tantrums, depression, and withdrawals. In older children, allowing the child to participate in providing wound care can help the child to have some control and alleviate fear and pain. Various combinations of analgesics with anxiolytic medications are used effectively during procedures and wound dressing changes (Table 26-8). A successful pain management regimen for burned children requires understanding by the entire burn team on how the pain is associated with burn depth and the phase of wound healing. Pain management protocols should be tailored to control background pain as well as that incurred with procedures, such as dressing changes, vascular access placement, and physical therapy. Physical therapy rehabilitation, which is vital to optimize good functional outcome, can more effectively be used if there is appropriate pain control. However, caution must be exercised to prevent any potential injury because of overmedication. Scheduled administration of acetaminophen can often address background pain, and it is not uncommon for dose escalation to occur as patients experience tolerance to a particular pain regimen. Morphine sulfate or fentanyl is frequently used to manage postoperative pain. The use of ketamine (0.5 to 2.0 mg/kg IV) is quite effective and ideal for short procedures, such as dressing changes and vascular access placements. For burned children requiring deeper sedation and analgesia, a combination of propofol and ketamine has also been shown to be effective. Advanced pain management protocols can be administered safely by those experienced with the use of conscious sedation. Physical therapy, which is vital to optimize good functional outcome, can more effectively be used if there is appropriate pain control. However, caution must be exercised to prevent any potential injury because of overmedication. In children as young as 5 years of age, a patient-controlled analgesia may be used to provide steady-state background infusion of narcotic with additional bolus regimen.[83] Burn injuries are traumatic for the burned child as well as for the family. Burn care professionals must do everything possible to make the experience as tolerable as possible in assisting burn patients to a successful recovery.

**TABLE 26-8**
**Pharmacotherapy Agents**

| *Agent* | *Dosages* | *Indications* |
|---|---|---|
| Morphine Sulfate | 0.05-0.1 mg/kg IV or 0.3 mg/kg PO | Acute pain; procedures and dressing changes |
| Demerol | 1-2 mg/kg PO or IV | Acute pain; procedures and dressing changes |
| Ketamine | 1-2 mg/kg IV or 5-7 mg/kg IM | Surgery; procedures and dressing changes |
| Diazepam | 1-2 mg PO or IV | Preoperative; anxiety |
| Chloral hydrate | 250-500 mg PO | Preoperative; insomnia |
| Midazolam | 0.25-0.5 mg/kg PO or IV | Anxiety; used in combination with narcotics |
| Lorazepam | 0.03 mg/kg PO or IV | Background anxiety |

As mentioned earlier, the physiologic changes that occur with a burn injury alter metabolism and pharmacodynamics of many medications, including narcotics. In one study, 20 adult patients with a mean burn size of 49% TBSA were compared with a control group after receiving 200 μg of fentanyl. Plasma concentrations were sampled at various times after administration, and it was noted that the burn patients had lower fentanyl concentrations at all time points, with no difference in clearance. This is likely related to the increased volumes of distribution in burn patients, which further suggests that the volume of distribution needs to be carefully considered when administering narcotics and titrating to clinical effect.[84]

## SEDATIVES AND ANXIOLYTICS

Ketamine is a commonly used procedural sedative/anesthetic in burn patients. Derived from phencyclidine, it is characterized by dissociative anesthesia and has excellent analgesic properties. Given at a dose of 1 to 2 mg/kg IV or 5 to 7mg/kg IM, an effect is achieved rapidly with a relatively short duration of action. In addition, ketamine is also frequently used as an anesthetic agent for operative procedures without compromising airway reflexes. The use of ketamine is contraindicated in patients with increased intracranial pressure. Benzodiazepines are commonly used to control burn-related anxiety as well as to enhance the effects of narcotics for pain control. Lorazepam (Ativan) at a dosage of 0.03 mg/kg PO or IV, is an effective anxiolytic agent. It is also useful as a hypnotic agent to improve patient restfulness in the acute care setting. Diazepam (Valium) has a longer duration of action than

lorazepam and therefore is useful in more chronic settings. Diazepam also improves muscle relaxation, which can be beneficial to facilitate rehabilitative therapy. Midazolam (Versed) has a rapid onset of action, with peak plasma levels achieved within 30 minutes and a half-life of 2 to 5 hours. It is commonly used to achieve a desired level of sedation for procedures and dressing changes. Because of the anterograde amnesia property, it is used commonly as a premedication agent on operative days.

Dexmedetomidine (DEX) is another adjunct being used in the pediatric population for pain and sedation management. It is a selective $\alpha_2$-adrenergic agonist that can provide sedation, anxiolysis, and analgesia with less respiratory depression than other sedatives. In one retrospective review of 65 ventilated pediatric burn patients, DEX was continuously infused after loading, and patients were noted to be "adequately sedated," which was in contrast to their sedation failure with opioids and benzodiazepines alone. The patients were successfully extubated while on the DEX infusion, and no patient showed evidence of DEX-induced respiratory depression.[85] In another study, intranasal DEX or oral midazolam was administered to 100 pediatric burn patients preoperatively. Ninety-four percent of the patients who received DEX were appropriately sedated as opposed to 82% in the midazolam group. There were no significant differences in narcotic requirements during the operation, nor increased adverse effects in patients receiving DEX.[86] Thus DEX may prove to be a safe alternative to benzodiazepines in burn patients.

### INTRAVENOUS ANTIBIOTICS

The use of perioperative IV antibiotics has significantly contributed to an overall improvement in the survival of major burn patients during the past 2 decades. Bacteria colonized in the burn eschar can potentially shed systemically at the time of eschar excision and contribute to sepsis. Perioperatively, IV antibiotics against *Streptococcus*, *S. aureus*, and *Pseudomonas* are generally administered until quantitative cultures of the excised eschar are finalized. The antibiotic regimen can then be guided by culture results and used under the appropriate clinical conditions. In acute burns, gram-positive cocci are generally the predominate organism involved, but colonization with gram-negative bacteria, and even fungi, are frequently encountered in chronic burn wounds and therefore must be covered with appropriate IV antibiotics during excision and grafting. In addition to burn wound sepsis, graft loss may be attributed to the presence of an infected wound at the time of skin grafting or colonization of the grafted bed shortly after surgery. The most common organisms responsible for graft loss are beta-hemolytic streptococci (*S. pyogenes, S. agalactiae, or S. viridans*). They are generally sensitive to third-generation cephalosporin and fluoroquinolones. The emergence of multiresistant bacteria, such as methicillin-resistant *S. aureus*, has become a serious problem for burn centers. Hence, IV antibiotics should be used with diligence, limiting their use for perioperative coverage and treatment of identified sources of infection.

One consideration that should be taken into account is the tissue penetration of IV antibiotics in burned tissue. One study compared the distribution of cephalothin in burned and nonburned tissue, and cephalothin levels were found to be elevated with decreased clearance in both tissues when compared with controls. It was postulated that this resulted from altered blood flow in injured tissue, an increase in capillary leakage, or leakage of albumin-bound cephalothin into the interstitium.[87] This finding suggests that antibiotic pharmacodynamics may need to be re-interpreted in burned patients.

## Nonthermal Injuries

### CHEMICAL BURNS

Children accidentally come in contact with various household cleaning products. Treatment of chemical burns involves immediate removal of the causative agent and lavage with copious amount of water, with caution for potential hypothermia. Fluid resuscitation is started, and care should be taken to ensure that the effluent does not contact uninjured areas. Decontamination is not performed in a tub, but rather, the wounds are irrigated toward a drain as in a shower. After completion of copious irrigation, wounds should be covered with a topical antimicrobial dressing and appropriate surgical plans made. The rapid recognition of the offending chemical agent is crucial to the proper management. When in doubt, a local poison control center should be contacted for identification of chemical composition of the product involved. The common offending chemical agents can be classified as alkali or acid. Alkali, such as lime, potassium hydroxide, sodium hydroxide, and bleach, are among the most common agents involved in chemical injury.[88] Mechanisms of alkali-induced burns are saponification of fat resulting in increased cell damage from heat, extraction of intracellular water, and formation of alkaline proteinates with hydroxyl ions. These ions induce further chemical reaction into the deeper tissues. Attempts to neutralize alkali are not recommended, because the chemical reaction can generate more heat and add to injury. Acid burns are not as common. Acids induce protein breakdown by hydrolysis, resulting in formation of eschar, and therefore do not penetrate as deeply as the alkaline burns. Formic acid injuries are rare but can result in multiple systemic organ failures, such as metabolic acidosis, renal failure, intravascular hemolysis, and acute respiratory distress syndrome. Hydrofluoric acid burns are managed differently from those of other acid burns in general.[89] After copious local irrigation with water, fluoride ion must be neutralized with topical application of 2.5% calcium gluconate gel. If not appropriately treated, free fluoride ion causes liquefaction necrosis of the affected soft tissues, including bones. Because of potential hypocalcemia, patients should be closely monitored for prolonged QT intervals.

### ELECTRICAL BURNS

Three to five percent of all admitted burn patients are injured from electrical contact. Fortunately, electrical burns are rare in children. Electrical burns are categorized into high- and low-voltage injuries. High-voltage injuries are characterized by varying degree of local burns, with destruction of deep tissues.[90] The electrical current enters a part of the body and travels through tissues with lowest resistance, such as nerves, blood vessels, and muscles. Heat generated as electrical current passes through deep tissues with relatively high resistance, such as bone, and damages adjacent tissues that may not be readily visible. Skin is mostly spared because of its high resistance to electrical current. Primary and secondary surveys, including electrocardiography, should be completed. If the initial electrocardiogram is normal, no further monitoring

is necessary; however, any abnormal findings require continued monitoring for 48 hours and appropriate treatment of dysrhythmias when detected. The key to management of electrical burns lies in the early detection and proper treatment of injuries to deep structures. Edema formation and subsequent vascular compromise is common to extremities. Fasciotomies are frequently necessary to avoid potential limb loss. Intra-abdominal complications can arise from bowel perforation. If myoglobinuria is present, vigorous hydration with administration of sodium bicarbonate, to alkalinize the urine and mannitol to achieve diuresis and as a free radical scavenger, is indicated. Repeated wound exploration and debridement of affected areas are required before ultimate wound closure, because there is a component of delayed cell death and thrombosis. The mechanism of electrical burn injury is to overwhelm the cellular systems that operate at millivolt/milliamp levels, so that cells that survive the initial injury may slowly die during a week's time as ion gradients deteriorate while thrombosis of the microvasculature proceeds. Electrical injuries may also have a thermal, nonconductive component as clothes burn or the electricity flashes. This is treated as if it were a conventional thermal burn. Low-voltage injury is similar to thermal injury, without transmission of electrical current to deep tissues, and usually only requires local wound care.

## Outpatient Therapy

The majority of pediatric burns are minor, often resulting from scald less than 10% TBSA or isolated small areas of thermal injuries from contact with hot objects. Such injuries are usually limited to partial thickness of the skin and can be treated on an outpatient basis. After an initial assessment, the burn wound is gently washed with water and a mild bland soap with appropriate pain control. Blisters can be left intact when they are small and not likely to spontaneously rupture, especially when present on the palm of hand. Blisters can provide a natural barrier against the environment and are beneficial in avoiding daily dressing changes. Spontaneous resorption of the fluid occurs in approximately 1 week, concomitant with the re-epithelialization process. Larger areas of blisters should be debrided and topical antimicrobial dressings applied. Silvadene is most commonly used because of its broad-spectrum antimicrobial property as well as its soothing effect on superficial second-degree burns. However, because silver sulfadiazine can impede epithelialization, its use should be discontinued when healing partial-thickness wounds are devoid of necrotic tissue and evidence of re-epithelialization is noted. Alternatively, antimicrobial dressings with triple antibiotic ointment (neomycin, bacitracin, and polymyxin B sulfate) and Polysporin, which do not have any negative effects on epithelialization, are commonly used. For small superficial partial-thickness burns, nonmedical white petrolatum-impregnated fine mesh, porous mesh gauze (Adaptic; Johnson & Johnson, New Brunswick, NJ), or fine mesh absorbent gauze impregnated with 3% bismuth tribromophenate in a nonmedicinal petrolatum blend (Xeroform, Covidien) are usually sufficient without the need for topical antimicrobials.

Superficial burns to the face can be treated with application of triple antibiotic ointment alone, without any dressings. The frequency of dressing change varies from twice daily to once a week, depending on the size, depth of burns, and drainage. Those who advocate twice daily dressing changes base their care on the use of topical antimicrobials whose half-life is about 8 to 12 hours. Others who use petrolatum-based or bismuth-impregnated gauze recommend less frequent, once every 3- to 5-day dressing changes. The use of synthetic wound dressings (e.g., Biobrane) is also ideal for treatment of superficial partial-thickness burns as an outpatient.[91] When applied appropriately to fresh, partial-thickness wounds, Biobrane adheres to the wound rapidly and is very effective in promoting re-epithelialization in 1 to 2 weeks (see Fig. 26-6). Although daily dressing changes are eliminated, Biobrane-covered wounds should still be monitored closely for signs of infection.

## Rehabilitation

Rehabilitation therapy is a vital part of burn care. During the acute phase of burn care, splints are used to prevent joint deformities and contractures. By using thermoplastic materials, which are amenable to heat manipulation, splints are fitted individually to each patient. Application of splints at all times, except during an exercise period, can potentially prevent severe contractures that occur in large-burn patients. Patients are mobilized out of bed immediately after the graft takes, and aggressive physical therapy is implemented. After the acute phase, hypertrophic scar formation is of major concern. The burn depth, patient's age, and genetic factors all play an important role in hypertrophic scar formation. In general, deep second-degree burn wounds, requiring 3 weeks or more to heal, will produce hypertrophic scarring. Children are more prone to hypertrophic scar formation than adults, probably because of the high rate of cell mitosis associated with growth. Continuously applied pressure 24 hours a day is the most effective method to minimize the hypertrophic scar formation. Pressure garments should be worn until scars mature, but they may be associated with skin breakdown and patient discomfort. Silicone gel is a commonly used treatment modality, even though its mechanism of action is poorly understood. Silicone treatment is reported to soften, increase elasticity, and improve the appearance of hypertrophic scars, but conflicting results remain in the literature that may be attributed to patient compliance.[92] Nonetheless, scar maturation usually occurs 6 to 18 months after injury. In younger patients, scars mature at a much slower rate. In addition to splints and pressure garments, physical therapy is a crucial component of rehabilitation therapy. Families should be thoroughly instructed on a program of active and passive range-of-motion exercises and muscle strengthening. It is not uncommon for patients to require inpatient or outpatient rehabilitation to return them to a functional quality of life. Burned survivors and families need rehabilitation therapy for extended periods of time both on a physical and psychological level. All must deal with feelings ranging from guilt to post-traumatic stress. A program such as *summer camp for children with burn injuries* has played an important role during the chronic phase of rehabilitation by helping children to improve self-esteem and to promote coping, social skills.[93]

*The complete reference list is available online at www.expertconsult.com.*

# CHAPTER 27

# Child Abuse and Birth Injuries

Dennis W. Vane

## Child Abuse

Child abuse encompasses physical abuse, sexual abuse, emotional abuse, and neglect. This maltreatment of children has become a significant focus of attention in our society. The media routinely publish accounts of the alleged traumatic and sometimes fatal abuse of children among all socioeconomic classes and levels of celebrity. The myth that child abuse and other violence in the home occur only among the poor and the uneducated has been debunked. Child abuse is a worldwide problem that affects all levels of society. Prevention and effective treatment depend on the timely detection of epidemiologic situations that lend themselves to the maltreatment of children.

Unfortunately, the "minor" status of children leads to the justifiable issue of the relative rights of parents and guardians. In most societies, it is an accepted premise that parents have the authority and responsibility to provide for their children. This is based on the assumption that parents have the best interests of their children in mind when making these decisions. Unfortunately, not all parents are willing or capable of basing their care decisions on their children's best interests; rather, they make these decisions in a more self-centered manner. As a result, these children may become victims of abuse and neglect through actions or the lack of actions by these parents.

Religious and societal "norms" have created barriers to the identification of child abuse victims in many nations. Around the globe, relatively few nations have addressed this problem at all.[1] In the United States and Canada, legislation aimed at identifying child abuse and neglect was enacted beginning in the 1960s.[2] Since that time, the reporting of child abuse to civil authorities has been mandated for almost all professionals dealing with children. The legislation protects the reporting individual from liability (usually by using the phrase "suspicion of" or "injuries consistent with"), supersedes all professional–client privilege, and sometimes even imposes penalties for failure to report abuse.[3]

### EPIDEMIOLOGY

In 2007 in the United States, Children's Protective Services investigated 3.5 million reports of child abuse. Of these investigations, 794,000 children were found to be victims of abuse. Thirty percent of all the children were less than the age of 4 years, 20% were between the ages of 4 and 7 years, and 20% were between 8 and 11 years.[4] In about 160,000 children, this maltreatment is considered physically serious or life threatening. Between 1,000 and 2,000 deaths are attributed to child abuse each year in the United States, and 80% of those children are younger than 5 years. Forty percent of the deaths occur in the first year of life and occur in an equal sex distribution.[5] Although deaths occur predominantly in the younger age groups, maltreatment of children is felt to increase with age. In teenagers, the incidence of abuse is thought to be twice that in preschool children; however, that statistic includes sexual abuse.[6] Intentional physical injury is most common in children less than 2 years of age, because they are essentially defenseless victims.[4] Patterns of child abuse occur with differing frequencies over the social strata. Sexual and emotional abuse have no socioeconomic associations, whereas physical abuse and neglect are more frequently associated with poverty.[6] Often, several types of abuse are perpetrated on the same child or within the same family. Additionally, abuse commonly occurs in families with other forms of intrafamilial violence, such as spousal abuse and violence among siblings.[7]

There is no single cause for abuse. However, multiple factors have been described that place a child at high risk to be abused. Commonly, more than one risk factor is present in a family at one time. It is important to remember, however, that the presence of risk factors in a child's environment does not necessarily indicate that abuse has or will occur. It is important to identify those situations where risk factors for child abuse exist. Local family services can often provide assistance to high-risk homes to aid families that may be in crisis. These early interventions potentially reduce or eliminate the risk of abuse.[4]

Risk factors for abuse are generally classified into four broad categories. First, there are the character and personality traits of the caregiver or parent; second, the individual characteristics of the child; third, the family dynamics; and finally, the environment in which the family is living.

#### Caregiver or Parent

Approximately 80% of all abusers are the parents.[4] Often, the abuser is described as having poor impulse control, antisocial behavior, and low self-esteem. Commonly, they were victims of abuse or witnessed domestic violence in the home themselves. Often, the abuser will have substance abuse problems. In many cases the parent's or caregiver's perception of the child is

negative and associated with unrealistic expectations of the child's abilities. The age of the parent is another risk factor—the younger the parent or caregiver, the greater the risk of abuse.

### The Child

The profile of the victim related to abuse rates has been studied in great depth.[4] The age of the child clearly impacts the risk, with children less than 3 years of age having the highest rates of abuse. These children require constant care and attention. They are small in stature compared with the adult and clearly are unable to adequately defend themselves. The child may be in a learning phase, such as toilet training, and may not be responding as the caregiver expects. Subsequently, children with cognitive, physical, or emotional disabilities are at significantly greater risk to suffer abuse. This higher risk holds true for premature and low-birth-weight infants as well. Some authors suggest that these factors interfere with appropriate parental bonding early in the child's life.

### Family Dynamics

The existing family structure clearly impacts the risk for abuse.[4] A single-parent household significantly increases the risk for abuse, particularly when the father is absent. Households where there are large numbers of individuals living together, including family and nonfamily members, compounds the potential risk for abuse as well. In families where domestic violence has been documented, reports indicate that children suffer a 30% to 60% risk of abuse.

Finally, environmental factors, such as poverty, unemployment, lack of education, and living in high-crime areas, have all been identified as predisposing to potential child abuse. These factors are often coupled with a scarcity of social services to aid these families in these areas, thus adding stress to the dynamics fostering the environment for abuse.[4]

Child abuse is a self-perpetuating social and economic problem. Problems with substance abuse and depression are reportedly 2 to 3 times more likely in abused children than in the general population, and abused children are likely to be far more physically aggressive with their peers.[8,9] It is estimated that approximately 30% of abuse victims eventually abuse their own children.[10] Some authors have suggested that this perpetual cycle of abuse is attributable, in part, to changes in the neuroendocrine system, influencing arousal, learning, growth, and the individual's pain threshold.[10]

What is clear is that the incidence of child abuse is significantly underreported, because professional contact or recognition is often required to identify abuse in the first place. Physicians must recognize not only abuse that has already occurred but also the factors indicating a high potential for abuse, if this dramatic worldwide problem is to be prevented.

## Presentation

Physicians must be aware that abused children are often withdrawn and avoid eye contact with their interviewers. Interviewers must be cognizant of the fact that children often respond with answers that they think will please the interviewer; so, care must be taken not to influence the child's responses. Young children are prone to associative fabrication, which may influence or even alter reality. The clinical history in suspected child abuse cases should include a detailed history of the family situation, unrelated caregivers, substance abuse in the household, and any history of past abuse. Even with these indicators, child abuse is extremely hard to accurately diagnose.

Given the wide spectrum of abuse, presenting symptoms vary accordingly. In the youngest victims, the diagnosis often depends on physical signs, such as bruising, patterned burn injuries, retinal hemorrhages, and long-bone fractures. Among all children, presentations that should raise a high level of suspicion in the clinician include multiple injuries in different stages of healing; injuries not consistent with the history provided by the caregiver; a history that changes when retold, particularly when the incident was "unwitnessed"; and injuries to the perineum. Wisslow[2] provided an excellent summary of the presenting physical injuries in cases of child abuse and neglect (Table 27-1). In children,

**TABLE 27-1**
**Signs and Symptoms Suggesting Child Abuse or Neglect**

| |
|---|
| Subnormal growth |
| Weight, height, or both less than 5th percentile for age |
| Weight less than 5th percentile for height |
| Decreased velocity of growth |
| Head injuries |
| Torn frenulum of upper or lower lip |
| Unexplained dental injury |
| Bilateral black eyes with history of single blow or fall |
| Traumatic hair loss |
| Retinal hemorrhage |
| Diffuse or severe central nervous system injury with history of minor to moderate fall (< 3 m) |
| Skin injuries |
| Bruise or burn shaped like an object |
| Bite marks |
| Burn resembling a glove or stocking, or with some other distribution, suggests an immersion injury |
| Bruises of various colors (in different stages of healing) |
| Injury to soft tissue areas that are normally protected (thighs, stomach, upper arms) |
| Gastrointestinal or genitourinary injuries |
| Bilious vomiting |
| Recurrent vomiting or diarrhea witnessed only by parent |
| Chronic abdominal or perineal pain with no identifiable cause |
| History of genital or rectal pain |
| Injury to genitals or rectum |
| Sexually transmitted disease |
| Bone injuries |
| Rib fracture in the absence of major trauma, such as a motor vehicle accident |
| Complex skull fracture after a short fall (< 1.2 m) |
| Metaphyseal long-bone fracture in an infant |
| Femur fracture (any configuration) in a child younger than 1 year |
| Multiple fractures in various stages of healing |
| Laboratory studies |
| Implausible or physiologically inconsistent laboratory results (polymicrobial contamination of body fluids, sepsis with unusual organisms, electrolyte disturbances inconsistent with the child's clinical state or underlying illness, wide and erratic variations in test results) |
| Positive toxicologic tests in the absence of a known ingestion or medication |
| Bloody cerebrospinal fluid (with xanthochromic supernatant) in an infant with altered mental status and no history of trauma |

From Wissow LS: Child abuse and neglect. N Engl J Med 1995;332:1425-1431.

essentially any injury can be the result of abuse; however, particular injuries and injury patterns have a high degree of association with abuse.

### Traumatic Brain Injury

Head injury is the most common injury associated with child abuse, and is responsible for the majority of deaths.[11–16] Penetrating head injury is rare in abuse victims, and most head injuries occur in younger children.[14] Blunt head injury most commonly manifests as "shaken baby syndrome" or, more accurately, "shaken impact syndrome," in which the insult is caused by an acceleration and deceleration of the brain within the cranial compartment resulting from violent shaking (Fig. 27-1). Recent studies indicate that some sort of contact with an object is necessary for the classical brain injury to occur, but that object may be relatively soft and produce no external indication of trauma (Fig. 27-2).[17] Angular forces created during shaking and eventual percussion against an object result in rotation of the brain within the skull. This causes diffuse axonal injury and tearing of the subdural bridging veins, often resulting in subdural hematoma. Spontaneous subdural hematoma or its occurrence from unintentional trauma is uncommon in children; so, its presence should raise the suspicion of child abuse (Fig. 27-3). Acute contact with stationary objects results in the characteristic multiple skull fractures associated with repetitive injury. Secondary brain injury is also frequently associated with abuse, resulting in intracranial hemorrhage, anoxia secondary to apnea, hypoperfusion, cardiac arrest, and potentially, herniation of the brainstem.[18] Brain injury secondary to abuse carries a reported mortality rate of 15% to 38%, which is significantly higher than that of similar injuries caused by unintentional trauma.[17] Nonfatal outcomes in abused children with traumatic brain injuries are also significantly worse than in those whose injuries were sustained unintentionally.[19] Nonenhanced computed tomography is considered the most appropriate diagnostic tool for the identification of intentional head injury. Intracranial lesions are easily identified, as are the often associated skull fractures.[20]

Although most commonly seen in younger children, head injury associated with child abuse occurs in older children as well. Whereas external signs of trauma are infrequent in


FIGURE 27-1 **A** and **B,** Shaken baby syndrome is often recognizable by external bruising about the chest, shoulders, and neck caused by the fingers and hands. (Used with permission of the American Academy of Pediatrics: Visual Diagnosis of Child Abuse CD-ROM, ed. 3, American Academy of Pediatrics, 2008.)

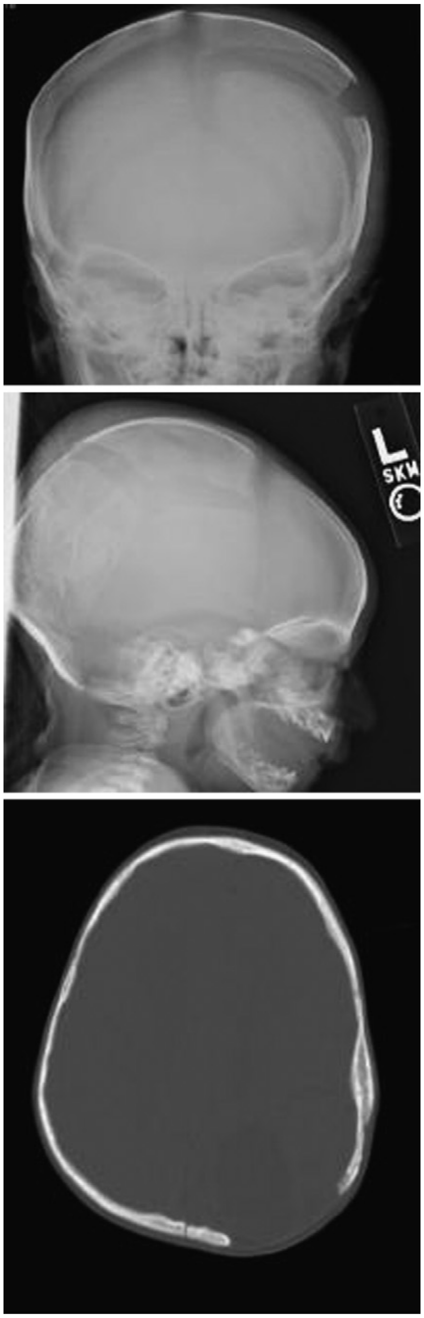

**FIGURE 27-2** The radiographs demonstrate a diastatic skull fracture secondary to forcibly striking the child's head against a hard object. These fractures are often associated with later complications from healing and development of leptomeningeal cysts. (Used with permission of the American Academy of Pediatrics: Visual Diagnosis of Child Abuse CD-ROM, ed. 3, American Academy of Pediatrics, 2008.)

younger children, older children usually present with visible injuries secondary to violent external trauma. These injuries are often severe, with poor outcomes.[21]

The identification of retinal hemorrhage has been deemed almost pathognomonic of child abuse[22]; however, recent studies indicate that retinal hemorrhage occurs in cases of nonintentional injury as well, including normal vaginal delivery, which can cause compression of the baby's soft skull.[23,24] The presence of retinal hemorrhage from nonintentional injury is so rare, however, that it should stimulate a high

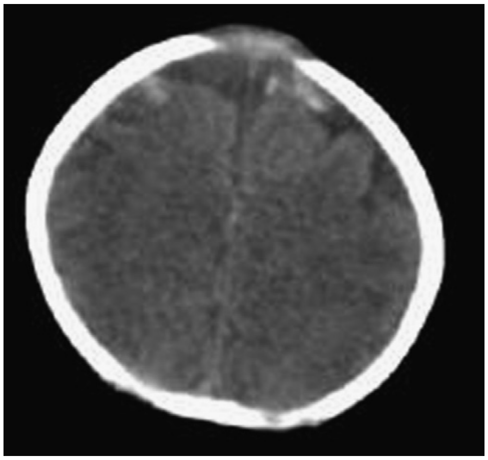

**FIGURE 27-3** The computed tomography (CT) scan demonstrates a subdural hematoma in a 6-week-old infant. Subdural hematomas may not present as space-occupying lesions but may cause significant morbidity when evacuated because of significant brain swelling. (Used with permission of the American Academy of Pediatrics: Visual Diagnosis of Child Abuse CD-ROM, ed. 3, American Academy of Pediatrics, 2008.)

level of suspicion for child abuse. When it is identified, the physician should begin an appropriate workup to investigate that possibility.

## Fractures

It is postulated that approximately 80% of child abuse cases in the United States are identified radiographically.[25] Fractures secondary to child abuse can be found in any age group, although fractures in older children are more commonly from high-impact unintentional injury.[26] This is the reverse of what is found in younger children where 55% to 70% of fractures associated with abuse occur in children less than 1 year of age; yet, only 2% of unintentional fractures occur in this age group.[12,14,27] The presence of a long-bone fracture in any child younger than 2 years of age has a high association with intentional injury.[28,29] Investigators have historically associated several fracture types with abuse, but it is probably more accurate to state that all fracture types can be associated with multiple causes. Spiral fractures, once reported as the most common type of fracture in abuse victims, have been replaced in more recent studies with single transverse fractures.[30] Spiral fractures are the result of torsional force applied to the extremity secondary to rotation of some sort. Transverse fractures are the result of a direct injury to the bone. This information should be used by the evaluating physician in conjunction with the history of injury to determine whether the history coincides with the presenting injury.

Diaphyseal fractures of the long bones are the most common fractures associated with child abuse, particularly those of the tibia, femur, and humerus. If the child is not ambulatory, the association between these fractures and abuse is extremely high.[30] Epiphyseal-metaphyseal fractures, although much less common than diaphyseal injuries, are reportedly far more specific for intentional injury.[31] The forces required to sustain these injuries greatly exceed the forces normally associated with falls and other minor trauma. Epiphyseal-metaphyseal fractures are also commonly known as corner fractures or bucket-handle fractures.

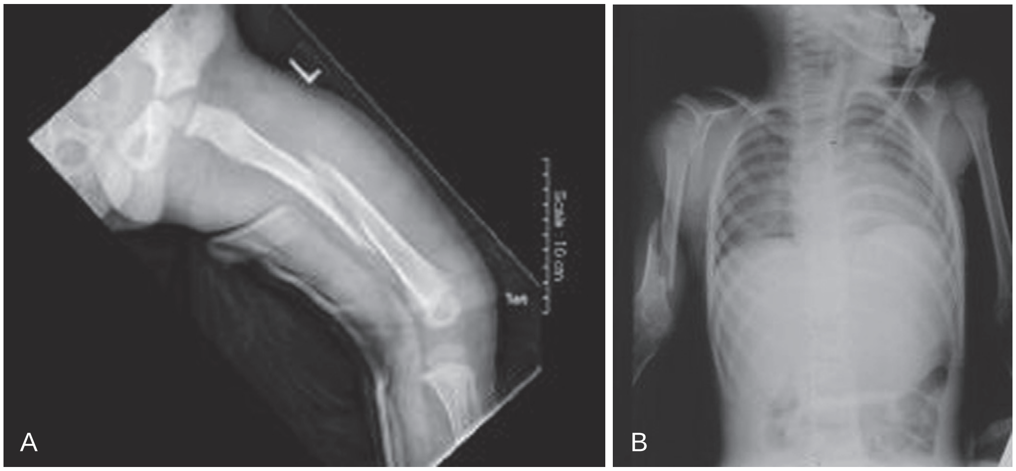


**FIGURE 27-4** **A,** The radiograph demonstrates a fracture of the femur in a 2-year-old child. Femur fractures are highly suspicious in this age group. The parents brought the child in, because it would not bear weight on its leg. **B,** The right humerus fracture in this child was accompanied by significant pulmonary contusions. The history of falling on the arm is inconsistent with this level of injury. (Used with permission of the American Academy of Pediatrics: Visual Diagnosis of Child Abuse CD-ROM, ed. 3, American Academy of Pediatrics, 2008.)

Type 1 fractures of the femur and humerus have a high association with abuse when encountered outside of the neonatal period.[32] This is particularly true if the history of injury does not contain significant high-force violent trauma. These injuries require considerable force to occur and, when nonintentional, are commonly associated with significant soft tissue damage and other injuries. Other types of Salter-Harris injuries do not appear to have a strong association with intentional abuse (Fig. 27-4).

Clavicular fractures can also be associated with abuse, but there is a low specificity. Clavicular fractures of either end, rather than the midshaft, are usually the result of significant traction or the trauma of shaking.[15] Rib fractures, in contrast, have an extremely high association with abuse. It is postulated that the relatively elastic rib cage in children prevents most fractures secondary to accidental trauma. When fractures of the ribs do occur, the association with abuse is high—up to 82%.[33] In general these fractures occur at the posterior segment of the rib near the costovertebral junction (Fig. 27-5).

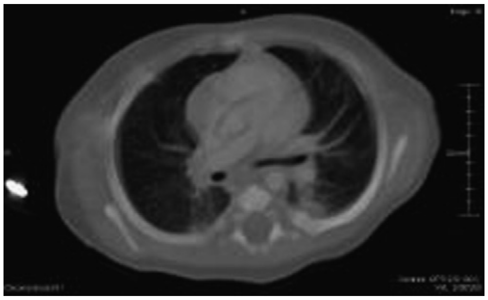

**FIGURE 27-5** Posterior rib fractures in children are rare results of accidental injury. Their presence most commonly indicates intentional injury. (Used with permission of the American Academy of Pediatrics: Visual Diagnosis of Child Abuse CD-ROM, ed. 3, American Academy of Pediatrics, 2008.)

Spinal fractures are rare in children, as is cord injury. The difficulty in diagnosing vertebral body injuries and the relatively protected spine make any association with abuse difficult to determine. Suffice it to say that any injury of the spine or spinal cord requires an extremely violent force, and the cause must be carefully investigated.

It is critical for any physician treating children to investigate all fractures, particularly in the younger age groups. Minimal trauma does not commonly cause fractures, except when associated with other pathology. Getting an accurate history is critical. The presence of multiple fractures associated with a history of minimal trauma always requires an investigation for potential child abuse. The identification of multiple fractures, particularly when the age of the fractures is different, is almost pathognomonic of abuse. When abuse is suspected, skeletal surveys are indicated. The American College of Radiology has published standards for these surveys.[34]

## Burns

Burns are a fairly common indication of child abuse, representing approximately 20% of pediatric burn injuries. Most commonly, the victims are less than 2 years of age.[35] Abuse victims often have characteristic patterns of burn infliction of which physicians should be aware.[36] Common patterns include circumferential burns, particularly when the burns are on more than one extremity; "pattern" burns or branding; burns to the buttocks, genitalia, or perineum; and punctate or cigarette burns (Figs. 27-6 and 27-7). Burn victims who are abused are usually younger than unintentional burn victims and have a history of being burned in the bathroom.[37] The demographics of intentionally burned children are striking. These children are often being raised by single mothers or are in foster care, they are in homes where other children have previously been removed because of abuse, and there is an almost 40% chance that past abuse has already been investigated.[37]

With burns, the history of injury is critical and is often inconsistent with the burn pattern. The burn itself often exhibits uncharacteristic features, such as lack of splash marks from falling liquids, consistent depth throughout the burn rather than the normal "feathering" of depth, and larger surface areas than expected based on the history. These burns, which are often the result of immersion, present with clear lines of demarcation, indicating that the child was unable to move during the incident and was probably restrained. Inflicted burns to the buttocks and perineum often occur in children being toilet trained when a caregiver becomes frustrated about an

**FIGURE 27-6** Pattern burns are almost pathognomonic of intentional injury. In this case, the silverware found in the home directly matches the injury seen here. (Used with permission of the American Academy of Pediatrics: Visual Diagnosis of Child Abuse CD-ROM, ed. 3, American Academy of Pediatrics, 2008.)

**FIGURE 27-7** Bilateral foot and ankle burns accompanied by burns to the perineum indicate abuse. These burns are commonly seen in children being toilet trained, who are in the care of a nonbiologic parent. (Used with permission of the American Academy of Pediatrics: Visual Diagnosis of Child Abuse CD-ROM, ed. 3, American Academy of Pediatrics, 2008.)

"accident." Burns on the dorsum of the hand are suggestive of abuse, whereas burns to the palm are more likely unintentional. Children, similar to adults, explore with the palmar surface, not the back of the hand. The depth of burn is also important. It takes approximately 1.5 seconds to cause a second-degree burn in adult skin immersed in water at

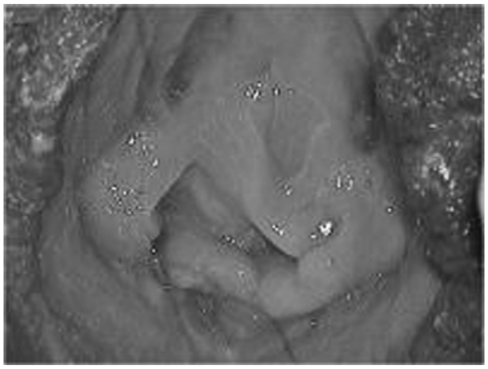

**FIGURE 27-8** Total lateral disruption of the hymen pictured here indicates forceful penetration. (Used with permission of the American Academy of Pediatrics: Visual Diagnosis of Child Abuse CD-ROM, ed. 3, American Academy of Pediatrics, 2008.)

150° F. That is certainly more time than anyone would keep his or her hands immersed volitionally.

Flame burns, while not usually the result of a direct intentional infliction, often do represent potential abuse by neglect or an unsafe habitation. These types of injuries require a high degree of suspicion and may warrant reporting.

A complete history and physical examination are necessary in any child seen for burns or the suspicion of abuse. Other signs of abuse are often discernible, such as healed or healing fractures or, possibly, perineal injuries. Additionally, recent data indicate that some burn injuries mimic chronic skin conditions.[38] Thus a high level of suspicion must be maintained when clinicians see lesions that do not present in characteristic locations or do not respond to normal therapy. Given the high incidence of recurrence in burn injury, physicians must ensure that the child is discharged to a safe environment.[39]

## Thoracoabdominal Injury

Fortunately, significant thoracoabdominal injury secondary to child abuse is uncommon, estimated to occur in about 5% of abused children.[40] Unfortunately, thoracoabdominal injury is the second leading cause of death in these children, following head injury, and has a significantly higher associated mortality than similar unintentional injury.[25,40] Any type of blunt or penetrating abdominal injury can be caused intentionally.[6,34,41–43] Injuries commonly result from severe blows to the abdomen or chest cavity, and as previously stated, rib fractures in children should raise the suspicion of abuse.[33] Most important, the clinician must ascertain the history of injury to determine whether the injury is consistent with the mechanism described. For example, recent reports indicate that a simple fall down a flight of stairs does not generate the force or dynamics necessary for a hollow viscus perforation.[44] Similarly, significant head injury requires a mechanism generating more force than simply rolling out of bed. Studies indicate that a child must fall at least 3 feet onto a hard surface to sustain a skull fracture. This includes wood floors, tile, or cement. Falls on to carpets and mattresses provide adequate cushioning to make a fracture unlikely from this height.[45–47]

Treatment of intentionally inflicted intra-abdominal injuries follows the algorithms of unintentional injuries. Mortality from these intentional injuries exceeds those found with unintentional injuries, mainly because of delay in presentation. Specific organ injuries, such as to the pancreas, carry with

FIGURE 27-9 Lacerations of the anal area, often first noted as blood in the underwear, indicate penetration. (Used with permission of the American Academy of Pediatrics: Visual Diagnosis of Child Abuse CD-ROM, ed. 3, American Academy of Pediatrics, 2008.)

FIGURE 27-10 Bruising in the perineum, scrotum, and penis secondary to intentional injury. (Used with permission of the American Academy of Pediatrics: Visual Diagnosis of Child Abuse CD-ROM, ed. 3, American Academy of Pediatrics, 2008.)

them an increased association of hollow viscus injury versus those of unintentional injury patterns. These associations should prompt a high degree of suspicion for abuse.[49,50]

Injuries to the perineum should always lead to a consideration of child abuse. Aside from burns to the perineum, discussed previously, injuries in this area resulting from abuse tend to be penetrating. Rectal or vaginal trauma resulting in laceration should routinely be investigated, as should lacerations in the penile and scrotal region (Figs. 27-8 to 27-10). Abuse may involve retained foreign bodies as well. The physician should always investigate anal and vaginal orifices that appear to be dilated, particularly those that may result in incontinence. Signs of abuse to the perineum are often chronic, and areas of scar and old lacerations should be noted.

The radiographic and diagnostic workup for children suffering thoracoabdominal abuse is identical to that for unintentional injury. Recommendations for appropriate scans and diagnostics have been updated by the American Academy of Pediatrics.[51] Management of these injuries is also the same as for unintentional thoracoabdominal injuries.[42,52]

# Birth Injuries

Birth injury is estimated to occur in 6 to 8 of every 1000 live births in the United States, but it is responsible for about 2% of the perinatal mortality.[53] Injury most commonly occurs in babies with macrosomia but can also be associated with fetal organomegaly, mass lesions, prematurity, protracted labor, precipitous delivery, breech presentation, and cephalopelvic dissociation. The development and widespread use of prenatal ultrasonography, along with other advances in perinatal care, have allowed the early identification of many of these factors, together with recommendations for the delivery of such high-risk infants.[54]

## SOFT TISSUE INJURY

The most common birth injury encountered is injury to the soft tissue. This can present as a hematoma (often cephalohematoma), simple cutaneous bruising, or fat necrosis manifesting as subcutaneous masses. These lesions resolve spontaneously within months and require no treatment other than reassurance of the parents. Less commonly, lacerations secondary to instrumentation may occur. These lacerations can usually be closed with adhesive strips or cutaneous glue rather than sutures. Suturing may be necessary, however, when adhesive closure cannot achieve the appropriate cosmetic result. Fine material should always be used, and healing is usually excellent. Lacerations are rarely deep, but if they are, standard precautions for wound exploration should be followed.

Torticollis has been ascribed to birth trauma or intrauterine malpositioning.[55] The cause is debatable, because torticollis has been found in infants who were delivered by cesarean section, as well as in those delivered vaginally. The classical presentation is a small, firm mass in the body of the sternocleidomastoid muscle. The head is tilted toward the mass, with the face classically turned to the contralateral side. Physical therapy performed by the parents is successful in the vast majority of cases, and surgical intervention is rarely indicated. Facial asymmetry may result in untreated lesions. Torticollis has been misdiagnosed as a malignancy in the neck. Careful examination and taking a complete history can often prevent this error.[56]

## FRACTURES

The most common fracture associated with birth trauma is clavicular, occurring in about 2.7 of every 1000 births.[57] The fracture is noticed when the infant does not move the arm or swelling occurs over the clavicle. The fracture is commonly in the midshaft and generally requires no treatment, although some authors recommend figure-of-eight splints or pinning the baby's shirtsleeve to the chest on the affected side.[58] Occasionally, because of shoulder dystocia, the clavicle may be intentionally fractured.[59]

Fractures of the humerus usually occur in either the shaft or the proximal epiphysis. Epiphyseal fractures are difficult to diagnose because of a lack of ossification points in the neonatal epiphysis. Associated neurologic findings may be noted with fractures of the humerus, including Erb palsy and radial nerve palsy.[59,60] Shoulder dislocation is most likely not related

to birth trauma but rather to intrauterine causes or therapy for Erb palsy.[61] Distal fractures and dislocations of the radial head may also occur and are often associated with breech delivery.[62,63] Proximal fractures of the humerus can be successfully treated by bandaging the arm to the chest in a neutral position for epiphyseal injuries and by strapping the arm to the chest with an abduction device or possibly a posterior splint for shaft fractures.[64]

Birth trauma can cause fractures of the femur at almost any location. Breech delivery and high birth weight are predisposing factors.[65] Presentation consists of abnormal rotation of the lower extremity, pain, or swelling. Treatment involves application of a traction device, spica cast, or both.[66] Reduction should be close to anatomic, because overgrowth and remodeling of the femur are not usually dramatic.[67]

## NEUROLOGIC INJURY

Brachial plexus injury is the most common neurologic birth injury.[68] Approximately 21% of these injuries are associated with a shoulder dystocia at birth. Erb palsy (C3 to C5) is the most common of the brachial plexus injuries and usually resolves spontaneously, with little residual effect. Presentation involves a lack of motion of the affected shoulder, with the limb adducted and internally rotated to the prone position. Distal sensation and hand function are usually normal. Even after aggressive physical therapy, about 2% of cases are permanent.[69] Lower injuries of the C6 to T1 cervical roots (Klumpke palsy) present with a lack of hand and wrist function. These lesions may be accompanied by Horner syndrome, with the associated physical findings. Microsurgical repair has been described for recalcitrant brachial plexus injuries, with relatively good success, but this should be reserved only for infants failing aggressive physical therapy.[70] Phrenic nerve paralysis is a commonly associated finding and should be investigated whenever brachial plexus injury is identified. Isolated brachial plexus injury can cause significant shoulder abnormalities, and therapy should not be delayed.[71]

Phrenic nerve injury can also occur in isolation.[53] Treatment of phrenic nerve injury depends on the severity of the respiratory embarrassment experienced by the child. Asymptomatic injuries should not be treated; injuries resulting in respiratory impairment should be treated with diaphragmatic plication or other procedures designed to reduce the paradoxical movement of the diaphragm with respiration.[21]

Certainly the most devastating neurologic birth injuries involve the central nervous system. Lesions of the cervical spine are rare but are devastating when they occur. The cause of injury is usually a vaginal delivery with a breech or transverse lie.[72] As with all cervical spine injuries, high lesions require mechanical ventilation, and lower lesions have devastating physical sequelae. Survival is poor in neonates with complete transection. Partial injury may mimic cerebral palsy.[73]

Subdural, subarachnoid, intraventricular, and intraparenchymal bleeds have also been associated with birth trauma. Outcome is dependent on the extent of the lesion and the presentation. Usually these lesions are secondary to vacuum extraction,[74,75] which is also implicated as the cause of subgaleal cephalohematoma. Although most hematomas resolve without incident or sequelae, approximately 25% have been reported to cause death in affected neonates.[76] Traction injury to the internal carotid artery has also been reported in difficult births. Outcome from these injuries is varied and depends on the extent of vascular damage and collateral perfusion.[77] Similarly, direct injury to the optic nerve has been described.[78]

The most common central nervous system injury during childbirth is anoxic brain damage, and the resultant "cerebral palsy." The cause is controversial, but difficult delivery is a common association.

Treatment of neurologic birth trauma is usually expectant, with aggressive physical therapy. Recalcitrant peripheral injuries have responded to surgical repair.

## THORACOABDOMINAL INJURY

Injuries to the chest are believed to be the result of pressure on the thoracic cavity. Pneumothorax, pneumomediastinum, and chylothorax have been described.[53,79] Perforation of the esophagus or cricopharyngeus can also occur. In most cases of birth trauma to the chest, expectant observation is indicated. The clinical course dictates the need for operative intervention. High perforations of the esophagus and cricopharyngeus can usually be treated by observation or occasionally drainage.[53] Lower lesions require drainage or operative repair. With early identification, results are excellent. Perforation of the esophagus can also result from placement of a gastric tube in the neonatal period. The management of these lesions remains controversial and varies from immediate intervention to expectant observation, based on the child's clinical situation.

Liver hematoma is the most common intra-abdominal injury secondary to birth trauma (Fig. 27-11). The usual presentation is anemia, but it can also be shock.[80] Diagnosis is usually made by ultrasonography, but a thorough investigation may be necessary to rule out other hepatic masses in a newborn. Treatment is usually expectant and includes volume resuscitation and correction of any hypothermia or coagulopathy. Occasionally, operative intervention is necessary when the baby is unstable or continued hemorrhage occurs. Hemostatic agents appear to be more helpful than attempts at suture repair in stopping hepatic bleeding in newborns.[81] In any case, control of hepatic hemorrhage is very difficult in this age group.

Splenic injury is rare and presents much like hepatic injury. Intra-abdominal blood may be the only presenting sign, and,

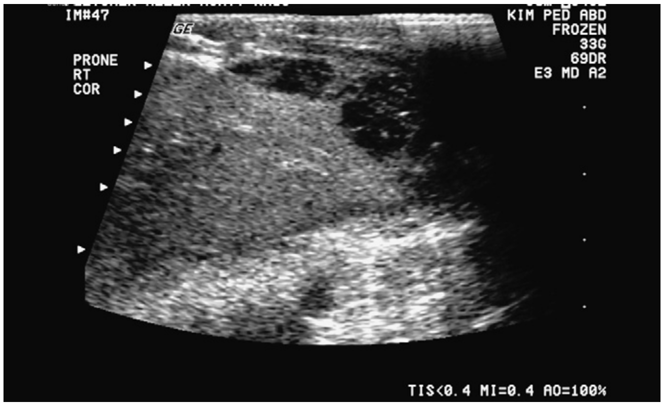


**FIGURE 27-11** Ultrasonography of the abdomen clearly demonstrates this hepatic hematoma caused by birth trauma, which resolved spontaneously. Lesions such as this can be followed by ultrasonography; if they persist, other causes, such as neoplasm, must be investigated.

as in hepatic injury, other pathology must be ruled out.[82] Treatment includes expectant observation and correction of coagulopathy or hypothermia. Operative intervention is difficult and usually results in splenectomy. Hemostatic agents may also be useful.

As with splenic injury, injury to the adrenal glands is uncommon because of the relative protection provided by the thoracic ribs. The presentation may be hemorrhage or adrenal insufficiency in severe cases. Injury can also be identified from calcifications found on a radiograph taken later in life. As with all intra-abdominal solid organs, investigation of hematomas requires a workup to rule out other pathology, such as underlying tumor.

*The complete reference list is available online at www.expertconsult.com.*

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# Part III

# MAJOR TUMORS OF CHILDHOOD

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CHAPTER 28

# Principles of Pediatric Oncology, Genetics of Cancer, and Radiation Therapy

Matthew J. Krasin and Andrew M. Davidoff

A number of milestones in the evolution of cancer therapy have come from the field of pediatric oncology. The first clear evidence that chemotherapy could provide effective treatment for childhood malignancy occurred in 1950 when Farber reported temporary cancer remission in children with acute lymphoblastic leukemia (ALL) treated with the folic acid antagonist aminopterin.[1] The first successful use of a multidisciplinary approach to cancer treatment occurred in the 1960s and 1970s through the collaborative efforts of pediatric surgeons, radiation therapists, and pediatric oncologists aiming to improve the treatment of Wilms' tumor in children.[2] Such a multidisciplinary approach is now used throughout the field of oncology. The successful use of a combination of chemotherapeutic agents to cure Hodgkin disease and ALL during the 1960s led to the widespread use of combination chemotherapy to treat virtually all types of cancers. Since the late 1980s, neuroblastoma has been the paradigm for the use of therapies of variable intensity, depending on risk stratification determined by clinical and biological variables, including molecular markers. Other advances in pediatric oncology have included the development of interdisciplinary, national cooperative clinical research groups to critically evaluate new therapies, the efficacy of dose-intensive chemotherapy programs in improving the outcome of advanced-stage solid tumors, and the supportive care necessary to make the latter approach possible. The development and application of these principles and advances have led to substantially increased survival rates for children with cancer and profound improvements in their quality of life.

Additionally, advances in molecular genetic research in the past 3 decades have led to an increased understanding of the genetic events in the pathogenesis and progression of human malignancies, including those of childhood. A number of pediatric malignancies have served as models for molecular genetic research. Chromosomal structural changes, activating or inactivating mutations of relevant genes or their regulatory elements, gene amplification, and gene imprinting may each play a role in different tumor types. In some instances, these genetic events occur early in tumorigenesis and are specific for a particular tumor type, such as the chromosomal translocation t(11;22)(q24;q12) in Ewing sarcoma; other aberrations occur in a variety of different tumor types and are almost always associated with additional genetic changes, such as chromosome 1p deletion in neuroblastoma and Wilms' tumor. Some alterations involve oncogenes—genes that, when activated, lead directly to cancer—whereas others involve tumor suppressor genes, whose inactivation allows tumor progression. The result of alterations in these genetic elements, regardless of the mechanism, is disruption of the normal balance between proliferation and death of individual cells. These discoveries have highlighted the utility of molecular analysis for a variety of purposes, including diagnosis, risk stratification, and treatment planning; the understanding of syndromes associated with cancer; genetic screening and genetic counseling; and prophylactic treatment, including surgical intervention. Soon, treatment regimens are likely to be individualized on the basis of the molecular biological profile of a patient's tumor. In addition, molecular profiling will lead to the development of new drugs designed to induce differentiation of tumor cells, block dysregulated growth pathways, or reactivate silenced apoptotic pathways.

## Epidemiology and Survival Statistics

Cancer in children is uncommon; it represents only about 2% of all cancer cases. Nevertheless, after trauma, it is the second most common cause of death in children older than 1 year. Each year, approximately 130 new cases of cancer are identified per million children younger than 15 years (or about 1 in 7000). This means that in the United States, about 9,000 children younger than 15 years are diagnosed with cancer each year, in addition to 4,000 patients aged 15 to 19 years.[3] Leukemia is the most common form of cancer

**TABLE 28-1**
**Frequency of Cancer Diagnoses in Childhood**

| *Type of Cancer* | *Percentage of Total* |
|---|---|
| Leukemia | 30 |
| Brain tumors | 25 |
| Lymphoma | 15 |
| Neuroblastoma | 8 |
| Sarcoma | 7 |
| Wilms' tumor | 6 |
| Osteosarcoma | 5 |
| Retinoblastoma | 3 |
| Liver tumors | 1 |

in children, and brain tumors are the most common solid tumor of childhood (Table 28-1). Lymphomas are the next most common malignancy in children, followed by neuroblastoma, soft tissue sarcomas, Wilms' tumor, germ cell tumors, osteosarcoma, and retinoblastoma. A slightly different distribution is seen among 15- to 19-year-olds, in whom Hodgkin disease and germ cell tumors are the most frequently diagnosed malignancies; non-Hodgkin lymphoma, nonrhabdomyosarcoma soft tissue sarcoma, osteosarcoma, Ewing sarcoma, thyroid cancer, and melanoma also occur with an increased incidence.

In general, the incidence of childhood cancer is greatest during the first year of life, peaks again in children aged 2 to 3 years, and then slowly declines until age 9. The incidence then steadily increases again through adolescence. Each tumor type shows a different age distribution pattern, however. Variations by gender are also seen. For example, Hodgkin disease, ALL, brain tumors, neuroblastoma, hepatoblastoma, Ewing sarcoma, and rhabdomyosarcoma are more common in boys than in girls younger than 15 years, whereas only osteosarcoma and Ewing sarcoma are more common in boys than in girls older than 15 years. However, girls in the older age group have Hodgkin disease and thyroid cancer more frequently than boys do. Distribution also varies by race: White children generally have a 30% greater incidence of cancer than do black children. This difference is particularly notable for ALL, Ewing sarcoma, and testicular germ cell tumors. The probability of surviving childhood cancer has improved greatly since Farber induced the first remissions in patients with ALL. In the early 1960s, approximately 30% of children with cancer survived their disease. By the mid-1980s, about 65% of children with cancer were cured, and by the mid-1990s, the cure rate had increased to nearly 75%.[4] Currently, greater than 80% are cured. These great strides have resulted from three important factors: (1) the sensitivity of childhood cancer, at least initially, to available chemotherapeutic agents; (2) the treatment of childhood cancer in a multidisciplinary fashion; and (3) the treatment of most children in major pediatric treatment centers in the context of a clinical research protocol using the most current and promising therapy. Although progress in the treatment of some tumor types, such as ALL and Wilms' tumor, has been outstanding, progress in the treatment of others, such as metastatic neuroblastoma and rhabdomyosarcoma, has been modest. Therefore there is still a need for significant improvement in the treatment of childhood cancer.

# Molecular Biology of Cancer

During normal cellular development and renewal, cells evolve to perform highly specialized functions to meet the physiologic needs of the organism. Development and renewal involve tightly regulated processes that include continued cell proliferation, differentiation to specialized cell types, and programmed cell death (apoptosis). An intricate system of checks and balances ensures proper control over these physiologic processes. The genetic composition (genotype) of a cell determines which pathway(s) will be followed in exerting that control. In addition, the environment plays a crucial role in influencing cell fate: Cells use complex signal transduction pathways to sense and respond to neighboring cells and their extracellular milieu.

Cancer is a genetic disease whose progression is driven by a series of accumulating genetic and epigenetic changes influenced by hereditary factors and the somatic environment. These changes result in individual cells acquiring a phenotype that provides them with a survival advantage compared with surrounding normal cells. Our understanding of the processes that occur in malignant cell transformation is increasing; many discoveries in cancer cell biology have been made by using childhood tumors as models. This greater understanding of the molecular biology of cancer has also contributed significantly to our understanding of normal cell physiology.

## NORMAL CELL PHYSIOLOGY

### Cell Cycle

Genetic information is stored in cells and transmitted to subsequent generations of cells through nucleic acids organized as genes on chromosomes. A gene is a functional unit of heredity that exists on a specific site or locus on a chromosome, is capable of reproducing itself exactly at each cell division, and is capable of directing the synthesis of an enzyme or other protein. The genetic material is maintained as DNA formed into a double helix of complementary strands. The cell must ensure that replicated DNA is accurately copied with each cell division or cycle. DNA replication errors that go uncorrected potentially alter the function of normal cell regulatory proteins. The molecular machinery used to control the cell cycle is highly organized and tightly regulated.[5] Signals that stimulate or inhibit cellular growth converge on a set of evolutionarily conserved enzymes that drive cell-cycle progression. Various "checkpoints" exist to halt progression through the cell cycle during certain environmental situations or times of genetic error resulting from inaccurate synthesis or damage. Two of the most well-studied participants in the cell-cycle checkpoint system are TP53 and retinoblastoma (RB) proteins.[6] In normal circumstances, cells divide and terminally differentiate, thereby leaving the cell cycle, or they enter a resting state. Inactivation of the effectors of cell-cycle regulation or the bypassing of cell-cycle checkpoints can result in dysregulation of the cell cycle, a hallmark of malignancy.

### Signal Transduction

Signal transduction pathways regulate all aspects of cell function, including metabolism, cell division, death, differentiation, and movement. Multiple extracellular and intracellular

signals for proliferation or quiescence must be integrated by the cell, and it is this integration of signals from multiple pathways that determines the response of a cell to competing and complementary signals. Extracellular signals include growth factors, cytokines, and hormones; the presence or absence of adequate nutrients and oxygen; and contact with other cells or an extracellular matrix. Signaling mediators often bind to membrane-bound receptors on the outside of the cell, but they may also diffuse into the cell and bind receptors in the cytoplasm or on the nuclear membrane. Binding of a ligand to a receptor stimulates the activities of small-molecule second messengers—proteins necessary to continue the transmission of the signal. Signaling pathways ultimately effect the activation of nuclear transcription factors that are responsible for the expression or silencing of genes encoding proteins involved in all aspects of cellular physiology.

Receptors with tyrosine kinase activity are among the most important transmembrane receptors. Several important transmembrane receptors with protein kinase activity have been identified and grouped in families on the basis of structural similarities.[7] These families include the epidermal growth factor receptors (EGFRs), fibroblast growth factor receptors, insulin-like growth factor receptors (IGFRs), platelet-derived growth factor receptors (PDGFRs), transforming growth factor receptors, and neurotrophin receptors (TRKs). Abnormalities of members of each of these families are often found in pediatric malignancies and therefore are thought to play a role in their pathogenesis. Characteristic abnormalities of these receptors often form the basis of both diagnostic identification of certain tumor types and, more recently, targeted therapy for tumors with these specific abnormalities.

### Programmed Cell Death

Multicellular organisms have developed a highly organized and carefully regulated mechanism of cell suicide to maintain cellular homeostasis. Normal development and morphogenesis are often associated with the production of excess cells, which are removed by the genetically programmed process of cell death called apoptosis. Apoptosis limits cellular expansion and counters cell proliferation. Apoptosis is initiated by the interaction of "death ligands," such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$), FAS, and TNF-related apoptosis-inducing ligand (TRAIL), with their respective receptors. This interaction is followed by aggregation of the receptors and recruitment of adapter proteins to the plasma membrane, which activate caspases.[8] Thus the fate of a cell is determined by the balance between death signals and survival signals.[9]

An alternative to cell death mediated by receptor–ligand binding is cellular senescence, which is initiated when chromosomes reach a critical length. Eukaryotic chromosomes have DNA strands of unequal length, and their ends, called telomeres, are characterized by species-specific nucleotide repeat sequences. Telomeres stabilize the ends of chromosomes, which are otherwise sites of significant instability.[10] With time and with each successive cycle of replication, chromosomes are shortened by failure to complete replication of their telomeres. Thus telomere shortening acts as a biological clock, limiting the life span of a cell. Germ cells, however, avoid telomere shortening by using telomerase, an enzyme capable of adding telomeric sequences to the ends of chromosomes. This enzyme is normally inactivated early in the growth and development of an organism. Persistent activation or the reactivation of telomerase in somatic cells appears to contribute to the immortality of transformed cells.

### Malignant Transformation

Alteration or inactivation of any of the components of normal cell regulatory pathways may lead to the dysregulated growth that characterizes neoplastic cells. Malignant transformation may be characterized by cellular de-differentiation or failure to differentiate, cellular invasiveness and metastatic capacity, or decreased drug sensitivity. Tumorigenesis reflects the accumulation of excess cells that results from increased cell proliferation and decreased apoptosis or senescence. Cancer cells do not replicate more rapidly than normal cells, but they show diminished responsiveness to regulatory signals. Positive growth signals are generated by proto-oncogenes, so named because their dysregulated expression or activity can promote malignant transformation. These proto-oncogenes may encode growth factors or their receptors, intracellular signaling molecules, and nuclear transcription factors (Table 28-2). Conversely, tumor suppressor genes, as their name implies, control or restrict cell growth and proliferation. Their inactivation, through various mechanisms, permits the dysregulated growth of cancer cells. Also important are the genes that regulate cell death. Their inactivation leads to resistance to apoptosis and allows the accumulation of additional genetic aberrations.

Cancer cells carry DNA that has point mutations, viral insertions, or chromosomal or gene amplifications, deletions, or rearrangements. Each of these aberrations can alter the context and process of normal cellular growth and differentiation. Although genomic instability is an inherent property of the evolutionary process and normal development, it is through genomic instability that the malignant transformation of a cell may arise. This inherent instability may be altered by inheritance or exposure to destabilizing factors in the environment. Point mutations may terminate protein translation, alter protein function, or change the regulatory target sequences that control gene expression. Chromosomal alterations create new genetic contexts within the genome and lead to the formation of novel proteins or to the dysregulation of genes displaced by aberrant events.

Genetic abnormalities associated with cancer may be detected in every cell in the body or only in the tumor cells. Constitutional or germline abnormalities either are inherited or occur de novo in the germ cells (sperm or oocyte). Interestingly, despite the presence of a genetic abnormality that might affect growth regulatory pathways in all cells, people are generally predisposed to the development of only certain tumor types. This selectivity highlights the observation that gene function contributes to growth or development only within a particular milieu or physiologic context. Specific tumors occur earlier and are more often bilateral when they result from germline mutations than when they result from sporadic or somatic alterations. Such is often the case in two pediatric malignancies, Wilms' tumor and retinoblastoma. These observations led Knudson[11] to propose a "two-hit" mechanism of carcinogenesis in which the first genetic defect, already present in the germline, must be complemented by an additional spontaneous mutation before a tumor can arise. In sporadic cancer, cellular transformation occurs only when two (or more) spontaneous mutations take place in the same cell.

Much more common, however, are somatically acquired chromosomal aberrations, which are confined to the malignant cells.

**TABLE 28-2**

**Proto-oncogenes and Tumor Suppressor Genes in Pediatric Malignancies**

| *Oncogene Family* | *Proto-oncogene* | *Chromosome Location* | *Tumors* |
|---|---|---|---|
| Growth factors and receptors | *ERBB2* | 17q21 | Glioblastoma |
| | *TRK* | 9q22 | Neuroblastoma |
| Protein kinase | *SRC* | 7p11 | Rhabdomyosarcoma, Osteosarcoma, Ewing sarcoma |
| Signal transducers | *H-RAS* | 11p15.1 | Neuroblastoma |
| Transcription factors | c-*MYC* | 18q24 | Burkitt lymphoma |
| | *MYCN* | 2p24 | Neuroblastoma |
| ***Syndrome*** | ***Tumor Suppressor Gene*** | ***Chromosome Location*** | ***Tumors*** |
| Familial polyposis coli | *APC* | 5q21 | Intestinal polyposis, colorectal cancer |
| Familial retinoblastoma | *RB* | 13q24 | Retinoblastoma, osteosarcoma |
| WAGR* | *WT1* | 11p13 | Wilms' tumor |
| Denys-Drash† | *WT1* | 11p13 | Wilms' tumor |
| Beckwith-Weidemann‡ | *WT2* (?) | 11p15 | Wilms' tumor, hepatoblastoma, adrenal |
| Li-Fraumeni | *TP53* | 17q13 | Multiple (see text) |
| Neurofibromatosis type 1 | *NF1* | 17q11.2 | Sarcomas, breast cancer |
| Neurofibromatosis type 2 | *NF2* | 22q12 | Neurofibroma, neurofibrosarcoma, brain tumor |
| von Hippel-Lindau | *VHL* | 3p25-26 | Renal cell cancer, pheochromocytoma, retinal angioma, hemangioblastoma |

*WAGR: Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation.
†Denys-Drash: Wilms' tumor, pseudohermaphroditism, mesangial sclerosis, renal failure.
‡Beckwith-Weidemann: multiple tumors, hemihypertrophy, macroglossia, hyperinsulinism.

These aberrations affect growth factors and their receptors, signal transducers, and transcription factors. The general types of chromosomal alterations associated with malignant transformation are shown in Figure 28-1. Although a low level of chromosomal instability exists in a normal population of cells, neoplastic transformation occurs only if these alterations affect a growth-regulating pathway and confer a growth advantage.

## Abnormal DNA Content

Normal human cells contain two copies of each of 23 chromosomes; a normal diploid cell therefore has 46 chromosomes. Although cellular DNA content, or ploidy, is accurately determined by karyotypic analysis, it can be estimated by the much simpler method of flow cytometric analysis. Diploid cells have a DNA index of 1.0, whereas near-triploid (also termed *hyperdiploid*) cells have a DNA index ranging from 1.26 to 1.76. The majority (55%) of primary neuroblastoma cells are triploid or near triploid (e.g., having between 58 and 80 chromosomes), whereas the remainder are near diploid (35 to 57 chromosomes) or near tetraploid (81 to 103 chromosomes).[12] Neuroblastomas consisting of near-diploid or near-tetraploid cells usually have structural genetic abnormalities (e.g., chromosome 1p deletion and amplification of the *MYCN* oncogene), whereas those consisting of near-triploid cells are characterized by three almost complete haploid sets of chromosomes with few structural abnormalities.[13] Of importance, patients with near-triploid tumors typically have favorable clinical and biological prognostic factors and excellent survival rates compared with those who have near-diploid or near-tetraploid tumors.[14]

## Chromosomal Translocations

Many pediatric cancers, specifically hematologic malignancies and soft tissue neoplasms, have recurrent, nonrandom abnormalities in chromosomal structure, typically chromosomal translocations (Table 28-3). The most common result of a nonrandom translocation is the fusion of two distinct genes from different chromosomes. The genes are typically fused within the reading frame and express a functional, chimeric protein product that has transcription factor or protein kinase activity. These fusion proteins contribute to tumorigenesis by activating genes or proteins involved in cell proliferation. For example, in Ewing sarcoma the consequence of the t(11;22)(q24;q12) translocation is a fusion of *EWS*, a transcription factor gene on chromosome 22, and *FLI-1*, a gene encoding a member of the ETS family of transcription factors on chromosome 11.[15] The resultant chimeric protein, which contains the DNA binding region of *FLI-1* and the transcription activation region of *EWS*, has greater transcriptional activity than does *EWS* alone.[16] The EWS–FLI-1 fusion transcript is detectable in approximately 90% of Ewing sarcomas. At least four other *EWS* fusions have been identified in Ewing sarcoma; fusion of *EWS* with *ERG* (another ETS family member) accounts for an additional 5% of cases.[17] Alveolar rhabdomyosarcomas have characteristic translocations between the long arm of chromosome 2 (75% of cases) or the short arm of chromosome 1 (10% of cases) and the long arm of chromosome 13. These translocations result in the fusion of *PAX3*

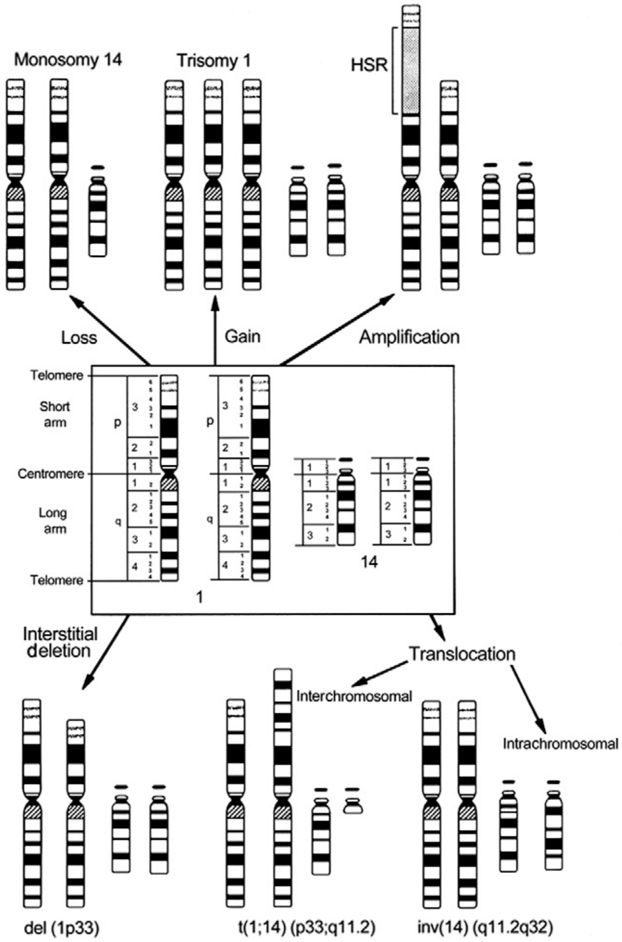


**FIGURE 28-1** Spectrum of gross chromosomal aberrations using chromosomes 1 and 14 as examples. HSR, homogeneously staining regions. (From Look AT, Kirsch IR: Molecular basis of childhood cancer. In Pizzo PA, Poplack DG [eds]: Principles and Practices of Pediatric Oncology. Philadelphia, Lippincott-Raven, 1997, p 38.)

(at 2q35) or *PAX7* (at 1p36) with *FKHR*, a gene encoding a member of the forkhead family of transcription factors.[18] The *EWS-FLI-1* and *PAX7-FKHR* fusions appear to confer a better prognosis for patients with Ewing sarcoma and alveolar rhabdomyosarcoma, respectively.[19,20] Translocations that generate chimeric proteins with increased transcriptional activity also characterize desmoplastic small round cell tumor,[21] myxoid liposarcoma,[22] extraskeletal myxoid chrondrosarcoma,[23] malignant melanoma of soft parts,[24] synovial sarcoma,[25] congenital fibrosarcoma,[26] cellular mesoblastic nephroma,[27] and dermatofibrosarcoma protuberans.[28]

### Proto-oncogene Activation

Proto-oncogenes are commonly activated in transformed cells by point mutations or gene amplification. The classical example of proto-oncogene activation by a point mutation involves the cellular proto-oncogene *RAS*. RAS-family proteins are associated with the inner, cytoplasmic surface of the plasma membrane and function as intermediates in signal transduction pathways that regulate cell proliferation. Point mutations in *RAS* result in constitutive activation of the RAS protein and therefore the continuous activation of the RAS signal transduction pathway. Activation of RAS appears to be involved in the pathogenesis of a small percentage of pediatric malignancies, including leukemia and a variety of solid tumors.

**TABLE 28-3**
**Common, Recurrent Translocations in Soft Tissue Tumors**

| *Tumor* | *Genetic Abnormality* | *Fusion Transcript* |
|---|---|---|
| Ewing sarcoma/primitive neuroectodermal tumor | t(11;22)(q24;q12)<br>t(21;22)(q22;q12)<br>t(7;22)(p22;q12)<br>t(17;22)(q12;q12)<br>t(2;22)(q33;q12) | *FLI1-EWS*<br>*ERG-EWS*<br>*ETV1-EWS*<br>*E1AF-EWS*<br>*FEV-EWS* |
| Desmoplastic small round cell tumor | t(11;22)(p13;q12)<br>t(11;22)(q24;q12) | *WT1-EWS*<br>*FLI1-EWS* |
| Synovial sarcoma | t(X;18)(p11.23; q11)<br>t(X;18)(p11.21; q11) | *SSX1-SYT*<br>*SSX2-SYT* |
| Alveolar rhabdomyosarcoma | t(2;13)(q35;q14)<br>t(1;13)(p36;q14) | *PAX3-FKHR*<br>*PAX7-FKHR* |
| Malignant melanoma of soft part (clear cell sarcoma) | t(12;22)(q13;q12) | *ATF1-EWS* |
| Myxoid liposarcoma | t(12;16)(q13;p11)<br>t(12;22)(q13;q12) | *CHOP-TLS(FUS)*<br>*CHOP-EWS* |
| Extraskeletal myxoid chondrosarcoma | t(9;22)(q22;q12) | *CHN-EWS* |
| Dermatofibrosarcoma protuberans and giant cell fibroblastoma | t(17;22)(q22;q13) | *COL1A1-PDGFB* |
| Congenital fibrosarcoma and mesoblastic nephroma | t(12;15)(p13;q25) | *ETV6-NTRK3* |
| Lipoblastoma | t(3;8)(q12;q11.2)<br>t(7;8)(q31;q13) | ?<br>? |

From Davidoff AM, Hill DA: Molecular genetic aspects of solid tumors in childhood. Semin Pediatr Surg 2001;10:106-118.

Gene amplification (i.e., selective replication of DNA sequences) enables a tumor cell to increase the expression of crucial genes whose products are ordinarily tightly controlled. The amplified DNA sequences, or amplicons, may be maintained episomally (i.e., extrachromosomally) as double minutes-paired chromatin bodies lacking a centromere or as intrachromosomal, homogeneously staining regions. In about one third of neuroblastomas, for example, the transcription factor and proto-oncogene *MYCN* is amplified. The *MYCN* copy number in neuroblastoma cells can be amplified 5-fold to 500-fold and is usually consistent among primary and metastatic sites and at different times during tumor evolution and treatment.[29] This consistency suggests that *MYCN* amplification is an early event in the pathogenesis of neuroblastoma. Because gene amplification is usually associated with advanced stages of disease, rapid tumor progression, and poor outcome, it is a powerful prognostic indicator.[30,31] The cell surface receptor gene *ERBB2* is another proto-oncogene that is commonly overexpressed because of gene amplification, an event that occurs in breast cancer, osteosarcoma, and Wilms' tumor.[32]

### Inactivation of Tumor Suppressor Genes

Tumor suppressor genes, or antioncogenes, provide negative control of cell proliferation. Loss of function of the proteins encoded by these genes, through deletion or mutational inactivation of the gene, liberates the cell from growth constraints

and contributes to malignant transformation. The cumulative effect of genetic lesions that activate proto-oncogenes or inactivate tumor suppressor genes is a breakdown in the balance between cell proliferation and cell loss because of differentiation or apoptosis. Such imbalance results in clonal overgrowth of a specific cell lineage. The first tumor suppressor gene to be recognized was the retinoblastoma susceptibility gene *RB*. This gene encodes a nuclear phosphoprotein that acts as a "gatekeeper" of the cell cycle. *RB* normally permits cell-cycle-progression through the $G_1$ phase when it is phosphorylated, but it prevents cell division when it is unphosphorylated. Inactivating deletions or point mutations of *RB* cause the protein to lose its regulatory capacity. The nuclear phosphoprotein gene *TP53* has also been recognized as an important tumor suppressor gene, perhaps the most commonly altered gene in all human cancers. Inactivating mutations of the *TP53* gene also cause the TP53 protein to lose its ability to regulate the cell cycle. The *TP53* gene is frequently inactivated in solid tumors of childhood, including osteosarcoma, rhabdomyosarcoma, brain tumors, anaplastic Wilms' tumor, and a subset of chemotherapy-resistant neuroblastoma.[33–35] In addition, heritable cancer-associated changes in the *TP53* tumor suppressor gene occur in families with Li-Fraumeni syndrome, an autosomal dominant predisposition for rhabdomyosarcoma, other soft tissue and bone sarcomas, premenopausal breast cancer, brain tumors, and adrenocortical carcinomas.[36] Other tumor suppressor genes include Wilms' tumor 1 *(WT1)*, neurofibromatosis 1 *(NF1)*, and von Hippel-Lindau *(VHL)*. Additional tumor suppressor genes are presumed to exist but have not been definitively identified.

### Epigenetic Alterations

As stated previously, the hallmark of cancer is dysregulated gene expression. However, not only do genetic factors influence gene expression but epigenetic factors do as well, with these factors being at least as important as genetic changes in their contribution to the pathogenesis of cancer. Epigenetic alterations are defined as those heritable changes in gene expression that do not result from direct changes in DNA sequence. Mechanisms of epigenetic regulation most commonly include DNA methylation and modification of histones, although the contribution of microRNAs (miRNA), a class of noncoding RNAs, is becoming increasingly recognized.

***DNA Methylation*** DNA methylation is a reversible process that involves methylation of the fifth position of cytosine within CpG dinucleotides present in DNA. These dinucleotides are usually in the promoter regions of genes; methylation of these sites typically causes gene silencing, thereby preventing expression of the encoded proteins. This process is part of the normal mechanism for imprinting, X-chromosome inactivation, and generally keeping large areas of genomic DNA silent, but it may also contribute to the pathogenesis of cancer by silencing tumor suppressor genes. However, both abnormal hypomethylation and hypermethylation states exist in human tumors, resulting in both dysregulated expression and silencing, respectively, of affected genes. These modifications of the nucleotide backbone of human DNA are becoming increasingly recognized in human cancer, both for their frequency and importance. For example, promoter methylation resulting in silencing of caspase 8, a protein involved in apoptosis, likely contributes to the pathogenesis of *MYCN*-amplified neuroblastoma[37] as well as Ewing sarcoma.[23]

***Histone Modification*** Histones are the proteins that give structure to DNA and, together with the DNA, form the major components of chromatin. The functions of histones are to package DNA into a smaller volume to fit in the cell, to strengthen the DNA to allow replication, and to serve as a mechanism to control gene expression. Alterations in histones can mediate changes in chromatin structure. The compacted form of DNA, termed heterochromatin, is largely inaccessible to transcription factors and therefore genes in the affected regions are silent. Other modifications of histones can cause DNA to take a more open or extended configuration (euchromatin), allowing for gene transcription. The N-terminal tails of histones can be modified by a number of different processes including methylation and acetylation, mediated by histone acetyl transferases (HAT) and deacetylases (HDAC), and histone methyltransferases (HMT). Each of these processes alters histone function, which, in turn, alters the structure of chromatin and therefore the accessibility of DNA to transcription factors. Methylation of the DNA itself can also effect changes in chromatin structure.

***MicroRNA*** As stated above, miRNAs are a group of small, regulatory noncoding RNAs that appear to function in gene regulation. These miRNAs are single-stranded RNA fragments of 21 to 23 nucleotides that are complementary to encoding mRNAs.[25] Their function is to down-regulate expression of target mRNAs; it is estimated that miRNAs regulate the expression of about 30% of all human genes.[38] These miRNAs regulate gene expression primarily by incorporating into silencing machinery called RNA-induced silencing complexes (RISC). MiRNAs are involved in a number of fundamental biological processes, including development, differentiation, cell-cycle regulation, and senescence. However, broad analyses of miRNA expression levels have demonstrated that many miRNAs are dysregulated in a variety of different cancer types, including neuroblastoma and other pediatric tumors,[39] frequently losing their function as gene silencers/tumor suppressors. The activity of miRNAs, like gene expression, is also under epigenetic regulation.

## METASTASIS

Metastasis is the spread of cancer cells from a primary tumor to distant sites and is the hallmark of malignancy. The development of tumor metastases is the main cause of treatment failure and a significant contributing factor to morbidity and mortality resulting from cancer. Although the dissemination of tumor cells through the circulation is probably a frequent occurrence, the establishment of metastatic disease is a very inefficient process. It requires several events, including the entry of the neoplastic cells into the blood or lymphatic system, the survival of those cells in the circulation, their avoidance of immune surveillance, their invasion of foreign (heterotopic) tissues, and the establishment of a blood supply to permit expansion of the tumor at the distant site. Simple, dysregulated cell growth is not sufficient for tumor invasion and metastasis. Many tumors progress through distinct stages

that can be identified by histopathologic examination, including hyperplasia, dysplasia, carcinoma in situ, invasive cancer, and disseminated cancer. Genetic analysis of these different stages of tumor progression suggests that uncontrolled growth results from progressive alteration in cellular oncogenes and inactivation of tumor suppressor genes, but these genetic changes driving tumorigenicity are clearly distinct from those that determine the metastatic phenotype.

Histologically, invasive carcinoma is characterized by a lack of basement membrane around an expanding mass of tumor cells. Matrix proteolysis appears to be a key part of the mechanism of invasion by tumor cells, which must be able to move through connective tissue barriers, such as the basement membrane, to spread from their site of origin. The proteases involved in this process include the matrix metalloproteinases and their tissue inhibitors. The local environment of the target organ may profoundly influence the growth potential of extravasated tumor cells.[40] The various cell surface receptors that mediate interactions between tumor cells and between tumor cells and the extracellular matrix include cadherins, integrins (transmembrane proteins formed by the noncovalent association of alpha and beta subunits), and CD44, a transmembrane glycoprotein involved in cell adhesion to hyaluronan.[41] Tumor cells must decrease their adhesiveness to escape from the primary tumor, but at later stages of metastasis, the same tumor cells need to increase their adhesiveness during arrest and intravasation to distant sites.

### ANGIOGENESIS

Angiogenesis is the biological process of new blood vessel formation. This complex, invasive process involves multiple steps, including proteolytic degradation of the extracellular matrix surrounding existing blood vessels, chemotactic migration and proliferation of endothelial cells, the organization of these endothelial cells into tubules, the establishment of a lumen that serves as a conduit between the circulation and an expanding mass of tumor cells, and functional maturation of the newly formed blood vessel.[42,43] Angiogenesis involves the coordinated activity of a wide variety of molecules, including growth factors, extracellular matrix proteins, adhesion receptors, and proteolytic enzymes. Under physiologic conditions, the vascular endothelium is quiescent and has a very low rate of cell division, such that only 0.01% of endothelial cells are dividing.[42–44] However, in response to hormonal cues or hypoxic or ischemic conditions, the endothelial cells can be activated to migrate, proliferate rapidly, and create tubules with lumens.

Angiogenesis occurs as part of such normal physiologic activities as wound healing, inflammation, the female reproductive cycle, and embryonic development. In these processes, angiogenesis is tightly and predictably regulated. However, angiogenesis can also be involved in the progression of several pathologic processes in which there is a loss of regulatory control, resulting in persistent growth of new blood vessels. Such unabated neovascularization occurs in rheumatoid arthritis, inflammatory bowel disease, hemangiomas of childhood, ocular neovascularization, and the growth and spread of tumors.[45]

Compelling data indicate that tumor-associated neovascularization is required for tumor growth, invasion, and metastasis.[46–49] A tumor in the prevascular phase (i.e., before new blood vessels have developed) can grow to only a limited size, approximately 2 to 3 $mm^3$. At this point, rapid cell proliferation is balanced by equally rapid cell death by apoptosis, and a nonexpanding tumor mass results. The switch to an angiogenic phenotype with tumor neovascularization results in a decrease in the rate of apoptosis, thereby shifting the balance to cell proliferation and tumor growth.[50,51] This decrease in apoptosis occurs, in part, because the increased perfusion resulting from neovascularization permits improved nutrient and metabolite exchange. In addition, the proliferating endothelium may supply, in a paracrine manner, a variety of factors that promote tumor growth, such as IGF-I and IGF-II.[52]

In experimental models, increased tumor vascularization correlates with increased tumor growth, whereas restriction of neovascularization limits tumor growth. Clinically, the onset of neovascularization in many human tumors is temporally associated with increased tumor growth,[53] and high levels of angiogenic factors are commonly detected in blood and urine from patients with advanced malignancies.[107] In addition, the number and density of new microvessels within primary tumors have been shown to correlate with the likelihood of metastasis, as well as the overall prognosis for patients with a wide variety of neoplasms, including pediatric tumors such as neuroblastoma and Wilms' tumor.[54,55]

## Molecular Diagnostics

The explosion of information about the human genome has led not only to an improved understanding of the molecular genetic basis of tumorigenesis but also to the development of a new discipline: the translation of these molecular events into diagnostic assays. The field of molecular diagnostics has developed from the need to identify abnormalities of gene or chromosome structure in patient tissues and as a means of supporting standard histopathologic and immunohistochemical diagnostic methods. In most instances, the result of genetic testing confirms light microscopic- and immunohistochemistry-based diagnosis. In some instances, however (e.g., primitive, malignant, small round cell tumor; poorly differentiated synovial sarcoma; lipoblastic tumor), molecular analysis is required to make a definitive diagnosis.

The molecular genetic methods most commonly used to analyze patient tumor material include direct metaphase cytogenetics or karyotyping, fluorescence in situ hybridization (FISH), and reverse transcriptase polymerase chain reaction (RT-PCR). Additional methods, such as comparative genomic hybridization, loss of heterozygosity analysis, and complementary DNA (cDNA) microarray analysis, may eventually become part of the routine diagnostic repertoire but are currently used as research tools at referral centers and academic institutions. Each standard method is summarized in Table 28-4. As with any method, molecular genetic assays have advantages and disadvantages, and it is important to understand and recognize their limitations.

The value of molecular genetic analysis of patient tissue is not limited to aiding histopathologic diagnosis. Many of the most important markers provide prognostic information as well. *MYCN* amplification in neuroblastomas,[13] for example, is strongly associated with biologically aggressive behavior. Amplification of this gene can be detected by routine

**TABLE 28-4**

**Comparison of the Cytogenetic and Molecular Methods Routinely Used as Aids in Pathologic Diagnosis of Soft Tissue Tumors**

| *Method* | *Purpose* | *Advantages* | *Disadvantages* |
|---|---|---|---|
| Cytogenetics | Low resolution analysis of metaphase chromosomes of cells grown in culture | Does not require a priori knowledge of genetic abnormalities<br>Available in most diagnostic centers | Requires fresh, sterile tumor tissue for growth in culture<br>Low sensitivity; will only detect large structural abnormalities<br>No histologic correlation<br>Slow and technically demanding (takes up to several weeks to perform) |
| In situ hybridization | Detection of translocations, amplifications, and gene deletions by hybridization of nucleic acid probes to specific DNA or mRNA sequences | Can be applied to chromosomal preparations as well as cytologic specimens, touch preparations, and paraffin sections<br>Morphologic correlation is possible<br>Multiple probes can be assayed at the same time<br>Rapid (usually only requires 2 days) | Cannot detect small deletions or point mutations<br>Interpretation can be difficult, especially with formalin-fixed, paraffin-embedded material<br>Only a limited number of specific nucleic acid probes are available commercially |
| PCR and RT-PCR | Extremely sensitive detection of DNA sequences and mRNA transcripts for the demonstration of fusion genes, point mutations, and polymorphisms | Highest sensitivity and specificity of all the molecular diagnostic techniques<br>DNA sequencing of PCR products can confirm result and provide additional information<br>Requires minimal tissue<br>Versatile; can be applied to fresh tissue as well as formalin-fixed, paraffin-embedded tissue<br>Morphologic correlation is possible<br>The presence of normal tissue will usually not affect test results<br>Rapid (usually requires 3-5 days) | Formalin-fixation diminishes sensitivity<br>Combinatorial variability within fusion gene partners requires appropriate redundant primer design to avoid false-negative test results<br>Extreme sensitivity requires exacting laboratory technique to avoid false-positive test results |

From Davidoff AM, Hill DA: Molecular genetic aspects of solid tumors in childhood. Semin Pediatr Surg 10: 2001;106-118.
PCR, polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction.

metaphase cytogenetics or by FISH, and current neuroblastoma protocols include the presence or absence of *MYCN* amplification in their stratification schema. Some fusion gene variants are also thought to influence prognosis. In initial studies, two examples noted to confer relatively favorable prognoses are the type 1 variant fusion of *EWS-FLI1* in Ewing sarcoma or primitive neuroectodermal tumor[20] and the *PAX7-FKHR* fusion in alveolar rhabdomyosarcoma.[19]

New technologies are emerging that permit accurate, high-throughput analysis or profiling of tumor tissue: Gene expression can be analyzed by using RNA microarrays, and proteins by using proteomics. These approaches identify a unique fingerprint of a given tumor that can provide diagnostic or prognostic information. Proteomic analysis can also identify unique proteins in patients' serum or urine; such a profile can be used for early tumor detection, to distinguish risk categories, and to monitor for recurrence. Additional types of "omics" that are currently being used to evaluate tumor or patient specimens include transcriptomics (RNA and gene expression), metabolomics (metabolites and metabolic networks), and pharmacogenomics (how genetics affects host drug responses). Information from each of these areas of investigation provides an increasingly precise and unique perspective on the biology, clinical behavior, and responsiveness to specific therapeutic interventions of individual patient tumors. It is through these analyses that personalized therapy is likely to be realized. In addition, it is anticipated that with the identification of new, critical components of oncogenesis and tumor progression will come new "druggable" targets for cancer therapy. Drugs that act on these targets will not only be effective anticancer agents but, because of their specificity, will also have a broader therapeutic window, thereby improving safety and minimizing toxicity.

## Childhood Cancer and Heredity

Advances in molecular genetic techniques have also improved our understanding of cancer predisposition syndromes. Constitutional gene mutations that are hereditary (i.e., passed from parent to child) or nonhereditary (i.e., de novo mutations in the sperm or oocyte before fertilization) contribute to an estimated 10% to 15% of pediatric cancers.[56] Constitutional chromosomal abnormalities are the result of an abnormal number or structural rearrangement of the normal 46 chromosomes and may be associated with a predisposition to cancer. Examples are the predisposition to leukemia seen with trisomy 21 (Down syndrome) and to germ cell tumors with Klinefelter syndrome (47XXY). Structural chromosomal abnormalities include interstitial deletions resulting in the constitutional loss of one or more genes.

Wilms' tumors may be sporadic, familial, or associated with specific genetic disorders or recognizable syndromes. A better understanding of the molecular basis of Wilms' tumor has been achieved largely through the study of the latter two types of tumors. The WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation) provides an easily recognizable phenotype for grouping children likely to have a common genetic abnormality. Constitutional deletions from chromosome 11p13 are consistent in children with

WAGR syndrome[57] and also occur in approximately 35% of those with sporadic Wilms' tumor.[58] A study of a large series of patients identified the gene deleted from chromosome 11p13 as *WT1*.[59] This gene encodes a nuclear transcription factor that is essential for normal kidney and gonadal development[60] and appears to act as a tumor suppressor, but its precise role is unclear at this time. Aniridia in patients with WAGR syndrome is thought to occur after the loss of one copy of the *PAX6* gene located close to *WT1* on chromosome 11.[61] Denys-Drash syndrome, which is characterized by a very high risk of Wilms' tumor, pseudohermaphroditism, and mesangial sclerosis leading to early renal failure, is associated with germline mutations in the DNA binding domain of *WT1*.[62] The mutated WT1 protein appears to function by a dominant negative effect. Only 6% to 18% of sporadic Wilms' tumors have *WT1* mutations.[62,63]

In another subset of patients with Wilms' tumor, there is loss of genetic material in a region distal to the *WT1* locus toward the telomeric end of chromosome 11 (11p15).[39] It has therefore been suggested that there is a second Wilms' tumor susceptibility gene, tentatively named *WT2,* in 11p15. Loss of heterozygosity at this locus has also been described in patients with Beckwith-Wiedemann syndrome, a congenital overgrowth syndrome characterized by numerous growth abnormalities as well as a predisposition to a variety of malignancies, including Wilms' tumor.[64]

Neurofibromatosis type 1 (NF1) is one of the most common genetic disorders. The NF1 protein normally inhibits the proto-oncogene *RAS,* but in patients with NF1, mutation of one copy of the gene combined with deletion of the other permits uncontrolled RAS pathway activation. These patients are then susceptible to myelogenous disorders, benign tumors, gliomas, and malignant peripheral nerve sheath tumors. An inherited predisposition to pediatric cancers is also associated with Li-Fraumeni syndrome (which results from mutations which inactivate the *TP53* gene and put patients at risk for osteosarcoma, rhabdomyosarcoma, adrenocortical carcinoma, and brain tumors, among other tumors), familial retinoblastoma (which results from mutations that inactivate the *RB* gene and put patients at risk for osteosarcoma as well as retinoblastoma), familial adenomatous polyposis, and multiple endocrine neoplasia syndromes. Another set of inherited risk factors is represented by mutations of DNA repair genes (so-called caretaker genes), as seen in xeroderma pigmentosa and ataxia-telangiectasia.[65] Understanding these complex syndromes and their pathogenesis is important in efforts to screen for early detection and, possibly, for prophylactic therapy.

Recently, the germline mutation associated with hereditary neuroblastoma has been identified as activating mutations in the tyrosine kinase domain of the anaplastic lymphoma kinase (*ALK*) oncogene on the long arm of chromosome 2 (2p23).[66] Further molecular studies have revealed that common genetic variation at chromosome bands 6p22[1] and 2q35[67] are associated with susceptibility to, and likely contribute to the etiology of, high-risk neuroblastoma, providing the first evidence that childhood cancers also arise because of complex interactions of polymorphic variants. Finally, the same group has also shown that inherited copy number variation at chromosome 1q21.1 is associated with neuroblastoma, implicating a neuroblastoma breakpoint family gene in early neuroblastoma genesis.[68]

## Genetic Screening

Along with an increased understanding of the molecular basis of hereditary childhood cancer has come the opportunity to identify children who are at high risk of malignancy and, in some cases, to intervene before the cancer develops or when it is still curable. Two examples include familial adenomatous polyposis and familial thyroid cancer.

Familial adenomatous polyposis is an autosomal dominant inherited disease in which hundreds to thousands of adenomatous intestinal polyps develop during the second and third decades of life. Mutations of the adenomatous polyposis coli *(APC)* gene on chromosome 5q21 occur in approximately 80% of kindreds of persons who have the disease.[69,70] These mutations initiate the adenomatous process by allowing clonal expansion of individual cells that, over time, acquire additional genetic abnormalities that lead to the development of invasive colorectal carcinoma.[71] Prophylactic colectomy is recommended for patients with this germline mutation, although the most appropriate timing for this intervention in children with familial adenomatous polyposis is controversial. These patients are also at increased risk of hepatoblastoma.[72]

Medullary thyroid carcinoma (MTC) is a rare malignancy that may occur sporadically or as part of two syndromes: multiple endocrine neoplasia (type 2A or 2B) syndrome or familial MTC syndrome. In children, MTC is much more likely to occur in association with a familial syndrome. An apparently 100% association between germline *RET* mutations[73] and MTC guides the recommendation for prophylactic thyroidectomy in affected patients. There is no effective adjuvant treatment other than surgery for MTC, highlighting the need for early intervention. Patients with germline *RET* mutations should also be screened for pheochromocytoma, which occurs in 50% of patients with multiple endocrine neoplasia type 2A, and hyperparathyroidism, which occurs in 35% of such patients, although these entities generally arise in older patients beyond the pediatric age range.[74] In addition, patients who are at risk for MTC or have newly diagnosed MTC, as well as their relatives, should be screened for the germline *RET* mutation so that appropriate surgical and genetic counseling can be given.

## General Principles of Chemotherapy

Cytotoxic agents were first noted to be effective in the treatment of cancer in the 1960s, after alkylating agents, such as nitrogen mustard gas, used during World War II, were observed to cause bone marrow hypoplasia. Chemotherapy is now an integral part of nearly all cancer treatment regimens. The overriding goal of cancer chemotherapy is to maximize the tumoricidal effect (efficacy) while minimizing adverse side effects (toxicity). This goal can be difficult to achieve, however, because the dose at which tumor cells are affected is often similar to the dose that affects normal proliferating cells, such as those in the bone marrow and gastrointestinal tract. Despite the early promise of chemotherapy and the observation that most tumor types are initially sensitive to chemotherapy, often

exquisitely so, the successful use of chemotherapy is often thwarted by two factors: the development of resistance to the agent and the agent's toxicity to normal tissues. Nevertheless, chemotherapy remains an integral part of therapy when used as an adjunct to treat localized disease or as the main component to treat disseminated or advanced disease.

A number of principles and terms are essential to the understanding of chemotherapy as a therapeutic anticancer modality. Adjuvant chemotherapy refers to the use of chemotherapy for systemic treatment following local control generally by surgical resection or radiation therapy of a clinically localized primary tumor. The goal in this setting is to eliminate disease that is not detectable by standard investigative means at or beyond the primary tumor's site. Neoadjuvant chemotherapy refers to chemotherapy delivered before local therapeutic modalities, generally in an effort to improve their efficacy; to treat micrometastatic disease as early as possible, when distant tumors are smallest; or to achieve both of these aims. Induction chemotherapy refers to the use of chemotherapeutic agents as the primary treatment for advanced disease. In general, chemotherapy given to children with solid tumors and metastatic disease at the time of first examination has a less than 40% chance of effecting long-term, disease-free survival. Exceptions include Wilms' tumor with favorable histologic features, germ cell tumors, and paratesticular rhabdomyosarcoma, but most children with metastatic disease are at high risk of disease recurrence or progression. Combination chemotherapy refers to the use of multiple agents, which generally have different mechanisms of action and nonoverlapping toxicities, that provide effective, synergistic antitumor activity and minimal side effects.

The mechanisms of action and side effects of commonly used agents are listed in Table 28-5. Alkylating agents interfere with cell growth by covalently cross-linking DNA and are not cell-cycle specific. Antitumor antibiotics intercalate into the double helix of DNA and break the DNA strands. Antimetabolites are truly cell-cycle specific, because they interfere with the use of normal substrates for DNA and RNA synthesis, such as purines and thymidine. The plant alkaloids can inhibit microtubule function (vinca alkaloids, taxanes) or DNA topoisomerases (camptothecins inhibit topoisomerase I; epipodophyllotoxins inhibit topoisomerase II), and these actions also lead to breaks in DNA strands. Topoisomerases are a class of enzymes that alter the supercoiling of double-stranded DNA. They act by transiently cutting one (topoisomerase I) or both (topoisomerase II) strands of the DNA to relax the DNA coil and extend the molecule. The regulation of DNA supercoiling is essential to DNA transcription and replication, when the DNA helix must unwind to permit the proper function of the enzymatic machinery involved in these processes. Thus topoisomerases maintain the transcription and replication of DNA.

The common toxic effects of these agents are also listed in Table 28-5. Most toxicity associated with chemotherapy is reversible and resolves with cessation of treatment. However, some chemotherapeutic agents may have lifelong effects. Of particular concern is that certain drugs can lead to a second malignancy. Most notable is the development of leukemia after the administration of the epipodophyllotoxins and cyclophosphamide.[75]

Finally, understanding the metabolism of chemotherapeutic agents is important. Certain agents require metabolism at a specific site or organ for their activation or are eliminated from the body by a specific organ (see Table 28-5). The processes of activation and elimination require normal organ function (e.g., the liver for cyclophosphamide); therefore children with liver or kidney failure may not be able to receive certain agents.

## RISK STRATIFICATION

Major advances in the variety of chemotherapeutic agents and dosing strategies used to treat pediatric cancers in the past 30 years are reflected in improved patient survival rates. Regimen toxicity (including late effects, which are particularly important in the pediatric population) and therapeutic resistance are the two main hurdles preventing further advancement. As more information about diagnostically and prognostically useful genetic markers becomes available, therapeutic strategies will change accordingly. With molecular profiling, patients can be categorized to receive a particular treatment on the basis of not only the tumor's histopathologic and staging characteristics but also its genetic composition. Some patients whose tumors show a more aggressive biological profile may require dose intensification to increase their chances of survival. Patients whose tumors do not have an aggressive biological profile may benefit from the lower toxicity of less intensive therapy. Such an approach may allow the maintenance of high survival rates while minimizing long-term complications of therapy in these patient populations.

The paradigm for the use of different therapeutic intensities on the basis of risk stratification drives the management of pediatric neuroblastoma. There is increasing evidence that the molecular features of neuroblastoma are highly predictive of its clinical behavior. Most current studies of the treatment of neuroblastoma are based on risk groups that take into account both clinical and biological variables. The most important clinical variables appear to be age and stage at diagnosis, and the most powerful biological factors appear to be *MYCN* status, ploidy (for patients younger than 1 year), and histopathologic classification. These variables currently define the Children's Oncology Group risk strata and therapeutic approach, which are further refined by determining whether there is 1p/11q LOH. At one extreme, patients with low-risk disease are treated with surgery alone; at the other extreme, patients at high risk for relapse are treated with intensive multimodality therapy that includes multiagent dose-intensive chemotherapy, radiation therapy, and stem cell transplantation. Other factors, such as 17q gain, caspase 8 inactivation, and TRKA/B expression, are currently being evaluated and may help further refine risk assessment in the future. The management of other solid pediatric tumors is also shifting to risk-defined treatment. For example, the current protocol for the management of patients with Wilms' tumor includes risk stratification and therapy adjustment based on molecular analysis of the primary tumor for 16q and 1p deletions.

## TARGETED THERAPY

Another major change in the approach to the treatment of cancer has been the concept of targeted therapy. Until recently, the development of anticancer agents was based on the empirical screening of a large variety of cytotoxic compounds without particular regard to disease specificity or mechanism of action. Now, one of the most exciting prospects for improving the

**TABLE 28-5**

**Common Chemotherapeutic Agents**

| *Class of Drug* | *Agent* | *Synonyms* | *Brand Name* | *Mechanism of Action* | *Common Toxic Effects* | *Site of Activation* | *Method of Elimination* | *Susceptible Solid Tumors* |
|---|---|---|---|---|---|---|---|---|
| Alkylating agents | Carboplatin | CBCDCA | Paraplatin | Platination, intrastrand and interstrand DNA cross-linking | A, H, M, (esp. thrombocytopenia), N/V | | R | BT, GCT, NBL, STS |
| | Cisplatin | CDDC | Platinol | Platination, intrastrand and interstrand DNA cross-linking | A, N/V, R (significant), ototoxicity, neuropathy | | R | BT, GCT, NBL, OS |
| | Cyclophosphamide | CTX | Cytoxan | Alkylation, intrastrand and interstrand DNA cross-linking | A, N/V, SIADH, M, R, cardiac, cystitis | Liver | H, R (minor) | Broad, BMT |
| | Ifosfamide | IFOS | Ifex | Alkylation, intrastrand and interstrand DNA cross-linking | A, CNS, N/V, M, R, cardiac, cystitis | Liver | H, R (minor) | Broad |
| | Dacarbazine | | DTIC | Methylation | H, N/V, M, hepatic vein thrombosis | Liver | R | NBL, STS |
| | Temozolomide | TMZ | Temodar | Methylation | CNS, N/V, M | Spontaneous | R | BT |
| | Nitrogen Mustard | Mechlorethamine | Mustargen | Alkylation, intrastrand and interstrand DNA cross-linking | A, M (significant), N/V, mucositis, vesicant, phlebitis, diarrhea | | Spontaneous hydrolysis | BT |
| | Melphalan | L-PAM | Alkeran | Alkylation, intrastrand and interstrand DNA, cross-linking | M, N/V, mucositis, diarrhea | | Spontaneous hydrolysis | NBL, RMS, BMT |
| | Busulfan | | Busulfex | Alkylation, intrastrand and interstrand DNA cross-linking | A, H, M, N/V, P, mucositis | | R | BMT |
| Antimetabolites | Cytarabine | Ara-C | Cytosar | Inhibits DNA polymerase, incorporated into DNA | M, N/V, diarrhea, CNS | Target cell | Biotransformation | Limited |
| | Fluorouracil | 5-FU | (Several) | Inhibits thymidine synthesis, incorporated into DNA/RNA | CNS, N/V, M, cardiac, diarrhea, mucositis, skin, ocular | Target cell | Biotransformation, renal (minor) | GI carcinomas, liver tumors |

*Continued*

**TABLE 28-5**

**Common Chemotherapeutic Agents—cont'd**

| *Class of Drug* | *Agent* | *Synonyms* | *Brand Name* | *Mechanism of Action* | *Common Toxic Effects* | *Site of Activation* | *Method of Elimination* | *Susceptible Solid Tumors* |
|---|---|---|---|---|---|---|---|---|
| | Mercaptopurine | 6-MP | Purinethol | Inhibits thymidine synthesis, incorporated into DNA/RNA | H, M, mucositis | Target cell | Biotransformation, renal (minor) | Limited |
| | Methotrexate | MTX | Trexall | Blocks folate metabolism, inhibits purine synthesis | CNS, H, M, R, mucositis, skin | | R, H (minor) | OS |
| Antibiotics | Dactinomycin | Actinomycin-D | Cosmegen | DNA intercalation, strand breaks | A, H, M, N/V, mucositis, vesicant | | H | RMS, Wilms' |
| | Bleomycin | BLEO | Blenoxane | DNA intercalation, strand breaks | P, skin, mucositis | | H, R | GCT |
| | Anthracyclines | | | | | | | |
| | Daunomycin | Daunorubicin | Cerubidine | DNA intercalation, strand breaks, free radical formation | A, M, N/V, cardiac, diarrhea, vesicant, potentiate XRT reaction | | H | Limited |
| | Adriamycin | Doxorubicin | Adriamycin | DNA intercalation, strand breaks, free radical formation | A, M, N/V, cardiac, diarrhea, mucositis, vesicant, potentiate XRT reaction | | H | Broad |
| Plant Alkaloids | Epipodophyllotoxins | | | | | | | |
| | Etoposide | VP-16 | VePesid | Topoisomerase II inhibitor, DNA strand breaks | A, M, N/V, mucositis, neuropathy, diarrhea | | R | Broad |
| | Teniposide | VM-26 | Vumon | Topoisomerase II inhibitor, DNA strand breaks | A, M, N/V, mucositis, neuropathy, diarrhea | | Degraded | Broad |
| | Vinca alkaloids | | | | | | H | |
| | Vincristine | VCR | Oncovin | Inhibits tubulin polymerization, blocks mitosis | A, SIADH, neuropathy, vesicant | | H | Broad |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Vinblastine | VLB | Velban | Inhibits tubulin polymerization, blocks mitosis | A, M, mucositis, vesicant | | H | GCT |
| | Taxanes | | | | | | | |
| | Paclitaxel | | Taxol | Interferes with microtubule formation | A, M, cardiac, mucositis, CNS, neuropathy | | | |
| | Docetaxel | | Taxotere | Interferes with microtubule formation | A, neutropenia, cardiac, mucositis, CNS, neuropathy | | | |
| | Camptothecins | | | | | | | |
| | Topotecan | TPT | Hycamtin | Topoisomerase I inhibitor, DNA strand breaks | A, H, M, N/V, mucositis, diarrhea, skin | | R | NBL, RMS |
| | Irinotecan | CPT-11 | Camptosar | Topoisomerase I inhibitor, DNA strand breaks | A, H, M, N/V, diarrhea | H, GI | H, R (minor) | NBL, RMS |
| Miscellaneous | L-Asparaginase | Erwinia | Elspar | L-Asparagine depletion, inhibits protein synthesis | CNS, H, coagulopathy, pancreatitis, anaphylaxis | | degraded | Limited |
| | Corticosteroids | | | Nuclear receptor–mediated apoptosis | avascular necrosis, hyperglycemia, hypertension, myopathy, pancreatitis, peptic ulcers, psychosis, salt imbalance, weight gain | H | H, R (minor) | BT |

Toxic effects: A, alopecia; CNS, central nervous system toxicity; H, hepatotoxicity; M, myelosuppression; N/V, nausea and vomiting; P, pulmonary toxicity; R, renal toxicity; SIADH, syndrome of inappropriate antidiuretic hormone; XRT, x-ray therapy.
Solid tumors: BMT, conditioning for bone marrow transplantation; BT, brain tumor; EWS, Ewing sarcoma; GCT, germ cell tumors; NBL, neuroblastoma; OS, osteosarcoma; RMS, rhabdomyosarcoma; STS, soft tissue sarcoma; W, Wilms' tumor.

therapeutic index of anticancer agents, as well as overcoming the problem of therapy resistance, involves targeted therapy. As the molecular bases for the phenotypes of specific malignancies are being elucidated, potential new targets for therapy are becoming more clearly defined. The characterization of pathways that define malignant transformation and progression has focused new agent development on key pathways involved in the crucial processes of cell-cycle regulation, receptor signaling, differentiation, apoptosis, invasion, migration, and angiogenesis, which may be perturbed in malignant tissues. Information about the molecular profile of a given tumor type can be assembled from a variety of emerging methods, including immunohistochemistry, FISH, RT-PCR, cDNA microarray analysis, and proteomics. This information can then be used to develop new drugs designed to counter the molecular abnormalities of the neoplastic cells. For example, blocking oncogene function or restoring suppressor gene activity may provide tumor-specific therapy. In addition, molecular profiling may lead to the development of drugs designed to induce differentiation of tumor cells, block dysregulated growth pathways, or reactivate silenced apoptotic pathways.

Some agents target alterations in the regulation of cell proliferation. Trastuzumab (Herceptin) is a monoclonal antibody that binds to the cell surface growth factor receptor ERBB2 with high affinity and acts as an antiproliferative agent when used to treat ERBB2-overexpressing cancer cells.[76] Pediatric high-grade gliomas that overexpress EGFR may be amenable to a similar therapeutic agent, gefitinib (Iressa), a small-molecule inhibitor of EGFR (ERBB1).[77] In addition, small-molecule tyrosine kinase inhibitors, such as imatinib (Gleevec), designed to block aberrantly expressed growth-promoting tyrosine kinases—ABL in chronic myelogenous leukemia[78] and c-KIT in gastrointestinal stromal tumors[79]—are being evaluated in clinical trials. Imatinib may also be useful in treating pediatric tumors in which PDGF signaling plays a role in tumor cell survival and growth. Also of potential therapeutic utility are small-molecule inhibitors that recognize antigenic determinants on unique fusion peptides or one of the fusion peptide partners in tumors that have chromosomal translocations (e.g., sarcomas). Tumors that depend on autocrine pathways for growth (e.g., overproduction of IGF-II in rhabdomyosarcoma or PDGF in dermatofibrosarcoma protuberans) may be sensitive to receptor blocking mediators (e.g., antibodies to the IGF-II or PDGFR).

Other agents target alteration of the cell death and differentiation pathways. Caspase 8 is a cysteine protease that regulates programmed cell death, but in tumors such as neuroblastoma, DNA methylation and gene deletion combine to mediate the complete inactivation of caspase 8, almost always in association with *MYCN* amplification.[80] Caspase 8-deficient tumor cells are resistant to apoptosis mediated by death receptors and doxorubicin; this resistance suggests that caspase 8 may be acting as a tumor suppressor. However, brief exposure of caspase 8–deficient cells to demethylating agents, such as decitabine, or to low levels of interferon gamma can lead to the reexpression of caspase 8 and the resensitization of the cells to chemotherapeutic drug-induced apoptosis. Histone deacetylase also seems to have a role in gene silencing associated with resistance to apoptosis[81]; therefore histone deacetylase inhibitors, such as suberoylanilide hydroxamic acid (SAHA), are also being tested for the treatment of certain pediatric malignancies. Finally, cells with alterations in programmed cell death as a result of the persistence or reactivation of telomerase activity, which somatic cells normally lose after birth, can be targeted by various telomerase inhibitors.

Several methods of targeting tumor cell differentiation are being used for the treatment of neuroblastoma. Treatment with 13-cis-retinoic acid, a vitamin A derivative that signals through receptors that mediate transcription of different sets of genes of cell differentiation, including *HOX* genes, is now standard of care for maintenance therapy in patients with high-risk neuroblastoma.[82,83] Also, different neurotrophin receptor pathways appear to mediate the signal for both cellular differentiation and malignant transformation of sympathetic neuroblasts to neuroblastoma cells. Neurotrophins are expressed in a wide variety of neuronal tissues and other tissues that require innervation. They stimulate the survival, maturation, and differentiation of neurons and exhibit a developmentally regulated pattern of expression.[84,85] Neurotrophins and their TRK tyrosine kinase receptors are particularly important in the development of the sympathetic nervous system and have been implicated in the pathogenesis of neuroblastoma. Three receptor–ligand pairs have been identified: TRKA, TRKB, and TRKC, which are the primary receptors for nerve growth factor, brain-derived neurotrophic factor (BDNF), and neurotrophin 3 (NT-3), respectively.[84] TRKA appears to mediate the differentiation of developing neurons or neuroblastoma in the presence of nerve growth factor ligand and to mediate apoptosis in the absence of nerve growth factor.[85] Conversely, the TRKB-BDNF pathway appears to promote neuroblastoma cell survival through autocrine or paracrine signaling, especially in *MYCN*-amplified tumors.[86] TRKC is expressed in approximately 25% of neuroblastomas and is strongly associated with TRKA expression.[87] Studies are ongoing to test agonists of TRKA in an attempt to induce cellular differentiation. Conversely, blocking the TRKB-BDNF signaling pathway with TRK-specific tyrosine kinase inhibitors such as CEP-751 may induce apoptosis by blocking crucial survival pathways.[66,86] This targeted approach has the attractive potential for increased specificity and lower toxicity than conventional cytotoxic chemotherapy.

## Inhibition of Angiogenesis

Because tumor growth and spread appear to be dependent on angiogenesis, inhibition of angiogenesis is a logical anticancer strategy. This approach is particularly appealing for several reasons. First, despite the extreme molecular and phenotypic heterogeneity of human cancer, it is likely that most, if not all, tumor types, including hematologic malignancies, require neovascularization to achieve their full malignant phenotype. Therefore antiangiogenic therapy may have broad applicability for the treatment of cancer. Second, the endothelial cells in a tumor's new blood vessels, although rapidly proliferating, are inherently normal and mutate slowly. They are therefore unlikely to evolve a phenotype that is insensitive to an angiogenesis inhibitor, unlike the rapidly proliferating tumor cells, which undergo spontaneous mutation at a high rate and can readily generate drug-resistant clones. Finally, because the new blood vessels induced by a tumor are sufficiently distinct from established vessels to permit highly specific targeting,[88,89] angiogenesis inhibitors should have a

high therapeutic index and minimal toxicity. The combination of conventional chemotherapeutic agents with angiogenesis inhibitors appears to be particularly effective.

The first clinical demonstration that an angiogenesis inhibitor could cause regression of a tumor came with the use of interferon alpha in a patient treated for life-threatening pulmonary hemangioma.[90] An increasing number of natural and synthetic inhibitors of angiogenesis, which inhibit different effectors of angiogenesis, have since been identified, and many of these agents have been tested in clinical trials. Examples include drugs that directly inhibit endothelial cells, such as thalidomide and combretastatin; drugs that block activators of angiogenesis, such as bevacizumab (Avastin), a recombinant humanized anti-VEGF antibody, or "VEGF trap"; drugs that inhibit endothelium-specific survival signaling, such as Vitaxin, an anti-integrin antibody; and drugs with nonspecific mechanisms of action, such as celecoxib and interleukin-12 (IL-12).

# Immunotherapy

The immune system has evolved as a powerful means to detect and eliminate molecules or pathogens that are recognized as "foreign." However, because tumors arise from host cells, they are generally relatively weakly immunogenic. In addition, malignant cells have evolved several mechanisms that allow them to elude the immune system. These mechanisms include the ability to down-regulate the cell surface major histocompatibility complex molecules required for activation of many of the immune effector cells, to produce immunosuppressive factors, and to variably express different proteins that might otherwise serve as targets for the immune system in a process known as antigenic drift. Nevertheless, because of the large number of mutations and chromosomal aberrations occurring in cancer cells, which results in the expression of abnormal, new, or otherwise silenced proteins, it is likely that most, if not all, cancers contain unique tumor-associated antigens that can be recognized by the immune system. Examples include the fusion proteins commonly found in pediatric sarcomas and the embryonic neuroectodermal antigens that continue to be produced by neuroblastomas.

Recruiting the immune system to help eradicate tumor cells is an attractive approach for several reasons. First, circulating cells of the immune system have ready access to even occult sites of tumor cells. Second, the immune system has powerful effector cells capable of effectively and efficiently destroying and eradicating targets, including neoplastic cells. Initial efforts to recruit the immune system to recognize and destroy tumor cells by using cytotoxic effector mechanisms that are T-cell dependent or independent focused on recombinant cytokines. Cytokines act by directly stimulating the immune system[66] or by rendering the target tumor cells more immunogenic.

Neuroblastoma has been a popular target for immunotherapy in the pediatric population. Although a particular neuroblastoma antigen has not been defined, murine monoclonal antibodies have been raised against the ganglioside GD2, a predominant antigen on the surface of neuroblastoma cells. These antibodies elicited therapeutic responses,[37,91] but with substantial toxicity, particularly neuropathic pain.[92] Because the induction of antibody-dependent cell-mediated cytotoxicity with anti-GD2 antibodies is enhanced by cytokines, such as granulocyte-macrophage colony-stimulating factor[92] and interleukin-2 (IL-2),[93] current antineuroblastoma antibody trials are evaluating the use of a humanized, chimeric anti-GD2 antibody (ch14.18) with these cytokines and a fusion protein (hu14.18:IL2) that consists of the humanized 14.18 antibody linked genetically to human recombinant IL-2. A recently completed randomized phase III trial using ch14.18 alternating with cycles of granulocyte-macrophage colony-stimulating factor (GM-CSF) or interleukin-2 added to maintenance therapy of cis-retinoic acid demonstrated a significant improvement in 2-year event-free survival for those who received immunotherapy in addition to retinoic acid.[94]

# General Principles of Radiation Therapy

Radiation therapy is one of the three primary modalities used to manage pediatric cancers in the modern era. Radiation therapy is delivered to an estimated 2000 or more children per year for the primary treatment of tumor types as diverse as leukemia, brain tumors, sarcomas, Hodgkin disease, neuroblastoma, and Wilms' tumor.[95] Delivery of radiation therapy in the pediatric setting differs from that in the adult setting because of the balance between curative therapy and an anticipated long life span during which long-term morbidity may result from the therapy.

## CLINICAL CONSIDERATIONS

Radiation therapy for the management of pediatric cancer is most frequently combined with surgery and chemotherapy as part of a multidisciplinary treatment plan. The sensitive nature of pediatric tumors requires the use of a combined therapy approach to maximize tumor control while minimizing the long-term side effects of treatment. Radiation may be delivered preoperatively, postoperatively (relative to a definitive surgical resection), or definitively without surgical management. Systemic therapy may also be integrated into this management approach.

### Definitive Irradiation

Definitive radiation therapy is an alternative local approach to surgical resection of primary solid tumors. It is often the only local therapeutic approach for children and adolescents with leukemia or lymphoma.[96,97] Definitive radiation therapy for rhabdomyosarcoma has been used as an alternative to surgical resection, which has potentially greater morbidity; it has achieved high rates of local tumor control while allowing preservation of function.[38] The Ewing sarcoma family of tumors may also be considered candidates for definitive radiation therapy as an alternative to surgery. With careful patient selection, excellent local tumor control rates can be maintained while reducing or avoiding the morbidity associated with difficult surgical resections.[98,99]

### Preoperative Irradiation

Targeting of a localized tumor is straightforward in the preoperative setting; the tumor has clearly defined margins undisturbed by a surgical procedure. The volume of normal, healthy tissues receiving high doses of radiation may be

reduced, because the areas at risk for disease involvement can be better defined. Preoperative radiation therapy has been used rarely in the management of Wilms' tumor to decrease the chance of tumor rupture[100] and in the management of nonrhabdomyosarcoma soft tissue sarcoma and Ewing sarcoma to facilitate surgical resection.[101,102] One of the limitations may be the slightly higher incidence of postoperative wound complications noted in the sarcoma population.[102]

### Postoperative Irradiation

Postoperative radiation therapy combined with surgical resection is the most common application of adjuvant radiation treatment in the United States. Despite some degree of difficulty in targeting, a postoperative approach allows a review of tumor histology from the complete tumor specimen, including identification of the tumor margins and the response to any previous therapy. Wound healing complications appear to be reduced with this approach, and the radiation dose can be more accurately tailored to the pathologic findings after primary resection.

### Interactions of Chemotherapy and Radiation

Most children's cancers are managed with systemic chemotherapy. In children receiving radiation therapy as well as systemic chemotherapy, issues of enhanced local efficacy and enhanced local or regional toxicity need to be considered. Solid tumors that are frequently treated with combined chemotherapy and radiation therapy include Wilms' tumor, neuroblastoma, and sarcomas. These tumors are subdivided into those in which chemotherapy is given concomitantly with radiation therapy[103,104] and those in which it is given sequentially, before or after radiation therapy.[83,100,105] When delivering radiation therapy concurrently with or temporally close to a course of chemotherapy, several issues must be considered.

### Chemotherapeutic Enhancement of Local Irradiation

Several systemic chemotherapeutic agents used against pediatric tumors may enhance the efficacy of radiation therapy when delivered concomitantly. Cisplatin, 5-fluorouracil, mitomycin C, and gemcitabine, for example, are well-known radiation sensitizers.[106–108] Concomitant delivery of any of these drugs with radiation therapy may require that they be administered at a dose and schedule different from those typically used when the drugs are delivered alone. Despite the potential of increased toxicity, significant improvements in local tumor control have been shown in randomized studies of concomitant drug and radiation therapy.[106,107]

### Irradiation Combined with Agents Having Limited or No Sensitizing Effect

In the management of pediatric malignancies, radiation is often combined with systemic therapy not to increase its local efficacy but to allow continued delivery of systemic therapy to control micrometastatic or metastatic disease. Agents combined with radiation therapy in this setting are common in the management of pediatric sarcomas and include ifosfamide and etoposide, which are delivered concurrently with radiation therapy for Ewing sarcoma, and vincristine and cyclophosphamide, which are delivered concurrently with radiation therapy for rhabdomyosarcoma.[103,104] Although local toxicity may be increased by such an approach, this risk is often outweighed by the benefit of continuously delivered systemic therapy, particularly in tumors associated with a high incidence of micrometastatic disease.

### Agents That Increase Radiation Toxicity

Several agents significantly increase the local toxicity of radiation. For this reason, these agents are not given concomitantly with irradiation and are often withheld for a period after the completion of radiation therapy. The two most notable agents are doxorubicin and actinomycin, both of which can induce significant skin and mucosal toxicity when delivered concurrently with radiation therapy.[38,109] The camptothecins (including irinotecan and topotecan) also potentiate mucosal toxicity when delivered concurrently with radiation therapy.[110,111] Although this increase in toxicity suggests a possible increase in local efficacy, this benefit has not been noted with current treatment approaches and chemotherapeutic dosing guidelines. For this reason, these agents are avoided during the delivery of radiation therapy and are withheld for 2 to 6 weeks after the completion of treatment.

The current era of systemic therapy continues to broaden with the availability of many new agents that target molecular pathways. It is important to consider the possibility of new toxicities when combining novel agents with a known therapy such as radiation.

## FRACTIONATION OF RADIATION THERAPY

Conventional, external beam irradiation is delivered in a fractionated form. Fractionation implies daily doses of radiation delivered 5 days per week and amounting to the prescribed dose for a particular tumor type. Radiation delivered once daily at a fraction size between 1.5 and 2.0 Gy on 5 days per week is considered "conventionally" fractionated. This daily dose is well tolerated by normal tissues adjacent to the tumor and appears to effect local tumor control in many tumor systems. Though adult malignancies may be treated with increased doses per fraction to overcome the radioresistance of many carcinomas (termed hypofractionation), nearly all the literature describing radiation therapy, its efficacy, and its toxicity in children is based on conventional fractionation.

## RADIATION THERAPY TREATMENT TECHNIQUES

### Traditional Radiation Therapy

The planning and delivery of traditional, or conventional, radiation therapy are based on nonvolumetric imaging studies (i.e., conventional radiographs). Patients are positioned in a manner that allows the orientation of radiation beams from the conventional directions: anterior, posterior, and lateral. Limitations of this approach are related to the ability of conventional radiographs to accurately convey the location of tumor-bearing tissue. Although treatment beams are oriented around the tumor, adjacent normal tissues also receive high doses of radiation. Depending on the accuracy of the delineation of adjacent normal tissues on radiographs, the dose to those tissues may not be known. Radiation is delivered by a photon beam generated by a linear accelerator.

### Focal Radiation Therapy

Focal radiation therapy comprises a group of techniques that deliver radiation to a defined volume, usually delineated by computed tomography (CT) or magnetic resonance imaging (MRI). Relatively low doses may be incidentally delivered to surrounding normal tissues. Radiation therapy may be described as image guided when four criteria are met: (1) three-dimensional imaging data (CT or MRI) are acquired with the patient in the treatment position; (2) imaging data are used to delineate and reconstruct the tumor volume and normal tissues in three dimensions; (3) radiation beams can be freely oriented in three dimensions in the planning and delivery processes, and structures traversed by the beam can be visualized with the eye of the beam; and (4) the distribution of doses received by the tumor volume and any normal tissue is computable on a point-by-point basis in three-dimensional space. Several different methods of delivering image-guided photon radiation are currently in use and are discussed here.

### Conformal Radiation Therapy

The delivery of three-dimensional conformal radiation therapy allows specific targeting of tumor volumes on the basis of imaging studies performed with the patient in the treatment position. This method of delivery uses multiple fields or portals, with each beam aperture shaped to the tumor volume, and it is performed daily. Beam modifiers, such as wedges, are used to conform the radiation beam to the tumor and to ensure that the tumor volume receives a homogeneous dose. Conformal radiation therapy has been intensively studied in adults with head and neck cancer, lung cancer, and prostate cancer and has been shown to excel when the target volume is convex and crucial structures do not invaginate the target volume. Available data demonstrate that it has low toxicity despite high doses of radiation to the target volume.[112]

### Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy is another method of delivering external beam radiation that requires imaging of the patient in the treatment position and delineation of target volumes and normal tissues. Radiation is delivered to the target as multiple small fields that do not encompass the entire target volume but collectively deliver the prescribed daily dose. Intensity-modulated radiation therapy differs from conformal radiation therapy in that it (1) increases the complexity and time required for the planning and delivery of treatment, (2) increases the amount of quality-assurance work required before treatment is delivered, (3) increases dose heterogeneity within the target volume such that some intralesional areas receive a relatively high dose, and (4) can be used to treat concave targets while sparing crucial structures that invaginate the target volume. The last point holds promise for better protecting normal tissue and reducing late toxic effects. Preliminary data from adult patients given intensity-modulated radiation therapy demonstrate its potential for reducing treatment toxicity when applied to pediatric brain tumors and other adult tumors.[113]

### Proton Beam Radiation Therapy

Proton radiation therapy and other approaches using heavy charged particles have been investigated at a limited number of centers. The primary benefit of therapy with proton or other heavy charged particle beams is the capacity to end the radiation beam at a specific and controllable depth. This may allow the protection of healthy, normal tissues directly adjacent to tumor-bearing tissues.[114] However, the use of proton therapy has been limited because of the expense of constructing a suitable treatment facility. Several new facilities have opened in the United States, and pediatric malignancies are always noted as one of the tumors systems on which the centers will focus their research efforts. With appropriately designed studies and comparisons with current state-of-the-art focal radiation therapy delivered with photon beams, a determination of the potential benefits of this treatment modality may be made.

### Brachytherapy

Brachytherapy is a method of delivering radiation to a tumor or tumor bed by placing radioactive sources within or adjacent to the target volume, usually at the time of surgical resection and under direct vision. Planning of the dose to be delivered to the target volume is accomplished after resection and may use CT or MRI studies; the appropriate strength of the radioactive source is determined prospectively. Sources commonly used in children include iridium 192 and iodine 125. Brachytherapy may consist of either low dose-rate treatments (approximately 40 to 80 cGy per hour) or high dose-rate treatments (approximately 60 to 100 cGy per minute). Low dose-rate treatments are delivered during a period of days, often while the patient remains hospitalized, whereas high dose-rate treatments are divided into fractions and delivered on several days during 1 to 2 weeks. The primary advantage of brachytherapy is that a radiation source can be placed into or adjacent to the tumor, often at the time of resection. Preoperative planning and cooperation between the surgical and radiation oncology teams are necessary to ensure the appropriate and accurate implementation of brachytherapy. Nonrhabdomyosarcoma soft tissue sarcomas and some rhabdomyosarcomas are the pediatric tumors most commonly treated with brachytherapy.[115,116] Most other pediatric solid tumors are not amenable to brachytherapy, however, because of the tumor's behavior (e.g., radioresistance) or its anatomic location (e.g., retroperitoneal).

Intraoperative radiation therapy has been used intermittently after resection in the management of localized tumors.[117] Although of limited availability in the United States, intraoperative radiation therapy has the distinct advantage of allowing the operative tumor bed to be visible in the operating theater while radiation is delivered, thereby enhancing the accuracy of delivery and providing the opportunity to displace or temporarily move mobile crucial structures (e.g., bowel, bladder) from the field of delivery. The primary limitation of intraoperative radiation therapy is that it can deliver only a single fraction of radiation, usually in the 10 to 20 Gy range. Radiation tolerances of normal tissues that cannot be removed from the treatment field must be respected and may limit the ability to deliver an effective treatment dose.

## PALLIATIVE RADIATION THERAPY

Despite substantial success in the management of pediatric cancer, some children experience disease recurrence and ultimately die from their malignancy. Palliative radiation therapy is often a valid intervention for these patients.[118] The ultimate goal of a palliative approach is to maintain quality of life for

patients who will not survive their disease by palliating their symptoms while minimizing the number of disruptive interventions they must undergo. Painful sites of disease, particularly those with bony involvement, and symptoms resulting from compression of vital structures, including spinal cord, peripheral nerves, and respiratory tract are often palliated with radiation. A palliative course of therapy is highly individualized, and its success or failure depends on the histologic diagnosis, previous therapy, duration of symptoms, and symptom(s) being treated.

## ACUTE AND LATE TOXICITIES OF RADIATION THERAPY

The treatment-related effects of radiation therapy, both acute and chronic, are well described for pediatric and adult patients, but unfortunately, their incidence and relation to the dose and volume of treatment are poorly characterized.[119] Historically, treatment-related effects have been classified as acute or late; an arbitrary time point of 90 days after the completion of treatment defines the division between the two classifications. Current guidelines for assessing adverse events related to treatment no longer recognize this arbitrary distinction, but the use of early and late time points is instructive in the discussion of radiation-related effects. Essentially all such effects originate from within the confines of the treatment beams, usually the high-dose regions of treatment. The most common early and late treatment-related effects arising from radiation are listed in Table 28-6. Despite the arbitrary nature of the division into early and late effects, this classification distinguishes effects from which the patient is likely to recover completely from those that are likely to be permanent. Early treatment-related effects, if managed appropriately, will resolve as normal, healthy tissues adjacent to the tumor-bearing tissues, gradually recovering from the effects of radiation. The period of recovery can range from days to months, but the patient is often left with minimal sequelae. Treatment-related effects that are observed later, after the completion of radiation therapy, are more likely to be chronic or permanent. They appear to be related to the normal healing response of healthy irradiated tissue, resulting in the formation of an unwanted effect such as fibrosis. Many late treatment effects can be managed but are not reversible. For children receiving curative therapy, long-term effects are a primary concern and are best managed with a preventive approach. Some of the long-term effects of treatment in children should be ameliorated by limiting the volume of normal tissue irradiated at high doses and by implementing approaches that minimize the radiation dose to adjacent healthy tissues.

**TABLE 28-6**

**Radiation-Related Adverse Events in Children and the Associated Radiation Doses**

| *Organ/Site* | *Acute* | *Chronic* | *Dose Relation* | *Reference* |
|---|---|---|---|---|
| Skin | Erythema<br>Desquamation | Atrophy<br>Hyperpigmentation | Doses more than 40 Gy increase incidence of moist desquamation | 121 |
| Subcutaneous tissue | Edema | Fibrosis | – | |
| Mucosa | Mucositis | Ulceration | – | |
| Central nervous system | Headache<br>Edema | Necrosis<br>Myelitis<br>Decline in cognition | 2.5% incidence of brainstem necrosis with doses of 59.4 Gy<br>Reduction in intelligence quotient with younger age and doses of radiation to the supratentorial brain more than 30 Gy | 122, 123 |
| Eye | Conjunctivitis | Cataract<br>Retinopathy<br>Dry eye | 43% incidence of cataract with doses of total body irradiation of $\geq$ 12 Gy | 124 |
| Thyroid | – | Hypothyroidism | 20% incidence at $\leq$ 21 Gy; 61% incidence when $>$ 21 Gy | 125 |
| Heart | – | Pericarditis<br>Myocarditis<br>Valvular disease | 2.5% incidence of pericarditis at doses of 30 Gy to the heart | 126, 127 |
| Lung | Pneumonitis | Pulmonary fibrosis | Increasing risk of pneumonitis with volume of lung receiving 24 Gy and bleomycin chemotherapy | 128 |
| Bowel | Nausea<br>Diarrhea | Necrosis | – | |
| Kidney | – | Nephritis<br>Renal insufficiency | – | |
| Bladder | Dysuria<br>Urgency<br>Frequency | Hemorrhagic cystitis | – | |
| Muscle | Edema | Fibrosis<br>Hypoplasia | Acute edema in adjacent muscle receiving doses above 40 Gy<br>Volume of jaw muscles $>$ 40 Gy increases chronic fibrosis | 129 |
| Bone | – | Hypoplasia<br>Fracture<br>Premature physis closure | Increasing reduction in growth above 35 Gy, but effects seen even at 23.4 Gy<br>Weight-bearing bones in patient radiated for sarcomas have a 29% incidence of fracture | 130–132 |

## General Principles of Stem Cell Transplantation

Infusion or transplantation of hematopoietic cells capable of reconstituting the hematopoietic system is used in two broad instances. First, hematopoietic stem cell transplantation (HSCT) can be used to replace missing or abnormal components of a defective hematopoietic system. Second, HSCT can be used to reconstitute elements of the hematopoietic system destroyed by intensive chemotherapy or radiation therapy for solid tumors or disorders of the hematopoietic system itself. The transplanted cells can be the patient's own (i.e., autologous), in which case the cells are obtained before the administration of myelosuppressive therapy, or they may come from a donor (i.e., allogeneic) who is generally a histocompatibility leukocyte antigen (HLA)–identical sibling, a mismatched family member, or a partially matched unrelated donor. The latter two circumstances require immunosuppressive and graft engineering strategies to permit successful engraftment and avoid graft-versus-host disease. Hematopoietic progenitor cells are usually obtained from the bone marrow or peripheral blood. They are the crucial component of the transplant, because they are capable of self-renewal and therefore long-term production of cells of the various hematopoietic lineages. Occasionally, when available, banked umbilical cord blood may be used as the source of hematopoietic stem cells (HSCs). In general, although autologous cells are the safest to use for HSCT, they may be contaminated with tumor cells. Graft-versus-host disease, which may occur with allogeneic HSCT, can be life threatening, but a modest graft-versus-host reaction may be beneficial if directed against the host's tumor cells.

Bone marrow is normally harvested from the posterior iliac crest to a total volume of 10 to 20 mL/kg body weight of the recipient. Peripheral blood stem cells are harvested after their mobilization with recombinant granulocyte colony-stimulating factor, given daily for up to a week before harvest. The exact nature of the crucial cellular component responsible for the reconstitution of the hematopoietic system is unknown, but the number of cells having the surface marker CD34 has been shown to be related to the rate of engraftment.[120] Before HSCT, the recipient receives a preparative (or "conditioning") chemotherapeutic regimen. This treatment serves several purposes, including killing residual tumor cells, providing immunosuppression for allogeneic HSCT, and providing "space" in the marrow into which transplanted HSCs can engraft. Before reinfusion, the HSC product may be manipulated ex vivo to enrich it for putative progenitor cells (e.g., $CD34^+$ or $CD133^+$ cells), using positive or negative selection methods to facilitate hematopoietic reconstitution; to remove donor T lymphocytes, thereby decreasing the risk of graft-versus-host disease in allogeneic HSCT; or to purge contaminating tumor cells from the product used in autologous HSCT.

Complications of HSCT can be significant. The most common early complication is infection, which results from the transient but profound immunosuppression of the patient, combined with the breakdown of mucosal barriers. Another common complication is veno-occlusive disease, which is characterized clinically by painful enlargement of the liver, jaundice, and fluid retention. Ultrasound examination shows reversal of flow in the portal vein. Liver biopsy samples show a classic histologic appearance of obliterated hepatic venules and necrosis of centrilobular hepatocytes. There is no specific treatment for this condition; only supportive care can be given, and mild or moderate veno-occlusive disease is self limited. Other acute complications of HSCT include graft-versus-host disease, a process mediated by donor T cells targeting host cells with antigenic disparities, and graft failure. Late complications include chronic graft-versus-host disease, endocrine insufficiency, secondary malignancies, growth failure, and other sequelae related to the use of total-body irradiation as part of some preparatory regimens. Nevertheless, despite the toxicity, HSCT is now an integral part of successful therapy for many high-risk malignancies in children.

## Clinical Trials

As previously stated, the past 40 years have seen a significant increase in overall survival rates for children with cancer. This increase has been achieved through the development of new drugs and treatment approaches, improved supportive care, and better diagnostic modalities to permit earlier cancer detection. The benefits of these advances have been confirmed by carefully designed and analyzed clinical trials. Because childhood cancer is relatively rare, excellent organization and planning of these trials are essential. In the United States and other participating countries, clinical trials are largely conducted by the Children's Oncology Group, with smaller pilot studies being run by large individual institutions or small consortia.

Clinical trials are generally divided into three phases. Phase I studies are designed to evaluate the potential toxicity of a new diagnostic or therapeutic agent. Small numbers of patients are usually required for a phase I study, which typically uses a dose-escalating design in which cohorts of patients are observed for signs of toxicity before they advance to higher doses. The end point of this type of study is generally a determination of the safety of the agent or the maximum tolerated dose (or both). However, the increasing number of biologic reagents being introduced and tested may require a shift to the assessment of the optimal biologic dose. Enrollment in a phase I toxicity study is often restricted to patients whose disease has not responded to conventional, or standard-of-care, therapy. Phase II trials are conducted to determine whether a new agent or treatment approach is sufficiently efficacious to warrant further study. Phase II agents are often given to newly diagnosed patients before they begin or just after they complete standard therapy. The testing of new agents in an "upfront window" (i.e., before standard therapy) has been shown not to have an adverse effect on the efficacy of delayed standard therapy. Finally, phase III studies are designed to compare the efficacy of an experimental therapy with that of standard therapy. They are best done as prospective, randomized trials, but often, because of small patient numbers, a phase III study is done by comparing the efficacy of an experimental therapy with that of standard therapy given to historical control subjects. It is through such systematic assessment of the risks and benefits of new therapies that approaches are rejected or accepted as the new standard of care and the field of pediatric oncology is advanced.

## Conclusion

Advances in molecular genetic research in the past 3 decades have led to an increased understanding of the genetic events in the pathogenesis and progression of human malignancies, including those of childhood. A number of pediatric malignancies serve as models for the molecular genetic approach to cancer. The pediatric experience highlights the utility of molecular analysis for a variety of purposes. Demonstration of tumor-specific translocations by cytogenetics, FISH, and RT-PCR confirms histopathologic diagnoses. Detection of chromosomal abnormalities, gene overexpression, and gene amplification is used in risk stratification and treatment planning. Elucidation of pathways involving tumor suppressor genes has increased our understanding of syndromes associated with cancer and has led the way for genetic screening and counseling and prophylactic surgical intervention. And in the near future, translation of the molecular profile of a given tumor will form the basis of a new therapeutic approach. Treatment will be tailored such that patients with biologically high-risk tumors receive intensified regimens to achieve a cure, whereas patients with biologically low-risk tumors may experience a cure and benefit from the lower toxicity of nonintensive therapy. Elucidation of the complex molecular pathways involved in tumorigenesis will also encourage the production of targeted anticancer agents with high specificity, efficacy, and therapeutic index.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 29

# Biopsy Techniques for Children with Cancer

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The importance of biopsy techniques in the management of children with cancer has increased as the use of preoperative chemotherapy has become commonplace for many childhood cancers. Historically, definitive diagnosis was made at the time of surgical resection of the primary tumor. Currently, many children will undergo percutaneous, minimal access surgical, or open incisional biopsy rather than initial resection. Moreover, with increasing understanding of the molecular changes associated with these malignancies, definitive diagnosis can be accomplished with smaller specimens. This should allow a decrease in the morbidity associated with establishing the diagnosis of solid malignancies in children.

Ironically, this progression to less invasive biopsy has complicated rather than simplified the selection of technique in individual cases, as multiple factors must be considered. Percutaneous needle biopsy,[1,2] minimal access surgical biopsy,[3] and open biopsy have all been demonstrated to be effective in safely establishing initial diagnosis as well as verification of recurrent or metastatic disease. However, the success of these techniques is obviously dependent upon local institutional experience, which must be considered in the selection. In addition, it is critical to realize that many of the advances in risk stratification and improved therapy of pediatric malignancies has been facilitated by the development of large accessible tumor banks and the associated biology studies. Without large biopsy specimens, these tumor banks and the development of research cell lines would not have been possible. For a number of tumors, including neuroblastoma and Wilms' tumor, collection of such specimens remains important to further our understanding of the disease.

Biopsies may be required in a variety of settings including primary diagnosis, determination of metastatic disease, and assessment for viable tumor in residual masses after therapy. Therefore a biopsy must be considered as a component of the overall plan of care and not simply as a surgical procedure. It is, therefore, essential that the surgeon have a thorough understanding of the therapeutic plan prior to performing a biopsy. This is well-illustrated in the current management of a child with a Wilms' tumor and a solitary pulmonary nodule. Standard therapy for a pulmonary metastasis is lung irradiation. It could, therefore, be important to histologically confirm this metastasis by excisional biopsy prior to proceeding. This approach is complicated, however, by a current Children's Oncology Group research question of whether children in whom the pulmonary lesions respond completely after 6 weeks of chemotherapy can be spared lung irradiation and more intensive chemotherapy. In this research protocol setting, resection of this solitary lesion would be contraindicated, because it would commit the child to lung irradiation and more intensive medical treatment.

Current pediatric oncology protocols use risk-stratified treatment regimens.[4] Information needed from biopsy specimens is disease specific. The surgeon must be knowledgeable about the stratification schema that will be used for multimodality therapy to select the biopsy method that will be least morbid and yet yield all essential information. This concept is demonstrated by considering two patients with abdominal masses suggestive of neuroblastoma with apparent bone marrow involvement as they would be treated under the current Children's Oncology Group schema. The first patient is less than 1 year of age. This patient's treatment group could be low, intermediate, or high risk. Risk group assignment will require MYC-N amplification status, Shimada histology status, and DNA ploidy to determine stratification. This will require sampling of the primary lesion with an adequate sample of the tumor to allow Shimada staging. In contrast, an older child with similar presentation would be classified as high risk, regardless of any of the previous factors. Therefore one could confirm the diagnosis and assign a risk group with bone marrow biopsy alone.[5] Clearly, knowledge of the multimodality therapy decision making is essential in selection of biopsy technique.

## Handling of Specimens

Historically most diagnoses were made based on hematoxylin and eosin histology performed on permanent sections. This was supplemented by immunohistochemistry, which could similarly be performed on formalin fixed specimens. There has been extensive progress made in the molecular diagnosis of childhood malignancies, including recognition of genetic

aberrations, which has both diagnostic and prognostic significance.[6–9] Techniques used to detect these changes include reverse transcriptase–polymerase chain reaction (rt-PCR),[10] fluorescence in situ hybridization (FISH), microarray analysis, and flow cytometry. Inappropriate specimen handling can preclude these analyses. For example, phenotypic classification of lymphoma cannot be performed using flow cytometry on formalin-fixed lymph nodes. Given the rapidly evolving field of molecular diagnosis, it is essential that the surgeon consult with the pathologist regarding specimen handling prior to performing the biopsy. Additionally, if the patient is eligible for a research protocol, care must be taken to assure the specimen is handled in accordance with the protocol requirements. This requires a coordinated effort by the surgeon, medical oncologist, and pathologist.

## Percutaneous Needle Biopsy

Fine-needle aspiration was first introduced as a technique to obtain specimens for cytopathology by Grieg and Gray in 1904. Jereb and colleagues reported success with the use of needle biopsy for the diagnosis of pediatric solid tumors in 1978.[11] Subsequently, extensive experience from multiple institutions has confirmed the accuracy and safety of both needle aspiration and core needle biopsy techniques. The appeal of these techniques is that they both may provide diagnosis without requiring a significant delay in therapy and can be performed as outpatient procedures. Needle biopsies are often performed under either general anesthesia or sedation. In selected older children, some sites may be biopsied under local anesthesia alone.[12]

Percutaneous needle biopsies may be performed by palpation in the extremities and other superficial locations such as lymph nodes. However, deeper biopsies require guidance with either ultrasonography or CT scan. Ultrasonography that can be supplemented with Doppler mode allows clear identification of large vessels and other structures and provides real-time visualization as the needle is advanced.[13] Some core needle devices also deposit a small air bubble that allows verification of the site that was biopsied. CT scan, on the other hand, allows clear visualization of aerated lung and is not obscured by bowel gas.[14] It also allows measurement and planning of depth of biopsy.[1] Decision making regarding image guidance is made in conjunction with the radiologist, and ideally, biopsies should be performed with both modalities available if required.

## Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB) holds the obvious appeal of being the least invasive of all biopsy techniques. It is typically performed using a 22- to 25-gauge needle with multiple passes into the lesion if necessary. Successful diagnosis using FNAB requires coordination with an experienced cytopathologist. To improve the diagnostic yield, the specimens should be examined immediately by the cytopathologist. Additional aspirations may be taken if initial samples are inadequate.[15] Large series with fine-needle aspirates in both children and adults have confirmed the safety of the technique.[16,17]

Historically, diagnosis using fine-needle aspiration was based primary on cytologic appearance with conventional stains and light microscopy. Successful diagnosis using FNAB is dependent upon the availability of an experienced cytopathologist. In adult patients with the higher prevalence of carcinomas, FNA is a popular method for confirming the presence of malignancy in suspicious lesions. Often, in these adult cases, a diagnosis of carcinoma and primary site are sufficient to make initial treatment decisions. However, given the fact that multimodality therapy is histiotype-specific in pediatric patients, FNAB has been used less frequently in children. Recent application of molecular techniques and electron microscopy to supplement light microscopy has increased the histiotype specificity of FNAB and may lead to increased application in pediatric solid malignancies.[18,19] FNAB has been used in several pediatric settings with sufficient data reported for consideration.

The use of FNAB in the evaluation of thyroid nodules in adults is well-established. Although thyroid nodules are less common in children, the techniques and interpretation of FNAB are similar to those used in adults.[20] Given the good degree of specificity, FNAB may be considered a standard component of evaluation of thyroid nodules in children.[21]

Another relatively straight forward application and interpretation of fine-needle aspirate biopsy is in the verification of metastatic or recurrent disease in the setting of a previously characterized primary tumor.[22] In this context, the verification of the presence of malignant cells may be sufficient to guide further clinical decisions. This least invasive biopsy method is particularly appealing in these patients who may already be immunologically or physiologically compromised.

There is a limited body of literature on the use of FNAB in the diagnosis of sarcomas. Osteosarcoma has been diagnosed by the use of fine-needle aspirates, with definitive diagnosis being obtained in 65% to 92% of patients. The technique is as accurate in children as it is in adults.[23] The use of FNAB in soft tissue tumors has been facilitated by the recognition of cytogenetic abnormalities and fusion proteins that are specific to these tumor types.[17,19,24] However, caution should be exercised in the use of FNAB in this setting, because the reported series come from a limited number of institutions with extensive experience in cytologic interpretation. The use of FNAB in diagnosing sarcoma has not gained widespread use.

Fine-needle aspiration has not been widely used for the diagnosis of small, round, blue cell tumors of childhood. However, with the increasing availability of ancillary studies, such as electron microscopy, immunocytochemistry, DNA ploidy, cytogenetics, and fluorescent in situ hybridization, its use may become more common.[25] Use of FNAB for the evaluation of head and neck masses in children has been reported to have good sensitivity and specificity.[26,27] The results of these series, however, should be interpreted with caution, because the majority of aspirates diagnosed as reactive lymphadenopathy and the number of new malignant diagnoses was small. In addition, false-negative FNAB diagnosis occurred frequently in patients ultimately diagnosed with lymphoma in other series (not specifically isolated to the head and neck).[15]

## Core Needle Biopsy

The advantage of core needle biopsy versus fine-needle aspiration is that it provides a sample sufficient in size to allow histologic examination rather than only cytologic examination. In addition, it can provide sufficient tissue for molecular

evaluation. Despite the widespread use of this technique in adults, its application in children has not been as common.

Various core needle devices may be used. These typically range in size from 14 to 18 gauge. These needles are designed so that a cutting sheath advances over the core of the needle to obtain a biopsy that is protected within the sheath as the needle is withdrawn. This cutting sheath may be advanced either manually (e.g., Tru-Cut, Baxter Travenol, Deerfield, Ill.) or by a spring-loaded firing system (e.g., Biopty, Bard Urological, Murray Hill, NJ) (Fig. 29-1). There are no data directly comparing the quality of specimens obtained with these two systems in pediatric malignancies. The faster deployment of the spring-loaded systems may result in less crush artifact, which has been demonstrated in pediatric kidney biopsies. Regardless of the system used, visual inspection of the core biopsy is necessary to verify adequate sampling. The number of passes required with a core needle is dependent upon the purpose of the biopsy and the consistency of the tissue being biopsied. For primary tumor diagnosis, multiple cores are typically required to obtain sufficient tissue for biological studies. Alternatively, in pulmonary lesions evaluated for metastatic disease, a single pass was usually sufficient in most series.

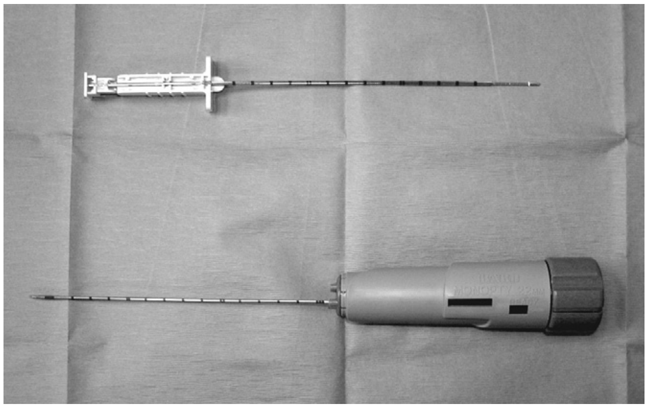

FIGURE 29-1 Two commonly used core needle biopsy devices. The upper device is a 14-gauge Tru-Cut needle (Allegiance, Cardinal Health). It is advanced into the region of interest, and then the inner needle is advanced. The outer sheath is manually advanced over the inner needle to obtain a core. The lower device is a 16-gauge Monopty biopsy device (Bard). It is spring-loaded and is activated after the tip is advanced into the region of interest. The spring-loaded mechanism automatically sequentially advances the obturator and the cannula.

Several large series have demonstrated the utility of core needle biopsies in children. The larger, more recent series are summarized on Table 29-1. The three most common scenarios for which percutaneous biopsies in children with malignancies are used are diagnosis of primary tumors, evaluation for possible recurrent disease, and evaluation of pulmonary lesions.

Success with core needle biopsy has been demonstrated in a wide variety of anatomic locations. These include neck, mediastinum, lung, peritoneal cavity, liver, retroperitoneum, kidney, adrenal, pelvis, and extremities.[1,2,12,13,28] Core needle biopsies have been demonstrated to be effective in obtaining adequate tissue for both primary diagnoses and confirmation of recurrence in these series. In the largest series of pediatric oncologic core needle biopsies, multiple passes were typically performed (median = 6 and maximum = 17). With this repetitive sampling, adequate diagnostic tissue was obtained for histologic and biological studies, obviating the need for operative biopsy in a wide variety of pediatric cancers. No patients in these series suffered procedure-related deaths or required operative therapy for procedural complications.[28]

The other common use of percutaneous core biopsies in pediatric oncology patients is in the evaluation of pulmonary nodules. Pulmonary nodules can be biopsied under either CT scan[29] or ultrasound guidance, often determined by the size and location of the lesions.[30] These procedures may be performed under either sedation or general anesthesia with

**TABLE 29-1**
**Series of Percutaneous Biopsies in Children**

| *Author (Year)* | *Number of Children* | *Number of Biopsies (Total/ Malignancy)* | *Method* | *Diagnostic Yield* | *Comments* |
|---|---|---|---|---|---|
| Skoldenberg (2002)[13] | 110 | 147/84 | US-guided core biopsies of wide range of tumors for initial diagnosis and evaluation for recurrence | 89% | |
| Hayes-Jordan (2003)[52] | 32 | 35/23 | US- or CT-guided core needle biopsies of pulmonary lesions under general anesthesia | 80% | Patients with nondiagnostic biopsy underwent repeat core needle or thoracoscopic biopsy; 10% small pneumothorax or hemothorax—none required drainage |
| Cahill (2004)[29] | 64 | 75/24 | CT-guided core or FNAB of pulmonary lesions with sedation or general anesthesia | 85% | One false negative for Ewing sarcoma; one tension pneumothorax required drainage |
| Fontalvo (2005)[30] | 33 | 38/32 | US-guided core needle of peripheral pulmonary lesions with general anesthesia and controlled ventilation | 84% | Included small lesions (24% $<$ 5 mm); 10% pneumothorax—none required drainage *(series partially overlaps with Hayes-Jordan, 2003)* |
| Garrett (2005)[28] | | 202/202 | US-/CT- or fluoroscopic-guided core needle biopsies of wide range of tumors for initial diagnosis and evaluation for recurrence | 93% overall 98% initial diagnosis 88% suspected recurrence | Multiple passes typically taken (median = 6); accomplished diagnosis, including biological studies without operative biopsies |

CT, computed tomography; FNAB, fine-needle aspiration biopsy; US, ultrasonography.

controlled ventilation. Typically, general anesthesia would be used in younger children or in children with smaller or deeper pulmonary lesions. Current series report success in more than 80% of lesions, including lesions less than 1 cm in size. Surprisingly, pneumothoraces are relatively uncommon, occurring in only 10% of children. The majority of these are managed without placement of a thoracostomy tube.

Needle tract recurrence represents an oncologic complication specific to this biopsy technique. Estimates of this complication in adults vary widely, ranging from 3.4% in hepatocellular carcinoma[31] to 1:8500 in thoracic tumors.[32] Obviously, the incidence of this complication is influenced by several factors. Immunologic, chemotherapeutic, and radiotherapeutic effects will decrease the likelihood of needle tract recurrence. The larger needles used for core needle biopsies are associated with a greater risk than the fine needles used for aspiration.[33] The cases series cited previously report no needle track recurrences in children.

# Minimal Access Surgery

Laparoscopy and thoracoscopy have become commonplace in general pediatric surgery, and both techniques are now used in cancer diagnosis and therapy. Gans and Berci first reported experience with multiple endoscopic techniques in children in 1971.[34] Interestingly, one of the chief applications for laparoscopy, which they advocated, was for guidance of biopsy of metastatic implants. Subsequently, the application of both laparoscopy and thoracoscopy has grown in the initial diagnostic technique for childhood malignancies and for the assessment of refractory or metastatic disease.

## LAPAROSCOPY

Laparoscopy affords several advantages for the evaluation of the abdominal cavity in children with childhood cancer. First, it provides the opportunity to completely examine the peritoneal cavity. A systematic examination of all peritoneal surfaces can be performed. The entire length of the bowel may be examined along with mesenteric lymph nodes. Multiple biopsies can easily be obtained. The second chief advantage of laparoscopy is decreased physiologic stress in children who may already be critically ill. Finally, as in all minimally invasive procedures, postoperative pain is reduced and recovery is hastened.[35] The main disadvantages of laparoscopy are the limited ability to assess retroperitoneal structures and the loss of tactile evaluation of deep lesions.

Diagnostic laparoscopy with biopsy has been used in several settings in the management of children with solid malignancies.[3,35] Biopsies obtained using laparoscopic techniques have a high rate of success in yielding diagnostic tissue.[3,36] Laparoscopy allows the surgeon to obtain larger tissue samples than may be obtained with core needle biopsy. This is particularly relevant if larger samples are required for biological studies. In the initial diagnosis, laparoscopy aids in the identification of site of origin of large abdominal masses. Laparoscopy has been shown to be superior to computerized tomography in assessing intraperitoneal neoplasms and for the evaluation of ascites. For example, laparoscopy allows direct assessment of whether a pelvic mass arises from the ovary or bladder neck, which may be difficult to distinguish by radiographic studies. Direct visualization with laparoscopy has been used to assess the resectability of hepatoblastoma. During the course of treatment, laparoscopy may be used to assess new metastatic disease or to assess initial tumor response as a second-look procedure.[3]

One area of concern with the use of laparoscopy in oncology has been the issue of port-site recurrence. There are relatively limited data on this issue in children. The Children's Cancer Group retrospective study of 85 children noted no port-site recurrences.[3] A survey of Japanese pediatric laparoscopic surgeons reported 85 laparoscopic and 44 thoracoscopic procedures with no port-site recurrences.[37] It should be noted, however, that 104 of these tumors were neuroblastomas, with many being detected by mass screening. The general applicability of this data may, therefore, be limited. A port-site metastasis has been reported in a child with Burkitt lymphoma.[38] Given the difference in tumor biology between adult adenocarcinomas and pediatric neoplasms, which often have a marked response to neoadjuvant therapy, it is difficult to draw conclusions from the adult literature. Certainly additional surveillance for this issue in pediatric tumors is merited.

Laparoscopy in children is typically performed under general anesthesia to facilitate tolerance of pneumoperitoneum. The only absolute contraindication to laparoscopic evaluation is cardiopulmonary instability, which would preclude safe insufflation of the peritoneal cavity. The supine position is used most commonly and affords a complete view of the peritoneal cavity. To facilitate visualization, a 30-degree laparoscope is used along with at least two additional ports for manipulation and retraction. Ascites should be collected for cytologic analysis and all peritoneal surfaces inspected. Incisional biopsies can be performed using laparoscopic scissors. Hemostasis is achieved with a combination of electrocautery and hemostatic agents (as discussed later in the section on open incisional biopsy) or by tissue approximation via laparoscopic suturing. Biopsy specimens are typically retrieved using a specimen bag. This reduces the chance of specimen destruction during retrieval and may decrease the risk of port-site recurrence. Cup biopsy forceps can be used to obtain specimens as well. Core needle biopsies can be directed by laparoscopy and be used to sample retroperitoneal, intraperitoneal, or hepatic masses. For deep-seated lesions, such as intrahepatic lesions, laparoscopic ultrasonography can be used to guide biopsy procedures and to compensate for the inability to palpate tissues.[39,40]

Complications associated with laparoscopic diagnosis and treatment of solid tumors in children are infrequent. The need for conversion to unplanned open operation has similarly been low.[3,35,41,42]

# Thoracoscopy

The initial experience with thoracoscopy in children was reported by Rodgers in 1976 and included two oncology patients (Ewing sarcoma and recurrent Hodgkin lymphoma).[43] Since this initial report, thoracoscopy has become widely used for the evaluation of thoracic lesions in children for several reasons. Postoperative pain associated with thoracoscopic biopsy or resection is markedly decreased compared with that seen with thoracotomy. Moreover, thoracoscopy allows near-complete visualization of all parietal and visceral pleural

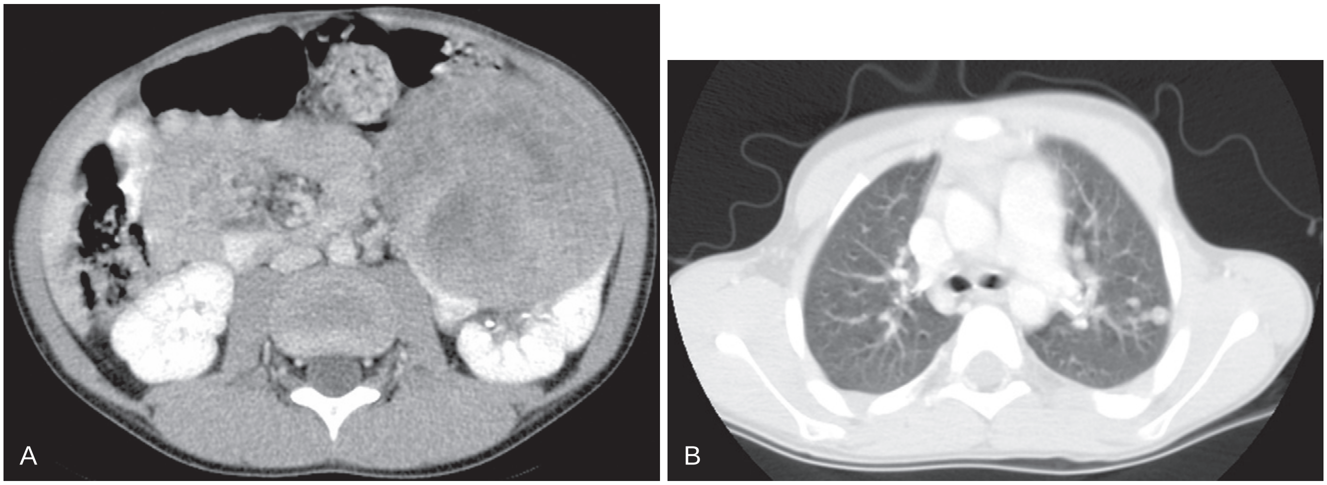


**FIGURE 29-2** Computed tomography (CT) scans obtained at the time of diagnosis of a new abdominal mass in a 5-year-old boy. **A,** Abdominal and pelvic CT scan shows a large left-sided renal mass. **B,** Chest CT scan demonstrates a single 8-mm pulmonary nodule in the left upper lobe. No other pulmonary lesions were identified. At the time of nephrectomy, a thoracoscopic excisional biopsy of the lung lesion was performed. Final pathology of the kidney demonstrated a stage II-favorable-histology Wilms' tumor, and the lung pathology showed a hyalinized granuloma.

surfaces, which cannot be accomplished with a thoracotomy. Additionally, in most children the mediastinum does not contain a significant amount of adipose tissue and, therefore, can be inspected thoracoscopically.

Although primary neoplasms of the lung are rare in children, pulmonary lesions are often a confounding issue in the treatment of children with cancer.[44] The most common tumor to have early pulmonary metastases is Wilms' tumor. Pulmonary metastases are also common with bone and soft tissue sarcomas, hepatic tumors, teratocarcinomas, and melanomas. Thoracoscopy is frequently used to evaluate for the presence of metastases either at the time of initial diagnosis or after follow-up imaging. Difficulty in distinguishing an opportunistic infection versus new metastatic disease is a common clinical scenario during the course of therapy. In areas with endemic granulomatous disease, thoracoscopy can also be helpful at the time of diagnosis (Fig. 29-2; case with histoplasmosis granuloma with new diagnosis of a Wilms' tumor). The diagnostic accuracy for thoracoscopic biopsies in this setting is very high.[41,44,45]

Mediastinal lesions may also be biopsied or resected using thoracoscopy.[46,47] Thoracoscopy provides clear visualization of both the anterior and posterior mediastinum, even in small children; therefore we prefer it rather than mediastinoscopy for evaluation of mediastinal lesions in children.

The only absolute contraindications to thoracoscopy are complete obliteration of the pleural space and the inability to tolerate single-lung ventilation when complete collapse of the lung is required.

Thoracoscopy in children is typically performed under general anesthesia with mechanical ventilation. Visualization is facilitated by single-lung ventilation if possible and supplemented with insufflation. In older children, this may be accomplished with a double-lumen endotracheal tube and, in smaller children, by mainstem intubation of the contralateral side. If selective ventilation is difficult to achieve or poorly tolerated by the patient, low-pressure insufflation (5 to 8 cm of water pressure) with carbon dioxide assists with visualization. The anesthesiologist must monitor for any adverse effects from this controlled tension pneumothorax. It can be evacuated rapidly if need be, but it is typically well tolerated. The child is positioned in the lateral thoracotomy position. Hyperextension of the chest increases the intercostal spaces and will facilitate movement of the thoracoscopy ports. This positioning should be adjusted for mediastinal lesions. For anterior lesions, a more supine position is used, and for posterior lesions the patient is positioned more prone. The initial port is placed in the midaxillary line using blunt dissection. Additional ports are placed under thoracoscopic guidance at sites based upon the location of the lesion of interest. A 30-degree thoracoscope is helpful to achieve complete visualization of all pleural surfaces. Complete inspection is also facilitated by the use of multiple port sites.

Careful correlation with cross-sectional imaging is essential to successful thoracoscopic sampling, particularly of smaller lesions. Pleural-based or subpleural pulmonary lesions are often apparent when the lung is deflated. These can be resected using endoscopic stapling devices and retrieved using specimen bags. Identification of deeper lesions is more challenging. Complete collapse of the lung allows identification of larger lesions. Biopsy of smaller lesions can be based on anatomic location if the location by CT scan is specific, such as apical, lingular, or basilar. CT-guided localization may be performed immediately before surgery to assure correct identification of the area of concern. The lesion may be marked by injection with methylene blue or, preferably, stained autologous blood, which is less prone to diffuse.[48,49] Lesions can be concomitantly marked with placement of a fine wire[50] or microcoils,[51] which can facilitate identification under intraoperative fluoroscopy. These localization techniques have been very effective in obtaining accurate biopsies in children.[48,49,52] Intrathoracic ultrasonography may be helpful in localizing deeper parenchymal lesions.[53] However, this technique is not widely used, and assessment of its efficacy in children is limited.

After sampling of tissues of interest is completed, the pneumothorax may be evacuated with a small catheter to

form a water seal. Unless extensive pulmonary biopsies are performed or the lung is otherwise diseased, a thoracostomy tube is often not required. Most children may be discharged the next day, and chemotherapy may be started promptly.[49]

Thoracoscopic techniques are highly effective in achieving diagnosis. Most pediatric series report a rate of success in obtaining accurate diagnostic tissue in almost all cases.[3,41,44,52] Complications during diagnostic thoracoscopy are rare. Pneumothorax or persistent air leakage may occur in children with underlying parenchymal lung disease or those requiring high-pressure ventilatory support.[52]

## Open Incisional Biopsy

Incisional biopsy remains the gold standard regarding the quality of tissue sampling if complete excision is not to be performed. Laparotomy or thoracotomy allows large samples to be obtained under direct vision, which can provide improved diagnosis compared with needle biopsies. For example, in the National Wilms' Tumor Study Group-4, open biopsy was more successful than core needle biopsies at identifying anaplasia in children with bilateral Wilms' tumor. Correlation with preoperative imaging allows multiple samples to be obtained if there is inhomogeneity within the tumor, which would raise concerns about sampling error.

The ability to obtain larger specimens is beneficial not only in providing tissue for molecular diagnosis and prognosis, but in providing samples for tissue banking and creation of cell lines. Samples obtained from these biopsies have provided the clinical material that allowed the development of the molecular diagnosis and prognosis techniques referred to earlier in this chapter. Further stratification of risk to allow more precise risk-based therapy remains a major focus for pediatric oncology trials. Finally, specimens that are tissue-banked from these larger specimens may be used for investigational therapies, such as tumor vaccines.

Several important factors should be considered in performing an open biopsy. The initial biopsy should consider the ultimate operative treatment of the tumor. For example, the incision for biopsy of an extremity mass should be oriented parallel to the axis of the limb, and care should be taken to avoid undermining subcutaneous or fascial planes. This allows subsequent wide local excision to be performed with minimal additional resection of tissue because of the biopsy. Likewise, testicular masses should only be biopsied through an inguinal approach, because a scrotal biopsy incision could require the addition of a hemiscrotectomy to the subsequent orchiectomy. Laparotomy for biopsy should be planned to allow subsequent resection through extension of the same incision.

Significant distortion of anatomic relations can occur with large retroperitoneal tumors and attention must be paid to avoid injury to structures, such as ureters or the bile duct, which may be distended over the mass. The most common intra-abdominal tumors in children tend to be vascular, and bleeding from the biopsy site is the most common serious complication. Strategies to reduce perioperative hemorrhage include normalization of coagulation parameters preoperatively and adequate operative exposure. Cauterization of the tumor capsule may help control bleeding, but we have found direct pressure after packing the biopsy site with oxidized cellulose combined with procoagulants, as described later, to be more efficient than generous cautery applied to the base of the biopsy site. If possible, closure of the tumor capsule can help with hemostasis.

Supplements to achieving hemostasis include topical agents and fibrin sealants. Commercially available topical products include gelatin foam pads, microfibrillar collagen, and oxidized cellulose, which is available as fabric and cottonoid. Fibrin sealants are composed of fibrinogen, thrombin, and calcium, which are mixed as they are delivered to the tissue to rapidly form a fibrin clot.

## Conclusion

Prior to performing a biopsy of a potential malignancy, the surgeon should consider the likely possible diagnoses. The biopsy should then be planned so that adequate tissue is obtained and preserved to determine not only diagnosis but also risk stratification. Percutaneous, minimal access surgical, and open surgical techniques each have an appropriate place in the evaluation of potential pediatric malignancies. The use of these techniques in a systematic, stepwise fashion is appropriate in some patients. The selection of the appropriate biopsy technique should be driven by both the specific question to be answered by the biopsy and individual institutional experience and resources. Planning an operative biopsy must account for the anticipated operative approach for definitive resection.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 30

# Wilms' Tumor

Peter F. Ehrlich and Robert C. Shamberger

Renal tumors account for 6.3% of cancer diagnoses for children younger than 15 years of age, with a reported incidence of 7.9 per million. Including adolescents younger than 20 years of age, this drops slightly to 4.4% of cancer diagnoses, with an incidence of 6.2 per million.[1] Renal tumors include Wilms' tumor (WT) (also referred to as nephroblastoma or renal embryoma), renal cell carcinoma (RCC), clear cell sarcoma of the kidney (CCSK), rhabdoid tumor of the kidney (RTK), congenital mesoblastic nephroma, cystic renal tumor, and angiomyolipoma.[2,3] WT is by far the most common, accounting for approximately 91% of all renal tumors in childhood. CCSK and RTK were originally considered subtypes of WT, but are now recognized as separate tumors. RCC comprises 5.9% of renal malignancies in children and adolescents.[1,4]

The treatment strategy for children with renal tumors evolved in conjunction with the definition of these pathologic subtypes. Treatment is based on traditional risk factors, stage and histology, and, more recently, on genetic markers. The goal of "risk-based management" is to maintain excellent outcomes but at the same time spare children with low-risk tumors intensive chemotherapy and radiation, with their long-term side-effects, and to intensify therapy for children with high-risk tumors in an effort to increase their survival. Despite these advances, children with rhabdoid, renal cell carcinoma, and anaplastic tumors still do poorly. This chapter reviews the most frequent renal tumors in children, including their biologic properties, multidisciplinary therapies, and future challenges.

## Wilms' Tumor

WT is the most common primary malignant renal tumor of childhood and comprises 6% of all pediatric tumors.[5,6] Outcomes for children with WT improved dramatically over the last 50 years, with long-term survival in both North American and European trials approaching 85% (Fig. 30-1). Survival rates for many of the low-stage tumors are 95% to 99%.[7,8] Current treatment protocols for children with WT were developed through a series of multidisciplinary cooperative group trials in both North America and Europe by the Children's Oncology Group (COG), formerly the National Wilms' Tumor Study Group (NWTSG), and the Société Internationale d'Oncologie Pédiatrique (SIOP). Their series of well-designed prospective randomized studies provide a large body of evidence-based knowledge to establish the optimal surgical, radiotherapy, and chemotherapy treatments for tumors based on the early studies on stage and histology and, more recently, also on cytogenetic and response-based factors. There are differences between the approaches of these two groups that affect staging and risk classification that are critical to understand when considering outcomes that will be discussed later in the chapter (Table 30-1).

## History

WT is named after Carl Max Wilhelm Wilms, a German pathologist and surgeon. He was one of the first to propose that tumor cells originate during the development of the embryo. He published his findings in 1897 and 1899 in an influential monograph titled "Die Mischgeschwülste der Niere," which described seven children with nephroblastoma as part of a monograph on "mixed tumors."[9,10] Although reports of successful excision of renal tumors in children appeared in the end of the 19th century, his name has been indelibly applied to them. Dr. Thomas Jessop (1837 to 1903), probably performed the first successful nephrectomy at the General Infirmary in Leeds, England, on June 7, 1877, on a 2-year-old child with hematuria and a tumor of the kidney.[11,12]

At the beginning of the 20th century, survival for a child with WT was 5%. Surgery was the first effective treatment for nephroblastoma and continues to be a critical component of successful multimodality therapy. Although surgery at that time was the only option for cure, it carried a significant operative mortality. In 1916, radiation therapy was added by Friedlander.[13] In the late 1930s, Ladd described removing renal tumors in selected children. His technique included a large transverse transabdominal approach with early ligation of the renal vessels and removal of the surrounding Gerota fat and fascia. This modification improved the outcome in children with nonmetastatic nephroblastoma to a 32.2% survival at 3 years, with an operative mortality reduced from 23% to 7%. The basic tenets of this operative procedure described by Ladd are used today, with the exception of early ligation of the renal vessels.[12–15]

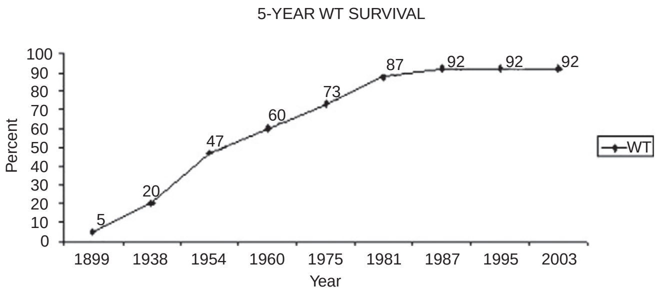


**FIGURE 30-1** This graph shows the improved survival of children with Wilms' tumor (WT) over time.

# Epidemiology

In the United States, there are 500 to 550 cases of WT per year. It is the second most common malignant abdominal tumor in childhood after neuroblastoma. The risk of developing WT in the general population is 1:10,000.[16] The incidence is slightly elevated for American and African blacks compared with whites and is significantly lower in Asians. The mean age at diagnosis is 36 months, with most children presenting between the ages of 12 and 48 months. Tumors tend to occur about 6 months later in girls than in boys. WT is rare at greater than 10 years and at less than 6 months of age. Tumors can be unilateral or bilateral (Figs. 30-2 and 30-3). Bilateral Wilms' tumors (BWT) occur in 4% to 13% of patients.[5,17–19] Children with congenital syndromes associated with WT, such as Beckwith-Wiedemann, have a higher risk of developing BWT.

Congenital anomalies, either isolated or as part of a congenital syndrome, occur in about 10% of children with WT.[20] WAGR syndrome (WT, aniridia, genitourinary malformation, mental retardation) is a rare genetic syndrome associated with a chromosomal defect in 11p13. Children with WAGR syndrome are at a 30% higher risk of developing WT than a normal child. Because of the presence of aniridia, most children with WAGR syndrome are diagnosed at birth. Children with WAGR account for about 0.75% of all children with WT.[21]

Beckwith-Wiedemann syndrome (BWS) is a congenital disorder of growth regulation, affecting 1 in 14,000 children. Children with BWS have visceromegaly, macroglossia, omphalocele, and hyperinsulinemic hypoglycemia at birth. They also have an increased risk of tumor development. The risk is greatest in the first decade of life and thereafter approaches that of the general population. Three large studies of children with BWS reported tumor frequencies of 7.1% (13/183), 7.5% (29/388), and 14% (22/159).[22–25] The most frequently observed tumors in BWS are WT and hepatoblastoma, which comprise 43% and 12% of reported cancers, respectively.[22,26] Denys-Drash syndrome (DDS) (nephropathy, renal failure, male pseudohermaphroditism, and WT) is also associated with an increased risk of WT. Some investigators have recommended prophylactic nephrectomy in children with this syndrome once they develop renal failure.[27,28] Other

**TABLE 30-1**
**Children's Oncology Group (COG) and Société Internationale d'Oncologie Pédiatrique (SIOP) Staging Systems**

**COG Wilms' Tumor Staging**

| *Stage* | *Criteria* |
|---|---|
| I | The tumor is limited to the kidney and has been completely resected.<br>The tumor was not ruptured or biopsied prior to removal.<br>There is no penetration of the renal capsule or involvement of renal sinus vessels. |
| II | The tumor extends beyond the capsule of the kidney but was completely resected with no evidence of tumor at or beyond the margins of resection.<br>There is penetration of the renal capsule or invasion of the renal sinus vessels. |
| III | Gross or microscopic residual tumor remains postoperatively, including inoperable tumor, positive surgical margins, tumor spillage surfaces, regional lymph node metastases, positive peritoneal cytology, or transected tumor thrombus.<br>The tumor was ruptured or biopsied prior to removal. |
| IV | Hematogenous metastases or lymph node metastases outside the abdomen (e.g., lung, liver, bone, brain). |
| V | Bilateral renal involvement is present at diagnosis, and each side may be considered to have a stage. |

**SIOP Staging**

| *Stage* | *Criteria* |
|---|---|
| I | The tumor is limited to the kidney or surrounded with a fibrous pseudocapsule, if outside the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface, and it is completely resected. The tumor may be protruding (bulging) into the pelvic system and dipping into the ureter, but it is not infiltrating the walls. The vessels of the renal sinus are not involved. Intrarenal vessels may be involved. |
| II | The tumor extends beyond the kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into the perirenal fat, but it is completely resected. The tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma, but it is completely resected. The tumor infiltrates adjacent organs or vena cava, but it is completely resected. The tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery. |
| III | There is incomplete excision of the tumor, which extends beyond resection margins (gross or microscopic tumor remains postoperatively). Any positive lymph nodes are involved. Tumor ruptures before or during surgery (irrespective of other criteria for staging). The tumor has penetrated the peritoneal surface. Tumor implants are found on the peritoneal surface. The tumor thrombi present at resection, margins of vessels or ureter are transected or removed piecemeal by surgeon. |
| IV | Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases are outside the abdominopelvic region. |
| V | Bilateral renal tumors present at diagnosis. Each side has to be substaged according to above classifications. |

**FIGURE 30-2** A computed tomography (CT) scan of a unilateral Wilms' tumor.

syndromes associated with WT include hemihypertrophy and Perlman syndrome. Urologic abnormalities, such as hypospadias, cryptorchidism, and nephromegaly, are also associated with WT.

# Molecular Biology and Genetics

A number of important advances in WT development have occurred since the early 1990s. A detailed description is beyond the scope of this chapter. Table 30-2 summarizes some of the key genes and more detailed references are cited.[29–56] There are several candidate genes that are been investigated and evaluated or are being evaluated in the clinical setting. These are described later.

## LOSS OF HETEROZYGOSITY AND DNA PLOIDY

Loss of heterozygosity (LOH) refers to loss of genetic material and allelic uniqueness. LOH was found initially in children with WT on chromosomes 11p (33% of tumors), 16q (20%), and 1p (11%). A major aim of the fifth National Wilms' Tumor Study (NWTS-5) was to determine if tumor-specific LOH for chromosomes 11p, 1p, or 16q was associated with an adverse prognosis for children with favorable-histology (FH) WT, a finding suggested in earlier retrospective studies.[34] Chromosomes 11p, 16q, and 1p were prospectively evaluated. Results demonstrated that outcomes for patients with LOH at 1p and 16q were at least 10% worse than those without LOH (Figs. 30-4 and 30-5). These findings are used as determinants of therapy on the current renal tumor studies of the COG.

A similar but smaller study was reported from the United Kingdom (United Kingdom Children Cancer Study Group Wilms Tumor trials 1 to 3) in which a comparable incidence of LOH for 16q (14%) and 1p (10%) was found, but in this study there was no association between poor outcomes and LOH at 1p.[42] The reasons for the different results are unclear; possible explanations include a smaller sample size of the British study or that the larger doses of doxorubicin used in the U.K. studies served to eliminate part of the adverse impact on prognosis.

Analyses from patients with WT have also identified recurrent deletions and translocations involving the short arm of chromosome 7.[43,48,55] Studies suggest a locus of interest between 7p13 and 7p21, perhaps the *POU6F2* gene at 7p14.[57–59] Clinical correlates of 7p LOH have not been published, and so the exact prognostic role of this possible Wilms' locus, if any, has yet to be determined.

Another aim of NWTS-5 was to determine whether DNA ploidy status is associated with worse outcome in children

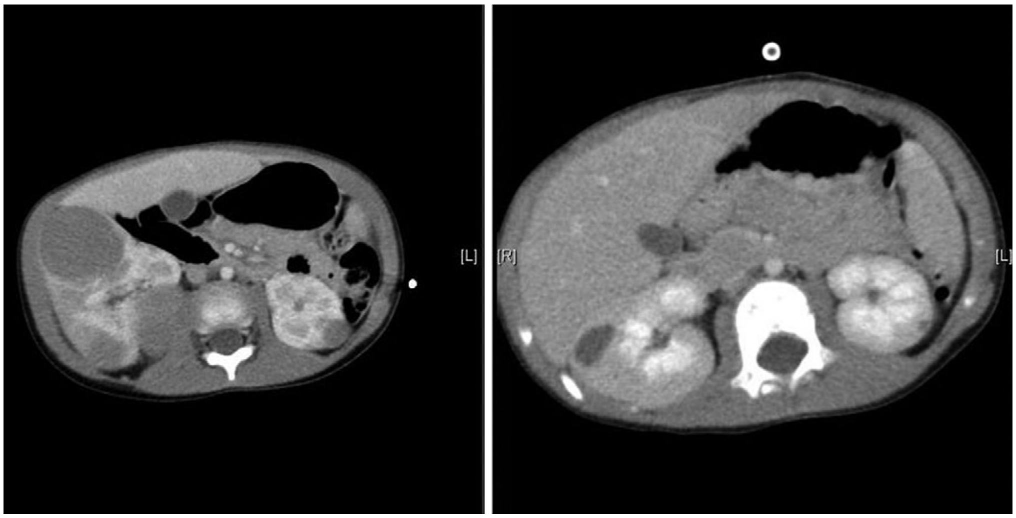


**FIGURE 30-3** Two computed tomography (CT) scans of bilateral Wilms' tumor at presentation and after 6 weeks of chemotherapy.

**TABLE 30-2**
**Summary of Current Genes Being Investigated in Wilms' Tumor**

| *Gene(s)* | *Location* | *Function* | *Clinical Relevance* |
|---|---|---|---|
| *WT1* | 11.13 | Tumor Supressor Functions in normal kidney development | WAGR syndrome Deletions Denys-Drash point mutation |
| *WT2* | 11p15.5 | Several gene loci IGF-2<br>Cell growth and encodes an embryonal growth factor that is highly expressed in fetal kidney and WT<br>Genomic imprinting | BWS syndrome Genomic imprinting |
| Cadherin-associated protein β1 gene[4] | 3p21 | Cellular adhesion protein that also associates with members of the T-cell factor (TCF) family of transcription factors to promote expression of growth-related genes such as c-*MYC* and *CYCLIN D1* | Highly correlated with *WT1* genes |
| *WTX* | Xq11.1 | *WTX* inhibits the Wnt signal transduction to promote post-translational modification and degradation | Unknown |
| Familial Wilms' genes | 17q and 19q13.3-q13.4 | Unknown | Unknown |

BWS, Beckwith-Wiedemann syndrome; IGF, insulin growth factor; WAGR, Wilms' tumor, aniridia, genitourinary malformation, mental retardation.

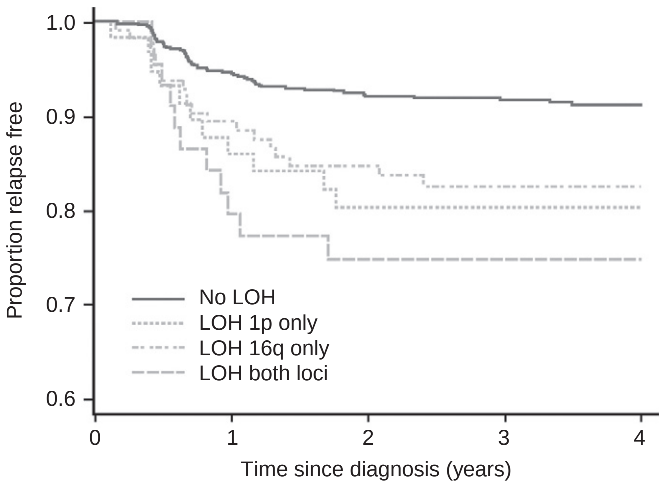


**FIGURE 30-4** Relapse-free survival by joint loss of heterozygosity (LOH) at chromosomes 1p and 16q for stage I/II favorable-histology Wilms' tumor patients. (From Grundy PE, Breslow N, Li S, et al: Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: A report from the National Wilms Tumor Study Group. J Clin Oncol 2005;23:7312-7321.)

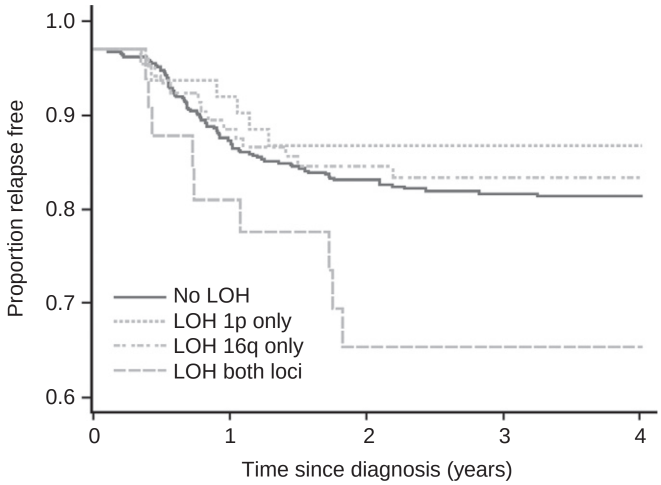


**FIGURE 30-5** Relapse-free survival by joint loss of heterozygosity (LOH) at chromosomes 1p and 16q for stage III/IV favorable-histology Wilms' tumor patients. (From Grundy PE, Breslow N, Li S, et al: Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: A report from the National Wilms Tumor Study Group. J Clin Oncol 2005;23:7312-7321.)

with favorable-histology DNA index as a prognostic marker: DNA index greater than 1.5 was strongly associated with anaplastic histology and predictive of poor outcome. However, DNA content was not predictive of outcome when stratified by stage and histology.[60]

## *TP53* GENE

The *TP53* gene is located on chromosome 17. The Tp53 protein is a negative regulator of cell proliferation and a positive regulator of apoptosis in response to DNA damaging agents. *TP53* is the most common mutated gene associated with human cancer. Li-Fraumeni syndrome is a multicancer predisposition syndrome that has constitutional *TP53* mutations.[61] However, WT rarely develops in Li-Fraumeni syndrome, and the majority of WT develop in the presence of wild-type *TP53*.[62] *TP53* mutations in WT are almost exclusively found in tumors with anaplastic histology. Seventy-five percent of anaplastic WT have *TP53* mutations. In the current COG study, one of the aims of the high-risk protocol is to study the incidence and association of *TP53* mutations.

# Clinical Presentation

Most children with WT present with an asymptomatic abdominal mass, often discovered by either a parent or pediatrician. Nonpalpable tumors are typically discovered by ultrasonography during evaluation for abdominal pain. Gross hematuria has been reported in 18.2% of patients and microscopic hematuria in 24.4%. Ten percent of children with WT have coagulopathy, and 20% to 25% present with hypertension because of activation of the renin-angiotensin system.[63] Fever, anorexia, and weight loss occur in 10%. Extension of tumor thrombus into the renal vein can obstruct the spermatic vein and result in a left varicocele and, in rare cases, tumor

extension into the atrium may produce cardiac malfunction. Tumor rupture and hemorrhage are also infrequent events that can present as an acute abdomen.

The differential diagnosis for an abdominal mass includes neuroblastoma, hepatoblastoma, rhabdomyosarcoma, and lymphoma. Neuroblastoma is the most common solid abdominal tumor in children. One clinical observation to help distinguish between WT and neuroblastoma is that children with neuroblastoma are often ill because of extensive metastatic disease at presentation. In contrast, children with WT are generally healthy toddlers with a palpable abdominal mass.

## Diagnosis

After an abdominal mass is identified, radiographic imaging is performed to determine the anatomic location and extent of the mass. Ultrasonography (US) is a good screening examination of a mass to determine its site of origin and to assess for possible intravascular or ureteral extension. About 4% of WT present with inferior vena cava (IVC) or atrial involvement and 11% with renal vein involvement.[5,6] Embolization of a caval thrombus to the pulmonary artery can be lethal, and the presence of a thrombus must be identified preoperatively to prevent this occurrence. US is a sensitive technique to identify vascular extension.[64,65] A computed tomography (CT) scan of the abdomen will confirm the renal origin of the mass and determine whether there are bilateral tumors. Early generations of CT scans missed 7% to 10% of bilateral lesions. Hence, contralateral exploration of the kidney was recommended in NWTSG protocols to assess for bilateral lesions.[66] A recent review of children with bilateral WT, however, demonstrated that only 0.25% of bilateral tumors were missed with modern helical CT scans, all of which were small.[67] Based on these results, bilateral exploration is not recommended in current protocols from the COG. Although magnetic resonance imaging (MRI) avoids radiation exposure, it has not been shown to be superior to CT scanning in standard assessments. MRI is currently being evaluated as a method to help distinguish nephrogenic rests from WT and may be the preferred method to follow children with bilateral WT after resection.

The common sites of metastatic spread are the lungs and the liver. Therefore, in addition to abdominal imaging, pulmonary imaging must be performed. In NWTS-4 and NWTS-5, 13% of patients (575 of 4,006) with unilateral favorable-histology tumors presented with pulmonary disease. Initially this was routinely evaluated based upon a chest radiograph. In current protocols, it is based upon CT scans.

$^{18}$F-fluorodeoxyglucose positron emission tomography (FDG PET) has not been fully delineated in pediatric cancers.[65] It is recognized that FDG PET has an established role in Hodgkin lymphoma and increasingly in sarcomas in children, but its role in WT is unclear.[68,69]

## Screening

Screening is reserved for children at risk for developing WT. This includes children with genetic syndromes such as BWS, idiopathic hemihypertrophy (IHH), WAGR, DDS, and Perlman syndrome. Renal ultrasound examination is the preferred modality to screen for WT. It is widely available, noninvasive, does not involve radiation exposure, and generally does not require use of sedation. It is recommended that children be scanned every 3 to 4 months. Debaun and colleagues assessed the cost effectiveness of screening for WT and hepatoblastoma in children with Beckwith-Wiedemann syndrome (BWS).[70] In this analysis, screening a child with BWS from birth until 4 years of age resulted in a cost per life-year saved of $9,642, while continuing until 7 years of age resulted in a cost per life-year saved of $14,740, although it is not truly established that the rate of cure or event-free survival (EFS) is higher based on this early monitoring protocol. Three retrospective studies have evaluated screening in children at risk for WT. One study from the United Kingdom of 41 children with WT and aniridia, BWS, or IHH showed no difference in outcome or stage distribution between screened and unscreened populations.[71] In a second study of BWS/IHH, Choyke and colleagues demonstrated that evaluation by US every 3 months until age 8 years in 12 children with BWS lowered the proportion of patients with late-stage tumors to 0%, which was significantly reduced compared with the 42% incidence of late-stage tumors in 59 unscreened patients with BWS/IHH.[72] A third study analyzed the impact of surveillance in children with aniridia, BWS, and IHH who had developed WT.[73] There was a higher proportion of stage I tumors identified in children who underwent routine screening than in those who did not. Although ultrasonography is easy, false-positive results have been reported and have led to unnecessary investigations and surgery in patients who had benign lesions, such as cysts, nephrogenic rests, or foci of renal dysplasia, supporting the use of either MRI or CT to further define the lesions before surgical intervention.[72–74] The U.K. Wilms' Tumor Surveillance Working Group suggests that surveillance should be offered to children who are at a greater than 5% risk of WT.[75]

Children with Perlman syndrome are at a significantly increased risk of WT; therefore surveillance specifically for WT is warranted. Based on a review by Tan and colleagues, there is currently insufficient evidence to justify tumor surveillance in Sotos, Weaver, Proteus, and Bannayan-Riley Ruvalcaba syndromes or the syndrome of macrocephaly-cutis marmorata telangiectatica congenita. Of interest, children with Klippel-Trenaunay syndrome (KTS) had been considered to be at increased risk for developing WT. In a 2004 study by Fishman and colleagues, the risk of developing WT in children was assessed using the NWTSG database.[76] The risk of WT in children with KTS was no different than in the general population, and thus routine ultrasonography surveillance is not recommended.

## Pathology

Tumor histology is a major determinant of therapeutic stratification for children with WT. The diagnostic classification of pediatric renal tumors has benefited from central review of tumors from patients treated in the cooperative group trials.[77] This success has enabled the introduction of disease-specific and risk-based therapy. For example, clear cell sarcoma of the kidney (CCSK) and malignant rhabdoid tumor (MRT) were initially considered to be variants of WT and were

managed with chemotherapeutic agents for WT, but they are now considered distinct entities with separate therapies.

WT are embryonal tumors containing components seen in normal developing kidneys. The classic WT consists of three elements: blastemal, stromal, and epithelial tubules. Tumors contain various proportions of each of these elements. Triphasic patterns containing blastemal, stromal, and epithelial cell types are the most characteristic, but biphasic and monophasic lesions occur.[78] Less frequently, abnormal mucinous or squamous epithelium, skeletal muscle, cartilage, osteoid, or fat are found in WT.[79]

When the tumors are monophasic, they can be very invasive and difficult to distinguish from other childhood tumors, such as primitive neuroectodermal tumor, neuroblastoma, and lymphoma. Monophasic undifferentiated stromal WT look like sarcomas, such as clear cell sarcoma of the kidney, congenital mesoblastic nephroma, or synovial sarcoma. Other WT may have differing amounts of skeletal-muscle differentiation, from well-differentiated (rhabdomyomatous) to poorly differentiated (rhabdomyoblastic) skeletal muscle. A WT that is entirely tubular and papillary can be difficult to distinguish from papillary renal cell carcinoma.[79]

WT are divided into two groups: those with “favorable” histology and those with “unfavorable” histology. Favorable-histology tumors comprise 90% of the unilateral and bilateral tumors.

Anaplastic histology is considered unfavorable histology along with the CCSK and rhabdoid tumors. Unfavorable histology is found in about 10% of childhood renal tumors. It is rare in the first 2 years of life (2%), then increases in patients older than 5 years to 13%. It is also more frequent in nonwhite (African-American and Latino populations) than in white patients.[80] In a report by Bonadio and colleagues, 30.1% of anaplastic tumors occurred in the nonwhite population. In a multivariate analysis, older age, being nonwhite, and lymph node positivity were the significant predictors of anaplastic WT histology. Finally, anaplasia has been strongly associated with the presence of *TP53* mutations.[81]

Different treatment protocols for children with anaplastic versus favorable-histology tumors were first used in NWTS-3. Anaplasia is defined by multipolar polyploid mitotic figures, marked nuclear enlargement (giant nuclei with diameters at least 3 times those of adjacent cells), and hyperchromasia.[82] Focal anaplasia is defined as the presence of one or a few sharply localized regions of anaplasia within a primary tumor, the majority of which contain no nuclear atypia. The cells must not be present in any sites outside of the kidney. Tumors with diffuse anaplasia must have at least one of the following four criteria. Anaplastic cells outside of the kidney, presence of anaplasia in a random kidney biopsy, anaplasia in more than one region of the kidney, and anaplasia in one region, with extreme nuclear pleomorphism in another site. The difference between focal and diffuse anaplasia has been demonstrated to have prognostic significance.[83] Anaplasia is a marker of resistance to therapy, not of tumor aggressiveness.[78,82,84] Although associations between histologic features and prognosis or responsiveness to therapy have been suggested, with the exception of anaplasia (unfavorable histology), none of these features have reached statistical significance and therefore have not been used to determine therapy.[78,84]

The classic WT is triphasic, but some tumors can have dominant blastemal, stromal, and epithelial elements. Stromal dominant tumors are associated with intralobar nephrogenic rests, and epithelial dominant tumors have been associated with perilobar nephrogenic rests.

## PRETREATED TUMORS AND PATHOLOGY

Tumors that have been treated with chemotherapy before resection differ in their histopathologic findings from tumors resected primarily. In the SIOP-9 study, the most common subtype of tumors resected without neoadjuvant chemotherapy was triphasic mixed histology (45.1%), followed by blastemal (39.4%) and epithelial dominant (15.5%), whereas in tumors that received preoperative chemotherapy, the most common histology was regressive (37.6%), followed by mixed (29.4%), stromal (14%), blastemal (9.3%), and epithelial predominant (3.1%); 6.6% of tumors were completely necrotic.[85,86] The SIOP risk classification uses these histologic findings as prognostic indicators to determine further therapies (Table 30-3). In addition, chemotherapy may produce tumor differentiation.[82,86,87] Anderson evaluated the histologic changes in tumors from 15 BWT patients that did not decrease in size radiographically following chemotherapy.[88] One had complete necrosis, 4 had rhabdomyomatous differentiation, and 10 had mature stromal differentiation. Despite their absence of regression in size, these patients had favorable outcomes, especially if there was rhabdomyomatous differentiation.

In SIOP-9, 10% of patients had postchemotherapy tumors that were completely necrotic. These patients had excellent outcomes. The SIOP-9 study also demonstrated that preoperative chemotherapy extensively ablates the blastemal component of WT.[87,89,90] The frequency of tumors with dominant blastemal components was markedly reduced (to 7.7%) by preoperative treatment compared with the no-treatment group (36%). Furthermore, this response is clearly an important prognostic factor. If predominant blastemal elements persist after initial therapy, the tumors were found to be highly aggressive. In SIOP-9, 5 of 16 (31%) of the postchemotherapy blastemal predominant tumors recurred, compared with none of the tumors that were predominantly epithelial or stromal after chemotherapy. Prior SIOP studies have also shown the prognosis for the purely blastemal group (after preoperative chemotherapy) to be inferior to that for the epithelial and stromal dominant tumors.

**TABLE 30-3**

**Revised International Société Internationale d'Oncologie Pédiatrique Working Classification of Renal Tumors of Childhood (2001)**

| *Stage* | *Risk* | *Histology* |
|---|---|---|
| I | Low | Mesoblastic nephroma<br>Cystic partially differentiated nephroblastoma |
| II | Intermediate | Nephroblastoma epithelial type<br>Nephroblastoma stromal type<br>Nephroblastoma mixed type<br>Nephroblastoma regressive type<br>Nephroblastoma focal anaplasia type |
| III | High | Nephroblastoma blastemal type<br>Nephroblastoma diffuse anaplasia type<br>Clear cell sarcoma of the kidney<br>Rhabdoid tumor of the kidney |

In the SIOP studies, postchemotherapy risk stratification and stage are used to determine additional therapy after resection. This categorization is different than the risk stratification used for tumors resected primarily in North America. *Low-risk* tumors are those that are completely necrotic following preoperative chemotherapy. *Intermediate-risk* tumors include all histologies other than completely necrotic, rhabdoid, anaplastic, or blastemal (less than 66%) dominant. *High-risk* tumors are those with diffuse anaplasia, rhabdoid, and blastemal dominance (greater than 66%) after chemotherapy (see Table 30-3).

### NEPHROGENIC RESTS AND NEPHROBLASTOMATOSIS

Nephrogenesis in the normal kidney is usually complete by 34 to 36 weeks' gestation. Nephrogenic rests (NR) are "areas of metanephric (embryonal tissue) persisting after the 36th week of life." The presence of multiple or diffuse nephrogenic rests is termed nephroblastomatosis.[91] Diffuse hyperplastic perilobar nephrogenic rests (DHPLNR) represent a unique category of nephroblastomatosis in which the rests form a thick rind around the kidney. The rests that cause the greatest diagnostic challenge are those that are actively proliferating or hyperplastic, and can be mistaken for WT. Hyperplastic NR can produce masses as large as conventional WT. Complicating things further is the fact that neoplastic induction of NR can occur. The diagnosis of DHPLNR is often made based on radiographs (Fig. 30-6). Histologically, a rest consists of predominantly small clusters of blastemal cells, but tubules and stromal components can be present. NRs are classified by their growth phase and location: perilobar or intralobar. Perilobar nephrogenic rests are limited to the periphery (subcapsular) of the lobes, while intralobar rests occur within the renal lobes and have an irregular margin. The growth phase of a rest is divided into (1) incipient or dormant nephrogenic rests that show few well-formed tubular structures but no evidence of proliferation and no mitoses, (2) hyperplastic nephrogenic rests that are composed of epithelial elements with nodular expansive growth, and (3) sclerosing rests that consist of stromal and epithelial elements with few blastemal nephrogenic elements (Fig. 30-7).

**FIGURE 30-6** Computed tomography (CT) scans showing diffuse hyperplastic perilobar nephrogenic rests.

NRs are considered precursor lesions to WT; however, only a small number develop clonal transformation into a WT. A child with a WT and NRs in the resected specimen is at increased risk of developing a metachronous tumor in the other kidney.[92] For a child less than 1 year of age, this risk is very significant, and these children need to be followed very carefully with sequential US examinations. A patient who has a unilateral tumor and a presumed nephrogenic rest is thought to be at increased risk of developing a metachronous tumor, but data to support that assumption does not exist. The prevalence of NRs in unilateral WT has been reported to be 28% to 41% in unilateral WT and close to 100% in bilateral WT.[93] Pathologic distinction between NR and WT can be very difficult. To make the diagnosis, it is critical to examine the juncture between the lesion and the surrounding renal parenchyma to distinguish between the two entities. Most hyperplastic NRs lack a pseudocapsule at the periphery, while most WT will have this feature. An incisional biopsy is of limited value, because it is uncommon for it to contain the interface between the lesion and the adjacent kidney. This is particularly true for patients with DHPLNR. In a study by Perlman and colleagues, pathology alone was insufficient to establish the diagnosis of DHPLNR in 21 of 33 cases that underwent biopsy at the time of initial diagnosis.[94] In addition, because rests are found within and adjacent to WT, a biopsy may result in the inadvertent pathologic diagnosis of WT. Alternatively, a small WT may be present within a large field of nephroblastomatosis, obscuring it for biopsy. Taken together, in these situations where a renal mass could be a tumor or a rest where a biopsy is performed, Perlman and colleagues suggest using the term "nephrogenic process, consistent with a WT or a nephrogenic rest."

## Staging

The COG/NWTS and SIOP staging systems are fundamentally different. In COG/NWTS protocols, initial surgical resection is recommended in most cases. Thus for unilateral tumors, the pathology of the tumor is established prior to administration of chemotherapy or radiotherapy. In contrast, SIOP protocols generally recommend chemotherapy followed by nephrectomy, and surgicopathologic staging is assessed at that time.

The COG/NWTS staging system has evolved as features associated with prognosis have been defined. A very important concept for this staging system is that there is a local stage and a disease stage. Local staging refers to the abdominal disease

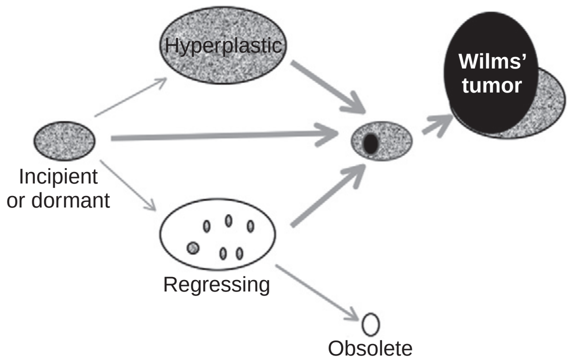


**FIGURE 30-7** Cartoon of growth phases and classification of nephrogenic rests.

only, whereas disease stage considers both the local and distant hematogenous metastatic disease. Both factors determine therapy; the use of local radiation therapy to the tumor bed is based on the local stage, and the use of additional chemotherapy is based on both stage III local disease or distant metastasis.[95] The current COG and SIOP staging systems are shown in Table 30-1.

# Treatment

The successful treatment for children with WT has been the direct result of prior multidisciplinary studies from cooperative group trials, including the NWTSG, SIOP, and the United Kingdom Children's Cancer Study Group (UKCCSG), that have defined the key components to therapy. These trials have identified several prognostic factors used for risk stratification in current protocols, including biologic markers. This section will review these prognostic factors, operative therapy, chemotherapy, and radiotherapy (with a focus on COG studies).

## PROGNOSTIC FACTORS

The current prognostic factors used in COG trials are histology, stage, age, tumor weight, response to therapy, and loss of heterozygosity at 1p and 16q. The two most important continue to be the histology and the stage of the tumor.[7,8,96]

*Histology:* The details and prognostic significance of tumor pathology have been previously discussed in the Pathology section.

*Stage:* The tumor stage is determined by the results of the imaging studies and both the surgical and pathologic findings at nephrectomy (see Table 30-1).

*Rapid response:* This is a prognostic category being evaluated in patients who have stage IV disease that is based on lung metastasis alone. The goal in these patients is to avoid lung radiation. Response to therapy is also being assessed in bilateral disease.

*Loss of heterozygosity:* LOH (described previously) at both 1p and 16q are now used as determinants of therapy on the current COG renal tumor studies.[96]

## OPERATIVE THERAPY

Surgical therapy is a primary component in the multidisciplinary treatment of WT or other neoplastic renal lesions. Irrespective of whether surgery is performed as a primary therapy or in a delayed fashion after chemotherapy, there are a number of fundamental tasks that are required of the surgeon. These are (1) safe resection of the tumor, (2) accurate staging of the tumor, (3) avoidance of complications that will "upstage the tumor" (rupture or unnecessary biopsy), and (4) accurate documentation of operative findings and details of the procedure in the operative note. Intraoperative events that negatively affect patient survival include tumor spill, failure to biopsy lymph nodes, incomplete tumor removal, failure to assess for extrarenal tumor extension and surgical complications.[97–99]

### Technical Concerns: Unilateral Tumors

Ladd and Gross established the basic principles for resection of a presumed malignant tumor of the kidney, including wide abdominal exposure, resection of the surrounding Gerota fat and fascia to remove potential sites of lymphatic spread and early control of the renal vessels.[12,100] Lymph node sampling is now established as crucial for accurate staging.[101] Understaging the extent of the tumor can increase a child's risk of relapse, and overstaging will result in increasing the intensity of chemotherapy or radiation. A transverse transabdominal or thoracoabdominal incision provide the best exposure and are associated with fewer complications than a flank incision.[98,102–104] The thoracoabdominal incision is best for large tumors, to optimize visualization of the plane between the tumor and the diaphragm to avoid rupture from excessive traction on the tumor. Intraoperative events that negatively affect patient survival include tumor spill and inadequate staging.[97–99]

Early examination for involvement of the liver, renal vein, or IVC or peritoneal surfaces is important, as is identification of preoperative rupture of the tumor. Routine exploration of the contralateral kidney for bilateral disease was mandated in NWTS-1 to NWTS-5. In 1995, Ritchey and colleagues reviewed the accuracy of imaging in assessing bilateral disease from NWTS-4 (1986 to 1994). He found that bilateral tumors were missed in 7% of children by using the preoperative imaging studies. Thus, for NWTS-5, routine contralateral exploration was mandated. In 2005, Ritchey and colleagues did a follow-up study to look at what happened in those patients whose lesions were missed by imaging on NWTS-4. The size of the missed lesions was less than 1 cm in six patients and 1 to 2 cm in three patients. Management of missed lesions included enucleation in two cases, biopsy in six, and no surgery in one. No patient underwent irradiation. The postoperative chemotherapy regimen consisted of doxorubicin, dactinomycin, and vincristine in six children, and dactinomycin and vincristine in three. Median follow-up was 9 years. There were no recurrences in any kidney with a missed lesion. All nine patients were alive and disease free at last follow-up. The results of this study in conjunction with the advances in imaging quality means that routine contralateral exploration in the presence of a negative CT is not mandated.[66,67] If a clear contralateral lesion is present, then the child should be treated on the bilateral protocol. If studies suggest a possible contralateral lesion on the kidney, the contralateral kidney should be formally explored prior to nephrectomy.

Ladd and Gross stressed the need for early vascular ligation prior to the development of chemotherapy. This is no longer practiced because of the risk of injury to the vessels, particularly to the superior mesenteric artery in large left-sided tumors. The tumor should be mobilized by opening the lateral peritoneal reflection and reflecting the colon and its mesentery off the anterior surface of the kidney. For right-sided tumors, a Kocher procedure is also helpful. When ligating the renal pedicle, it is best to ligate the renal artery first if it can be safely identified, to avoid increasing the venous pressure within the tumor, which can result in rupture of the capsule. Vascular control in most cases is best completed after the tumor is fully mobilized.[99,105,106] The renal vein should be palpated prior to ligation to be certain there is no venous extension of the tumor. The adrenal gland may be left in place if it is not abutting the tumor; but, if the mass arises in the upper pole of the kidney, the adrenal gland should be removed with the neoplasm. The ureter is ligated and divided as low as possible.[107] The tumor and kidney should be handled gently throughout the operation

to avoid rupture, which will increase the intensity of therapy and risk for local recurrence.[99,105,106]

Pathologic assessment of hilar and regional lymph nodes is critical to accurately stage a child with a renal tumor.[97,99] Routine lymph node sampling from the renal hilum, the pericaval, or para-aortic areas must be performed. Simply looking at the lymph nodes to determine whether they are positive is highly inaccurate.[108] Unfortunately, failure to sample lymph nodes (whether dealing with a unilateral or bilateral tumor) is the major technical error noted in WT surgery.[97] Furthermore, studies have demonstrated a higher risk of recurrence in children who did not have their lymph node status documented at the time of nephrectomy.[12,99,109]

WTs tend to displace rather than invade the surrounding vessels. This feature of WT has two implications. First, the surgeon must be certain of the identity of the vessels to ligate.[102] Second, most organs can be dissected away from the tumor, because actual invasion is rare. When actual invasion is identified, radical en bloc resection (e.g., partial hepatectomy or colectomy) is not warranted as primary therapy.[98,99] WTs are very chemosensitive, and, in these situations, prior adjuvant therapy will result in a lower rate of complications than a multiorgan resection.[98] A small section of diaphragm, psoas muscle, or tip of the pancreas, however, is acceptable.

Recent reports have suggested that hepatic metastasis should be resected at presentation.[110,111] To address this question, the COG renal tumor study group reviewed outcomes for patients with different sites of metastasis and found no significant difference in outcome for patients with liver versus lung metastasis. Primary resection of liver metastases prior to adjuvant therapy is not currently recommended.[112]

### Spill

"Spill" refers to a break in the tumor capsule during operative removal, whether accidental, unavoidable, or by design. Studies have shown a higher risk of recurrence in patients who had tumor spill or rupture, irrespective of the cause or extent of the soiling.[97–99] Spill is also considered to have occurred if the renal vein or ureter are transected where they contain tumor. In COG protocols, spill is also considered to have occurred if a preoperative or intraoperative needle/open biopsy was performed. This is not the case for those patients treated following Société Internationale d'Oncologie Pédiatrique protocols: Fine-needle or Tru-Cut needle biopsy is allowed in this study; however, incisional biopsies are considered as ruptures, automatically stage III, and are contraindicated. "Rupture" refers to either the spontaneous or post-traumatic rupture of the tumor preoperatively, with the result that tumor cells are disseminated throughout the peritoneal or retroperitoneal space.[101] Bloody peritoneal fluid may be a sign of rupture, and a thorough examination of the tumor surface is mandated. Rupture is also considered to have occurred if the tumor penetrates the kidney capsule, with open neoplastic tissue surface being in free communication with the peritoneal cavity. If found, all of these situations make the child stage III and must be carefully documented in the operative note.

### Unresectable Tumors

There are clinical situations where it is agreed that primary nephrectomy is contraindicated. These are when (1) there is extension of tumor thrombus above the level of the hepatic veins; (2) the tumor involves contiguous structures, whereby the only means of removing the kidney tumor requires removal of the other structures (e.g., spleen, pancreas, and colon but excluding the adrenal gland); (3) there are bilateral tumors; (4) the tumor is in a solitary kidney; or (5) there is pulmonary compromise resulting from extensive pulmonary metastases. Studies conducted by the cooperative groups have shown that pretreatment with chemotherapy almost always reduces the bulk of the tumor.[113–116] This makes tumor removal easier and may reduce the incidence of surgical complications.[117] Preoperative chemotherapy does not result in improved survival rates, and it may result in the loss of staging information and changes the histology of the tumor as noted previously.[118,119]

## SPECIAL CONSIDERATIONS

### Management of Tumor Extension in the Renal Vein, Inferior Vena Cava, and Atrium

WT patients may present with tumor extension through the renal vein to the IVC and even up to the right atrium. This is found in 4% to 11% of children. Surgical treatment is dependent on the extent of vascular invasion. Extension is usually asymptomatic, and many are detected preoperatively by US, CT, and/or MRI scans. However, those that extend just into the renal vein may only be detected at operation because of compression and distortion of the veins by the tumor, reinforcing the need to palpate the renal vein and IVC at the start of nephrectomy before any mobilization of the kidney that might dislodge the thrombus.[106,120,121] As noted previously, a primary resection when tumor thrombus extends into the inferior vena cava at the level of the liver or higher is discouraged. COG protocols recommend that these patients be managed initially with preoperative chemotherapy. This approach will often achieve significant shrinkage and regression of the intravascular thrombus, facilitating subsequent surgical removal.[106,122] The severity and number of operative complications are reduced with preoperative chemotherapy for those with vascular extension above the hepatic veins. Alternatively, if the tumor extends only into the renal vein or renal vein and IVC below the level of the liver, the tumor and thrombus can, in most cases, be removed en bloc with the kidney.

Control of renal veins and cava above and below the tumor with vessel loops is necessary, using standard vascular surgery techniques. The tumor should not be transected, if possible, because this will result in spill and upstaging of the patient. In some cases, the tumor may be adherent to the vessel wall. A similar technique used for removing plaque for a carotid endarterectomy is helpful to lift the tumor off the vein wall. It must be stated in the operative report if the intravascular tumor extension was removed en bloc or if tumor was transected, as well as if the tumor thrombus is removed completely and if there is evidence of either adherence to or invasion of the vein wall. If, after preoperative chemotherapy, the tumor still extends above the hepatic veins, cardiopulmonary bypass is generally needed to remove the vascular extension of the tumor.

### Management of Tumor Extension in the Ureter

Extension of WT into the ureter is a rare event.[107] In NWTS-5, the incidence of ureteral extension was 2%. Preoperative imaging detected ureteral extension in only 30% of these

patients; the rest were discovered at operation. Clinical presentations included gross hematuria, passage of tissue per urethra, hydronephrosis, and a urethral mass. The diagnosis should be suspected in these patients, and cystoscopy with retrograde ureterogram may aid in preoperative diagnosis. If extension of tumor into the ureter is detected or suspected, the ureter should be resected with clear margins.

### Horseshoe Kidney, Single Kidney, and Nonfunctioning Kidney

A WT in a horseshoe kidney presents unique challenges. Children with a tumor in a horseshoe kidney are treated as unilateral tumors, NOT as bilateral tumors. Children with horseshoe kidneys and WT must be carefully imaged prior to any surgery.[123] The blood supply to horseshoe kidneys is quite variable and must be carefully imaged prior to surgery.[123] At the time of operation, the blood supply to the kidney as well as the location of the ureters must be identified and isolated. Exposure and mobilization of the kidney on the side of the tumor is carried out as in unilateral resection. The side of the kidney containing the tumor, the isthmus, and the ipsilateral ureter are resected. As with other unilateral procedures, the lymph nodes are sampled for staging purposes. Children with a single kidney, or a situation where a tumor occurs in one kidney but the second kidney is nonfunctioning, should be managed using a renal-sparing approach, with preoperative chemotherapy to facilitate surgery and preserve more renal tissue.

### Patients with Wilms' Tumor Treated Only with Surgery

NWTS-5 evaluated a subset of very-low-risk patients with favorable-histology tumors who might be treated without chemotherapy. The criteria for this arm of the study was stage I FH in patients who had lymph nodes biopsied, had a specimen weight of less than 550 g, and who were less than 2 years of age. Seventy-five patients were enrolled before closure of the study, and 8 developed recurrent disease (lung involvement in 5 and the operative bed in 3). Three other patients developed metachronous contralateral WT. Stringent stopping rules for the study were designed to ensure closure of this arm of the study if the 2-year EFS was 90% or less based on the expectation that approximately 50% of the surgery-only children would be salvaged after recurrence, thus attaining the 95% predicted survival of these children treated with vincristine and dactinomycin (EE-4A). This limit was exceeded on June 14th, 1998, and this arm of the study was closed when the 2-year disease-free survival estimate reached 86.5%.[124] Subsequent patients were treated with EE-4A. A recent long-term follow-up study of the surgery-only cohort and the EE-4A group, with a median follow-up of 8.2 years, reported the estimated 5-year EFS for surgery only was 84% (95% confidence interval [CI]: 73% to 91%); for the EE-4A patients it was 97% (95% CI: 92% to 99%, $P = 0.002$). One death was observed in each treatment group. The estimated 5-year overall survival (OS) was 98% (95% CI: 87% to 99%) for surgery only and 99% (95% CI: 94% to 99%) for EE-4A ($P = 0.70$).[125] The surgery-only EFS was less than for EE-4A, consistent with the earlier report. The salvage rate for the surgery-only cohort, however, exceeded that seen with children who had received two-drug chemotherapy, which had been predicted to be 50%. Thus 85% of the infants avoided any chemotherapy, while those who did receive it for relapse were treated with three agents (DD-4A). A current study in the COG is assessing this cohort again and is evaluating biologic markers for this very-low-risk group.[126]

### Neonatal Tumors

Neoplastic renal lesions in the neonate are rare and include benign and malignant tumors.[127,128] Acute and long-term toxicity from therapy is a considerable concern in infants. The distribution of tumors is age dependent. In the perinatal period, congenital mesoblastic nephroma (CMN) is the leader, accounting for greater than 50% of the renal tumors, followed in rank by WT, RTK, and CCSK.[127–131] WT, CMN, and rhabdoid tumor of the kidney (RTK) are the principal neoplasms of the kidney occurring after 3 months, when CMN accounts for less than 10%. An international retrospective study of 750 neonatal renal tumors in children less than 7 months of age found that 63.4% were WT.[127] Eighty-two percent of these were stage I/II. In contrast, RTK presented with advanced disease (53% stage III/IV). RTK accounted for nine of eleven tumors presenting with metastases. Outcomes paralleled older children, with excellent results for neonates with WT (5-year OS of 93.4%) and poor for RTK (5-year OS of 16.4%).[127]

### Acquired von Willebrand Disease in Children with Wilms' Tumor

von Willebrand disease (vWD) is an inherited coagulation disorder characterized by mucocutaneous bleeding, a prolonged bleeding time (BT), and a reduced level of functional von Willebrand factor (vWF). Secondary laboratory abnormalities include a decreased level of procoagulant factor VIII (FVIII) and activity of ristocetin cofactor (FVIII:RCoF) activity.[132] Acquired vWD has been reported in patients with WT and other malignancies and has important implications for the surgeon.[133,134] A single prospective study of 50 WT patients found the incidence of acquired vWD was 8%.[134] However, the true incidence and prevalence in WT is unknown, because a full bleeding history and factor levels are rarely obtained. Until recently, the literature has suggested that, when identified, the bleeding has been clinically insignificant, characterized by epistaxis, hematuria, gingival bleeding, and easy bruising.[135] Recent reports of profuse intraoperative bleeding that only stopped after ligation of the renal vessels have contradicted this assumption.[136,137] Despite normalization of FVIII and vWF activity and antigen levels prior to surgery, during surgery profuse intraoperative bleeding occurred, requiring multiple transfusions with FVIII, FFP, cryoprecipitate, platelets, and packed red blood cells.[136] Immediately after ligation of the renal vessels, all abnormal bleeding stopped, with normalization of FVIII and vWF antigen activity.

The mechanism of acquired vWD in WT is unknown. Tumor adsorption of vWF has been reported in other malignancies; however, this was not seen in the WT cases where intraoperative bleeding was significant. vWF inhibitors, rapid abnormal clearance of vWF, and coagulopathy related to elevated levels of hyaluronic acid and consequent blood hyperviscosity have also been proposed.[138,139] Why some cases had intraoperative bleeding and others do not is also not known. Baxter[136] suggests that these tumors may be more hypervascular, but this is not proven. The risk of intraoperative bleeding highlights the importance of recognizing acquired vWD in children with WT. In all cases, the initial sign was a prolonged prothrombin time (PT) and partial thromboplastin

time (PTT). When found, this should mandate acquiring a further history for bleeding and factor analysis. Although correction of factor levels prior to surgery appears to help in most cases, it does not guarantee that significant intraoperative bleeding will not occur. In the case reports of profound intraoperative bleeding, it was observed that, once the renal vessels were ligated, the bleeding ceased. Thus preoperative embolization should be considered as a management strategy. Alternatively, preoperative chemotherapy may also be a safe option.

## BILATERAL WILMS' TUMOR

Bilateral Wilms' tumors BWT occur in 4% to 13% of patients (see Fig. 30-3).[5,17–19] Unfortunately, outcomes for children with bilateral tumors have not been as good as those of children with unilateral tumors. In NWTS-5, the 4-year OS was 80.8% for a child with favorable histology and 43.8% for a child with anaplastic histology.[84] In 1998, the United Kingdom Children's Cancer Study Group published their experience with BWT patients treated between 1980 and 1995.[140] In 57 patients, conservative surgical treatment with initial biopsy was followed by chemotherapy and delayed tumor resection, while 13 underwent initial surgical resection followed by chemotherapy. Overall survival was 69%, with similar survival in the patients with initial surgery versus neoadjuvant chemotherapy. BWT with an unfavorable histology was associated with a poor prognosis, with only one of seven patients surviving. Renal failure was seen in 6% of the survivors who were conservatively treated and in 20% of the survivors who underwent initial resection. In 2004, Weirich reported BWT outcomes from SIOP-9. Twenty-eight patients were evaluated. Although therapy was individualized, all 28 patients with BWT were treated with preoperative therapy. Overall survival at 5 years was 85.1% (95% CI: 71.6% to 98.6%; four deaths), and relapse-free survival was 80.5% (95% CI: 65.2% to 95.8%; five relapses).[141]

Renal failure is another concern of children with BWT (Figs. 30-8 and 30-9). The etiology of renal failure in WT patients is multifactorial.[142–144] Factors that contribute to renal failure include intrinsic progressive renal disease related to a genetic predisposition, inadequate renal parenchyma after one or more tumor resections, the nephrotoxic effects of chemotherapy and radiation, and the potential for hyperfiltration injury to the remaining renal parenchyma. Ritchey defined the incidence and etiology of renal failure in patients treated on NWTS-1 to NWTS-4. BWT was the greatest risk factor for renal failure (16.4% for NWTS-1 and NWTS-2, 9.9% for NWTS-3, and 3.8% for NWTS-4). Other risk factors identified were Denys-Drash syndrome, metachronous tumor, progressive disease in patients with bilateral tumors requiring bilateral nephrectomies and radiation nephritis.[144] Breslow reported the 20-year end-stage renal disease (ESRD) outcomes in children treated for WT (see Figs. 30-7 and 30-8).[142] The major risk factors he identified for renal failure were BWT and congenital syndromes—Denys-Drash, WAGR, and genital urinary anomalies (hypospadias or cryptorchidism). Thus preservation of renal tissue without sacrificing long-term survival is of particular importance for those with BWT.

Despite 40 years of clinical trials for WT, it was not until 2009 that a formal BWT trial was opened by COG. Several prior reports contributed to the development of this protocol. Shamberger and colleagues examined 38 of 188 patients with BWT with progressive or nonresponsive disease (PNRD).[145] The mean duration of chemotherapy was 7 months; 36 patients were treated with two regimens of chemotherapy, and 21 patients received three. Patients with PNRD fell into two categories: first, patients with anaplasia whose tumors were not sensitive to the therapy administered (4 patients); second, patients who had tumors with very mature rhabdomyomatous or differentiated stromal elements (14 patients) and 1 with complete necrosis. A second study from Anderson looked at the histologic changes in BWT patients who did not respond to chemotherapy and the relationship between these changes and prognosis.[146] Their results mirrored those of the NWTS study. Fifteen patients whose tumors did not respond were evaluated. One had complete necrosis, 4 had rhabdomyomatous differentiation, and 10 had mature stromal differentiation. Despite not radiographically responding to chemotherapy, these patients had favorable outcomes. Patients in these studies fell into two categories. First, there were patients with anaplasia whose tumors were not sensitive to the therapy administered. Anaplastic tumors respond poorly to chemotherapy and, once the diagnosis of anaplasia is made, a complete resection is needed.[84,140,147,148] Second,

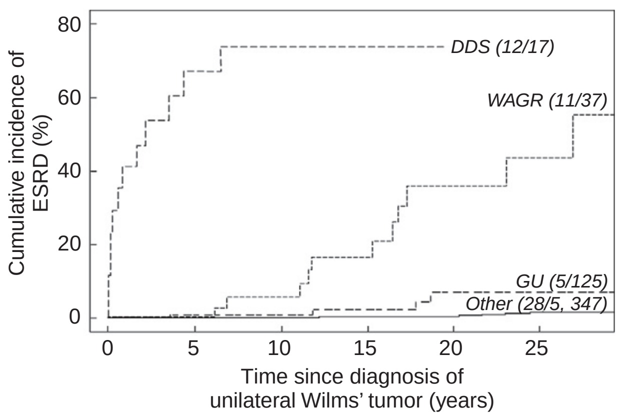


**FIGURE 30-8** Kaplan-Meier plot of renal failure rates at 20 years of age in children with a unilateral Wilms' tumor (WT). DDS, Denys-Drash syndrome; ESRD, end-stage renal disease; GU, genitourinary; WAGR (syndrome), Wilms' tumor, aniridia, genitourinary malformation, mental retardation.

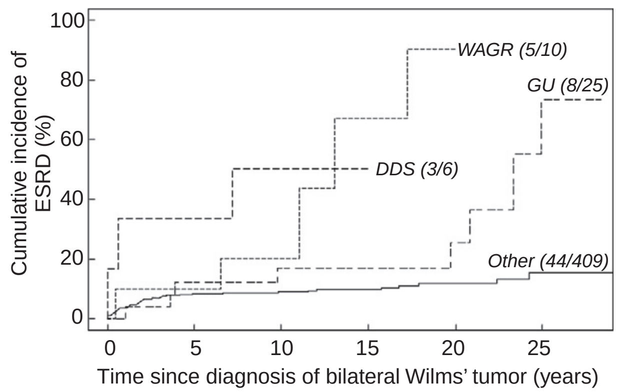


**FIGURE 30-9** Kaplan-Meier plot of renal failure rates at 20 years of age in children with bilateral Wilms' tumor (BWT). DDS, Denys-Drash syndrome; ESRD, end-stage renal disease; GU, genitourinary; WAGR (syndrome), Wilms' tumor, aniridia, genitourinary malformation, mental retardation.

there were patients who had tumors with very mature rhabdomyomatous or differentiated stromal elements and complete necrosis, all of whom had an excellent outcome. Again these patients are best served with resection.[146] Therefore if the bilateral lesions do not respond radiographically to therapy, it is critical to establish whether this is due to anaplasia or mature histology.

Hamilton and colleagues have demonstrated the difficulty in identifying anaplasia in patients with BWT.[148] Twenty-seven patients with anaplasia were reviewed from NWTS-4. Discordant pathology between the kidneys was seen in 20 patients, highlighting the importance of obtaining tissue from both kidneys. Seven children who were eventually found to have diffuse anaplasia had core needle biopsies, which failed to establish the diagnosis in all of these cases. Anaplasia was identified in only three of nine patients who had an open wedge biopsy and in seven of nine patients by partial or complete nephrectomy. Thus percutaneous biopsies rarely establish the diagnosis, and open biopsies were successful in only a third of the cases.

An important question is to determine how long to treat a child who has BWT with chemotherapy before intervening surgically. In SIOP-9, patients with unilateral tumors were randomized to receive either 4 or 8 weeks of dactinomycin and vincristine preoperatively. There was an average 48% reduction in tumor volume after 4 weeks that increased to 62% after 8 weeks of chemotherapy.[116,149] A review by the German Pediatric Hematology Group (GPOH) of their patients with BWT reported that maximum tumor shrinkage occurred in the first 12 weeks of chemotherapy.[150]

The two principal aims of the COG BWT study are to improve 4-year event-free survival and to prevent complete removal of at least one kidney in 50% of patients with BWT by using preoperative chemotherapy. This is a response-based protocol starting with chemotherapy, followed by evaluation at 6 and 12 weeks with definitive surgical therapy in all patients by 12 weeks (see Fig. 30-3). This protocol does not mandate an initial tissue diagnosis because bilateral renal tumors in children are invariably WT; biopsy does not change the therapy in most cases; anaplasia is hard to diagnose, and the biopsy will effectively increase the stage of the tumor and its risk for local recurrence.[148] In the current COG protocol, local spill of the tumor is designated as stage III. This classification was changed because of the finding of an increased incidence of abdominal recurrences in NWTS-4 patients with tumor spill.[99] First, for patients with BWT, the initial regimen will consist of regimen vincristine, actinomycin D, doxorubicin (VAD) (vincristine [VCR], dactinomycin [DACT], doxorubicin [DOX]), a more intensive combination of drugs based on regimens used with good results and minimal toxicities by both SIOP and the UKCCSG WT groups, which enables patients to receive two doses of DOX, in addition to six of VCR and two of DACT, during the first 6 weeks of therapy.[151] It differs from the standard three-drug regimen, DD-4A, in which the DOX and DACT are administered in separate cycles.[152] The three-drug chemotherapy regimen of VAD was chosen to give an enhanced therapy for possible stage III disease, because patients rarely have a lymph node biopsy before initiation of therapy. Second, it was elected to enhance the chemotherapy rather than administer radiotherapy, which might increase the occurrence of radiation nephritis in the remaining kidney. Third, a more intensive therapy was selected for treatment to avoid the use of a sequential regimen of increasing intensity, which was seen in the review of the prior cohort of NWTS-4 BWT patients.

## CHEMOTHERAPY

In 1963, Farber first reported that dactinomycin had activity against WT.[153] Today, dactinomycin continues to be part of the backbone of therapy for children with WT. Other active chemotherapeutic agents have been identified subsequently, including vincristine, doxorubicin, and cyclophosphamide. Clinical trials conducted by NWTSG and SIOP have evaluated, stage by stage, different chemotherapeutic protocols to assess the efficacy of various combinations and duration of therapy.[105,154–159] In NWTS-4, 4-year event-free survival and overall survival averaged 90% for patients with favorable histology.[154,159] Therefore NWTS-5 focused on evaluating biologic markers of prognosis, such as LOH, developing more effective therapy for recurrent disease, and reducing therapy in children with low-risk tumors.

Treatment on the current COG protocols for favorable-histology WT is determined by stage, histology, and LOH. For children with favorable-histology stage I and II tumors without LOH, 18 weeks of vincristine and dactinomycin (regimen EE-4A) is recommended. Results from NWTS-5 showed these children had an overall survival of 98.4% and 98.7%, respectively. For children with FH stage III and IV tumors without LOH, 24 weeks of vincristine, dactinomycin, and doxorubicin is recommended (regimen DD-4A). For those patients who have positive LOH at both loci (1p and 17q), treatment will be intensified. If they are stage I or II and LOH positive, they will receive DD-4A, and if they are stage III and IV LOH positive, they will receive vincristine, dactinomycin, and doxorubicin with alternating cycles of cyclophosphamide versus etoposide (regimen M). Dosing modifications are made for children less than 12 months of age.

Anaplastic tumors have been less successfully treated. NWTS-3 and NWTS-4 were the first studies to prospectively evaluate the benefit of additional/different chemotherapy therapy for these tumors. One randomized arm compared 15 months of vincristine, dactinomycin, and doxorubicin, with or without cyclophosphamide. For patients with stage II to IV diffuse anaplastic histology, the addition of cyclophosphamide resulted in a 4-year relapse-free survival estimate of 54.8% when treated with cyclophosphamide compared with 27.2% when treated without it ($P = 0.02$).[160] In NWTS-5, patients with focal anaplasia or diffuse stage I were treated with EE-4A. This was based on prior historical data, with a goal of reducing therapy. Unfortunately, the 4-year event-free and overall survival estimates for stage I (focal or diffuse) anaplastic WT were lower than previous studies (EFS 69.5% and OS 82.6%). Thus therapy with EE-4A is inadequate. Patients with focal anaplasia stage II to IV were treated with DD-4A. Children with stage II to IV diffuse anaplastic WT were treated with vincristine, doxorubicin, and cyclophosphamide (VDC) alternating with cyclophosphamide and etoposide (CyE) (regimen I). The 4-year event-free survival estimates for stage II to IV diffuse anaplastic WT on NWTS-5 were 82.6%, 64.7%, and 33.3%, respectively, with similar overall survival.[84] The current protocols and chemotherapy agents for unilateral tumors are shown in Table 30-4.

**TABLE 30-4**
**Current Children's Oncology Group Chemotherapy Regimens for Unilateral Wilms' Tumor**

| *Regimen* | *Agents* |
|---|---|
| EE-4A | Vincristine and dactinomycin |
| DD-4A | Vincristine, dactinomycin, doxorubicin, and radiation therapy (XRT) |
| Regimen I | Vincristine, dactinomycin, doxorubicin, cyclophosphamide (CPM1), and etoposide (ETOP), as well as radiation therapy (XRT) |
| Regimen M | Vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide; radiation therapy also to be administered as part of this regimen |
| Revised UH-1 | Vincristine, dactinomycin, doxorubicin, cyclophosphamide, carboplatin, etoposide, and radiation |
| Revised UH-2 | Vincristine, dactinomycin, doxorubicin, cyclophosphamide, carboplatin, etoposide, irinotecan, and radiation therapy (XRT) |
| Vincristine/irinotecan window therapy | Vincristine and irinotecan in conjunction with revised UH-1 or revised UH-2, depending on response |

### Recurrent Tumor

Treatment of recurrent disease in children with WT is challenging. Recurrence occurs in 15% of patients with favorable histology tumors and in 50% with anaplastic histology. Recurrence is most frequent within 2 years of the initial diagnosis and most common in the lungs, tumor bed, and liver.[161] Less common sites are bone, brain, and distant lymph nodes.

Recurrent disease is treated by chemotherapy, surgery, and radiotherapy. NWTS-5 evaluated two protocols for recurrent disease, avoiding use of agents included in the primary protocols. Stratum B was for patients with stage I and II disease initially treated with EE-4A. The chemotherapy for this relapse protocol was regimen I (alternating courses of vincristine/doxorubicin with cyclophosphamide), in addition to surgical resection and radiation therapy. Event-free survival at 4 years was 71.1%, and 4-year overall survival was 81.8% for all patients and was 67.8% and 81.0%, respectively, for those who relapsed only to their lungs.[162] Stratum C was for patients initially treated with DD-4A.[163] The chemotherapy protocol for this group was alternating cycles of cyclophosphamide versus etoposide and carboplatin versus etoposide. Four-year event-free survival and overall survival were 42.3% and 48.0%, respectively, for all patients and were 48.9% and 52.8% for those who relapsed in the lungs only. Bone marrow transplantations have been performed for patients with recurrent disease, with reported event-free or disease-free survival rates of 36% to 60% in these small series.[164–166] At present, there is no open relapsed study in SIOP or COG, because the groups are awaiting new and more effective agents for treatment of this disease.

## RADIOTHERAPY

Analogous to surgery and chemotherapy, the cooperative group trials have refined the indications for radiotherapy. In addition, technologic advances have helped to deliver irradiation with increased efficacy and less toxicity to surrounding tissues. The three principle fields for radiotherapy for renal tumors are whole abdominal, flank, and lung (metastatic lung disease). All five NWTSG studies and the current COG studies use radiotherapy as part of the multimodality treatment for advanced-stage tumors.

In 1950, Gross and colleagues demonstrated the efficacy of radiotherapy as an adjuvant therapy prior to the advent of chemotherapy. In this series, nephrectomy with postoperative radiation improved survival to 47%.[167] Favorable histology tumors are generally very radiosensitive. NWTS-1 to NWTS-3 helped define the indications, timing, and dose of radiotherapy. NWTS-1 established that irradiation provided no advantage in children younger than 24 months with stage I FH tumors who also received 15 months of dactinomycin.[168] That study also demonstrated that in stage III tumors with local tumor spill or previous biopsy, there was no need for irradiation of the whole abdomen, thus sparing patients the associated toxicity.[169] NWTS-2 showed that radiotherapy could be avoided in all children with stage I WT if they received vincristine and dactinomycin.[170] NWTS-3 established that radiotherapy could be avoided in children with stage II tumors given vincristine and dactinomycin and also demonstrated that children with stage III favorable-histology tumors who received 10.8 Gy radiotherapy and vincristine, dactinomycin, and doxorubicin had similar tumor control to those who received 20 Gy with vincristine and dactinomycin. This was an important finding, because it eliminated the need for an age-adjusted dose schedule and significantly reduced the recommended dose of radiation.[157]

Timing of radiation following nephrectomy was assessed on NWTS-2, where a delay of 10 days or more before initiation of radiotherapy was associated with a higher rate of abdominal relapse, particularly among patients with unfavorable-histology tumors and a small radiation field.[157,168,169] A recent review of this issue from NWTS-3 and NWTS-4 data confirmed this observation.[171] Thus, in the COG protocols, it is recommended that abdominal irradiation be delivered as soon as practical after nephrectomy and not later than 14 days after surgery. The current recommendation for radiation therapy for COG protocols is shown in Table 30-5.

In contrast to FH tumors, the ideal dose for patients with anaplastic tumors is unknown. Anaplastic tumors are more resistant to chemotherapy and seem to be more resistant to radiotherapy as well. Anaplastic tumors have not demonstrated a radiation dose response between 10 Gy and 40 Gy.[160]

The radiotherapy strategy for patients with anaplastic histology (AH) on NWTS-5 included no irradiation for stage I AH tumors and 10-Gy radiotherapy for AH stage II and III in conjunction with nephrectomy and regimen I. The outcomes for both of these treatment strategies were suboptimal. Stage 1 patients had a 4-year EFS and overall survival of only 69.5% and 82.6%, respectively. Stage II, III, and IV patients had a 4-year OS after immediate nephrectomy, irradiation, and regimen I chemotherapy of 82.6%, 64.7%, and 33.3%, respectively.[84] EFS was similar to OS in all groups. Fifty percent of stage III recurrences were local, suggesting that the dose of 10 Gy was not adequate. These results form the basis for the current COG study that recommends the addition of irradiation for patients with stage I anaplasia and augmentation of irradiation for patients with stage III anaplasia.

For liver metastases, only those that are unresectable at diagnosis are irradiated. The treatment portal includes that portion of the liver known to be involved as identified by CT or MRI studies. The whole liver is treated in children with diffuse metastases.

**TABLE 30-5**
**Radiotherapy for Favorable-Histology Wilms' Tumor**

| *Treatment Site* | *Clinical Presentation and Dose (Gy)* | |
|---|---|---|
| Flank irradiation<br>All instances of soilage will be classified as Stage III and require abdominal radiation. Flank radiation is given to all Stage III patients with three exceptions (the patients meeting any of these exceptions requiring whole abdominal radiation). | Stage III favorable histology<br>Recurrent Wilms' tumor | 10.8<br>10.8 |
| Whole abdomen irradiation (WAI) | Abdominal stage III<br>Preoperative tumor rupture<br>Peritoneal metastases are found at initial surgery<br>A large intraoperative tumor spill affecting areas outside the tumor bed as determined by the surgeon/ treating institution. | 10.5 |
| | Abdominal Stage III<br>Diffuse unresectable peritoneal implants | 21 |
| Liver irradiation<br>Patients with residual tumor will receive supplemental irradiation with 5.4 to 10.8 Gy. | Focal metastases<br>Diffuse metastases | 19.8<br>19.8 |

### Lung Radiotherapy

Historically, pulmonary metastases were diagnosed based on lesions found on routine chest radiographs and were treated with whole lung radiation. For COG studies, it is delivered in eight treatments of 12 Gy. From NWTS-5, the 5-year EFS (95% CI) for stage IV category was lung only 76% (72% to 80%) (513 patients) and liver and lung 70% (57% to 80%) (62 patients).[172] Advances in imaging have changed the assessment of lung disease from plain radiograph to widespread use of chest computed tomography. Lesions are detected on CT scan that are not found on standard radiographs.[173–175] Thus more lesions are being identified. Complicating the use of radiation therapy is the fact that it is a major cause of long-term morbidity, particularly to the lung and heart, producing congestive heart failure, pulmonary fibrosis, and second malignancy.[176–178] Recent studies suggest that the management for pulmonary nodules should be reexamined. In SIOP-9, by 70 days of therapy, resolution of pulmonary nodules on CT scan in children with FH tumors was a favorable prognostic indicator.[179] In SIOP-9, many of these patients were spared whole lung irradiation, if complete resolution of pulmonary metastases occurred after 6 weeks of prenephrectomy chemotherapy with vincristine, dactinomycin, and doxorubicin with or without surgical excision of residual metastases. The 5-year relapse-free survival (RFS) for stage IV patients receiving preoperative chemotherapy was 62.5%.[179] The results of this study have been controversial. The United Kingdom Children's Cancer Study Group (UKCCSG) Wilms Tumor Study 1 followed a similar protocol; yet, their 6-year EFS was only 50%.[180] In their second study, UKCCSG-Wilms Tumor Study (UKWT2), the majority of children with lung metastases received whole lung irradiation (WLI), and the 4-year survival rate improved to 75%.[181] A COG study of patients with pulmonary lesions detected by CT only (as opposed to CT and chest radiograph) and treated with only two chemotherapeutic agents showed an inferior outcome compared with those treated with three drugs *irrespective* of whether or not they received pulmonary radiation.[172] A fourth study examined the value of biopsy prior to treating patients with lesions detected only by CT.[175] Two thirds of the children had tumor on biopsy, suggesting that histologic evaluation may be valuable in directing therapy. The current COG study is evaluating the use of radiographic response to chemotherapy to predict the need for whole lung irradiation. Those patients with stage IV favorable-histology WT with pulmonary metastases who have complete CT resolution of the pulmonary lesions after 6 weeks of vincristine/dactinomycin/doxorubicin chemotherapy will continue the same chemotherapy without whole lung irradiation. Those who do not have resolution of pulmonary metastases by week 6 will have the addition of cyclophosphamide and etoposide to the other three drugs and will receive whole lung irradiation.

## LATE EFFECTS

The increasing numbers of survivors of WT have led to a better understanding of adverse medical conditions related to treatment of their disease that can develop over time.[182] Treatment for WT impacts renal function (discussed earlier), pregnancy, cardiac and pulmonary function, and second malignancies may develop.[178,183–187]

### Pregnancy

Treatment for WT impacts reproductive capacity and increases the risk of complications during pregnancy. The National Wilms' Tumor Long-Term Follow-Up Study evaluated 700 maternal/offspring pairs.[188] If a woman had received flank radiation for unilateral WT, the dose of radiation correlated with increased risk of hypertension, fetal malposition, and premature labor. The children were also more at risk for low birth weight and prematurity (birth before 37 weeks). Premature labor was seen in 10.2% of women who did not receive flank radiation and 22% of those who received 35Gy ($P = 0.001$). Radiation therapy to the abdomen has resulted in absent/abnormal function of the ovaries, a small uterus, and premature menopause.[189–193] Male infertility is not at risk unless alkylating agents were used.

### Secondary Malignancies

Patients who have been treated for pediatric cancer are known to have an increased risk of second malignancies. This is in part due to treatment with known carcinogens, such as alkylating agents and radiotherapy.[183,194,195] An international cohort of 13,351 children with WT diagnosed before 15 years of age, from 1960 to 2004, was established to determine the risk of second malignant neoplasms (SMN).[178] One hundred and seventy-four solid tumors and 28 leukemias were found in 195 people. Median survival after a secondary malignancy was diagnosed 5 years or more from WT was 11 years; it was 10 months for leukemia. Age-specific incidence of secondary solid tumors increased from approximately 1 case per 1,000 person-years at age 15 years to 5 cases per 1,000 person-years at age 40 years. The cumulative incidence of solid tumors at age 40 years was 6.7%. In those patients whose

WT was diagnosed after 1980, there was a lower age-specific incidence rate for second tumors compared with those treated before 1980. Paradoxically, the incidence of leukemia was higher in those diagnosed after 1990. This may be due to decreasing use of radiation therapy and increasing intensity of chemotherapy in modern protocols for treatment of WT.

### Congestive Heart Failure

Congestive heart failure has been identified as a significant morbidity in children treated with doxorubicin, and this is exacerbated in patients who receive thoracic radiation. The cumulative frequency of congestive heart failure in patients treated on NWTS-1 to NWTS-4 was 4.4% at 20 years for patients treated initially with doxorubicin, but that percentage is expected to be lower with current cumulative doses.[184,185,196] The relative risk of congestive heart failure was found to be increased in females (risk ratio [RR] = 4.5; $P = 0.004$), and by cumulative doxorubicin dose (RR = 3.2/100 mg/m$^2$; $P < 0.001$), lung irradiation (RR = 1.6 for every 10 Gy; $P = 0.037$), and left abdominal irradiation (RR = 1.8/10 Gy; $P = 0.013$).[185] Preliminary results suggest that cardiotoxicity is lower with current radiation doses, but patients still have a substantial lifetime risk of developing cardiac disease.[183,196]

### Thoracic

Radiotherapy (RT) has been implicated as a major contributor to late complications. Acute lung injury is relatively uncommon, occurring in a minority of children.[197] The late effects of pulmonary RT include pneumonitis and restrictive lung disease, scoliosis, kyphosis, reduced lung capacity, and secondary tumors. In girls, breast hypoplasia and cancer have been described.[176,177] Paulino and his colleagues reported on the late complications of pulmonary RT in 55 long-term survivors of WT.[176] Two thirds of the patients had at least one complication. Forty-three percent had scoliosis or kyphosis, and 10% developed benign chest tumors (osteochondromas). Secondary tumors were noted in three patients within the lung field (two osteogenic sarcomas of the rib and one breast cancer), and all succumbed to these tumors. Pulmonary function was examined by Attard-Montalto and colleagues.[177] Subjectively, 63% percent of patients had mild to moderate exercise intolerance, and objective measurement of vital capacity and total lung capacity was decreased compared with age and height predicted values in all. All of the females had breast hypoplasia. In another study of long-term survival of females, all developed breast hypoplasia and one had breast cancer.[198]

# Other Renal Tumors

## CLEAR CELL SARCOMA OF KIDNEY

CCSK accounts for 3% of renal tumors reported to the COG studies. Each year, approximately 20 new cases of CCSK are diagnosed in the United States. CCSK was recognized as a distinct clinicopathologic entity by Kidd in 1970.[199] CCSK has been described as nests of ovoid, epithelioid, or spindled cells separated by fibrovascular tissue with a "chicken wire" pattern of small blood vessels. Most tumors show evidence of this "classical" pattern, but other reported histologic patterns seen include myxoid, sclerosing, cellular, epithelioid, palisading, spindle-cell, storiform, and anaplastic patterns.[200] Immunohistochemistry is used to exclude other renal tumors. CCSK is nonspecifically vimentin and Bcl-2 positive. Gene-expression profiling studies demonstrate the expression of neural markers (e.g., nerve growth factor receptor), expression of member genes of the Sonic Hedgehog pathway and the phosphoinositide-3-kinase/Akt cell proliferation pathway.[201,202] Recently, a translocation t(10;17) and deletion 14q have also been described in CCSK, suggesting that they may play a role in its pathogenesis.[203] CCSK is characterized by bone and brain metastases and the increased tendency for late recurrences. Long-term follow-up of CCSK patients is needed because 30% of relapses occurred more than 3 years after diagnosis, and some occurred as late as 10 years after diagnosis.[204] The tumor is generally unilateral and unicentric, with solid and, occasionally, cystic areas. On NWTS-1 to NWTS-3, treatment for CCSK was the same as for WT, and the outcomes were poor. In NWTS-4, patients were treated with vincristine, dactinomycin, doxorubicin, and RFS, and overall survival was improved versus NWTS-3 (RFS 71.6% versus 60.2% at 8 years, $P = 0.11$; OS 83% versus 66.9% at 8 years, $P < 0.01$).[204] To further improve survival, patients on NWTS-5 with CCSK were treated using regimen I (see Table 30-2), because etoposide and cyclophosphamide were active against CCSK in preclinical models.[205] Four-year OS for stage I patients was 100%. Stage II, III, and IV had 4-year OS of 88.9%, 94.8%, and 41.7%, respectively. LOH was not found in most cases of children with CCSK and is not predictive of outcomes. In the current COG study, patients with CCSK are treated according to the high-risk study. Patients with stage I disease will continue to be treated with regimen I but will not receive radiation therapy. The need to minimize unnecessary therapy in patients with stage I CCSK is highlighted by the fact that treatment-related deaths in the Argani series outnumbered tumor-related deaths, two versus one.[200] In addition, none of the stage I patients from NWTS-5 have relapsed, with a median follow-up of more than 4 years. To improve survival for children with higher-stage disease, they will be treated with revised UH-1 (see Table 30-4).

## RHABDOID TUMOR OF THE KIDNEY

RTK was initially described in 1978 as a "rhabdomyosarcomatoid" variant of WT.[206] Haas used the term "rhabdoid tumor" in 1981, because of the absence of muscle differentiation.[207] RTKs have been reported to occur throughout the body, including the brain, liver, soft tissues, lung, skin, and heart. RTK accounts for 2% of all renal tumors, and it is the most aggressive and lethal of all pediatric renal tumors. Clinical features that help distinguish an RTK from WT clinically include the presence of hypercalcemia and diffuse lymphatic and hematogenous spread in a young infant. Tomlinson and her colleagues reviewed 142 patients with RTK from NWTS-1 to NWTS-5.[208] Age at diagnosis was found to be a highly significant prognostic factor for survival of children with RTK. Infants have a dismal prognosis, whereas older children have a slightly more favorable outcome. Higher tumor stage and presence of a central nervous system (CNS) lesion were also predictive of a poor rate of survival. Unfortunately, these tumors tend to present at an advanced stage and are resistant to chemotherapy.[209] RTK is associated with second primary tumors in the brain, including cerebellar medulloblastomas, pineoblastomas, neuroblastomas, and subependymal giant cell astrocytomas.[210]

Grossly, the tumors are solid, unencapsulated, and often have extensive hemorrhage and necrosis. The tumors are very invasive. Microscopically, they consist of sheets of cells showing nuclear pleomorphism and characteristic morphologic features of open vesicular nuclei, prominent nucleoli, and scattered hyaline eosinophilic cytoplasmic inclusions composed of intermediate filaments in a "whorled" pattern. At present, no single immunohistochemical stain or profile is considered to represent a diagnostic criterion. Recently, genetic abnormalities of the *hSNF5/INI1* tumor suppressor gene on chromosome 22 have been shown to be characteristic for both renal and extrarenal rhabdoid tumors; the gene is important for chromatin remodeling. For all other renal tumors, except RTK, immunohistochemical staining for the wild-type integrase interactor 1 (INI-1) protein shows nuclear positivity. In renal and extrarenal rhabdoid tumors, this is absent.[211] This antibody is being evaluated for its diagnostic utility in the current COG renal tumor study.

Both SIOP and COG/NWTSG have reported poor outcomes for children with RTK.[208,212] The outcomes by stage from NWTS-5 are stage I = 50.5%, stage II and III = 33.3%, stage IV = 21.4%, stage V = 0%. Children with RTK, on the current COG study, will be treated using revised UH-1 if they are stage I to IV and have no measurable disease after surgery. If they have measureable disease (stage III, IV), they will receive a vincristine/irinotecan "window," followed by revised UH-2 if they have a partial or complete response (see Table 30-2). The rationale for this treatment strategy was based on reviewing the outcomes from the intergroup rhabdomyosarcoma (IRS) studies and several case reports that documented the successful treatment of advanced or metastatic rhabdoid tumor of the kidney.[213–215]

## RENAL CELL CARCINOMA

RCC in childhood accounts for 5% to 8% of all pediatric and adolescent renal malignancies. They are more common than clear cell sarcoma of the kidney and malignant rhabdoid.[1] The median age at presentation in children is 9 years. By age 15, RCC becomes as common as WT (Fig. 30-10). In the pediatric population, there have been limited therapeutic studies with no randomized controlled trials. Similar to WT, children with RCC generally present with an asymptomatic abdominal mass, although hematuria is a frequent finding.[216] Imaging studies cannot differentiate RCC from other solid

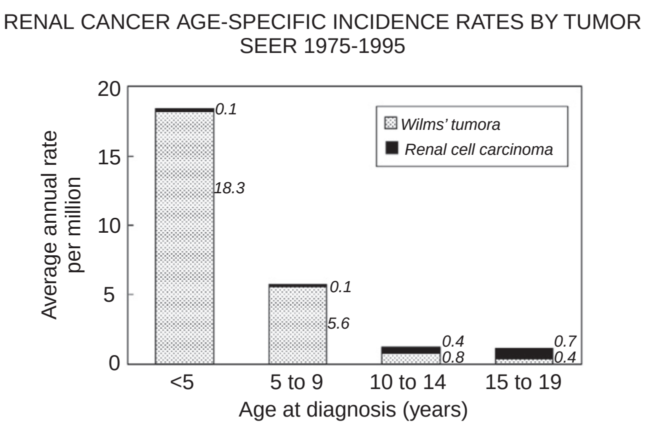


**FIGURE 30-10** Incidence of renal cell carcinoma and Wilms' tumor by age. SEER, Surveillance, Epidemiology, and End Results (Program).

renal tumors. RCC in children can be divided into two broad pathologic groups.[217] The first is the classical clear cell histology. This includes the adult-type RCC with 3p25 (VHL locus) genetic abnormalities and tumors in patients with tuberous sclerosis. In addition, there is a unique genetic subtype of clear cell that presents in adolescents and young adults, accounting for nearly one third of all cases. These tumors are characterized by the chromosomal translocations involving the *TFE3* gene on Xp11.2[217–219] or the *TFEB* gene on 6p21.[220,221] The abnormal gene fusions produce protein dysregulation and result in overexpression of either *TFE3* or *TFEB* transcription factors, which contribute to tumor pathogenesis. Immunohistochemistry can detect aberrant expression for TFE3 or TFEB and can thus be useful in establishing the diagnosis.[221,222] In addition, these translocation-positive RCCs have been described as second malignancies following previous chemotherapy.[223,224]

The second subgroup of pediatric RCCs are the papillary RCCs.[225–227] Papillary renal cell carcinoma appears more frequently than classical clear cell. Other RCC cell types include chromophobe or collecting duct types.[228] Renal medullary carcinomas are rare, but highly aggressive, malignancies that are associated with sickle cell hemoglobinopathy.[229,230] Approximately 25% of pediatric RCCs are not able to be classified because of atypical histologic features.[217]

Complete tumor resection is the most important determinant of outcome in RCC.[228] Younger age at diagnosis is also a favorable prognostic factor. It has been suggested that regional lymph node involvement does not portend the same grave prognosis as it does in adult renal cell carcinoma; however, because this impression was reached based on only 13 patients, further evaluation is required.[231] Data collected from RCC patients enrolled on NWTS-5 showed 5-year OS survival rates by stage: stage I 92.5%, stage II 73%, stage III 55%, and stage IV 9%. Similar to adult RCC, prognosis worsens with increasing stage, although direct comparisons of adult and pediatric data are confounded by the finding that most reviews of pediatric RCC used the modified Robson staging system rather than the tumor-node-metastasis (TNM) system. Neither chemotherapy nor radiation therapy have demonstrated activity in adult or pediatric patients with metastatic RCC. To address this lack of knowledge and experience, for the first time these tumors will be addressed in a COG protocol. To enable comparison with adult tumors, the staging system proposed by the World Health Organization will be used. The relatively good survival rate for children with localized RCC combined with the relative inefficacy of the known adjuvant therapies support treating children without adjuvant therapy. However, the provision of adjuvant chemotherapy is at the discretion of the local physicians. A major future thrust will be to identify novel agents with activity against RCC.

## CONGENITAL MESOBLASTIC NEPHROMA

Congenital mesoblastic nephroma (CMN) is the most frequent renal neoplasm of newborns and young infants, accounting for 5% of all renal tumors.[129,232–234] The median age at diagnosis is 2 months. In 1967, Bolande and colleagues were the first to describe the tumor as a separate entity from WT.[234] CMN are firm on gross examination, and the cut surface has the yellowish gray trabeculated appearance of a leiomyoma. To date,

three histologic subtypes have been described. The classical type, first identified by Bolande (24% of cases), cellular type (66% of cases), and mixed type (10% of cases) showing both classical and cellular patterns.[235] The classical variant is characterized by leiomyomatous histology, with spindle cells in bundles, rare mitoses, and the absence of necrosis. It is histologically similar to infantile myofibromatosis. The cellular variant consists of solid, cellular, sheetlike growth pattern of oval or round cells with little cytoplasm and frequent mitoses and necrosis, which resembles infantile fibrosarcoma. The mixed type of congenital mesoblastic nephroma features areas resembling both classical and cellular morphologies.[235–237] The relationship between mixed CMN and the two main histologic subtypes is not clear.[238]

The observation that classical CMN is similar to infantile myofibromatosis and cellular CMN resembles infantile fibrosarcoma suggests that these may be two distinct entities, and genetic studies provide evidence in support of this hypothesis. Cellular CMN is characterized by the t(12;15) translocation, resulting in the *ETV6-NTRK3* fusion gene, a genetic change that has not been identified in classical CMN, but is characteristic of infantile fibrosarcoma.[238,239] This led to the hypothesis that cellular CMN is an intrarenal occurrence of infantile fibrosarcoma, whereas classic CMN reflects intrarenal fibromatosis. The cloning of the resulting gene fusion has allowed the development of molecular detection assays for this subtype of congenital mesoblastic nephroma. The absence of the fusion product in classical congenital mesoblastic nephroma correlates with its demonstrated absence in infantile myofibromatosis. The challenge then is to explain the existence of the mixed lesions.

Clinically, most children with CMN have an excellent prognosis and are cured with a radical nephroureterectomy with lymph node sampling.[236,240] However, CMN tends to grow into the hilar and perirenal soft tissue, and recurrence or metastases are seen.[241,242] In 1973, the first reports of local recurrences in children with CMN appeared in the literature.[243–245] Since then, metastasis to the lung, liver, brain, and heart have been reported.[245–249] Recurrence and metastatic disease has lead to a debate concerning the need for adjuvant therapy to prevent these rare events in a subset of patients versus the risks of this therapy in infants.[237,241]

Subsequent investigations demonstrated that recurrences were seen preferentially in either the cellular or the mixed subtypes. Other suggested risk factors for recurrence included age (more than 3 months of age), stage (stage III resulting from incomplete surgical resection), and vascular invasion.[250,251] In 2006, the German Pediatric Oncology Group published their experience with 50 children with CMNs, suggesting that a subgroup of children more than 3 months of age with stage III cellular CMN tends to develop recurrences more often supporting the earlier findings.[252] Alternatively, Perlman and colleagues evaluated 396 cases of CMN from the database of the J.B. Beckwith Developmental Renal Tumor Collection.[253] Thirty CMNs were known to have recurred (7.6% overall recurrence rate and 9.3% recurrence rate for tumors with a cellular histologic component). Recurrences took place within 1 year of diagnosis (range, 2 to 11.5 months); 20 were local, 8 were metastatic, and 2 were both local and metastatic. None of the classical CMNs recurred, including 18 that were known or suspected to have residual disease. Recurrences were confined to tumors with a cellular component or cellular and mixed, which had the same risk of recurrence. Stage III disease was the second factor associated with recurrence. Intrarenal and renal sinus vascular invasion correlated with increased potential for recurrence; however, the correlation did not achieve independent statistical significance. Other clinical or pathologic features previously suggested as prognostic factors, including age at diagnosis, were not proven to be of additional prognostic significance. This study concluded that the most important risk factors for recurrence in CMNs are the presence of a cellular histologic component and stage III disease. However, in none of these reports has the efficacy of adjuvant therapy been established.

## SOLITARY MULTILOCULAR CYST AND CYSTIC PARTIALLY DIFFERENTIATED NEPHROBLASTOMA

Cystic renal tumors are a diagnostic and therapeutic challenge (Fig. 30-11). Cystic nephroma (CN), cystic partially differentiated nephroblastoma (CPDN), and cystic WT (CWT) are a spectrum with CN at the benign end, CWT at the malignant end (these must have both a solid and cystic component), and CPDN in the intermediate position. The three types cannot be differentiated using imaging techniques and can be confused with cystic clear cell sarcoma and cystic mesoblastic nephroma.[254] Multicystic dysplastic kidney can generally be distinguished radiographically from the other entities, because it lacks any normal renal parenchyma that the other lesions should contain.[255]

## CYSTIC NEPHROMA

CN is an uncommon benign renal lesion that occurs most commonly in children younger than 24 months of age, with a male to female ratio close to 2:1. A second peak incidence occurs in adults around 30 years of age, with an 8:1 female to male predominance.[255–258] Grossly, these masses are

FIGURE 30-11 A magnetic resonance scan of a cystic nephroma.

well-encapsulated multilocular tumors composed of various-sized cysts with thin septations that compress the normal kidney. Microscopically, the identifying feature is that of mature well-differentiated cell types within the septa of the cyst wall. There are no blastemal or embryonal elements.[254,255] Most cases are unilateral, but some are bilateral.[259] Although CN is benign, cases have been reported with pleuropulmonary blastoma as well. The relationship between these two entities is undefined.[260,261]

## CYSTIC PARTIALLY DIFFERENTIATED NEPHROBLASTOMA

Cystic partially differentiated nephroblastoma is a multilocular cystic WT composed entirely of cysts separated by delicate septa. The majority of these lesions occur in the first 2 years of life.[256,262,263] Cystic partially differentiated nephroblastoma is usually well circumscribed and sharply demarcated from the adjacent normal kidney. It can be large (up to 18 cm in diameter) and may produce visible abdominal distention. This neoplasm is composed entirely of variably sized cysts; unlike CN, the septal stroma contains small foci of blastema, primitive or immature epithelium, and/or immature-appearing stromal cells.[264,265] In addition, skeletal muscle fibers are commonly present in cystic partially differentiated nephroblastoma.

Both COG/NWTSG and SIOP have reported their experiences with CN and CPDN.[262,266,267] In the NWTSG study, 21 patients were evaluated.[262] Thirteen patients received chemotherapy, and 8 patients did not. In the chemotherapy group, the distribution by stage was 10 children with stage I, 2 children with stage II, and 1 child with stage V. The 8 no-chemotherapy patients were all stage I with a 100% survival. The SIOP evaluated 14 patients with diagnoses of cystic nephroma (7 patients) and cystic partially differentiated nephroblastoma (7 patients). Two patients received preoperative chemotherapy. Primary nephrectomy was performed in 12 patients. Two patients underwent partial nephrectomy. In 1 child, postoperative chemotherapy was administered. None of the patients had progression of disease or recurrence. Overall survival was also 100%.[267] There is some concern about doing partial nephrectomies because of recurrences after incomplete excision as well as distinguishing this tumor from other malignant lesions.[267,268]

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 31

# Neuroblastoma

Barrie S. Rich and Michael P. La Quaglia

Neuroblastoma is one of the most common solid tumors in infancy and childhood. This is a neoplasm of neural crest origin, arising in the adrenal medulla and along the sympathetic ganglion chain from the neck to the pelvis. The clinical course is quite variable, because this highly malignant tumor demonstrates unusual behavior. Although instances of spontaneous regression and tumor maturation from a malignant to a benign histologic form have been observed,[1–7] the disease is progressive in many cases. Survival in children with other malignancies, such as Wilms' tumor, rhabdomyosarcoma, acute lymphocytic leukemia, germ cell tumors, Hodgkin disease, and non-Hodgkin lymphoma, has been significantly improved by the intensive use of combined treatment modalities, but the outlook for many children with advanced neuroblastoma remains dismal.[1,5,8–12] This neoplasm exhibits great heterogeneity in its behavior and represents a significant challenge to practitioners.

Primitive neuroblasts can be identified in the fetal adrenal gland in the 10th to 12th intrauterine week. The nodules increase in number by 20 weeks' gestation but gradually diminish in number toward the end of gestation. Neuroblastoma in situ in the adrenal gland is seen in 1 of every 260 neonates who die of congenital heart disease and in as many as 1 in 39 infants who die from other causes in the first 3 months of life. The clinical incidence of the tumor is approximately 1 in 7,500 to 10,000 children.[1,10,13,14] Neuroblastoma is responsible for 10% of all childhood tumors and 15% of all cancer deaths. There are 700 cases diagnosed annually in the United States. Approximately 40% of cases are diagnosed by 1 year of age, 75% by 7 years, and 98% by 10 years.[1] More than half the patients are younger than 2 years at the time of diagnosis.[15] Neuroblastoma is slightly more common in boys than in girls, with a male-to-female ratio of 1.2:1.0.[1,10] It is the most common intra-abdominal malignancy in newborns, and the most frequently diagnosed malignancy in children less than 1 year of age.[16]

The embryonal nature of neuroblastoma has been well documented by its identification on prenatal ultrasonography, and the tumor has been known to invade the placenta during the antenatal period, though this is a rare occurrence.[17–24] More than 55 cases of antenatally discovered neuroblastoma have been reported in the literature since the original description by Fénart and colleagues in 1983.[25] The masses are usually identified during ultrasound examinations performed after 32 weeks' gestation. The earliest reported instance was observed at 18 weeks' gestation.[26]

Mothers of infants with congenital neuroblastoma occasionally experience flushing and hypertension during pregnancy as a result of catecholamine released from the fetal tumor in utero.

Neuroblastoma has been described in twins on many occasions, and familial occurrences in both mother and child and father and son have been reported.[23,27,28] Concordance for neuroblastoma in twins during infancy indicates that hereditary factors may be predominant in this age group, whereas discordance in older twins suggests that a random mutation may be more important for this population. The median age for the occurrence of familial neuroblastoma is 9 months, in contrast to 18 months in the general population. Maris and colleagues[29] observed that 20% of patients with familial neuroblastoma have bilateral or multifocal tumors and reported evidence for a hereditary neuroblastoma predisposition locus on chromosome 16p12-13. Neuroblastoma has been observed in infants with Beckwith-Wiedemann syndrome, neurofibromatosis (von Recklinghausen disease), Hirschsprung disease, central hypoventilation syndrome (Ondine's curse), and fetal alcohol syndrome, and in offspring of mothers taking phenytoin (fetal hydantoin syndrome) for seizure disorders.[30–34] Mutations in the *PHOX2B* gene, which is often seen in congenital central hypoventilation disorder, have been documented in those with familial neuroblastoma, and in 2.3% of those with sporadic neuroblastomas.[35] Recently, it has been determined that genetic mutations in the anaplastic lymphoma kinase (*ALK*) gene explain most hereditary neuroblastoma. However, activating mutations of this gene can also be somatically acquired.[36] This discovery has initiated the development of therapy based on *ALK* inhibition.[37] Although it is unlikely that environmental factors play an important role in causing this tumor, neuroblastoma has been noted among infants of mothers receiving medical therapy for vaginal infection during pregnancy and with paternal occupational exposure to electromagnetic fields.[1]

Neuroblastoma may occur at any site where neural crest tissue is found in the embryo. The neuroblast is derived from primordial neural crest cells that migrate from the mantle layer of the developing spinal cord. Tumors may arise in the neck, posterior mediastinum, retroperitoneal (paraspinal) ganglia, adrenal medulla, and pelvic organ of Zuckerkandl.[5,10,14,38] In 75% of cases, the tumor is located in the retroperitoneum,

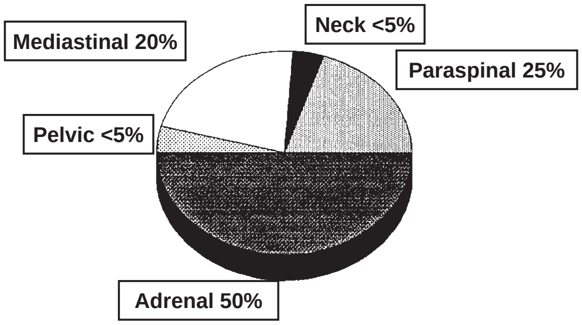


FIGURE 31-1 Distribution of cases of neuroblastoma at each of the primary tumor sites. Primary tumors most commonly occur in the adrenal gland.

in either the adrenal medulla (50%) or the paraspinal ganglia (25%). In 20% of cases, the primary tumor is in the posterior mediastinum. Less than 5% of tumors occur in the neck or pelvis (Fig. 31-1).[1,5,10,14] Primary intracranial cerebral neuroblastoma also occurs.[39,40] In addition, a teratoma in an infant may occasionally contain foci of neuroblastoma. Rare cases of neuroblastoma arising in the bladder have also been reported.[41]

The fate of the neuroblasts can follow 1 of 3 clinical pathways: (1) spontaneous regression, (2) maturation by differentiation from neuroblastoma to a benign ganglioneuroma, or most frequently, (3) rapid progression to a highly malignant tumor that is often resistant to treatment.

## Mass Screening

In an effort to identify early cases of neuroblastoma that were amenable to cure, mass screening programs were initiated in Japan in 1985, evaluating urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) levels in infants at 6 months of age. These studies identified a large number of infants with neuroblastoma. The survival in these cases was exceptionally high compared with the survival in patients who present with clinical disease diagnosed by conventional methods. The Japanese screening effort doubled the actual incidence of neuroblastoma in infants younger than 1 year of age, but neither decreased the number of cases observed in older children nor improved the survival of children older than 1 year of age.[1,42–44] Sawada and colleagues[43,44] reported a 96% survival rate in 170 cases of neuroblastoma identified by screening. These observations suggest that neuroblastomas identified by screening were most likely biologically favorable tumors that spontaneously regressed.[43] However, a small number of screened patients have had tumors with unfavorable biologic markers and a poor prognosis, and a few screened patients who tested negative at 6 months of age later (at 12 to 18 months of age) developed highly aggressive neuroblastomas.[45]

In general, mass screening has provided important information regarding the natural history of this enigmatic tumor and has identified a group of tumors that clearly regress and represent a biologically favorable form of tumor, in contrast to that noted in older children.[7] Prospective, population-based, controlled screening trials in Quebec minimized the rate of false-positive cases, but had an overall sensitivity of only 45%. The results were similar to the findings in Japan.[46] A German study offered screening to 2.6 million infants between 9 and 18 months of age. This effort identified 149 cases of neuroblastoma in 1,800 screened infants, demonstrating a predictive value of 8%.[47] The German investigators estimated that two thirds of the tumors detected by screening would have regressed spontaneously. The potential risks were highlighted by the fact that all 3 children who died in the group detected by screening had localized disease and succumbed from complications of treatment. These studies in North America, Japan, and Europe suggest that screening may result in an overdiagnosis of neuroblastoma and the performance of unnecessary therapies.[48] However, the results observed in screening studies are valuable and should help minimize treatment in the substantial subset of infants diagnosed with early-stage neuroblastoma that has an excellent chance of either maturing or spontaneously regressing.[49] Because of compelling medical and psychological reasons, especially among parents in false-positive cases, neuroblastoma screening was discontinued in many countries.[50,51] Following the cessation of screening elsewhere in the world, the Ministry of Health in Japan discontinued its mass screening program in April 2004.[52]

## Clinical Presentation

Neuroblastoma is a tumor with multiple clinical manifestations related to the site of the primary tumor, the presence of metastases, and the production of certain metabolic tumor byproducts. In 50% to 75% of reported cases, patients present with an abdominal mass. The tumor may be hard, nodular, fixed, and painful on palpation. Generalized symptoms include weight loss, failure to thrive, abdominal pain and distention, fever, and anemia.[1,5,10,14] Hypertension is found in 25% of cases and is related to the production of catecholamines by the tumor. Instances of hypercalcemia have been observed in association with neuroblastoma, and hemoperitoneum caused by sudden spontaneous rupture of the neoplasm has also been reported.[53,54]

Neoplasms arising in the upper mediastinum or neck may involve the stellate ganglion and cause Horner syndrome, which is characterized by ptosis, miosis, enophthalmos, anhydrosis, and heterochromia of the iris on the affected side.[5,10,14] Metastases to the bony orbit may produce proptosis or bilateral orbital ecchymosis—often referred to as "panda eyes" or "raccoon eyes" (Fig. 31-2). The latter finding in a child

FIGURE 31-2 Child with bilateral orbital ecchymoses ("panda eyes" or "raccoon eyes") resulting from orbital metastases from neuroblastoma.


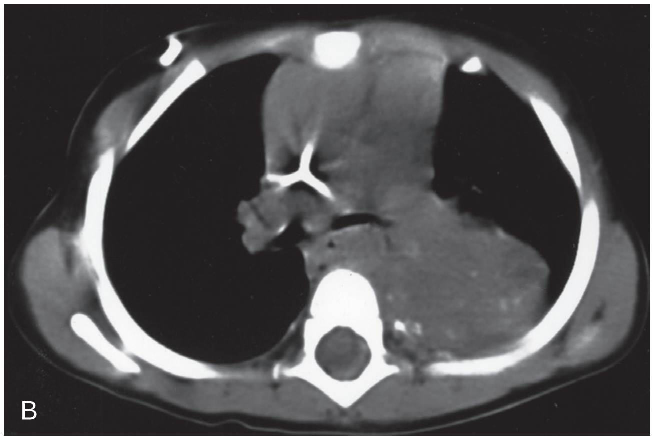


**FIGURE 31-3** **A,** Plain chest radiograph shows the presence of a left upper thoracic tumor. **B,** Computed tomography scan documents a mass in the posterior mediastinum that contains calcium, suggestive of a neuroblastoma.

without a history of trauma should always raise the index of suspicion for the presence of a malignancy. Mediastinal tumors may be associated with respiratory distress because of the tumor's interference with lung expansion and dysphagia caused by extrinsic pressure on the esophagus (Fig. 31-3).[10,55–57] Mediastinal and paraspinal retroperitoneal lesions may manifest with paraplegia related to tumor extension through an intervertebral foramen, resulting in a dumbbell- or hourglass-shaped lesion that may cause extradural compression of the spinal cord.[14,58–61] In a few patients, cauda equina syndrome has also been observed. Pelvic tumors may be associated with bladder and bowel dysfunction. They are usually palpable on rectal examination. They must be differentiated from presacral teratoma, yolk sac tumor, nonosseous Ewing tumor, and pelvic rhabdomyosarcoma.[5,10]

Anemia is often related to bone marrow invasion by the tumor. Excessive catecholamine production by the tumor may result in flushing, sweating, and irritability. Acute cerebellar ataxia, characterized by opsomyoclonus and nystagmus ("dancing eye syndrome"), has been observed.[62–66] This syndrome is seen more frequently (>60%) in patients with primary mediastinal tumors, in patients with stage I or II disease, and in infants younger than 1 year of age.[62,66] In addition, they are often more histologically mature. The involuntary muscular contractions and random eye movements are unrelated to metastases. The cause is suggested to be an autoimmune phenomenon related to an antigen–antibody complex involving antibodies that cross-react with Purkinje cells in the cerebellum.[62,64,66,67] Poor school performance and learning deficits may occur as sequelae.[64,65] The survival rate for patients who present with opsomyoclonus and nystagmus is approximately 90%. Presence of the dancing eye syndrome in patients who present with advanced tumors and N-myc overexpression, however, is associated with a poor outcome.[68] Despite tumor resection and adrenocorticotropic hormone treatment, the neurologic symptoms in survivors (including learning disabilities and attention deficits) may persist for many years.[63–65]

Infants with neuroblastoma, ganglioneuroblastoma, and, occasionally, benign ganglioneuroma may present with intractable diarrhea characterized by watery, explosive stools and hypokalemia.[69–71] The diarrhea is related to the production of vasoactive intestinal polypeptide (VIP) by the tumor.[10,69–71] Tumors associated with this syndrome often have somatostatin receptors and are differentiated, low-risk tumors. Serum VIP levels can serve as a tumor marker; the tumor often does not secrete catecholamines. These observations suggest that somatostatin receptor expression is a favorable prognostic factor.[72,73]

Children with advanced neuroblastoma frequently show evidence of protein-calorie malnutrition associated with immunoincompetence, based on anergy to a variety of skin test antigens.[74,75] Rickard and colleagues[74,75] demonstrated that patients with stage IV neuroblastoma who were malnourished at diagnosis had more treatment delays and a significantly worse outcome than adequately nourished counterparts with similar disease severity. These findings suggest that a nutritional assessment at diagnosis should be a component of the patient's staging.[74] In addition, Van Eys and colleagues[76] and Rickard and colleagues[74,75] showed that significant nutritional depletion occurs with multimodal cancer therapy and that total parenteral nutrition can replete and maintain the patient's nutritional status during intensive tumor therapy. In another study, Sala and colleagues[77] reported that the incidence of malnutrition in children with advanced neuroblastoma was 50%. They stressed the importance of nutritional status and its possible influence on the course of the disease and survival. Of interest is a study from Toronto, Canada, that implies that mandatory folic acid fortification of flour—initially intended to reduce the incidence of neural tube defects—was associated with a 60% decrease in the incidence of neuroblastoma in the province of Ontario.[78]

Neuroblastoma may spread by direct extension into surrounding structures, lymphatic infiltration, or hematogenous metastases. Regional and distant lymph nodes, liver, bone marrow, and bone cortex are frequently involved.[5,10,11,79–81] Patients with bone cortex metastases have an ominous prognosis. Bone metastases occur in sites containing red marrow and involve the metaphyseal areas of long bones in addition to the skull, vertebral column, pelvis, ribs, and sternum.[1,5,10,11] Bone lesions may cause extreme pain and may be first identified when a child refuses to walk because of leg pain. Hematogenous metastases to the brain, spinal cord, and heart are unusual. Brain metastases usually manifest in

older children with headaches and seizures.[8,82] Lung metastases are found on chest radiographs in only 4% of patients.[83] This may be the result of direct extension to the lung from mediastinal lymph nodes or diffuse hematogenous spread, presenting with a radiographic pattern that may be confused with pulmonary edema or interstitial pneumonia.[83] Lung involvement by intralymphatic metastases (not seen on chest radiographs) may be noted at autopsy. Occasionally, patients with advanced disease present with a bleeding diathesis related to thrombocytopenia from extensive involvement of bone marrow and interference with hepatic production of clotting factors by liver metastases. Multiple subcutaneous skin nodules and hepatomegaly may occur in infants with stage IV-S neuroblastoma.

# Diagnosis

Diagnosis of neuroblastoma is made through a variety of imaging and isotopic studies, serum and urine determinations, and histologic and genetic evaluation of tumor tissue. On the plain abdominal radiograph, approximately 50% of cases may show finely stippled tumor calcification.[10,11,14] Radiographs also may show displacement of bowel gas by a mass. Paraspinal widening is commonly found with celiac axis tumors. Chest radiographs may show a posterior mediastinal tumor, a paraspinal widening above the diaphragm from extension of an abdominal tumor, or a primary thoracic tumor. The diagnostic workup of patients with retroperitoneal tumors includes an initial upright radiograph of the abdomen, an ultrasound examination to distinguish a cystic from a solid lesion, and an evaluation for potential obstruction or compression of the inferior vena cava. As a rule, obstruction of the inferior vena cava in patients with neuroblastoma suggests the presence of an initially unresectable lesion.[10,84] Computed tomography (CT) can demonstrate tumor calcification in approximately 80% of cases (Fig. 31-4).[14,85] With CT studies using contrast enhancement, one can often distinguish kidney and liver from adrenal and paraspinal lesions and evaluate for intracranial extension of skull metastases.[10,85,86] Magnetic resonance imaging (MRI) is extremely useful in detecting intraspinal tumor extension and, in some instances, the tumor's relationship to major vascular structures. Helical (spiral) CT with three-dimensional reconstruction is also a useful method of evaluating this latter relationship. Abdominal CT is performed with intravenous contrast material, so that an intravenous urogram can be acquired during the same study.[84] In most instances, paraspinal or adrenal neuroblastoma causes lateral or downward displacement of the ipsilateral kidney or ureter (or both). A separate intravenous urogram is not necessary. Metaiodobenzylguanidine (MIBG) also images both soft tissue and bony disease. A recent study for the International Neuroblastoma Risk Group (INRG) task force proclaims MIBG the most sensitive and specific imaging modality for staging purposes for neuroblastoma, in addition to recognizing response to treatment, especially when a semiquantitative scoring method is used.[87] A long bone survey, isotopic bone scintigraphy (using the bone-seeking isotopes technetium and $^{131}$I-MIBG), and multiple bone marrow aspirates are also obtained.[10,11,84,85] Isotopic bone scans are also used to identify bone metastases; they show a close correlation with the radiographic skeletal survey and are occasionally more sensitive.[85] False-positive bone scans can occur in cases of recent bone trauma or inflammation. The bone-seeking isotopes are picked up by metastatic foci in the bone and by the punctate calcifications in the primary tumor (Fig. 31-5).[10,14] Demonstration of the bone-seeking isotope in a retroperitoneal or posterior mediastinal mass suggests that the lesion is a neuroblastoma. Although angiography was once performed to evaluate many childhood tumors, this test is rarely used today because vascular structures can be readily identified with less potential morbidity by other imaging studies such as helical CT or magnetic resonance angiography (Fig. 31-6).

Because neuroblastoma is a tumor derived from neural crest cells, it may secrete hormonal products and is likely a member of the amine precursor uptake and decarboxylation (APUD) family of tumors. More than 90% of children with neuroblastoma have tumors that produce high levels of catecholamines or their byproducts. Quantification of

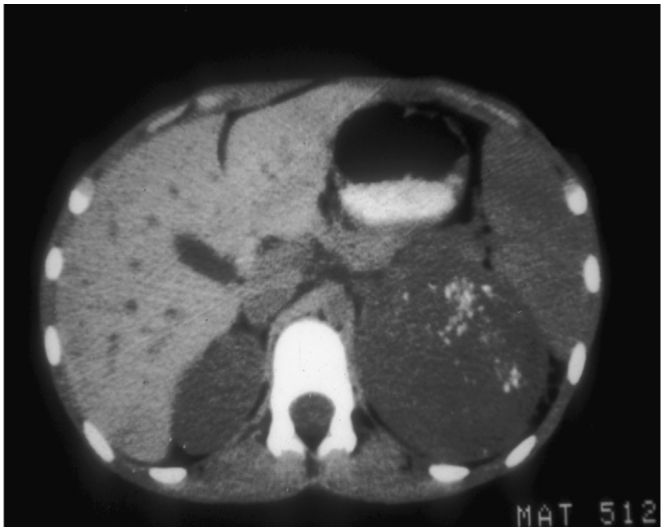


**FIGURE 31-4** Abdominal computed tomography shows a retroperitoneal mass with stippled calcification, consistent with neuroblastoma.

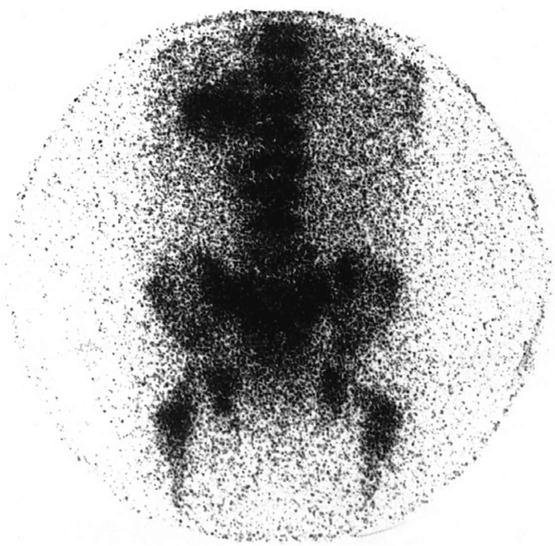

**FIGURE 31-5** $^{123}$I-MIBG scintiscan shows the presence of bone metastases and uptake of the isotope in a primary tumor in the adrenal gland.

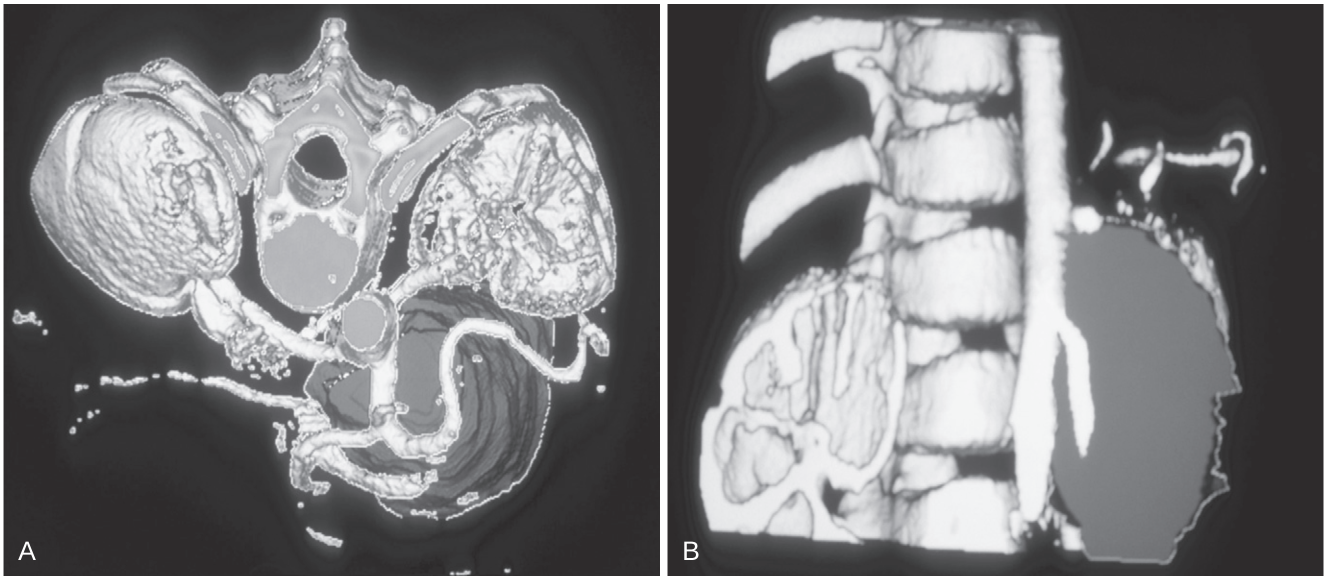


**FIGURE 31-6** Helical computed tomography scan with three-dimensional reconstruction of a neuroblastoma arising near the celiac axis. **A,** Anterior view indicates that the tumor does not involve the branches of the celiac axis. **B,** Lateral view demonstrates that the superior mesenteric artery passes through the tumor.

catecholamine byproduct secretion is best done by 24-hour urine collection.[86] Adrenaline, noradrenaline, dopamine, metanephrine, HVA, VMA, and vanillylglycolic acid levels are determined. Children with immature, more undifferentiated tumors tend to excrete higher levels of certain byproducts (e.g., HVA).[14] Patients with more mature tumors excrete more VMA. In rare instances, however, the tumor does not secrete excessive catecholamines. Prasad and colleagues[88] suggested that these are parasympathetic neuroblastomas that secrete increased levels of acetylcholine and fail to metabolize tyrosine to dopamine. Patients with advanced malignancy have elevated urine concentrations of cystathionine and homoserine; increased serum levels of neuron-specific enolase, ferritin, and lactic dehydrogenase; and, in 25% of cases, sera positive for carcinoembryonic antigen.[89–93] Hann and colleagues[89] reported that 63% of patients with stage IV disease had high serum ferritin levels, which was predictive of a poor prognosis, especially in girls older than 2 years. A number of studies showed that neuroblastic tumors produce increased serum levels of neuron-specific enolase.[90,92] Zeltzer and colleagues[93] documented that neuron-specific enolase levels are elevated in 96% of patients with metastatic disease and that high serum levels are associated with a poor prognosis, particularly in infants. Elevated serum lactic dehydrogenase levels are also associated with a poor prognosis in localized neuroblastoma.[91] Although these observations are of historical interest, none of these serum levels are independent prognostic factors, nor are they currently used to determine treatment. Although histologic examination of tissue is the key to the conclusive diagnosis of neuroblastoma, in advanced disease, rosettes of tumor cells in bone marrow aspirate and increased urinary excretion of VMA or other catecholamine byproducts are often considered indicative of the diagnosis. Immunologic analysis of bone marrow aspirate may be more sensitive than conventional analysis in detecting tumor cells.[94] Serial immunocytologic analysis of peripheral blood samples has also identified circulating neuroblasts, documenting tumor dissemination.

## Staging

Various staging schemes for neuroblastoma were used in the past. In 1988, an international staging system was devised, establishing a common set of criteria that could be used worldwide and would permit the accrual of large numbers of cases and allow valid comparisons of data (Table 31-1).[95] This system takes into account tumor size and location relative to the midline, in addition to the presence and degree of metastatic disease. It depends on the extent of surgical resection of the primary tumor in patients with nonmetastatic disease. Recently, the INRG developed a new staging system that takes into account pretreatment imaging of the tumor and bone marrow morphology, instead of surgical resection, which is dependent upon the approach of the surgeons and thus varies from institution to institution; this system appears in Table 31-2.[96] The aim of this system is to better evaluate pretreatment risk based on image-defined risk factors, and was developed to be used in tandem with the international system. In contrast to the International Neuroblastoma Staging System (INSS), infiltration across the midline is not included in this classification system.[96] Prospective analyses to validate this new system are ongoing.

## Pathology and Histology

The pathologic classification of neuroblastoma has been revised, and histologic features of the tumor that have important prognostic value have been established.[97–99] Previously, the Shimada classification system was used. The Shimada

**TABLE 31-1**
**International Neuroblastoma Staging System**

| Stage | Description |
|---|---|
| I | Localized tumor confined to area of origin; complete excision, with or without microscopic residual disease; ipsilateral and contralateral lymph nodes negative (nodes attached to primary tumor and removed en bloc with it may be positive) |
| IIA | Unilateral tumor with incomplete gross excision; ipsilateral and contralateral lymph nodes negative |
| IIB | Unilateral tumor with complete or incomplete excision; positive ipsilateral, nonadherent regional lymph nodes; contralateral lymph nodes negative |
| III | Tumor infiltrating across the midline with or without lymph node involvement; or unilateral tumor with contralateral lymph node involvement; or midline tumor with bilateral lymph node involvement or bilateral infiltration (unresectable) |
| IV | Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver, or other organs |
| IV-S | Localized primary tumor as defined for stage I or II with dissemination limited to liver, skin, or bone marrow (limited to infants younger than 1 yr) |

From Brodeur GM, Pritchard J, Berthold F, et al: Revision of the international criteria for neuroblastoma diagnosis, staging and response to treatment. J Clin Oncol 1993;11:1466-1477; Brodeur GM, Seeger RC, Barrett A, et al: International criteria for diagnosis, staging, and response to treatment in patients with neuroblastoma. J Clin Oncol 1988;6:1874-1881.

**TABLE 31-2**
**The New International Neuroblastoma Risk Group Staging System**

| Stage | Description |
|---|---|
| L1 | Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment |
| L2 | Locoregional tumor with presence of one or more image-defined risk factors |
| M | Distant metastatic disease (except stage MS) |
| MS | Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow |

Note: Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined in the table.
Reprinted from Monclair T, Brodeur GM, Ambros PF, et al: The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report. J Clin Oncol, 2009 10;27:298-303, with permission. 

system divided neuroblastic tumors into age-related favorable and unfavorable histologic categories, based on whether the tumor exhibited a stroma-rich or stroma-poor appearance (Table 31-3).[98] Stroma-rich tumors are characterized by extensive Schwannian stroma and signs of neuroblastic differentiation (i.e., developed nuclear and cytoplasmic features of ganglion cells). Stroma-poor tumors contain immature, undifferentiated neural crest cells and have a high mitotic karyorrhexis index (MKI). The MKI refers to nuclear fragmentation and is determined by the sum of the number of necrotic tumor cells; the number of cells with mitosis; and the number of cells with malformed, lobulated, or pyknotic nuclei per 5,000 cells examined. The MKI varies with age; a high MKI value in infants younger than 18 months is greater than 200/5,000 cells, and for those older than 18 months it is greater than 100/5,000 cells. All patients older than 5 years have unfavorable

**TABLE 31-3**
**Modified Shimada Pathologic Classification of Neuroblastic Tumors**

| | Age | *Favorable Histology* | *Unfavorable Histology* |
|---|---|---|---|
| Stroma-rich appearance | All | Well differentiated (ganglioneuroma) Ganglioneuro-blastoma, intermixed | Ganglioneuro-blastoma, nodular |
| Stroma-poor appearance (i.e., neuroblastoma) | Age $<$ 18 months | MKI $<$ 4% | MKI $>$ 4% or undifferentiated |
| | Age 18-60 months | MKI $<$ 2% and differentiating | MKI $>$ 2%, or undifferentiated or poorly differentiated |
| | Age $>$ 5 years | None | All |

From Shimada H, Chatten J, Newton WA Jr, et al: Histopathologic prognostic factors in neuroblastoma: Definition of subtypes of ganglioneuroblastoma and an age-linked classification of neuroblastoma. J Natl Cancer Inst 1984;73:405-416; Shimada H, Stram DO, Chatten J, et al: Identification of subsets of neuroblastomas by combined histopathologic and N-myc analysis. J Natl Cancer Inst 1995;87:1470-1476.
MKI, mitotic karyorrhexis index.

histology. Stroma-poor tumors often have *MYCN* amplification, a high MKI, and a dismal outcome. A report by Shimada and colleagues[99] documented that both histology and *MYCN* amplification provided prognostic information that was independent of staging. Neuroblastomas with *MYCN* amplification have a characteristic histopathologic phenotype and a rapidly progressive clinical course.

The International Neuroblastoma Pathology Classification (INPC) adopted the Shimada classification with some minor modifications.[90,100–102] This age-linked classification is both prognostically significant and biologically relevant. The current system subdivides the undifferentiated subtype into undifferentiated and poorly differentiated tumors; changes the name of "stroma-rich, well-differentiated" tumors to "ganglioneuroma intermixed"; and adds a descriptive Schwannian, stroma-dominant character to ganglioneuroma.[103] There is also a ganglioneuroblastoma nodular (GNBn) group that is both Schwannian stroma rich/stroma dominant and stroma poor. Age remains a critical prognostic factor, and the grade of differentiation and MKI have different prognostic effects, depending on the patient's age at diagnosis. Favorable tumors are those that are poorly differentiated in children younger than 1.5 years of age, differentiating in children younger than 5 years of age, ganglioneuroblastoma intermixed, and ganglioneuroma. MKI is low (in those less than 5 years of age) or intermediate (in those less than 1.5 years of age) in this group as well. Unfavorable tumors are those that are undifferentiated or poorly differentiated in children older than 1.5 years, or any subtype of neuroblastoma in children older than 5 years. Patients with high MKI, or patients older than 1.5 years with an intermediate MKI, also have an unfavorable prognosis.[101] Although the presence of calcification was thought to favorably influence survival, further studies demonstrated that calcification does not have an independent prognostic impact.[97,103] Favorable Shimada histology was associated with an 85% survival rate, compared with 41% for unfavorable histologic

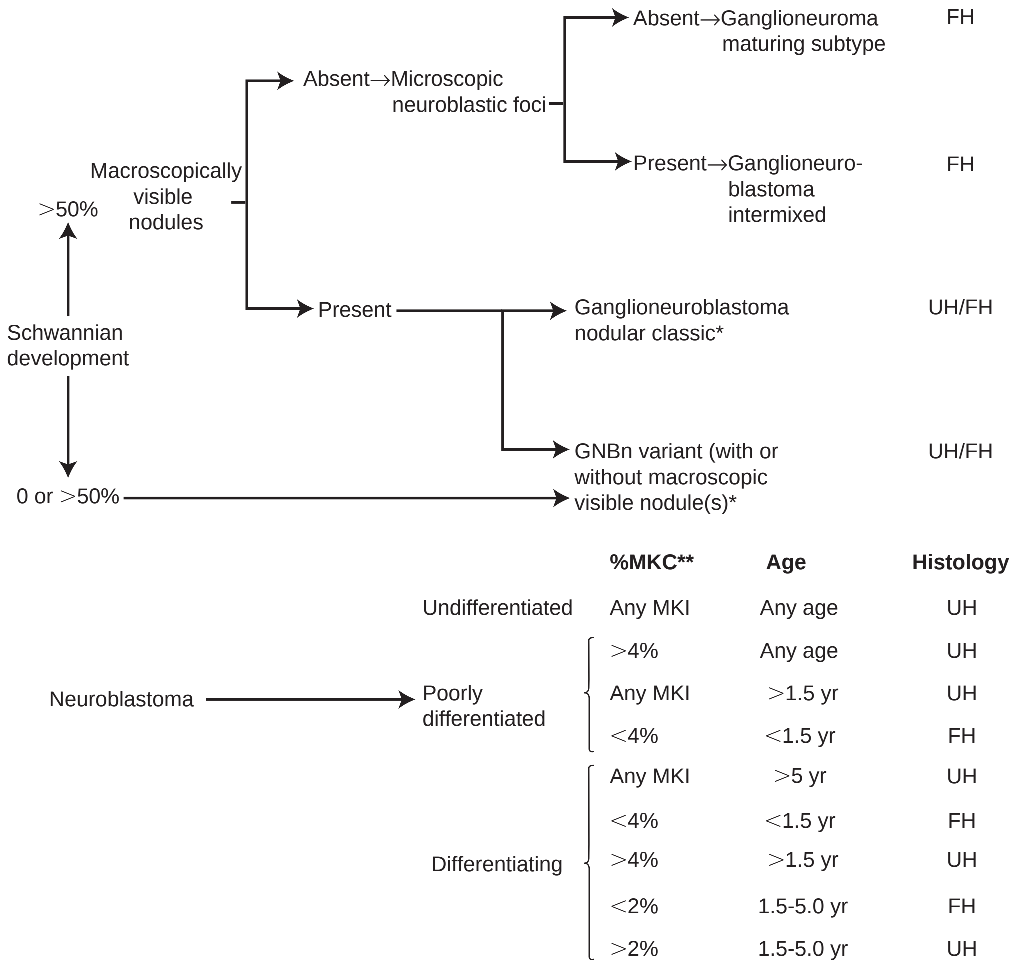


**FIGURE 31-7** International Neuroblastoma Pathology Classification. FH, favorable histology; GNBn, ganglioneuroblastoma nodular; MKI, mitotic karyorrhexis index; %MKC, mitotic and karyorrhectic cells; UH, unfavorable histology; *classic GNBn (single, macroscopically visible, usually hemorrhagic nodule in stroma-rich, stroma-dominant tissue background; **MKC 2%, 100 of 5,000 cells; MKC 4%, 200 of 5,000 cells. (From Peuchmaur M, d'Amore ES, Joshi VV, et al: Revision of the International Neuroblastoma Pathology Classification: Confirmation of favorable and unfavorable prognostic subsets in ganglioneuroblastoma, nodular. Cancer 2003;98:2274-2281.)

types. All GNBn cases were initially classified as unfavorable tumors. Umehara and colleagues[104] were the first to define subsets of these specific neoplasms that exhibit different behavior. Peuchmaur and colleagues[105] recently revised the INPC by dividing GNBn cases into two prognostic subsets—favorable and unfavorable. The favorable type was associated with an 86% event-free survival, whereas the unfavorable type (two thirds of cases) had only a 32% event-free survival. Children with the favorable subset of GNBn have an overall survival of greater than 90%, compared with 33.2% for those with the unfavorable GNBn subset (Fig. 31-7).[106] Large cell neuroblastoma has been identified as a distinct phenotype with aggressive clinical behavior.[107] These tumors have unfavorable histologic features, including monomorphous undifferentiated neuroblasts, a low incidence of calcification, and a high MKI. Immunohistochemical studies showed that large cell neuroblastoma cells stained positive for neuron-specific enolase, prodrug gene products, and tyrosine hydroxylase, and were negative for CD99.[107]

On gross examination, neuroblastoma usually appears as a highly vascular purple-gray mass that is often solid but occasionally cystic. The tumor has an easily ruptured, friable pseudocapsule that may lead to significant hemorrhage during operative manipulation. The tumor is often necrotic, especially the undifferentiated form. Mature tumors (ganglioneuromas) have a more solid consistency and frequently have a fleshy white color. The histologic pattern may be quite variable. Primitive stroma-poor neuroblastomas may be indistinguishable from other small, blue round cell tumors, such as Ewing tumor, rhabdomyosarcoma, or primitive neuroectodermal tumors. The neuroblast is a small round cell consisting predominantly of the nucleus without much cytoplasm. Immature, undifferentiated tumors are characterized by closely packed small spheroid cells without any special arrangement or differentiation.[108] Nuclei may appear cone shaped and are hyperchromic. Rosette formation may be observed and is considered a sign of early tumor differentiation (Fig. 31-8). The center of each rosette is formed by a tangle of fine nerve fibers. More mature-appearing, stroma-rich tumors may contain cells that resemble normal ganglion cells, with an admixture of histologic components characterized by abundant nerve filaments, neuroblastic rosettes, and ganglion cells all seen in a single microscopic field.[28,109] On electron microscopy, neurofibrils and electron-dense, membrane-bound neurosecretory granules may be observed. The neurosecretory granules may be the site of conversion of dopamine to norepinephrine.

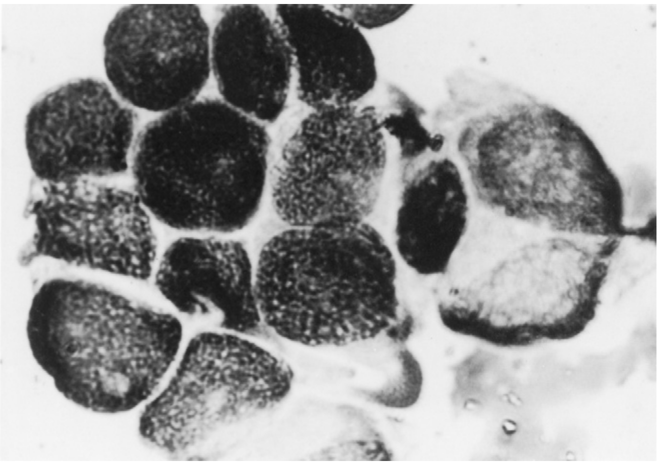

FIGURE 31-8 Histologic appearance of rosettes of neuroblastoma cells from a bone marrow aspirate, an early sign of tumor differentiation.

These ultrastructural findings and genetic identification of the tumor tissue can usually separate neuroblastoma from other small cell tumors. Segregation of neuroblastoma from other tumors can also be achieved by immunohistochemical staining that is positive for neurofilament proteins (S-100), synaptophysin, neuron-specific enolase, ganglioside GD2, chromogranin A, and tyrosine hydroxylase staining for these markers is negative in other small round cell tumors.[110]

Instances of spontaneous maturation from a highly malignant, undifferentiated neuroblastoma to a ganglioneuroblastoma, and subsequently to a benign ganglioneuroma, have been observed. Ambros and colleagues[111] reported that maturing neuroblastomas consist of both Schwann cells and neuronal cells, including ganglion cells. Schwann cells have normal numbers of chromosomes and triploid flow cytometry, in contrast to other neuronal cells, including ganglion cells.[102] These observations suggest that Schwann cells may be a reactive population of normal cells that invade a neuroblastoma, recruited or attracted by trophic factors, and may be responsible for tumor maturation and serve as an antineuroblastoma agent.[112,113] Schwann cells also produce angiogenesis inhibitors that induce endothelial cell apoptosis and may limit tumor growth by restricting angiogenesis.[1,114]

# Biologic and Genetic Alterations

Unique oncogenes are observed in tumors, such as *MYCN* and *RAS* oncogenes.[1,8] Amplification of *MYCN* (>10 copies) is associated with advanced disease, tumor progression, and a poor outcome, especially in children older than 1 year.[1,8,95,98,115,116] The *MYCN* proto-oncogene is located on the short arm of chromosome 2p24. Double minutes and long, nonbanding staining regions have been observed at this site and may represent amplified cellular genes. Studies have determined that the MycN protein binds DNA and leads to an increase in the level of endogenous Mdm2 mRNA and protein expression, with consequent p53 inhibition. This modification of Mdm2 levels by N-myc may partially explain its role in the aggressiveness of neuroblastoma.[117,118] Approximately 30% of patients with neuroblastoma have tumors with *MYCN* amplification. More than 90% of patients with *MYCN* amplification have rapidly progressive disease and are resistant to therapy.

Cellular DNA content is a predictor of response to chemotherapy in infants with unresectable neuroblastoma. DNA flow cytometry studies evaluating tumor ploidy indicate that children with diploid tumors have a worse outcome than those with aneuploid (hyperdiploidy or triploidy) tumors.[1,10] Similar to *MYCN* status, DNA ploidy is of prognostic value independent of stage and age, and the two factors (*MYCN* status, and ploidy) together provide important complementary prognostic information for infants.[1,111] DNA ploidy flow cytometry correlates well with response to chemotherapy and outcome. *MYCN* amplification is commonly associated with chromosome 1p deletion and diploidy.[119,120] Diploid tumors are commonly associated with an unbalanced gain of chromosome 17q, even in the absence of *MYCN*.[1,6,116,120] The most common cytogenetic abnormalities in neuroblastoma are 1p deletion and 17q gain.[119] Both abnormalities are poor prognostic factors and are associated with worse outcomes.[1,6,121–123] Allelic loss of 11q and 14q and gains of 4q, 6q, 11q, and 18q have also been observed (Table 31-4).[1]

**TABLE 31-4**
**Genetic Alterations in Neuroblastoma**

| *Genetic Feature* | *Associated Factor* | *Risk Group* |
|---|---|---|
| *MYCN* amplification | Diploidy or tetraploidy, allelic loss of 1p, high Trk-B, advanced stage (III, IV) | High |
| Allelic gain 17q | More aggressive tumor associated with *MYCN* amplification | High |
| Gain at 4q, 6p, 7q, 11q, 18q | Occurs concurrently with *MYCN* amplification | Risk related to *MYCN* status |
| Allelic loss 1p36 | Often associated with *MYCN* amplification | High |
| Allelic loss 11q | Few associated with *MCYN* amplification; correlates with LOH 14q | Intermediate decreased survival in patients without *MYCN* amplification |
| Allelic loss 14q | Correlates with LOH 11q, inverse relationship with allelic loss 1p and *MYCN* amplification | Intermediate |
| Predisposition of 16p12-13 | Familial neuroblastoma, multifocal and bilateral neuroblastoma | Low |
| Association with chromosome 10 (*RET*-oncogene) | Hirschsprung disease | Variable |
| Association with 11p15.5 | Beckwith-Weidemann syndrome | Low |

Note: This table does not include changes in the genetic expression of TRK-A, TRK-B, and TRK-C; the multidrug-resistant protein gene; telomerase; or others that are covered elsewhere in this chapter.
LOH, loss of heterozygosity.

High expression of the neurotropin Trk-A (a high-affinity nerve growth factor receptor) is associated with a good prognosis and is inversely related to N-myc.[116,124] Trk-A is observed in young infants and in those with stage I and stage IV-S tumors, and indicates a very favorable outcome.[116,124] Trk-A is associated with neural cell differentiation and tumor regression and may play a role in angiogenic inhibition. Trk-A downregulates angiogenic factor expression and decreases the number of microvessels in neuroblastoma tumor cell lines. Multivariate analysis, however, suggests that N-myc expression is a more important independent prognostic factor. The low-affinity nerve growth factor receptor gene is another proto-oncogene that has a prognostic effect similar to Trk-A and probably influences cellular maturation.[1,8,125] In contrast, high expression of Trk-B with its ligand BDNF may provide an autocrine survival pathway in unfavorable tumors, particularly those with *MYCN* amplification, possibly by providing a tumor cell survival or growth advantage.[1,126,127] The Trk-B–BDNF pathway also contributes to enhanced angiogenesis, tumorigenicity, cell survival, and drug resistance.[1,126] These patients have more advanced disease, are usually older than 1 year, and have a dismal outcome.[1,126,127] Trk-C expression has also been identified in neuroblastoma and is usually observed in lower-stage tumors that do not express N-myc.[1,128] A recent report identified targets of *TRK* gene expression, and recognized upregulation of proapoptotic factors and angiogenesis inhibitors. Conversely, Trk-B expression was associated with upregulation of genes related to invasion and therapy resistance. Its activation is associated with increased proliferation, migration, angiogenesis, and chemotherapy resistance of neuroblastoma cells.[126,129]

Another gene has been cloned, the multidrug resistance (MDR)-associated protein gene, that is associated with chemotherapy resistance, overexpression of N-myc, and a poor outcome.[130] The prognostic role of the *MDR* gene (*MDR-1*) in neuroblastoma is controversial.[130,131] High levels of the *MDR*-associated protein gene (located on chromosome 16), however, are associated with a poor outcome. This effect is independent of stage, N-myc expression, and Trk-A status.[130] Similarly, elevated P-glycoprotein levels are associated with progressive disease and a poor outcome.[132,133] Telomerase is increased in tumor cells and maintains cell viability by preserving the telomeres that protect the end of chromosomes.[1,134] There is an inverse relationship between telomerase levels and outcome in neuroblastoma and a direct correlation between telomerase levels and *MYCN* amplification.[1] CD44 is a glycoprotein found on the cell surface of a number of tumors, including neuroblastoma. High expression of CD44 is associated with a favorable outcome and is usually found in well-differentiated tumors. In contrast, Nm23 overexpression is observed in instances of advanced and aggressive neuroblastoma.[135] The ganglioside GD2 is found on human neuroblastoma cell membranes, and increased levels are associated with active disease and tumor progression. Gangliosides inhibit the tumor-specific immune response, and GD2 has become a target for immunotherapy.[136]

Evaluation of the relationship between tumor angiogenesis and outcome in infants with neuroblastoma demonstrates that increased tumor vascularity characterized by microvessel density correlates with advanced disseminated disease and the likelihood of metastases.[137–140] Angiogenesis is associated with *MYCN* amplification, unfavorable histology, and poor outcome. Neuroblastoma produces angiogenic factors that induce blood vessel growth, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF-A), stem cell factor, and their respective receptors—Flk-1, PDGFR, and c-Kit.[141] Komuro and colleagues[142] demonstrated that high VEGF-A expression correlated with stage IV disease and suggested that it could be a target for antiangiogenic therapy. Kaicker and colleagues[143] noted that vascular endothelial growth factor VEGF antagonists inhibit angiogenesis and tumor growth in experimental neuroblastoma in athymic mice with xenograft neuroblastoma cell line NGP. They also found that thalidomide suppressed angiogenesis and reduced microvessel density but not tumor growth. Kim and colleagues[144] and Rowe and colleagues[145] also demonstrated inhibition of tumor growth in experimental neuroblastoma models using antiangiogenic strategies. Imatinib mesylate, a compound used to treat patients with gastrointestinal stromal tumors, has been shown to decrease the growth of neuroblastoma in vivo and in vitro, decrease cell viability, and increase apoptosis (by ligand-stimulated phosphorylation of c-Kit and PDGFR) in a severe combined immunodeficiency (SCID) mouse model.[141] Davidoff and colleagues[138] demonstrated that gene therapy using in situ tumor cell transduction with retroviral vectors can deliver angiogenesis inhibitors for the Flk-1 receptor and restrict tumor-induced angiogenesis and tumor growth.

The Bcl-2 family of proteins is responsible for relaying apoptotic signals that influence tumor cell regression and is expressed in most neuroblastomas. The *BCL-2* gene produces a protein that prevents apoptosis. The level of Bcl-2 expression is high in advanced cases associated with a poor outcome and low in cases demonstrating tumor apoptosis (regression) and differentiation. High Bcl-2 expression may also play a role in acquired resistance to chemotherapy.[146] Subgroups of the Bcl family include Bcl-xL, which inhibits apoptosis, and Bcl-xS, which induces natural cell death. VEGF upregulates Bcl-2 expression and promotes neuroblastoma cell survival by altering apoptosis and its regulation proteins.[147] Elevated caspase levels (enzymes responsible for apoptotic signaling) are associated with an improved outcome in neuroblastomas that demonstrate favorable biologic features.[1] It has been shown that CpG–island hypermethylation inactivates caspase-8, TRAIL apoptosis receptors, the caspase-8 inhibitor, in addition to other proapoptotic factors.[148,149] In view of this finding that gene hypermethylation leads to resistance patterns, demethylating agents, including decitabine, are currently being investigated in preclinical studies.[150]

## Neuroblastoma in Infancy

For many years, the age of the patient and the stage of disease at the time of diagnosis were the two key independent variables determining prognosis in children with neuroblastoma. Evans and colleagues[3] and others found that infants younger than 1 year and those with stage I, II, or IV-S disease had a significantly better outcome.[5,11,34,151,152] Historically, patients older than 1 year and those with advanced disease (stages III and IV) did poorly. The worst survival data were observed in patients older than 1 year with stage IV disease and metastases to cortical bone.[1,5,11,14,153]

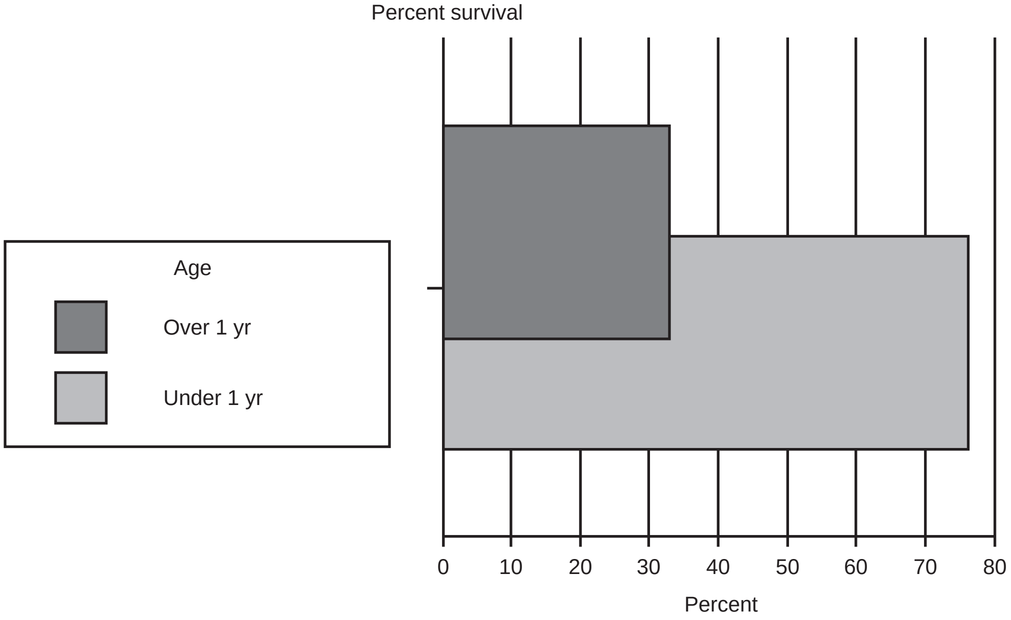


**FIGURE 31-9** Bar graph demonstrates the improved survival in infants with neuroblastoma who are younger than 1 year.

However, recent reviews have confirmed that 18 months serves as a better cutoff to predict outcome.[154–157]

Infants younger than 18 months at diagnosis have a significantly improved outcome. At the Riley Hospital for Children (Indianapolis, IN), the survival rate was 76% for infants younger than 1 year and only 32% for older patients (Fig. 31-9).[4] This favorable outlook for patients younger than 1 year extends across all stages, including infants with stage IV metastatic disease. The incidence of stage IV lesions in infants younger than 1 year is 30% compared with 60% to 70% in older patients.[4]

Infants with stage IV disease respond better to chemotherapy than do older children; 50% of infants have a complete response to treatment compared with 22% of older children.[158] This observation suggests that resolution of metastases may have a greater impact on length of survival than does the surgical excision. Further, this implies that surgical resection is beneficial in some infants and should be attempted when disseminated disease is controlled by chemotherapy. However, more intensive chemotherapy regimens and bone marrow transplantation (BMT) may be necessary to achieve a cure, especially in highly selected infants presenting with adverse biologic markers.

## Stage IV-S

The most unusual group of patients with neuroblastoma is those infants younger than 18 months with stage IV-S disease. This stage is characterized by hepatomegaly produced by extensive metastatic disease, subcutaneous metastases, and positive bone marrow with a primary tumor that would otherwise be classified as stage I or II. Stage IV-S cases account for approximately 30% of patients with neuroblastoma recognized in the first year of life.[4]

Some infants succumb from complications of their stage IV-S disease rather than progression of the tumor. Complications of severe hepatomegaly include respiratory insufficiency, caused by significant elevation of the diaphragm by the large, tumor-filled liver; coagulopathy; and renal compromise resulting from abdominal compartment syndrome produced by the mass (Fig. 31-10).[4,151,159–161] Vomiting may occur because of a change in the gastroesophageal angle related to the diaphragmatic elevation, resulting in gastroesophageal reflux, protein-calorie malnutrition, and aspiration pneumonia. Total parenteral nutrition may be a useful therapeutic adjunct.[74–76] Most fatalities in stage IV-S cases occur in infants younger than 2 months with severe symptoms related to hepatomegaly, who do not tolerate therapy as well as do older infants.[4,162] Symptomatic hepatomegaly caused by tumor infiltration may benefit from low-dose radiation to the liver in the range of 600 to 1,200 Gy, administered in doses of 100 to 150 Gy/day.[4,5,159] Although some early reduction in the size of the liver is seen, and peripheral edema may resolve in a few weeks, complete resolution may take 6 to 15 months.[4] Resolution of the liver mass is probably related more to the natural course of stage IV-S disease than to radiotherapy. Administration of low-dose cyclophosphamide 5 mg/kg per day is a reasonable treatment alternative. Although some investigators advocate the insertion of a Dacron-reinforced Silastic sheet to create a temporary ventral abdominal wall hernia to accommodate the enlarged liver and reduce intra-abdominal pressure, mortality resulting from septic complications has been observed.[4,159,163] To reduce the risk of infection, Lee and Applebaum[164] recommend the use of an internal polytetrafluorethylene patch to create a temporary ventral hernia. The graft can be removed in stages as the bulk of the hepatic mass regresses over time.

Survival of infants with remote metastases is greater than 80%, often without specific treatment. Most patients with stage IV-S disease (>90%) have favorable genetic and biologic factors, including high Trk-A expression, no *MYCN* amplification, favorable histology, and no evidence of allelic loss of chromosome 1p. This suggests that the majority of stage IV-S tumors undergo spontaneous regression. Although most patients with stage IV-S disease do well, Wilson and

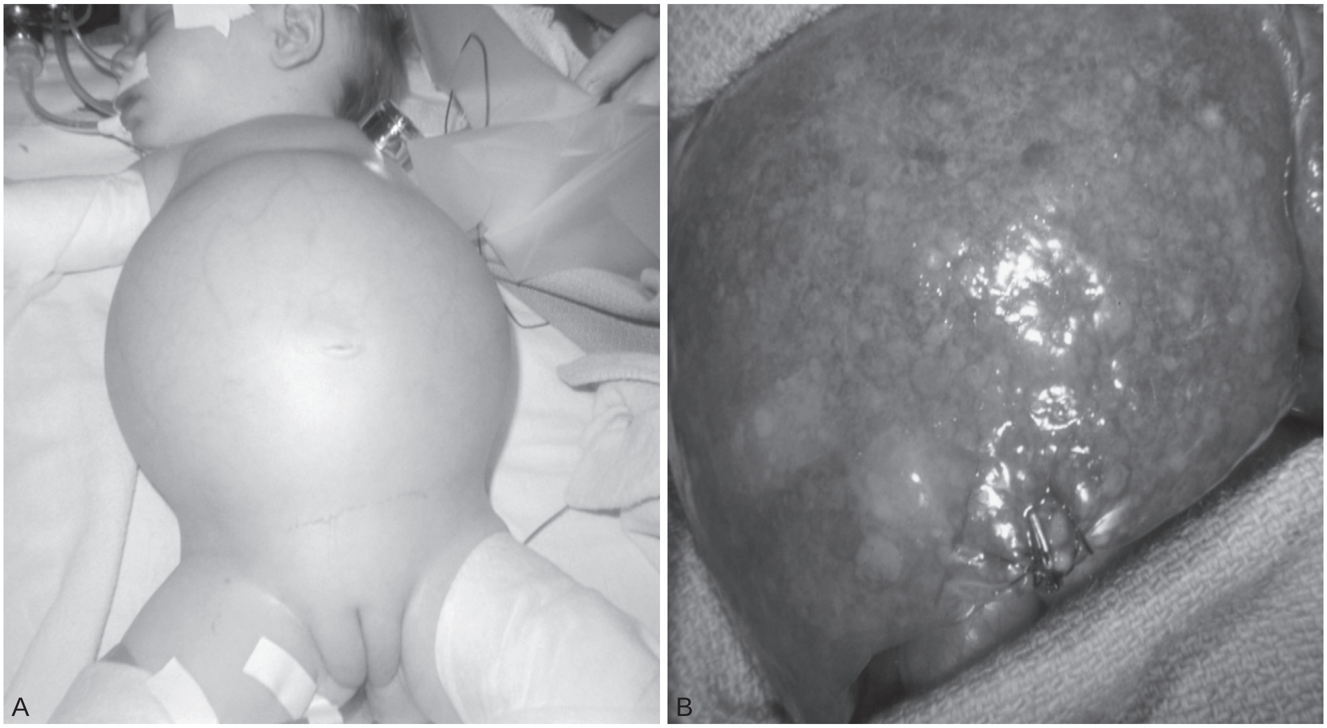


**FIGURE 31-10** **A,** Six-week-old infant presented with abdominal distention and hepatomegaly. **B,** Appearance of the liver at laparotomy. There were multiple metastatic nodules, and the biopsy confirmed the diagnosis of stage IV-S neuroblastoma.

colleagues[161] reported 18 cases with a heterogeneous tumor presentation and a survival rate of only 50%, including 3 patients with *MYCN* amplification. The presence of adverse genetic and biologic prognostic factors suggests that this subset of patients (<10%) requires more aggressive therapy. Of interest is that infants with multiple subcutaneous nodules seem to have the most favorable outlook. This may be because of increased immunologic activity as a result of tumor being present in multiple sites.[4] Increased uptake of major histocompatibility complex (MHC) class I antigen by neuroblastoma cells in vitro and in vivo may influence the outcome favorably.[165] Infants with stage IV-S disease have normal levels of MHC class I surface antigen expression, whereas those with stages I to IV have low levels.[165] Sugio and colleagues[166] reported that down-modulation of MHC class I antigen expression is associated with increased amplification of the *dMYCN* oncogene in patients with advanced disease.

In 2000, Nickerson and colleagues[162] described 80 infants with stage IV-S disease from the Children's Cancer Group (CCG). Fifty-eight cases were managed without specific therapy. All 44 asymptomatic patients survived without treatment. Symptomatic patients were treated with cyclophosphamide 5 mg/kg per day for 5 days and hepatic radiation at a dose of 4.5 Gy over 3 days. Five of six deaths occurred in symptomatic infants younger than 2 months. Event-free 5-year survival was 86%, and overall survival was 92%. Early intervention is imperative for stage IV-S patients with life-threatening complications (e.g., hepatosplenomegaly, coagulopathy, renal failure).[4,162] Surgical resection did not alter outcome. More aggressive chemotherapy is also required in those cases in which the tumor demonstrates more than 10 copies of *MYCN*, chromosome 1p deletion, or other adverse biologic markers.[4,162,167] Amplification of *MYCN* may be observed in 1 of 12 patients with stage IV-S tumors who develop progressive disease and die, despite having a favorable prognostic stage. In 2003, Schleiermacher and colleagues[167] reported on 94 infants with stage IV-S neuroblastoma in France; they observed an 88% overall survival and recommended a more intensive regimen using cisplatin and etoposide for those who require therapy. Some infants with stage IV-S disease have survived without resection of the primary tumor (in some, the primary tumor may not be identified).

## Cystic Neuroblastoma

Cystic neuroblastomas are relatively rare and are often identified on prenatal ultrasound examinations.[168] They characteristically occur in the adrenal gland, and almost all are diagnosed in early infancy (Fig. 31-11). Few are calcified, and only 10% are associated with elevation of urinary VMA and HVA levels.[169] They display a benign behavior and a favorable outcome. Some evidence suggests that they often regress and undergo spontaneous involution.[26] Some investigators have recommended observation alone, with close serial sonographic monitoring during the first few months of life. Operative resection should be reserved for tumors that fail to regress or that increase in size. Adjuvant chemotherapy is rarely required after resection. The Children's Oncology Group (COG) has performed a prospective study of observation alone for cases of perinatal neuroblastoma, with strict criteria for enrollment, including tumor volume (<16 mL, if solid, or <65 mL, if cystic). Results from the study are not yet available.

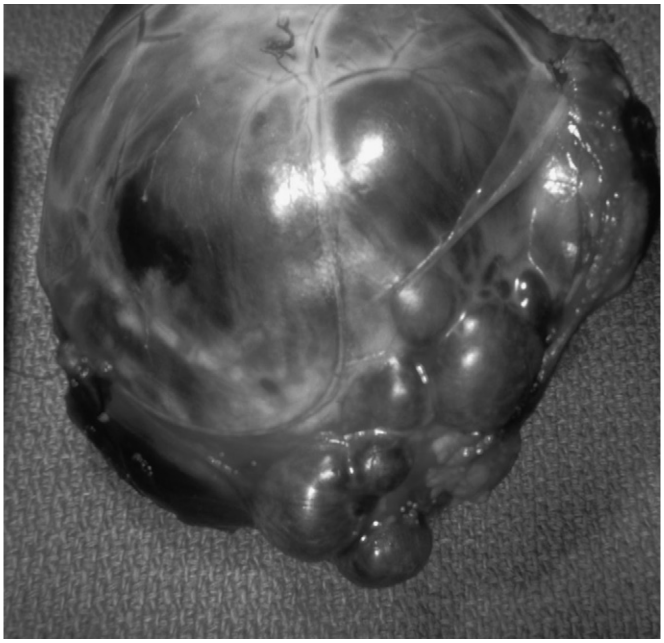

**FIGURE 31-11** Photograph of a cystic neuroblastoma of the adrenal gland in a 5-month-old baby who required complete excision. The patient was managed by surgery alone and is a long-term survivor.

# Multifocal and Bilateral Neuroblastoma

Bilateral neuroblastoma is relatively uncommon, occurring primarily in familial cases and young infants with alterations at the predisposition locus on chromosome 16p12-13.[29] Therapy has included observation alone; unilateral resection, with observation of the second (smaller) lesion or enucleation; and bilateral adrenalectomy, with postoperative hormonal replacement. Some bilateral tumors resolve spontaneously, while others persist and enlarge, requiring surgical intervention. The prognosis is generally good for these tumors, and most of the children survive. Occasionally these infants have other sites of multifocal disease. Tumor enucleation has been performed in cases with favorable biologic markers to preserve adrenal function. Hiyama and colleagues[170] described multifocal neuroblastoma in 8 of 106 cases (7.5%). Seven of eight cases had favorable histology, and all expressed Trk-A1 mRNA and the Ha-ras p21 protein. None of the tumors had *MYCN* amplification or elevated telomerase levels. Four had near-triploid DNA on flow cytometry, and all 8 had a proliferative index (percentage of cells in the S phase) of less than 25%. Four patients were treated with multistage resections. Five had bilateral neuroblastoma and were treated with tumor enucleation. All survived and are free of recurrence, and none require steroid replacement. The authors reviewed 53 additional cases of multifocal disease and noted that 18 had a family history of neuroblastoma and 25 were detected incidentally. Because of the excellent prognosis in patients with favorable biologic features, Hiyama's group recommended conservative surgical excision (enucleation) using minimally invasive surgical techniques.[170]

# Risk Stratification and Risk-Based Management

During the past 2 decades, a number of biologic and genetic factors have been identified that are important prognostic indicators and currently define therapy in North America. Based on the INSS, the use of the INPC, and the identification of numerous biologic and genetic characteristics as risk factors and predictors of outcome, a risk-based management system has been developed to determine treatment.[1,10,100–103] Newer treatment protocols individualize treatment using risk factors as predictors of outcome in an effort to maximize survival, minimize long-term morbidity, and improve the quality of life. Current protocols now categorize patients as low, intermediate, and high risk based on their prognostic factors (Table 31-5). Good outcomes are associated with stage I, II, and IV-S patients who are younger than 18 months and have hyperdiploid DNA flow cytometry, favorable histology, less than 1 copy of *MYCN*, high Trk-A expression, and absence of chromosome 1p abnormalities. In contrast, a poor prognosis is predicted in children older than 18 months with advanced tumors (stages III and IV), more than 10 copies of *MYCN*, low Trk-A expression, diploid DNA ploidy, allelic loss of 1p36, and unfavorable histology.

The site of the primary tumor was also considered predictive of survival by some investigators. Patients with tumors in cervical, pelvic, and mediastinal locations had an improved outlook compared with children with retroperitoneal (paraspinal or adrenal) tumors. Breslow and McCann[153] and Koop and Schnaufer,[152] however, suggested that the improved outlook in these cases can be explained by the patient's age and stage of disease. Despite these conflicting views, Filler and colleagues,[56] Young,[57] and Adams and colleagues[171] reported that site is a beneficial prognostic indicator for mediastinal lesions, and Haase and colleagues[5] noted the same for pelvic tumors, regardless of other factors.

Some early reports concerning neuroblastoma suggested that the more mature and differentiated the tumor, the better the prognosis.[108] Others noted that a more mature histology may be associated with the same dismal outcome as in patients with undifferentiated neuroblasts.[152] In patients with metastatic disease, the presence of more mature elements seemed to improve the outlook and was associated with increased survival.[9,11] Shimada and colleagues[101] subsequently classified the histopathology of neuroblastoma into favorable and unfavorable types, characterized by a stroma-rich appearance for the former and a stroma-poor appearance for the latter. The Shimada classification was also age related. The impact of Shimada histology class on prognosis proved to be important, especially when associated with other prognostic biologic variables, particularly amplification of the *MYCN* oncogene and allelic loss on the short arm of chromosome 1p (1p36).[99] The current INPC (which embraced and modified the Shimada classification) further divided cases into subsets of favorable and unfavorable histologic types and is a highly significant independent predictor of prognosis.[98,102,103,105,172] *MYCN* amplification is seen in approximately 30% of neuroblastoma cases and has an important role in modulating the malignant phenotype in neuroblastoma.[1,124,173] The prognostic value of *MYCN* status is independent of tumor stage and patient age. *MYCN* amplification is associated with a poor response to treatment,

**TABLE 31-5**
**Neuroblastoma Risk Groups***

| Risk Group | INSS Stage | Age | MYCN Amplification Status† | DNA Ploidy‡ | INPC (Modified Shimada) Histology |
|---|---|---|---|---|---|
| Low | 1 | Any | Any | Any | Any |
| Low | 2a/2b | Any | Not amplified | Any | Any |
| High | 2a/2b | Any | Amplified | Any | Any |
| Intermediate | 3 | $<$ 547 days | Not amplified | Any | Any |
| Intermediate | 3 | $\geq$ 547 days | Not amplified | Any | FH |
| High | 3 | Any | Amplified | Any | Any |
| High | 3 | $\geq$ 547 days | Not amplified | Any | UH |
| High | 4 | $<$ 365 days | Amplified | Any | Any |
| Intermediate | 4 | $<$ 365 days | Not amplified | Any | Any |
| High | 4 | 365 to $<$547 days | Amplified | Any | Any |
| High | 4 | 365 to $<$547 days | Any | DI $=$ 1 | Any |
| High | 4 | 365 to $<$547 days | Any | Any | UH |
| Intermediate | 4 | 365 to $<$547 days | Not amplified | DI $>$ 1 | FH |
| High | 4 | $\geq$ 547 days | Any | Any | Any |
| Low | 4 s | $<$ 365 days | Not amplified | DI $>$ 1 | FH |
| Intermediate | 4 s | $<$ 365 days | Not amplified | DI $=$ 1 | Any |
| Intermediate | 4 s | $<$ 365 days | Not amplified | Any | UH |
| High | 4 s | $<$ 365 days | Amplified | Any | Any |

*Courtesy Children's Oncology Group—Table 109.4 Children's Oncology Group Neuroblastoma Risk Stratification.
†*MYCN* nonamplified = 1 copy, amplified = greater than 1 copy.
‡DNA index > 1 (aneuploid) or = 1 (diploid).
DI, DNA index; FH, favorable histology; INPC, International Neuroblastoma Pathology Classification; INSS, International Neuroblastoma Staging System; UH, unfavorable histology.

rapidly progressive disease, and a dismal outcome. Although attempts to stimulate tumor maturation with nerve growth factor, adrenergic agonists, papaverine, prostaglandins, exogenous cyclic adenosine monophosphate, and hyperthermia were successful in the laboratory setting, there was minimal clinical evidence of their usefulness.[14,109,174–177] The use of retinoids as a promoter of differentiation, however, has rekindled interest in this concept and has been successful in prolonging survival in advanced cases during clinical trials.[174] The addition of cis-retinoic acid to the treatment protocol for high-risk cases of neuroblastoma following BMT or peripheral stem cell transplantation is now standard practice.[1]

A new pretreatment classification system based on 13 prognostic factors has recently been developed by the INRG, aiming to create international consensus for risk stratification. These factors include age, INRG stage, histology, DNA index, *MYCN* amplification status, and presence of 11q abnormality; they classify patients into 1 of 16 groups. Each group is categorized as very low, low, intermediate, and high risk, based on event-free survival rates of more than 85%, more than 75% to less than or equal to 85%, greater than or equal to 50% to less than or equal to 75%, or less than 50%, respectively.[178]

For low-risk patients, surgical excision of the tumor is usually curative and avoids the risks associated with chemotherapy. Intermediate-risk patients are usually treated with surgery and chemotherapy. Studies aimed at minimizing treatment regimens for this group of patients are ongoing. The poor prognosis in high-risk patients justifies a much more intense treatment regimen, including combination chemotherapy followed by complete surgical excision (if possible), radiotherapy to achieve local control, myeloablative treatments with bone marrow rescue, and biologic therapy.

## Operative Management

Initial surgery for extensive stage III and IV tumors should be limited to biopsy of tumor tissue, staging, and placement of a vascular access device. There is an increased rate of surgical complications when complete resection is attempted during initial surgery, with no improvement of survival.[179] After 4 or 5 cycles of chemotherapy, second-look surgery is performed. Although opinions vary regarding resection in high-risk patients, most investigators agree that complete gross resection, which is associated with excellent local control and improved outcome,[179,180] should be the goal of second-look procedures. Complete surgical removal of the primary tumor remains an essential component of treatment in the vast majority of cases.

During resection, adequate intravenous access is important because these tumors are quite vascular, and blood loss may be significant. Blood pressure must be carefully monitored intraoperatively to detect sudden hypertension caused by excessive catecholamine release from the tumor.

The surgical approach depends on the characteristics of the primary tumor. For upper abdominal lesions, particularly those involving major midline vessels, thoracoabdominal exposure is advantageous and well tolerated. The goal of resection is a complete dissection of the vasculature and should include the primary tumor site, in addition to all regional lymph nodes. Neuroblastoma often adheres to or surrounds the great vessels, and special care should be taken to identify and spare the blood supply to important visceral structures, such as the branches of the celiac axis and superior mesenteric artery.

In most children with localized disease, all or most of the tumor can be removed successfully. En-bloc contiguous resection of normal surrounding structures, such as the spleen,

stomach, pancreas, and colon, almost always can be avoided. In some cases, it is impossible to separate an adrenal or paraspinal neuroblastoma from the ipsilateral kidney, so nephrectomy may be necessary. It is important to excise any suspicious para-aortic and perirenal lymph nodes for staging purposes. A routine retroperitoneal lymph node dissection is usually not performed. The margins of the tumor resection are marked with titanium clips to guide the port if radiation is required and will reduce the scatter effect noted with other types of metal clips on follow-up CT scanning.

Because neuroblastoma may have a friable pseudocapsule, careful handling of the tumor during dissection is important to avoid tumor spill and hemorrhage. Primary adrenal tumors may be fed by a number of small arteries. The major venous drainage is usually constant, directly to the inferior vena cava on the right side, and into the left renal vein and subdiaphragmatic vessels on the left. Inferiorly located paraspinal and primary pelvic tumors often require careful dissection to separate the lesion from the bifurcation of the aorta and inferior vena cava. The tumor frequently extends into the intervertebral foramina (Fig. 31-12).

Minimally invasive surgical techniques have also been employed for selected cases of neuroblastoma.[180] Adrenal tumors initially detected by mass screening have been excised laparoscopically by a number of investigators.[181,182] Yamamoto and colleagues[49] described three cases of adrenal neuroblastoma in which the lesions were less than 20 mm in diameter. They used a 5-trocar technique and kept the intra-abdominal pressure for the pneumoperitoneum less than 4 mm Hg. The well-encapsulated tumors were completely excised; they were placed in a plastic bag and removed through the 10-mm trocar site. All had favorable

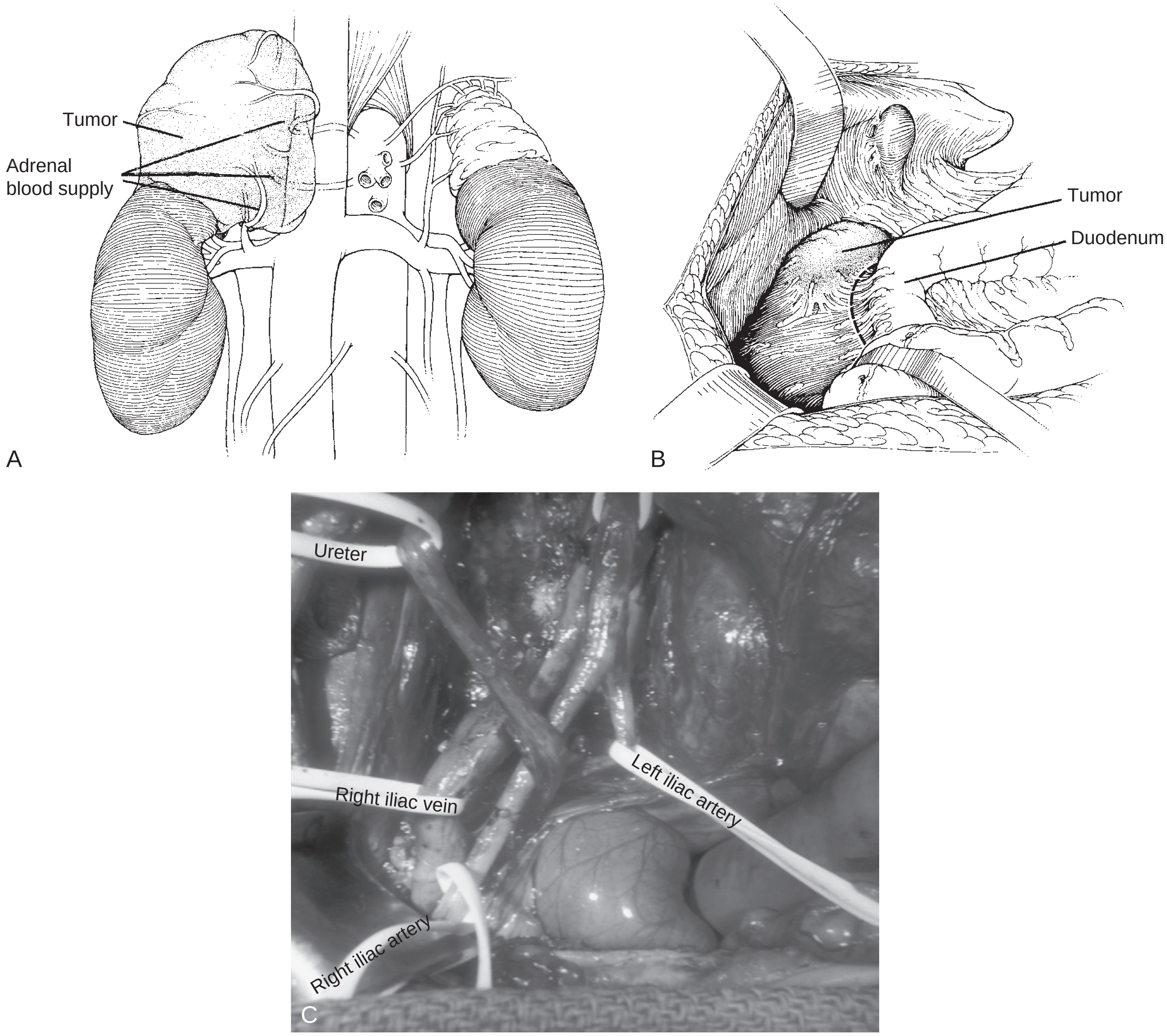


**FIGURE 31-12** **A,** Lower retroperitoneal paraspinal neuroblastoma and its relationship to the bifurcation of the aorta and ureter. **B,** Tumor may extend into the vertebral foramina. **C,** Photograph of the operative field after resection of a right-sided pelvic neuroblastoma. Note the vascular loops placed around the iliac arteries, right iliac vein, and ureter to facilitate a safe dissection.

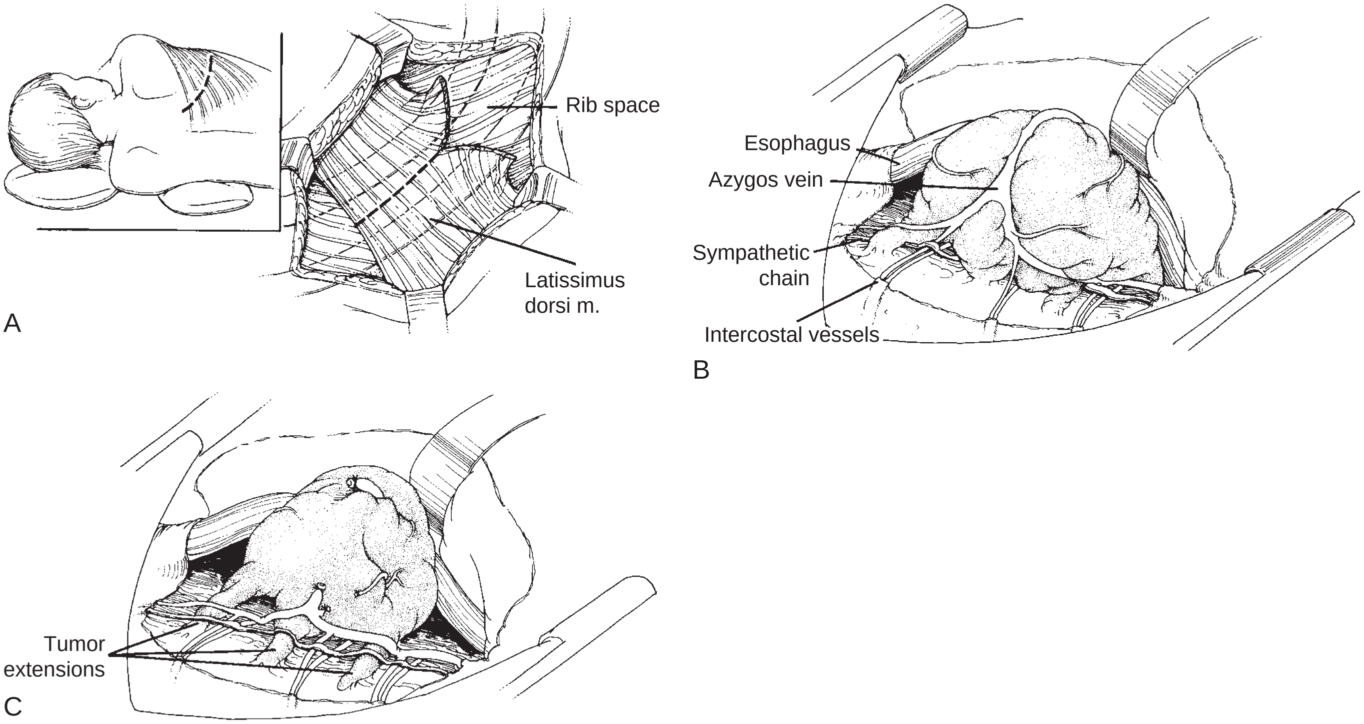


**FIGURE 31-13** **A,** Right posterolateral thoracotomy incision used for the excision of a posterior mediastinal neuroblastoma. **B,** Relationship of the tumor to surrounding tissues. **C,** The tumor is mobilized and retracted anteriorly, exposing numerous intervertebral extensions. The tumor extensions are divided at the vertebral foramina, leaving small remnants of residual tumor behind. This does not adversely influence the outcome.

histology, and none had *MYCN* amplification. No recurrences were observed. This and other reports suggest that, in selected cases, laparoscopic biopsy and tumor excision are both safe and effective.[181–183]

Mediastinal tumors are usually approached through a standard posterolateral thoracotomy incision. Excision of the pleura and the endothoracic fascia around the tumor usually allows entry into an appropriate plane of dissection. Mobilization of the tumor from the rib edges is accomplished with both sharp and blunt dissection. It is important to identify and either ligate or clip intercostal blood vessels feeding and draining the tumor. The tumor may be attached to a number of sympathetic ganglia and intercostal nerves and often extends, in one or more areas, into the intervertebral foramina (Fig. 31-13).[56,57,171,184] It may be impossible to remove every bit of tumor at the foraminal sites. Small primary tumors have been successfully removed by thoracoscopic techniques. Thoracoscopy is also useful in obtaining tissue for biopsy.

In patients with neurologic symptoms (including paraplegia) associated with dumbbell tumors, prompt MRI and an urgent laminotomy to excise extradural tumor and relieve cord compression are recommended before attempting intrathoracic resection of the tumor. The mediastinal resection can be delayed a short time to allow the patient's neurologic symptoms to improve. If extradural tumor is present on imaging studies but the patient is asymptomatic, chemotherapy is initiated and may shrink the tumor and avoid the need for laminotomy or laminectomy at the time of resection of the thoracic tumor. The choice of therapy for intraspinal tumor extension is still somewhat controversial. Plantaz and colleagues[59] reviewed 42 patients in France and recommended initial chemotherapy followed by surgical removal of residual disease. Yiin and colleagues[61] described 13 cases of neuroblastoma with symptomatic spinal cord compression and neurologic deficits. All the patients were treated initially with chemotherapy: 3 recovered, 4 improved, and 6 worsened and became paraplegic. Two of the six recovered after laminectomy. The authors recommended spinal cord decompression for patients who have neurologic deterioration on chemotherapy. Sandberg and colleagues[60] described the treatment of 46 patients with epidural or neural foraminal tumor involvement. Nine were low-risk patients with normal neurologic examinations who remained neurologically intact following operation or chemotherapy. Four low-risk patients with high-grade spinal cord compression improved or remained stable after surgical intervention, but 2 patients who were treated with chemotherapy had worsening deficits. Eleven of twelve high-risk patients with normal neurologic examinations and without radiographic high-grade spinal cord compression were treated with chemotherapy and had no neurologic deterioration. Of 16 high-risk patients with high-grade spinal cord compression, 7 of 10 were treated initially with chemotherapy, and all 6 who underwent initial surgery improved or remained stable. Spinal deformities occurred in 12.5% (2 of 16) treated nonsurgically and in 30% (9 of 30) who underwent surgery. The authors concluded that patients with high-risk tumors and spinal involvement but normal neurologic examinations should be offered chemotherapy, with the understanding that a small percentage may require operations for progressive neurologic deficits. Chemotherapy may be avoided in patients with low-risk tumors who can be offered a potentially curative procedure. Patients and their families should be made aware that operative intervention may be associated with subsequent spinal deformity in as many as 30% of cases.[60]

Cervical neuroblastoma is often localized and has a favorable outcome.[185] In a study of 43 cervical neuroblastomas,

Haddad and colleagues[186] identified four risk factors that were associated with increased operative morbidity: adherence to vascular structures, tumor size, friability, and dumbbell tumors. Imaging studies may show a solid mass with vascular displacement and narrowing.[187] Tumors arising in the neck or upper mediastinum often involve the stellate ganglion. If not present preoperatively, resection may result in postoperative Horner syndrome.[14,188] This is a relatively minor consequence outweighed by complete tumor excision and survival, but the patient's family should be made aware of this possible complication. Special attention should be given to protecting the brachial plexus and the phrenic, vagus, and recurrent laryngeal nerves.

Aggressive surgical management is occasionally associated with late complications in survivors, including ipsilateral atrophy of the kidney following adrenal resection and ejaculatory problems following pelvic tumor excision.[188] Of interest is the very favorable outlook noted in patients with stage III and IV tumors arising in the pelvis following complete tumor resection.[10]

# Chemotherapy

Although multiagent chemotherapy has significantly improved the survival rate of patients with many different types of tumors (e.g., Wilms' tumor), chemotherapy has no such effect in infants and children with resectable localized neuroblastoma with favorable biologic and genetic characteristics. For locoregional disease that does not have *MYCN* amplification, surgical resection alone is all that is necessary.[5,10,189] Patients with locoregional disease with poor prognostic biologic and genetic factors, however, are at higher risk and should be treated more aggressively with multiagent dose-intensive chemotherapy, in addition to a variety of therapies thereafter. Patients with stage IV disease who are younger than 18 months at diagnosis receive low-dose chemotherapy, in addition to surgery.[190]

Patients with stage IV disease who are *MYCN* amplified or older than 18 months at diagnosis remain the most difficult population to treat. Historically, these patients received cyclophosphamide, vincristine, and dacarbazine.[9,190,191] Patients in whom this treatment regimen failed received doxorubicin and teniposide (VM-26). Although these chemotherapy regimens did not effectively increase the cure rate of patients with stage IV disease, such treatment reduced the size of the primary tumor, often cleared the bone marrow of tumor cells, and was occasionally associated with histologic maturation from malignant neuroblastoma to benign ganglioneuroma.[9,11] Unfortunately, only 40% of patients with stage IV disease demonstrated a complete response to chemotherapy; 30% had a partial response; and 30% were unresponsive.[9] When the clinical estimation of response was subjected to confirmation by laparotomy, many patients thought to be responders to chemotherapy actually had persistent tumor not identified by preoperative testing.[15,76,172]

Numerous studies confirmed the limited effectiveness of chemotherapy regimens in patients with metastatic disease.[9,73] Using cell kinetic data, Hayes and colleagues[192] demonstrated that the proliferating fraction of the tumor cell population in neuroblastoma is exceedingly small. A large pool of nonproliferating resting cells is resistant to chemotherapy. Timed sequential administration of cell cycle–specific and nonspecific drugs (cyclophosphamide and doxorubicin, or cisplatin with teniposide or doxorubicin) was subsequently tested and resulted in improved response rates.[71,192] This improvement led to more aggressive, more intensive treatment protocols using multiple agents.

Currently, this patient population receives aggressive multimodality therapy, including induction chemotherapy to attain remission, followed by surgery and radiotherapy to further achieve local control. This treatment is followed by consolidation of remission with myeloablative therapy, autologous stem cell transplant, 13-cis-retinoic acid, and, possibly, the addition of immunotherapy.

The purpose of induction chemotherapy is to reduce tumor burden throughout the entire body, both at the primary site and at sites of systemic disease. Multiple agents are often used, including cyclophosphamide, ifosfamide, doxorubicin, cisplatin, carboplatin, etoposide, topotecan, and vincristine. These agents are now given as dose-intensive regimens.

# Radiotherapy

Neuroblastoma is a radiosensitive tumor, so radiotherapy remains an important part of the treatment regimen for patients with neuroblastoma. In general, in the management of neuroblastoma, radiotherapy is administered after both induction therapy and surgery, when minimal disease remains. It has also been used for bulky metastatic disease after a response is seen with chemotherapy, and for palliation in patients with refractory end-stage disease or painful metastases.[193–195] At our institution, a regimen that includes dose-intensive chemotherapy, surgery, and a dose of 2100 cGy of hyperfractionated radiotherapy to the primary site in patients with stage IV neuroblastoma resulted in a local control rate of greater than 90%.[46]

Although it is useful, external-beam radiotherapy is associated with considerable toxicity in growing children, resulting in growth disturbance, bony deformity, endocrine deficiency, hypoplastic soft tissue changes, skin atrophy, and, of greater concern, secondary malignancies in the radiation portal. Techniques used to decrease radiation-induced toxicity include hyperfractionation of the radiation dose, which usually does not reduce the desired antitumor effect, and avoiding the simultaneous administration of chemotherapy agents that may enhance the radiation effect. Brachytherapy and intraoperative radiotherapy can better confine the radiation effect to the target tissue and spare surrounding normal tissues.[196,197] Although early local control can be achieved, only 38% of patients with stage IV disease given intraoperative radiotherapy survived after 3 years. Some patients still require supplemental external-beam radiotherapy; postoperative ureteral stricture, renal artery stenosis, and neuropathies have been described.[5] Haas-Kogan and colleagues[196] described an experience using intraoperative radiotherapy in 23 cases of high-risk neuroblastoma and noted that this technique was effective only in patients who had gross total resection of the primary tumor.[196] All patients with partial tumor resection had recurrence, despite radiotherapy, and subsequently died. There are few data to support the efficacy of this therapy. Intraoperative radiotherapy is sometimes cumbersome to perform, especially in institutions that do not have an operative suite in the radiotherapy department or radiotherapy

equipment (including linear accelerators) in the operating room. Under these circumstances, after attempted tumor resection, the patient has to be transported under general anesthesia for the radiation treatment.

Children with refractory advanced neuroblastoma with widespread involvement often suffer severe pain due to metastases. Kang and colleagues[194] employed targeted radiotherapy using submyeloablative doses of $^{131}$I-MIBG to achieve disease palliation. The treatment stabilized disease, relieved pain, or improved performance status, with 31% of patients showing an objective response to treatment. They concluded that this modality is useful for treating end-stage neuroblastoma. Deutsch and Tersak[193] described the use of radiotherapy (300 to 1000 cGy) for palliative treatment of symptomatic metastases to bone. The most common treatment sites were the skull, spine, hip, and femur. In their study, 29% of patients survived 1 year or longer (range, 1 to 52 months); only 8% survived more than 3 years.

Targeted radiotherapy with MIBG has also been used in combination with myeloablative chemotherapy and proton therapy for recurrent and refractory neuroblastoma. Proton therapy has the advantage of delivering radiation more precisely than conventional radiotherapy. As it becomes more widely available, it may play a greater role in the management of children with neuroblastoma requiring radiation treatment.[1]

## Myeloablative Therapy

Myeloablative therapy, using near-lethal doses of phenylalanine mustard (melphalan) with autologous bone marrow rescue, has been shown to improve the tumor response rate. A combination of melphalan, doxorubicin, teniposide, and low-dose total-body irradiation followed by autologous BMT resulted in a relapse-free rate of 40% and, if deaths resulting from toxicity were excluded, there was a 2-year survival rate of 34% in patients with stage IV disease.[198] An alternative treatment was developed that relies on myeloablative chemotherapy using escalating doses of drugs given by constant infusion, followed by autologous (purged) bone marrow infusion but without total-body irradiation.[199]

Currently, stem cells are harvested during the induction phase of treatment, and stored for later use during the consolidation phase of treatment.[200] Chemotherapeutic agents used for this phase of treatment include carboplatin, etoposide, and melphalan. Peripheral blood stem cell infusion is used to reconstitute the marrow after myeloablative treatment. Immunoglobulin G levels are monitored and replaced with gamma globulin. Sulfamethoxazole and fluconazole are given prophylactically to avoid opportunistic *Pneumocystis carinii* and fungal infection.

The use of purged, peripheral blood hematopoietic stem cells has shown to have survival benefits over the use of allogeneic cells, mainly because of a higher toxic death rate and an increased incidence of graft-versus-host disease in the latter group.[94,201] Patients with high-risk stage IV disease have a better outcome with BMT, especially if they have amplification of the *MYCN* oncogene.[37,94,124] Preliminary reports are demonstrating improved event-free survival with rapid sequential tandem transplant consolidation therapy. This has initiated the ongoing COG phase III trial testing single versus tandem transplant as consolidation therapy.[201] However, to date, there are no prospective studies examining the use of myeloablative therapy in addition to dose-intensive induction therapy.[190] At our institution, the addition of myeloablative chemotherapy to dose-intensive chemotherapy did not decrease the rate of systemic or central nervous system recurrence.[202]

The addition of 13-cis-retinoic acid (isotretinoin), a biologic response modifier that causes tumor differentiation and decreases bone marrow tumor involvement, was shown to be useful.[199] Retinoids serve as multistep modulators of the MHC class I presentation pathway and sensitize neuroblastomas to cytotoxic lymphocytes.[202–204] In a phase III randomized trial in high-risk patients, Reynolds and colleagues[203,204] showed that high-dose pulse therapy with 13-cis-retinoic acid given after completion of intensive chemoradiation (with or without autologous BMT) significantly improved event-free survival. A CCG phase III randomized trial showed the use of 13-cis-retinoic acid after myeloablative chemotherapy had superior event-free survival in patients with remission, and this protocol is now commonly used for these particular patients.[199] A newly developed retinoid, fenretinide, has completed a COG phase I trial, and different oral formulations are being tested in the hopes of improving its bioavailability.[189,205]

## Immunotherapy

In the 1970s and 1980s, it was suggested that tumor regression in neuroblastoma involved an immunologic mechanism, resulting from an unusual tumor–host relationship.[206–208] Lymphocytes from children with neuroblastoma were observed to inhibit colonies of neuroblasts in culture but not cells from other tumors.[207] Sera from patients with progressive disease contain a blocking antibody that prevents a lymphocyte-mediated cytotoxic response and inhibits lymphocyte blastogenesis to phytohemagglutinins.[209,210] Lymphocytes from patients with neuroblastoma also have a decreased systemic and in situ natural killer activity.[211] In experimental studies, operative electrocoagulation and hyperthermia resulting from high-intensity focused ultrasonography induced immunity in mice with neuroblastoma.[206,207] A major problem is that advanced neuroblastoma cells are MHC class I deficient and evade immunorecognition.

The mainstay of current immunotherapy for neuroblastoma involves GD2. GD2 is a surface glycolipid antigen that is copiously found on all neuroblastoma cells. Raffaghello and colleagues[212] employed an anti-GD2 antibody in nude mice with neuroblastoma and noted increased long-term survival and decreased metastatic spread in a dose-dependent manner in treated mice compared with controls. Cheung and colleagues[213] suggested that immunotherapy using ganglioside GD2 monoclonal antibody should be directed at minimal disease and must be used in conjunction with dose-intensive chemotherapy to be effective. Kushner and colleagues[214] described the treatment of seven patients who relapsed with widespread disease after initial treatment with surgery alone for locoregional neuroblastoma. They received dose-intensive chemotherapy; anti-GD2 3F8 antibody; and targeted radiotherapy using $^{131}$I-labeled 3F8, if they had assessable disease, or 3F8, granulocyte-macrophage colony-stimulating factor, and 13-cis-retinoic acid, if they

were in remission. Five of the seven patients remained in remission between 4 and 8 years later.[214] The same group reported that high-dose cyclophosphamide, irinotecan, and topotecan were effective in achieving remission and inducing an immunologic state conducive to antibody-based passive immunotherapy (using 3F8 antibody) in resistant neuroblastoma.[215] Further studies have been completed that continue to show improved outcomes with the use of this antibody.

In contrast to 3F8, which is a mouse-derived monoclonal antibody, ch14.18 is a chimeric human/murine anti-GD2 antibody, and it has shown positive results in both phase I and II clinical trials (German NB90 and NB97 studies). Preliminary results from the COG randomized phase III trial using ch14.18 plus cytokines after autologous stem cell transplant versus control showed improved survival in the treatment group.[216]

Dendritic cells are potential targets for immunotherapy. They can enhance growth and differentiation of CD40-activated B lymphocytes, directly affect natural killer cell function, and act as antigen presenters.[217,218] Redlinger and colleagues[218] noted that advanced neuroblastoma impairs dendritic cell differentiation and function in adoptive immunotherapy. It has been shown that neuroblastoma-derived gangliosides inhibit dendritic cell function. Interleukin-12 (IL-12) is a potent proinflammatory cytokine that enhances the cytotoxic activity of T lymphocytes and resting natural killer cells.[217] In a murine model of neuroblastoma, Shimizu and colleagues[219] demonstrated that IL-12–transduced dendritic cell vaccine (with an adenoviral vector expressing IL-12) led to a complete and sustained antitumor response. Tumor regression was associated with a high infiltration of dendritic cells and viable T cells.

## Additional Therapies

$^{131}$I-MIBG infusion provides a way to specifically deliver radiotherapy to neuroblastoma cells, because it is taken up by more than 90% of neuroblastomas. The use of this treatment alone results in a response in 18% to 37% of patients with refractory or relapsed disease.[220] Rapamycin (mTOR) plays a significant role in cell growth and persistence of neuroblastomas, and phase II trials investigating rapamycin (mTOR) inhibitors are ongoing. Early results reveal a benefit in patients with recurrent neuroblastoma.[221] Additionally, trials are examining targeted therapies for the AKT pathway, as activation of AKT correlates with worse event-free and overall survival.[222–224] Biologic agents, such as histone deacetylase inhibitors, tyrosine kinase inhibitors, IGF-1 receptor inhibitors, N-myc inhibitors, ALK inhibitors, and various antiangiogenic agents, are also being investigated in ongoing clinical trials. The use of bisphosphonates is being explored as a possible treatment for bone metastases. Tumor vaccines and techniques of adoptive immunotherapy are also being evaluated in clinical trials.

## Summary and Future Directions

This common pediatric malignancy remains an enigma because of the high variability in tumor behavior. The primitive neuroblastic tumor may follow one of three possible pathways: spontaneous regression (apoptosis); differentiation and maturation to a benign ganglioneuroma; or, more commonly, tumor proliferation and rapid malignant progression. Fetal ultrasonography and infant screening programs have clearly demonstrated that some tumors spontaneously regress. Age-related histopathologic studies have clarified that some tumors (those with favorable histology) differentiate and mature, whereas others (those with unfavorable histology) are undifferentiated neoplasms that respond poorly to treatment and have a rapidly progressive course and fatal outcome.

Recognition of important biologic (and genetic) characteristics can help to categorize these tumors into risk groups (low, intermediate, and high) that determine future treatment protocols. Risk-based management permits individualized care for each patient based on age, INSS stage, INPC histology, and biologic and genetic characteristics that affect the behavior of each tumor.[1,10,102] This avoids unnecessary and potentially harmful treatment in patients categorized as having low-risk tumors and who may do well with surgery alone (and occasionally observation alone in highly selected cases). It allows the physician to reserve the most intensive treatment protocols for children with the highest-risk tumors and the most guarded prognosis. At present, the outlook is best in low-risk patients: infants younger than 18 months; patients with localized tumors that can be completely excised (stages I and II) with favorable INPC histology and low-risk biologic and genetic factors; and infants with stage IV-S disease. Infants with cystic or small solid neuroblastomas detected on prenatal sonograms also have a very favorable outcome. In patients with stage IV-S disease and those with cystic, multifocal, or bilateral tumors and favorable biologic characteristics, observation alone may be feasible. Close sonographic monitoring of these cases in the first year of life is important to ensure that the tumor shrinks and undergoes regression. Increase in tumor size is an indication for operative intervention.

Despite some improvements in outcome using high-intensity treatments, the outlook for patients with advanced neuroblastoma remains dismal, and less than half survive. A better understanding of factors influencing tumor regression and differentiation and tumor–host immune interactions is required. In children with high-risk tumors, identifying additional tumor markers and targeting effective monoclonal antibodies against the tumor, developing improved techniques to clear the bone marrow of tumor cells, using new and more effective chemotherapy regimens, and using growth factors (e.g., other biologic tumor modulators) to promote regression and differentiation may control disease progression and improve the outlook for this highly malignant tumor. Molecular profiling of the genetic changes that occur in neuroblastoma will likely permit a more precise classification system to predict outcome and further define the choice of specific therapy, which may include targeting the genes, proteins, and signaling pathways responsible for malignant progression of the tumor.[1] Also of concern are the long-term effects of neuroblastoma treatment, which include cardiac and renal toxicity, scoliosis, adverse effect on growth and development, delayed sexual maturation, learning disabilities, and occurrence of second neoplasms including renal tumors.[1,225,226]

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 32

# Nonmalignant Tumors of the Liver

Wolfgang Stehr and Philip C. Guzzetta, Jr.

Primary liver tumors constitute less than 3% of tumors seen in the pediatric population, and only one third of those tumors are benign.[1] Benign tumors may be epithelial (focal nodular hyperplasia, hepatocellular adenoma), mesenchymal (hepatic hemangioma, mesenchymal hamartoma), or other (teratoma, inflammatory pseudotumor). Nonparasitic cysts, although not technically neoplasms, are also discussed in this chapter. One of the more interesting aspects of benign liver tumors in children is their predilection to occur in patients with other conditions, and this phenomenon will be discussed with each tumor type.

## Clinical Presentation

Most children with benign liver tumors present with a painless right upper quadrant abdominal mass or hepatomegaly. Symptoms of gastrointestinal compression, such as constipation, anorexia, or vomiting, may also be present. If the mass is painful, the pain is usually dull and aching and is caused by expansion of the liver capsule or compression of the normal surrounding structures. Jaundice and weight loss are uncommon except in infants with symptomatic hemangiomas, and those signs should raise the suspicion that the lesion is malignant. Acute abdominal pain may be caused by bleeding into the mass or into the peritoneum,[2] particularly in hepatocellular adenomas, although this problem is rarely seen in children. Children may present with congestive heart failure (CHF) and thrombocytopenia, which is known as Kasabach-Merritt syndrome when associated with a vascular anomaly such as a liver hemangioma.[3] Cutaneous hemangiomas are seen in about half the children with a liver hemangioma,[4,5] and the rapid enlargement of the liver with a diffuse liver hemangioma can cause abdominal compartment syndrome and respiratory distress.[4] CHF without significant thrombocytopenia can also be seen with liver arteriovenous malformation (AVM)[6] or mesenchymal hamartoma.[7] Fetal hydrops has been identified by prenatal ultrasonography in some fetuses with liver hemangiomas[8] or mesenchymal hamartoma.[9]

## Diagnosis

### LABORATORY TESTS

Serum alpha fetoprotein (AFP) is present in very high concentrations at birth (48,000 $\pm$ 35,000 ng/mL) and rapidly declines to adult levels of less than 10 ng/mL by 8 months of age (Table 32-1).[10] Thus in infants younger than 8 months, AFP levels must be interpreted in the context of this dramatic change. Markedly elevated AFP levels in a child with a liver mass almost certainly means that the mass is malignant, although milder elevation may be encountered with some benign lesions, such as mesenchymal hamartoma[11] or teratoma.[12] As mentioned previously, significant thrombocytopenia associated with a liver mass is usually part of the Kasabach-Merritt syndrome resulting from a liver hemangioma. Hypothyroidism may also occur in multiple or diffuse forms of liver hemangioma[13]; thyroid function tests should be done routinely in these children, because hypothyroidism significantly impacts their management.[14]

### IMAGING TECHNIQUES

The initial imaging study in a child presenting with an abdominal mass should be a supine radiograph of the abdomen, looking for calcifications within the mass. The next imaging study should be an abdominal ultrasonogram with Doppler spectral analysis, followed by computed tomography (CT) with intravenous contrast (Fig. 32-1).[15] Magnetic resonance imaging (MRI) may be indicated, depending on the sonogram and CT scan results, especially when surgical resection is planned and more detailed information about the vascular anatomy relative to the tumor is desired or in infants with hemangiomas in whom another diagnosis is being considered because the MRI appearance may be diagnostic. Arteriography is reserved for children with a liver hemangioma, an AVM, or, rarely, a mesenchymal hamartoma with CHF, when embolization of the blood supply to the tumor is needed for treatment. The use of percutaneous biopsy under sonogram or CT guidance in children with benign tumors is generally discouraged, unless excision of the tumor would pose a major risk to the child, because establishing a diagnosis on the basis of a small sample may be problematic for the pathologist and because resection is the proper

**TABLE 32-1**
**Normal Serum Alpha Fetoprotein (AFP) Levels of Infants by Age**

| *Age* | *No. of Patients* | *AFP Level* ± *SD (ng/mL)* |
|---|---|---|
| Premature | 11 | 138,734 ± 41,444 |
| Newborn | 55 | 48,406 ± 34,718 |
| Newborn to 2 weeks | 16 | 33,113 ± 32,503 |
| 2 weeks to 1 month | 43 | 9452 ± 12,610 |
| 1 month | 12 | 2645 ± 3080 |
| 2 months | 40 | 323 ± 278 |
| 3 months | 5 | 88 ± 87 |
| 4 months | 31 | 74 ± 56 |
| 5 months | 6 | 46.5 ± 19 |
| 6 months | 9 | 12.5 ± 9.8 |
| 7 months | 5 | 9.7 ±?7.1 |
| 8 months | 3 | 8.5 ± 5.5 |

From Wu JT, Book L, Sudar K: Serum alpha fetoprotein (AFP) levels in normal infants. Pediatr Res 1981;5:50.

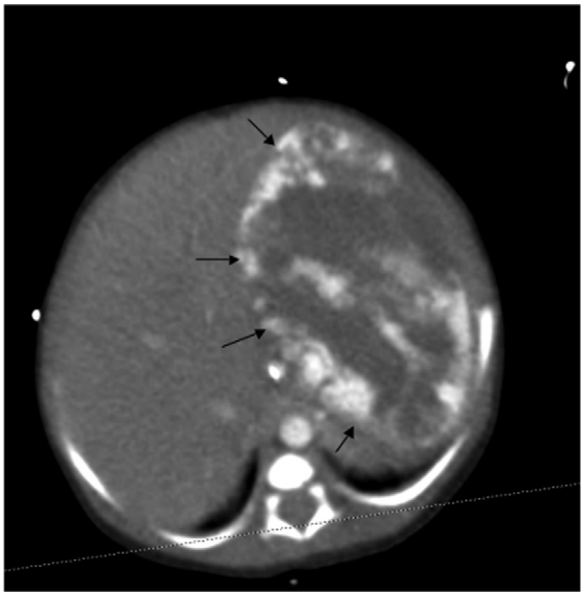

**FIGURE 32-1** Contrast-enhanced abdominal computed tomography scan of a 4-day-old infant with a large focal hemangioma of the left hepatic lobe. Note the central area of necrosis.

therapy for most of these tumors, with the exception of liver hemangiomas. The findings on imaging studies are discussed in the sections on each individual tumor.

# Hepatic Hemangioma

Hepatic hemangiomas are the most common benign liver tumor in children and are more common than all other benign liver tumors combined. Most of these lesions are identified in the newborn period or during prenatal ultrasound screening.[8] To facilitate discussion about treatment and prognosis, a new subtype classification was delineated in 2007.[4] This classification designates the hemangioma as either focal, multiple, or diffuse and eliminates confusing terms such as infantile hepatic hemangioendothelioma.

## FOCAL LIVER HEMANGIOMA

Focal lesions vary in size but can be as large as 8 cm in diameter.[5] They are usually asymptomatic. Some of the children will have cutaneous hemangiomas as well. On MRI, there is a solitary liver lesion that is hypodense on T1-weighted sequences and hyperintense on T2-weighted sequences compared with normal liver. CT scan similarly shows contrast enhancing in the periphery of the mass with little contrast in the center (see Fig. 32-1). These lesions seldom need treatment, may be a hepatic form of hemangioma similar to the cutaneous rapidly involuting congenital hemangioma (RICH), and have generally regressed spontaneously by 1 year of age.[4,5]

## MULTIFOCAL LIVER HEMANGIOMA

Multifocal lesions are generally widely dispersed, spherical, and homogeneously enhancing lesions on MRI. Flow voids may be present in the lesions and may indicate the presence of arteriovenous shunts that may lead to congestive heart failure (CHF).[15] Cutaneous hemangiomas are almost always present in these children.[5] Treatment by corticosteroids of patients with CHF is highly successful,[4,5] but if steroids fail to control CHF, embolization of the shunts may be necessary.[6,16] Children with this lesion may have evidence of hypothyroidism, and thyroid function tests (TFT) should be obtained in all children with multifocal lesions. Prognosis is excellent with 100% survival in one series.[5]

## DIFFUSE LESIONS

Diffuse lesions frequently replace nearly all of the liver with lesions showing centripetal enhancement on MRI or CT. The clinical course is more complicated and potentially lethal. Massive hepatomegaly may lead to abdominal compartment syndrome, multisystem organ failure, and death. Severe hypothyroidism may develop because of overproduction of type III iodothyronine deiodinase; therefore TFT must be obtained.[13] Despite the large tumor burden, CHF is rare. If corticosteroid therapy does not result in rapid improvement, then liver transplantation should be considered early,[17] because the prognosis is otherwise poor.[4] Medical therapy with vincristine has shown some success,[18] but this option is often limited by the rapid clinical deterioration of children with diffuse lesions. Interferon therapy has been abandoned because of the risk of spastic diplegia in infants.[19] Survival for all children with the diffuse form of liver hemangioma is approximately 75%.[5,13]

## ARTERIOVENOUS MALFORMATION

An AVM may occur within the liver parenchyma or outside the liver between the hepatic artery and the portal venous system. Similar to patients with diffuse liver hemangiomas, patients with hepatoportal AVMs usually present before 6 months of age, many in the newborn period, with hepatomegaly, CHF, and a bruit over the liver.[21] In older children and adults, hepatic AVM may occur as part of hereditary hemorrhagic telangiectasia, also known as Osler-Weber-Rendu disease.[15,22] Angiography is diagnostic, and embolization is therapeutic in some patients, but it is necessary to eliminate the extensive collaterals for successful closure of the AVM.[15,21] Fatal complications from the embolization of liver

AVMs have been reported in adults.[23] Steroids have no place in the management of these lesions, and AVMs not managed successfully with embolization may be controlled with ligation of the hepatic artery.[24,25]

## MESENCHYMAL HAMARTOMA

Mesenchymal hamartoma (MH) usually presents as a painless right upper quadrant abdominal mass in a child younger than 2 years.[20,26,27] Some patients may have evidence of CHF,[7] and, similar to liver hemangiomas, MH has been diagnosed prenatally.[20,9] Edmondson[28] proposed that MH arises from a mesenchymal rest that becomes isolated from the normal portal triad architecture and differentiates independently. The tumor grows along bile ducts and may incorporate normal liver tissue. Because the blood vessels and bile ducts are components of the mesenchymal rest, the biologic behavior of the tumor varies with the relative predominance of these tissues within the loose connective tissue stroma (mesenchyma) that surrounds them. Thus the tumor may present as a predominantly cystic structure (Fig. 32-2) that enlarges rapidly because of fluid accumulation,[29] or it may be predominantly vascular and present with CHF.[7] Von Schweinitz and colleagues[30] suggested that fat-storing (Ito) cells of the immature liver may be involved in the development of MH. There are reports of chromosomal translocations within mesenchymal hamartomas.[31]

Serum AFP levels are usually normal in children with MH, but they may be mildly elevated.[20,11,32] The radiographic features of these tumors are consistent and distinguishing; abdominal sonography and CT demonstrate a single, usually large, fluid-filled mass with fine internal septations and no calcifications.[33]

Management must be tempered by the understanding that MH usually follows a benign course,[34] although there have been reports of malignant transformation.[35,36] In general, complete operative resection is the procedure of choice, if it can be accomplished safely. Huge lesions or those that involve both lobes may be treated by unroofing and marsupializing the cysts, although the lesion may recur after incomplete resection.


**FIGURE 32-2** Cross section of a pathology specimen of a left hepatic lobectomy for mesenchymal hamartoma in a 10-month-old male infant.

MH is an entity distinct from the liver hamartomas associated with tuberous sclerosis. The latter are smaller, multifocal lesions that may be associated with angiomyolipomas in other locations, such as the kidney; they are rarely symptomatic and usually present in children older than 2 or 3 years. These hamartomas have little clinical significance, but their presence may be helpful in diagnosing tuberous sclerosis.[37]

## HEPATOCELLULAR ADENOMA

Although isolated lesions are encountered in childhood, hepatocellular adenoma (HCA) is most commonly observed in adults in association with the use of anabolic corticosteroids or estrogen. HCA has been described in children treated with anabolic steroids and multiple blood transfusions for chronic anemia,[38] and it is expected in children with type I glycogen storage disease.[39] Bianchi[40] proposed several mechanisms for the development of HCA in patients with type I glycogen storage disease, including (1) regional imbalance in insulin and glucagon metabolism, because these hormones are important in the regulation of hepatocyte proliferation and regeneration; (2) response to glycogen overload; and (3) oncogene activation. A giant hepatocellular adenoma has also been reported in a child treated with oxcarbazepine for a seizure disorder.[41]

Microscopic examination of adenomas reveals hepatocytes in sheets and cords oriented along sinusoids without a ductal component. The cells have glycogen-filled cytoplasm and small nuclei without mitoses. Adjacent liver and vessels are compressed but not invaded. Children usually do not have coexisting cirrhosis.[38] The histologic pattern is similar to that of a well-differentiated hepatocellular carcinoma, and development of hepatocellular carcinoma within an unresected HCA has been reported.[42,43]

In children, HCA generally presents as an asymptomatic hepatic mass. The mass is solid on ultrasonography and CT. Liver enzyme and AFP levels are normal. A feature unique to this lesion is its propensity for intraperitoneal hemorrhage from spontaneous rupture. In adults, intraperitoneal bleeding is almost always seen in patients receiving estrogen therapy, and tumor regression may occur with the cessation of hormone administration. In patients with glycogen storage disease and HCA, tumor regression may occur with the correction of metabolic disturbances.[40] Because of the known association between HCA and hepatocellular carcinoma, resection of HCA is recommended when it occurs in a child who is not receiving steroids and does not have glycogen storage disease. If resection cannot be accomplished without substantial risk, observation of the lesion while monitoring the serum AFP level may be appropriate. If the AFP level begins to increase or the lesion is significantly symptomatic, and if the risk of resection is unacceptably high, liver transplantation may be the best alternative.

## FOCAL NODULAR HYPERPLASIA

Focal nodular hyperplasia (FNH) in children presents as an irregularly shaped, nontender liver mass. It is frequently found incidentally at laparotomy for another cause or on radiographic studies performed for another indication. The female-to-male

FIGURE 32-3 Surgical view of focal nodular hyperplasia within the left lobe of the liver in a 2-year-old child treated by left lateral lobectomy.

ratio for FNH is approximately 4:1.[44] FNH is occasionally seen with vascular malformations and hemangiomas in the liver,[45] as well as in children with type 1 glycogen storage disease,[46] and it has been postulated that the lesions represent an unusual response to injury or ischemia.[28] On abdominal sonography, the lesions may be isoechoic, hypoechoic, or hyperechoic compared with normal liver parenchyma, and multiple lesions may occur in 10% to 15% of patients. The classic central scar may not be seen on ultrasonography. CT typically shows a hypervascular lesion with a dense stellate central scar. Conventional arteriography or magnetic resonance angiography show a hypervascular mass with feeding arteries entering the periphery and converging on the central portion of the tumor. Some cases of fibrolamellar hepatocellular carcinoma are radiographically indistinguishable from FNH, which is a cause for concern if the diagnosis is being made without a biopsy.[47] There are reports of adult patients who have FNH and hepatocellular carcinoma simultaneously.[48]

On gross examination, the lesions are nonencapsulated, occasionally pedunculated, and quite firm (Fig. 32-3). Microscopic examination shows proliferation of hepatocytes and bile ducts and the pathognomonic central fibrosis. These lesions rarely become malignant or hemorrhage. Therefore expectant therapy is appropriate when removal might be associated with significant morbidity, the child is asymptomatic, and the diagnosis has been made conclusively by radiographic studies, normal AFP levels, and biopsy.[49]

## TERATOMA

There have been fewer than 25 case reports of hepatic teratoma in children invariably younger than 1 year.[12,50] Calcification is usually present within the teratoma, helping to differentiate it from other tumors. Some have met the criteria for an intrahepatic fetus in fetu.[51] Serum AFP levels may be elevated with a teratoma, but only mildly elevated in comparison with the levels seen with hepatoblastoma. Resection is the procedure of choice for a teratoma because of the risk of malignancy in any immature elements of the tumor.

## INFLAMMATORY PSEUDOTUMOR

Inflammatory pseudotumor of the liver is rare and generally seen in children older than 3 years but has been reported in younger children as well. Because this lesion is predominantly solid, it is difficult to differentiate it from other benign or malignant tumors by imaging studies. Invariably, the serum AFP level is normal. Fever, leukocytosis, and high C-reactive protein level in a child with a solid liver mass and normal AFP level are suggestive of an inflammatory pseudotumor of the liver thought to be an inflammatory reaction to some insult, although the instigating cause is usually unknown. It is difficult to diagnose this lesion without a large biopsy. Most children undergo resection, which is curative.[52,53]

## NONPARASITIC CYSTS

Nonparasitic cysts of the liver are rare and occur more commonly in adults than in children. Although they may be present and symptomatic at birth, most are asymptomatic and are identified incidentally at autopsy or laparotomy. Symptoms are related to abdominal distention or displacement of adjacent structures. Nonparasitic cysts occur with equal frequency in males and females[54] and are generally unilocular lined by cuboidal or columnar epithelium characteristic of bile ducts. The cyst fluid is typically clear or brown, and bile is rarely present. Pathologic studies suggest that nonparasitic cysts arise from congenital or secondary obstruction of peribiliary glands. These glands normally arise from the ductal plate at the hepatic hilum around the 7th week of gestation and continue to proliferate until adolescence.[54] Symptomatic cysts can be effectively treated by simple unroofing, marsupialization,[55] or sclerotherapy.[56] If biliary communication is suspected, cholangiography may identify the source and allow the communicating ductule to be oversewn.

Cystic dilatation of the intrahepatic ducts may also present as a mass, although jaundice and cholangitis are often associated with this problem. Resection of the affected lobe is the preferred therapy.[57] If mesenchymal hamartoma appears to be completely cystic on imaging, it may be misdiagnosed as a nonparasitic cyst. Post-traumatic bile cysts result from ductal disruption and intrahepatic accumulation of bile. These lesions can be treated by percutaneous drainage or, in some cases, by biliary sphincterotomy to reduce the bile duct pressure and lessen the biliary leak.[58] Resection is rarely necessary for post-traumatic cysts. Multiple parenchymal cysts associated with hereditary polycystic kidney disease are generally asymptomatic and so small that they do not require intervention.

Epidermoid cysts differ from other nonparasitic cysts, in that the lining epithelium is squamous rather than cuboidal. This histologic characteristic has led to the theory that these lesions may be foregut bud anomalies trapped in the hepatic substance. Although they are rare, there has been a report of malignant degeneration. Thus resection is the appropriate management.[59]

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 33

# Malignant Liver Tumors

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## Historical Context

One hundred and thirteen years ago, the first case report of a hepatoblastoma (HB) was published in the English literature in 1898 by Misick in Prague.[1] He reports "A Case of Teratoma Hepatis" in a 6-week-old boy who died of respiratory problems. Autopsy showed a large tumor that occupied the lower half of the right liver lobe. Cysts, cartilaginous, and bony deposits were seen, as well as venous tumor infiltration. It was therefore not surprising that the tumor was described as a teratoma, with tissue representatives of the three embryonic germ cell layers. More than 60 years later in 1962, Willis introduced the term hepatoblastoma for this type of tumor that he defined as "an embryonic tumor that contains hepatic epithelial parenchyma."[2] At that time, hepatoblastoma usually was not distinguished from hepatocellular carcinoma (HCC). Through the work of Ishak and Glunz in 1967, morphologic criteria were defined for HB and HCC that were refined in the decennia that followed.[3,4]

Modern treatment dates to 1975 when Exelby published a landmark paper that has been cited in most reviews dealing with liver tumors in children. He reports the results of a survey of the American Academy of Pediatrics Surgical Section documenting the 1974 treatment practices and outcomes for liver tumors in children.[5] Through questionnaires sent to the members of the Surgical Section of the American Academy of Pediatrics (AAP), data on liver tumors in children operated upon during the previous 10 years were requested. From 110 replies, 375 liver tumors were reported, of which 252 were malignant (129 HB, 98 HCC), and 123 were benign. All patients with HB underwent primary surgical exploration, with biopsy only in 43 children and a subsequent attempt at definitive resection in 86. Seventy-eight of the 86 children in whom resection was attempted had complete excision of the tumor and 45 (60% of those resected) survived. Excessive blood loss was the most common complication during and immediately after operation, after which cardiac arrest occurred in 9 patients. There were 8 deaths in the operating room and 17 deaths in the immediate postoperative period attributable to the operation. Fifteen HB patients had irradiation of the liver; 53 patients had chemotherapy using a wide variety of agents. It was apparent that no cures were obtained from irradiation and/or chemotherapy in the absence of complete surgical resection. The overall survival for HB was 35%; for HCC it was 13%. With incomplete surgical excision no patient survived. There was no evidence that radiation therapy or chemotherapy controlled disease that could not be completely excised surgically. At this time, before the introduction of cisplatin-based chemotherapy and modern surgical techniques, it seemed that complete operative excision carried a high risk of morbidity, even mortality, but offered the only chance of cure.

The field has progressed considerably since Exelby's 1975 survey. With the introduction of cisplatin-based chemotherapy regimens in the 1980s, overall survival for HB increased from 35% to 70%[6] and has increased further to nearly 80% in the most recent trials.[7] Although our sophistication with chemotherapy and antiangiogenic regimens for both HB and HCC continues to evolve, the primary advantage of chemotherapy has been in a neoadjuvant setting to shrink the tumor and enable surgical resection. Although pediatric HCC is more likely to respond to chemotherapy than its adult counterpart, most HCC remains largely chemoresistant, and treatment efforts often focus on slowing tumor progression with the newest antiangiogenic agents. Complete surgical excision remains the cornerstone for cure in both HB and HCC as evidenced by the recent improvements in survival achieved with complete hepatectomy and liver transplantation.[8–10]

## Diagnosis

### CLINICAL PRESENTATION

Most liver tumors present with an asymptomatic abdominal mass palpated either by a parent or pediatrician.[11] In the youngest children (infants and toddlers) the most common malignant tumor is hepatoblastoma, which presents as an asymptomatic right upper quadrant or epigastric abdominal mass. Some children may have fatigue, fever, pain, anorexia, and weight loss. Rarely, HB may present with abdominal pain and hemorrhage after post-traumatic or "spontaneous" rupture of a previously occult tumor. Hepatocellular carcinoma and hepatic sarcomas are more common in older children and are more likely to present at an advanced stage. Nonspecific symptoms of inanition or respiratory failure may appear insidiously. As the cancer grows, the pain in the abdomen may

progress to shoulder or back pain and becomes more pronounced. The child may develop progressive anorexia and vomiting and appear thin and sickly. Tumor growth may compress or obstruct the normal hepatic architecture causing (1) ascites secondary to occlusion of the portal or hepatic veins, (2) gastrointestinal (GI) bleeding or splenomegaly from the portal hypertension of portal vein occlusion, or (3) jaundice, scleral icterus, and pruritus from obstruction of the biliary tree.[12] Symptoms of biliary obstruction are most common with biliary rhabdomyosarcoma.[13]

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis of a pediatric liver mass includes malignant tumors, benign tumors, and a wide assortment of congenital and acquired lesions of the liver, listed as "other masses" in Table 33-1. For many of the "other masses" listed in Table 33-1, the key to the diagnosis might lie in the underlying medical condition. For example, one might expect to see a bacterial hepatic abscess in a child with chronic granulomatous disease, a fatty deposit in the liver of a child with hyperlipidemia, or perhaps an inspissated bile lake in a child with biliary atresia as shown in Figure 33-1. Organizing intrahepatic hematoma should be suspected in any child with a history of hepatic trauma or in newborns with sepsis and coagulopathy, especially if there is a history of perinatal birth trauma or hemodynamic collapse requiring cardiopulmonary resuscitation. Congenital liver cysts are rare and represent a spectrum ranging from large simple cysts, intrahepatic choledochal cyst, and ciliated hepatic foregut cyst. Acquired cysts might be due to a bacterial, hydatid, or amoebic abscess. A simple, asymptomatic congenital liver cyst may be safely observed.[14] If infectious or large and symptomatic, cyst drainage, marsupialization, or excision may be needed to relieve pain and prevent risk of rupture. Recent literature suggests a risk of squamous cell carcinoma arising later in life in those congenital hepatic cysts with a ciliated epithelial lining (ciliated hepatic foregut cyst), and therefore these should probably be excised rather than observed or marsupialized.[15,16]

Neoplastic liver masses, including benign and malignant tumors, account for about 1.0% to 1.5% of all pediatric tumors.[17] Age at presentation is often the key to differential diagnosis (Table 33-2).[18] In newborns, the most common tumor is infantile hepatic hemangioma.[19] Infantile hepatic hemangioma is to be distinguished from the much rarer kaposiform hemangioendothelioma that may present in the extremities, chest, or retroperitoneum. Kaposiform hemangioendothelioma of the retroperitoneum may present with Kasabach-Merritt phenomenon and progress to obstruct the porta hepatis.[20] Hepatoblastoma is most commonly diagnosed between 4 months and 4 years of age. Benign tumors in toddlers are mesenchymal hamartoma and focal nodular hyperplasia. Hepatocellular carcinoma and hepatic adenoma are seen in older children. The other tumors listed in Table 33-2 are rare. Although the most common benign tumors often show classical distinguishing features on computed tomography, imaging is *not* usually a reliable way to differentiate benign from malignant tumors.[21]

## LABORATORY EVALUATION

Routine laboratory investigation should include complete blood count; many children with a malignant liver tumor will exhibit some degree of anemia and thrombocytosis.[22] In HB, the thrombocytosis is thought to be caused by tumor production of thrombopoietin, interleukin-6, and interleukin-1B.[23–25] Additional laboratory tests include a liver panel (albumin, transaminases, glutamyl transferase, alkaline phosphatase, total and conjugated bilirubin), lactate dehydrogenase, tumor markers (alpha-fetoprotein [AFP], beta-human chorionic gonadotropin [beta-HCG], ferritin, carcinoembryonic antigen [CEA], catecholamines), and viral titers (hepatitis A, B, and C, Epstein-Barr virus).[18]

The most important tumor marker is the serum AFP. AFP will be elevated in 90% of children with hepatoblastoma and in 50% of children with HCC.[26] Although AFP is elevated in most children with hepatoblastoma, increased AFP is *not* pathognomonic for a malignant liver tumor. European, German, and American multicenter trials have all concluded that hepatoblastomas that fail to express AFP at diagnosis (diagnosis AFP level less than 100) are biologically more aggressive with a worse prognosis.[27–31] Rarely, the opposite has been reported—a case of well-differentiated, fetal-type, favorable prognosis hepatoblastoma that did not express AFP.[32] AFP levels must be interpreted with caution in neonates, because AFP is the major protein produced by the fetal liver

**TABLE 33-1**
**Differential Diagnosis of Pediatric Liver Masses**

| *Malignant Tumors* | *Benign Tumors* | *Other Masses* |
|---|---|---|
| Hepatoblastoma | Mesenchymal hamartoma | Vascular malformations |
| Hepatocellular carcinoma | Biliary cystadenoma | Arteriovenous malformation |
| Sarcoma | Focal nodular hyperplasia | Blue rubber nevus syndrome |
| Biliary rhabdomyosarcoma | Infantile hemangioma | Congenital/acquired cysts |
| Angiosarcoma | Hepatic adenoma | Simple |
| Rhabdoid | Nodular regenerative hyperplasia | Ciliated foregut cyst |
| Undifferentiated | Teratoma | Polycystic liver disease |
| Metastatic/other | Inflammatory myofibroblastic tumor | Choledochal cyst |
| Wilms' tumor | | Inspissated bile lake/biliary atresia |
| Neuroblastoma | | Parasitic cysts |
| Colorectal | | Amoebic |
| Carcinoid tumor | | Abscess |
| Kaposiform hemangioendothelioma | | Bacterial |
| Hemophagocytic lymphohistiocytosis | | Chronic granulomatous disease |
| Langerhans' cell histiocytosis | | Hematoma |
| Megakaryoblastic leukemia | | Fatty liver |

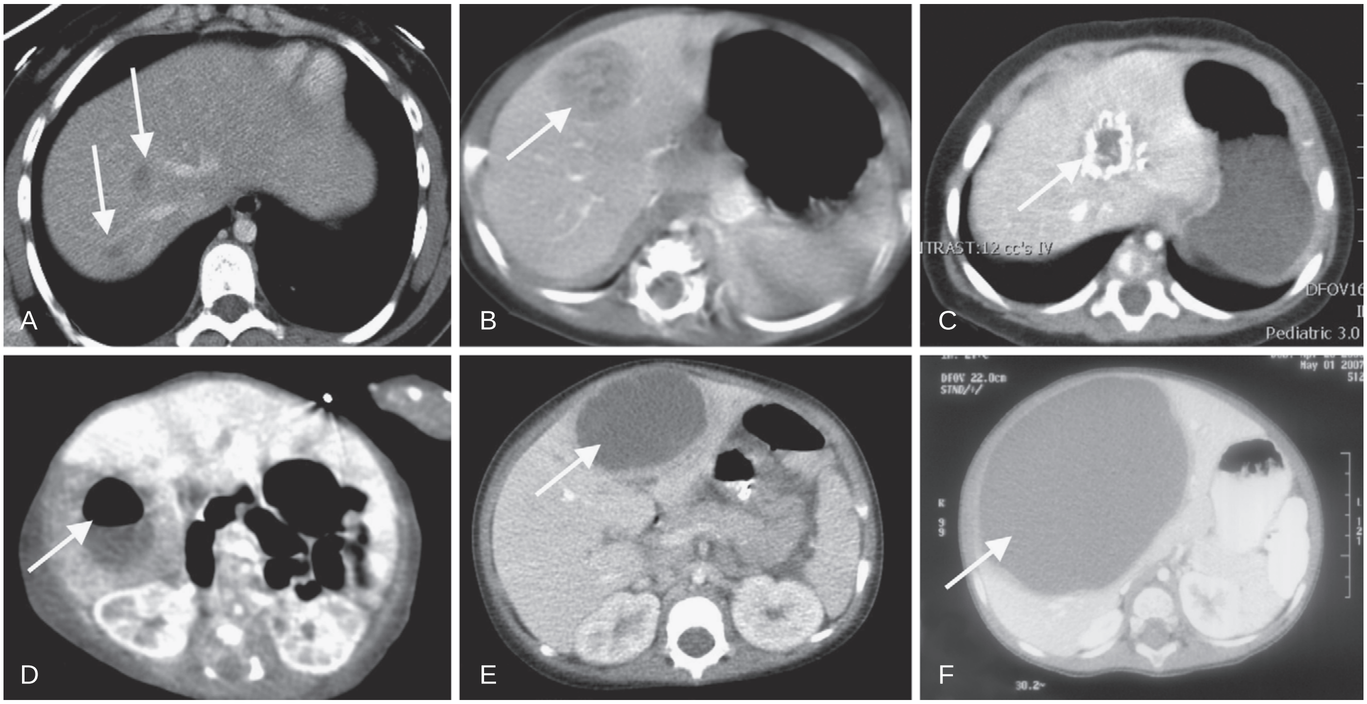


**FIGURE 33-1** Differential diagnosis: examples of non-neoplastic liver masses and cysts. **A,** Multiple small bacterial abscesses in a child with chronic granulomatous disease. **B,** Inspissated bile lake in a child with biliary atresia and cholangitis. **C,** Organizing hematoma in a newborn with sepsis and coagulopathy. **D,** Infarction of right lobe liver and hepatic abscess (with air fluid level) in a premature baby with necrotizing enterocolitis. **E,** Acquired cyst is an amoebic abscess in a toddler with fever. **F,** Congenital cyst is a ciliated foregut cyst in an infant with abdominal distension and feeding difficulties.

**TABLE 33-2**
**Age at Presentation, Most Common Liver Tumors of Childhood**

| *Age Group* | *Malignant* | *Benign* |
|---|---|---|
| Infant/toddler | Hepatoblastoma 43%<br>Rhabdoid tumor 1%<br>Malignant germ cell 1% | Hemangioma/vascular 14%<br>Mesenchymal hamartoma 6%<br>Teratoma 1% |
| School age/adolescent | Hepatocellular (including transitional cell tumors) 23%<br>Sarcomas 7% | Focal nodular hyperplasia 3%<br>Hepatic adenoma 1% |

From Von Schweinitz D: Management of liver tumors in childhood. Semin Pediatr Surg 2006;15:17-24.

and is thus produced in high amounts in the normal newborn. AFP may be especially high in neonates after hepatic damage and during regeneration of liver parenchyma. The half-life of AFP is 5 to 7 days, and levels fall throughout the first several months of life so that by 1 year of age the AFP should be less than 10 ng/mL.[33] Moreover, there are many reports of benign tumors, especially infantile hemangioma and mesenchymal hamartoma, in children presenting with high AFP levels.[34–36]

The other tumor markers useful in differential diagnosis are beta-HCG elevated in germ cell tumors, ferritin elevated in HCC and metastatic neuroblastoma; CEA elevated in HCC and metastatic colorectal, lactate dehydrogenase elevated in many malignant tumors, catecholamines elevated in metastatic neuroblastoma, hepatitis C in HCC, and Epstein-Barr viral titers in lymphoproliferative disease or lymphoma.

## RADIOLOGY

The radiographic appearance of the most common benign and malignant liver tumors is shown in Figure 33-2. Mesenchymal hamartoma is classically multicystic with the complex cysts separated by thick vascular septae. Focal nodular hyperplasia is generally well demarcated with a characteristic central stellate scar. Infantile hemangioma classically will demonstrate bright peripheral contrast enhancement. Infantile hepatic hemangioma may be focal, multifocal, or diffuse, as shown in Figure 33-2 in its diffuse form. Hepatoblastoma appears as a large multinodular expansile mass, usually unifocal, but occasionally multifocal. The tumor is generally well demarcated from the normal liver but is not encapsulated. HB may invade hepatic veins, disseminate to the lungs, or penetrate the liver capsule to reach contiguous tissues. An initial ultrasonogram will identify the liver as the organ of origin; additional testing, usually a contrast-enhanced abdominal computed tomography (CT) scan, is aimed at determining the extent of involved parenchyma and the presence or absence of macrovascular compression, displacement, or invasion. Metastatic liver tumors compared with primary malignant liver tumors have been reported to be more hypoechogenic on ultrasonography (US) and have less vessel invasion and contrast enhancement on abdominal CT.[37]

In hepatoblastoma and hepatocellular carcinoma, contrast-enhanced abdominal CT or magnetic resonance imaging

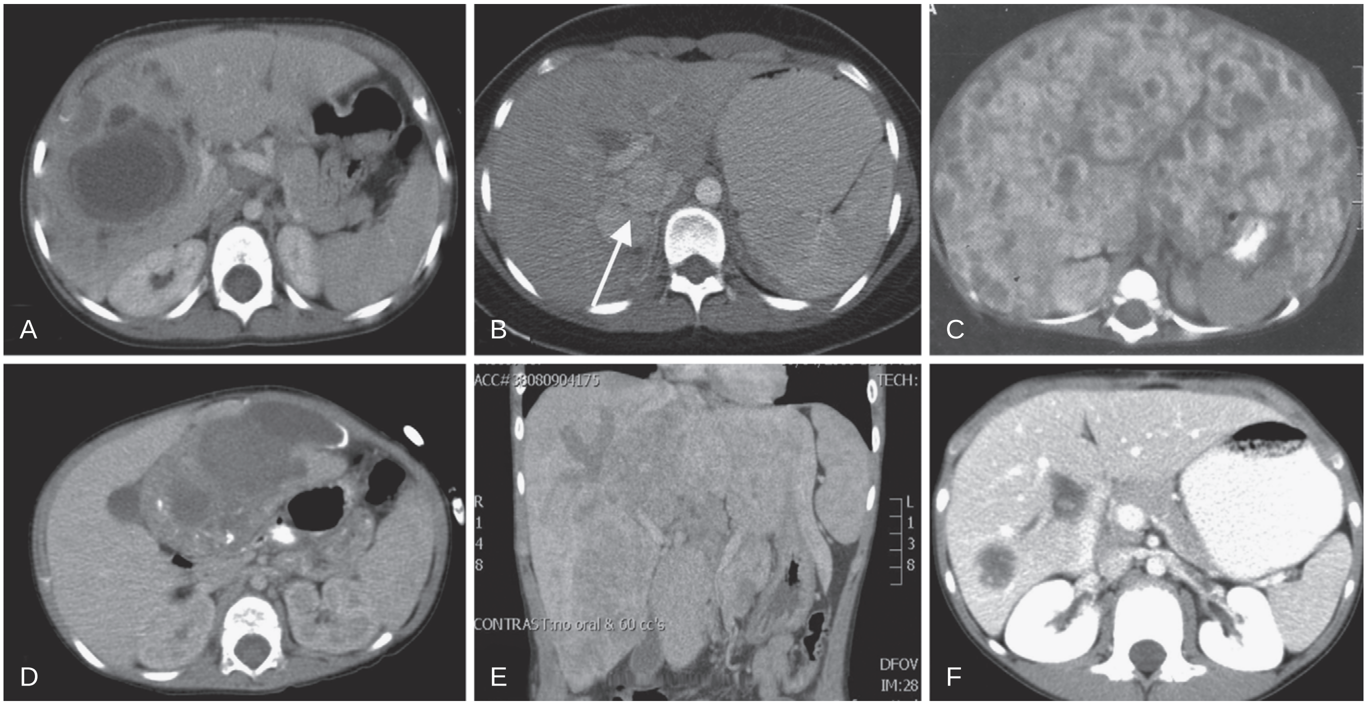


**FIGURE 33-2** Radiographic appearance of the most common hepatic benign and malignant neoplastic masses of the liver in children. **A,** Mesenchymal hamartoma, a complex multicystic mass with solid septae. **B,** Focal nodular hyperplasia with *arrow* pointing to classic stellate central scar. **C,** Diffuse infantile hepatic hemangioma with multiple nodules showing peripheral contrast enhancement. **D,** PRETEXT 2 hepatoblastoma. **E,** PRETEXT 4 +P hepatocellular carcinoma with involvement of main portal vein. **F,** Metastatic tumor, two nodules of metastatic colorectal carcinoma in right anterior and posterior sections.

(MRI) outlines the anatomic extent of the tumor, clarifies its relationship to the central venous structures, and evaluates for multicentricity.[38] The radiographic appearance of the tumor at diagnosis is used to assign the tumor *Pre*treatment *Ext*ent of tumor (PRETEXT) (Fig. 33-3). The radiographic appearance of the tumor after preoperative (neoadjuvant) chemotherapy has been called *Post*-treatment *Ext*ent of tumor (POST-TEXT).[39] A chest CT scan is an essential part of the initial radiographic evaluation, to rule out metastatic pulmonary disease. In children with HB, about 20% present with metastatic disease in the lungs. In HCC, the number of children who present with advanced disease is quite high and pulmonary metastases at diagnosis have been reported as high as 50% in some series.[40]

# Malignant Liver Tumors

After neuroblastoma and Wilms' tumor, primary tumors of the liver are the third most common intra-abdominal neoplasms in children.[41] HB is the most frequent liver tumor in children in Western countries, whereas in Asia and Africa, hepatocellular carcinoma (HCC) occurs more frequently than HB, probably as a consequence of the higher prevalence of hepatitis B infection on those continents.[42,43] Other less common malignant pediatric liver tumors are listed in Table 33-1.

## HEPATOBLASTOMA

### Epidemiology, Biology, and Genetics

Hepatoblastoma accounts for about 80% of the malignant liver tumors in children.[12,44] In the United States, the incidence of HB has increased from 0.6 to 1.2 cases per million population in the last 2 decades.[44] It comprises 1% of all pediatric malignancies and affects mostly young children between 6 months and 3 years old, but cases in neonates and school-age children are also seen.

Researchers at the University of Minnesota are conducting a large epidemiologic study, termed the "HOPE" study, aimed at elucidating possible environmental and genetic risk factors that might account for the increasing incidence of HB seen over the past 2 decades.[45] The HOPE study (hepatoblastoma origins and pediatric epidemiology) can be reached at www.cancer.umn.edu/hopestudy. A leading theory is that the increased incidence is due to the growing prevalence of premature birth and very-low-birth-weight (VLBW) babies. Both prematurity and very low birth weight have been associated with an increased risk for HB. The association between HB and prematurity or VLBW was first shown in Japan and has since been confirmed in multiple studies.[45–49] No association has yet been found between prematurity as a risk factor and the age at which the tumor diagnosis is eventually made or the histologic subtype of the tumor. Unproven, but postulated, environmental risk factors include occupational exposure of the father to metals, such as welding and soldering fumes, petroleum products, and paint.[50] The list of possible iatrogenic exposures of the premature or VLBW baby in the neonatal care unit includes light, oxygen, irradiation, electromagnetic fields, plasticizers, medications, and total parenteral nutrition.[51]

HB is also associated with fetal alcohol syndrome and hemihyperplasia (formerly termed hemihypertrophy).[52] Hemihyperplasia is associated with an increased risk of embryonal tumors, primarily Wilms' tumor and HB. Curiously, although there is clinical overlap between hemihyperplasia and Beckwith-Weidemann syndrome, the genetic abnormalities seen in HB patients with Beckwith-Weidemann syndrome are not

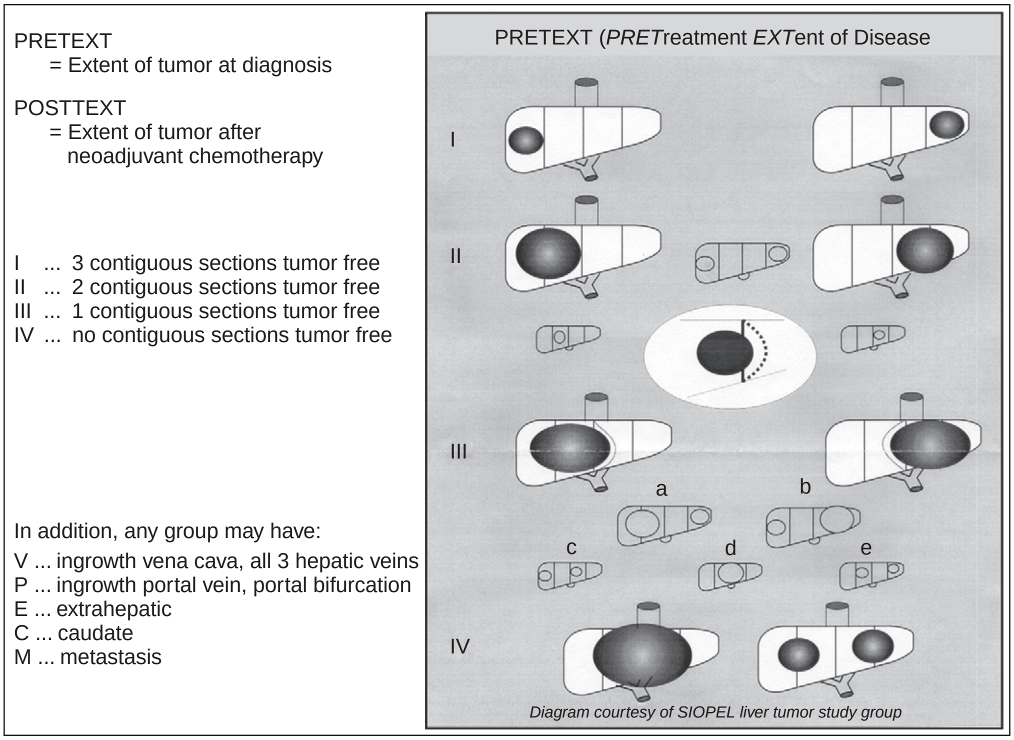


**FIGURE 33-3** PRETEXT.

seen in those with hemihyperplasia.[53] In addition to Beckwith-Weidemann syndrome, a number of other genetic syndromes have been associated with an increased risk of HB, including familial adenomatous polyposis (FAP), Li-Fraumeni syndrome, trisomy 18, and others as shown in Table 33-3.[54–68] Familial case reports of HB with familial adenomatous polyposis are striking and suggest a role in the pathogenesis of HB for chromosomes 5 and 11.[56,69] Additional screening for cases in familial adenomatous polyposis kindred families is recommended by testing for germline mutations in the adenomatous polyposis coli (APC) tumor suppressor gene.[55,70] Germline APC mutations are not commonly seen in children with sporadic HB.[71] The association between Beckwith-Weidemann syndrome and HB is so strong that experts recommend that children with Beckwith-Weidemann syndrome be screened with abdominal ultrasonography and AFP at regular intervals until they reach the age of 7 years.[72] The genetic abnormality in HB patients with Beckwith-Weidemann syndrome is mapped to the 11p15.15 locus and suggests the presence of a tumor suppressor gene at this location.[73] Additional biological markers may include trisomy 2, 8, 18, 20, and translocation of the *NOTCH2* gene on chromosome 1q12-21.[61] Up-regulation of insulin-like growth factor 2 may be mediated by overexpression of *PLGA1* oncogene, a transcriptional activator on the 8q chromosome.[74]

One of the most provocative genetic findings has been the association between HB and mutations of beta-catenin and activation of the WNT/beta-catenin signaling.[75–77] Microarray analysis of WNT/beta-catenin and MYC signaling has defined two tumor subclasses resembling distinct phases of liver development and characterized by a discriminating 16-gene signature. The highly proliferating tumor subclass showed gains of chromosome 8q and 2p and up-regulated MYC signaling.[78,79] Histologic subtypes of hepatoblastoma have also been characterized by different patterns of WNT and NOTCH pathway activation in DLK+ precursors.[80] The authors speculate that HB may arise from proliferating bipotential precursors with WNT activation most prevalent in embryonal and mixed histologic subtypes and NOTCH activation more prevalent in the differentiated pure fetal subtype.[80] In addition, deregulation of MAPK signaling pathway and antiapoptotic signaling is preferentially up-regulated in aggressive epithelial HB with a small cell undifferentiated component.[81] These gene expression signatures may provide prognostic and diagnostic markers, perhaps even therapeutic targets, in the future.[80,81]

Other genetic markers that have been associated with biological behavior include multidrug-resistance genes and the Hedgehog pathway.[82–85] Increased expression of multidrug-resistance genes is seen in response to chemotherapy in many childhood tumors, and this seems to be particularly true in HB.[82] Chemotherapy has been shown to induce overexpression of the multidrug-resistance gene *MDR1*, MDR-associated protein MRP1, and lung-related protein (LRP).[84]

## Pathology

According to the World Health Organization (WHO) Tumor Classification, hepatoblastoma is defined as a malignant tumor with divergent patterns of differentiation, ranging from cells resembling fetal epithelial hepatocytes, to embryonal cells, and with differentiated tissues, including osteoid-like material, fibrous connective tissue, and striated muscle fibers. In fact, the morphology of HB seems to reflect distinctive phases of hepatogenesis, recapitulating cell lineages derived from endoderm fated to become mature liver cells.[86] The neoplastic offspring of these cell systems is present in HB in a variety

**TABLE 33-3**
**Genetic Syndromes Associated with Pediatric Liver Tumors**

| *Disease* | *Tumor* | *Chromosome* | *Gene* | *Reference* |
|---|---|---|---|---|
| Familial adenomatous polyposis (FAP) | HB, HCC, adenoma | 5q21.22 | *APC* | Thomas 2003[54] Hirschman 2005[55] |
| Beckwith-Wiedemann syndrome (BWS) | HB, Infantile hemangioma | 11p15.5 | *P57KiP2, WNT, others* | Steenman 2000[56] Fukuzawa 2003[57] |
| Li-Fraumeni syndrome | HB, undifferentiated sarcoma | 17p13 | *TP53*, others | Fraumeni 1969[58] |
| Trisomy 18 | HB | 18 | – | Bove 1996[59] Maruyama 2001[60] |
| Other trisomies | HB | 2, 8, 20 | – | Tomlinson 2006[61] |
| Glycogen storage disease type I-IV | HB, HCC, adenoma | Several | – | Siciliano 2000[62] |
| Hereditary tyrosinemia | HCC | 15q23-25 | Fumarylaceto-acetate hydrolase | Demers 2003[63] |
| Alagille syndrome | HCC | 20p12 | *JAG1* | Keefe 1993[64] |
| Progressive familial intrahepatic cholestasis (PFIC) | HCC | 18q21-22, 2q24 | *F1C1, BSEP* | Alonso 1994[65] |
| Neurofibromatosis | HCC, schwannoma, angiosarcoma | 17q11.2 | *NF-1* | Kanai 1995[66] |
| Ataxia telangiectasia Hepatocellular carcinoma | HCC | 11q22-23 | *ATM* | Geoffroy-Perez[67] |
| Fanconi anemia | HCC, adenoma | 1q42, 3p, 20q13 | *FAA, FAC* | Touraine 1993[68] |

HB, hepatoblastoma; HCC, hepatocellular carcinoma.

of proportions, used as the basis of HB classifications, of which the current International Society of Pediatric Oncology (epithelial) liver tumor study group (SIOPEL) classification is shown in Table 33-4. Untreated HB presents as a lobulated mass up to more than 20 cm in diameter, being solitary tumors in 80% of the patients and located to the right lobe of the liver in about 60%. The lesions usually show an expanding growth pattern, but conglomerated masses with satellite nodules are also observed. The color of the cut surfaces is variegated in many HB, partly caused by necrosis and hemorrhage, with the exception of fetal HB, which has the tan color of normal liver. The gross presentation of HB postchemotherapy is characterized by firm and well-delineated and sometimes multinodular masses with whitish fibrotic areas and calcifications.

Histologically, the epithelial components range in their differentiation from a small cell undifferentiated (previously termed anaplastic) phenotype, resembling other cellular blue tumors, to cells that are close to mature hepatocytes (the fetal phenotype). The current, histology-based classification is not consistent regarding cellular differentiation, because one subtype (macrotrabecular) reflects a growth pattern rather than a distinct differentiation step. The fetal subtype, occurring in a purely fetal and a so-called crowded fetal variant, displays the highest level of differentiation. Pure fetal histology HB is associated with both a diploid DNA complement and a low proliferative activity. About 20% of epithelial HB shows a mixture of fetal and less differentiated, embryonal-type cells, with a more pronounced mitotic activity. The macrotrabecular subtype (less than 5% of the tumors) reveals a growth pattern with large cell plates consisting either of fetal-embryonal or hepatocyte-like cells. The latter variant, macrotrabecular type 1 (MT-1) is difficult to distinguish from hepatocellular carcinoma and may have an unfavorable biology.[18] Undifferentiated HB mostly occurs as a small cell neoplasm not associated with elevated serum AFP (small cell undifferentiated [SCU] HB), but variants with larger cells also occur. HB-SCU forms a complex group of tumors in that at least part of the lesions seem to have a relation to rhabdoid tumors and are INI1 protein negative.[87,88]

A large proportion of HB (about 45% when examined after chemotherapy) reveal a mixed epithelial and mesenchymal (MEM) phenotype (HB-MEM; see Table 33-4). Osteoid-like bone tissue is a common mesenchymal (heterologous) component. The same epithelial components as found in the wholly epithelial HB subtypes occur in variable expression. The relative proportions of the components in HB-MEM undergo marked changes subsequent to chemotherapy. After exposure to chemotherapy, often the osteoid dominates the histologic pattern. A small proportion of HB-MEM exhibit unusual tissues, such as glianeuronal, enteric, or melanocytic tissues. These tumors are termed HB-MEM with teratoid features. It has to be emphasized that this term is descriptive and does not imply that these neoplasms are germ cell tumors. The prognostic significance of these histologic types and subtypes is currently under study in large trials.

**TABLE 33-4**
**Classification of Hepatoblastoma Histologic Subtype***

| |
|---|
| Hepatoblastoma, Wholly Epithelial Type |
| Fetal |
| Embryonal/mixed fetal and embryonal |
| Macrotrabecular (MT) |
| Small cell undifferentiated (SCU; formerly anaplastic) |
| Hepatoblastoma Mixed Epithelial and Mesenchymal Type (HB-MEM) |
| Without teratoid features |
| With teratoid features |
| Hepatoblastoma, Not Otherwise Specified (HB-NOS) |

*This is the classification used by the SIOPEL (International Society of Pediatric Oncology [epithelial] liver tumor study group). Classification systems used by American, German, and Japanese study groups vary.

So far, a prognostic relevance has been worked out for the fetal subtype (favorable)[89] and for HB-SCU (unfavorable).[30,31,90] An unfavorable histology of HB-SCU is also present in cases where the SCU feature is expressed in a focal pattern only.[91] In addition to the lesions listed in Table 33-4, an increased number of variants of HB, or lesions thought to be related to HB, have been described, leading to the concept of *tumor families*.[92]

## PRETEXT, STAGING, AND RISK GROUP STRATIFICATION

"Risk Group" stratification determines treatment for hepatoblastoma (HB) in current multicenter group trials. As shown in Table 33-5, The Children's Oncology Group (COG) has low, intermediate, and high-risk treatment groups, whereas SIOPEL defines a standard-risk and a high-risk group. COG continues to use traditional COG (Evans) stage I to IV, and prognostic factors (pure fetal and small cell undifferentiated histology and AFP < 100) to assign risk groups. Although COG does not currently use PRETEXT to assign risk group, it does use PRETEXT to define surgical guidelines, where it determines whether or not a tumor should be resected at diagnosis. The timing of resection will determine the tumor stage for all nonmetastatic tumors. In contrast, SIOPEL uses PRETEXT and prognostic factors to define risk groups.

PRETEXT (see Fig. 33-3) was devised by SIOPEL 1.[93] Subsequent SIOPEL trials (SIOPEL 2, and SIOPEL 3) have used PRETEXT as a tool to stratify treatment, define risk categories, and report outcomes in HB. Although the risk stratification schema differs somewhat between groups, the three other major multicenter pediatric liver tumor study groups, Children's Oncology Group (COG), German Pediatric Oncology Hematology (GPOH), and the Japanese Pediatric Liver Tumor (JPLT) have all chosen to adopt PRETEXT in their current and future protocols. Although PRETEXT has been found to have a slight tendency to overstage patients, it is postulated to show good interobserver agreement (reproducibility.) PRETEXT may also be used to monitor the effect of preoperative therapy when it is applied serially to assess tumor response to neoadjuvant chemotherapy.[28] In North America, COG uses PRETEXT to define surgical resectability (i.e., surgical resection guidelines) in its current HB protocol (AHEP 0731). Building upon the Couinaud 8–segment anatomic structure of the liver, the PRETEXT system divides the liver into four parts, called "sections" (Fig. 33-4). The left lobe of the liver consists of a lateral (Couinaud segments II and III) and medial section (segment IV), whereas the right lobe is divided into an anterior (segments V and VIII) and posterior section (segments VI and VII). Couinaud segment I is the caudate lobe and when involved is shown in PRETEXT with the annotation "C."

As shown by the examples in Figure 33-5, the tumor is classified into one of the following four PRETEXT groups depending on the number of liver sections that are free of tumor: PRETEXT I, three adjacent sections free of tumor; PRETEXT II, two adjacent sections free of tumor (or one section in each hemiliver); PRETEXT III, one section free of tumor (or two sections in one hemiliver and one nonadjacent section in the other hemiliver); and PRETEXT IV, no tumor free sections. Extrahepatic growth and gross vascular involvement is

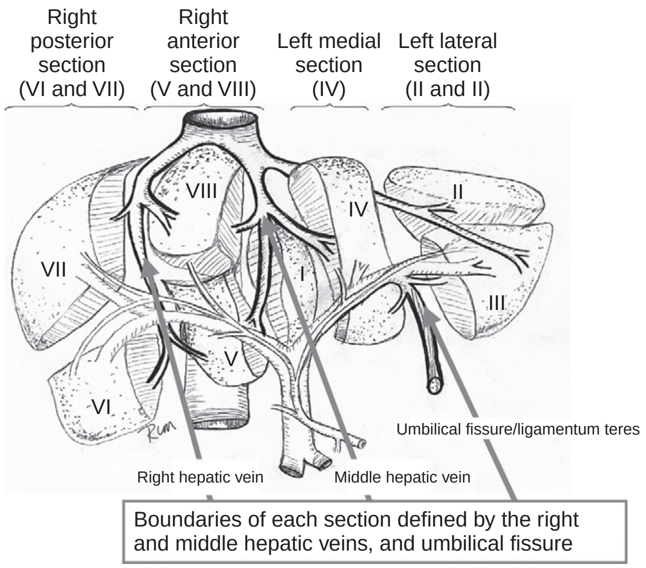


**FIGURE 33-4** PRETEXT is distinct from Couinaud 8–segments (I to VIII) anatomic division of the liver. PRETEXT defines four "sections." Boundaries of each section defined by the right and middle hepatic veins, and umbilical fissure.

**TABLE 33-5**
**Hepatoblastoma Staging and Risk Stratification**

| *Traditional COG (Evans) Staging System* | *Current COG Risk Stratification* | *Current SIOPEL Risk Stratification* |
|---|---|---|
| Stage I: complete gross resection at diagnosis with clear margins | Very low risk: pure fetal histology, resected at diagnosis (stage I/II); see resection guidelines below* | |
| Stage II: complete gross resection at diagnosis with microscopic residual disease at the margins of resection | Low risk: any histology resected at diagnosis (stage I/II); see resection guidelines below* | Standard risk: PRETEXT I, II, III |
| Stage III: biopsy only at diagnosis, or gross total resection with nodal involvement or tumor spill or incomplete resection with gross intrahepatic disease | Intermediate risk: stage III tumors (includes SCU histology) | |
| Stage IV: metastatic disease at diagnosis | High risk: stage IV tumors, AFP < 100 at diagnosis | High risk: PRETEXT IV, metastasis at diagnosis, SCU histology, AFP < 100 at diagnosis |

*COG surgical guidelines recommend resection of tumors at diagnosis (stage I/II) based upon PRETEXT. PRETEXT I and PRETEXT II resected at diagnosis if there is an anticipated greater than 1-cm surgical margin based upon preoperative imaging.

AFP, alpha-fetoprotein; COG, Children's Oncology Group; PRETEXT, pretreatment extent (of tumor) staging system; SCU, small cell undifferentiated; SIOPEL, International Society of Pediatric Oncology (epithelial) liver tumor study group.

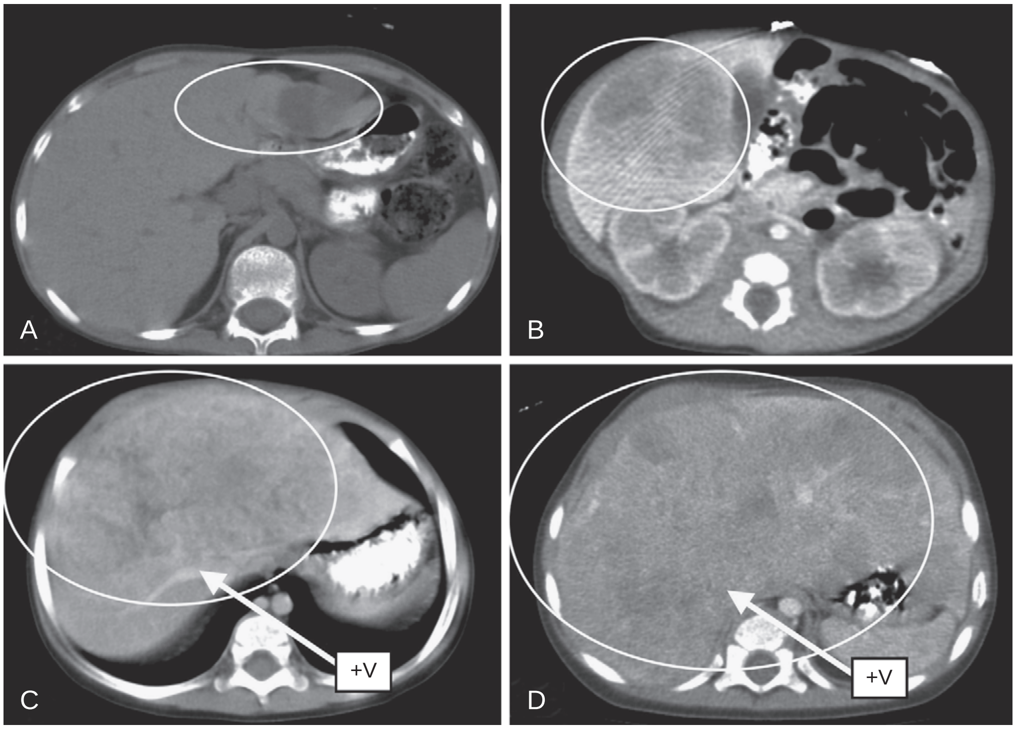


**FIGURE 33-5** Examples of PRETEXT for hepatoblastoma risk stratification. **A,** PRETEXT I, left lateral section. **B,** PRETEXT II, right anterior and right posterior sections. **C,** PRETEXT III, +V: left lateral section, left medial section, and right anterior section with invasion of all three hepatic veins (+V). **D,** PRETEXT IV, +V, +P: tumor involves all four sections and invades vena cava and portal bifurcation.

indicated by adding one or more of the following: V, vena cava or all three hepatic veins involved; P, main portal or *both* portal branches involved; C, involvement of the caudate lobe; E, extrahepatic contiguous growth (e.g., diaphragm or stomach), and M, distant metastases (mostly lungs, otherwise specify).[39]

### Treatment Strategy, Chemotherapy, and Surgery

In the treatment of hepatoblastoma, complete surgical resection remains the cornerstone of curative therapy. And yet, as has become increasingly clear in recent large multicenter trials, surgery alone cannot cure patients who present with advanced disease. More than half of the patients present with either an initial unresectable tumor or with distant metastases. In the early years when these children were treated with surgery alone, there was a 30% relapse rate in those patients whose tumor could be completely resected. Evidence that HB is a chemosensitive tumor began to accumulate in the early 1970s when responses were seen to combinations of cyclophosphamide, vincristine, 5-fluorouracil, and actinomycin-D,[94] but not until the introduction of cisplatin and doxorubicin–containing regimens in the 1980s was there a major impact of chemotherapy on survival.[6] Twenty years later, cisplatin remains the backbone of current chemotherapy regimen. In fact, in the most recent study of standard-risk HB by SIOPEL, SIOPEL 3, treatment results with cisplatin monotherapy were comparable to those achieved with cisplatin/doxorubicin combination chemotherapy (PLADO).[7] Chemotherapy may reduce tumor volume, making the tumor resectable, and may lead to the complete disappearance of lung metastases. The tumor response rate to the present cisplatin-containing chemotherapy regimens varies from 70% to 90%, according to the different series.[7,31,95–100] Neoadjuvant (preoperative) chemotherapy not only makes the tumor "smaller" and consequently more likely to be completely resected, but also more solid, less prone to bleeding, and better demarcated from the remaining healthy liver parenchyma.[101,102] Also, when chemotherapy is given as soon as possible after diagnosis, occult (micro)metastases in the lung have no delay in treatment. No matter how small the primary tumor, SIOPEL recommends preoperative chemotherapy in ALL patients as shown in Figure 33-6. This approach is hypothesized to increase the number of patients for whom complete surgical resection will be feasible, to reduce the surgical morbidity of resection, and to provide more time for making definitive surgical plans, including liver transplantation when indicated.[103,104] Because of the large number of countries participating in the SIOPEL studies, standardization of both sophisticated surgical approaches and supportive care measures has been difficult; therefore the use of preoperative chemotherapy in every case has permitted patients from countries with limited resources to participate in these studies.

In contrast to the SIOPEL approach, the North American "legacy groups" Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) (now COG) and the German Study Group (GPOH) have historically recommended primary surgery, *whenever prudently possible*, as the initial treatment. The decision about which tumors are "resectable," and which ones are not, has been subjectively made by the treating surgeon; hence, the approach has been criticized for being highly variable. Because traditional Evans staging relies on the surgical resection decision at diagnosis (see Table 33-5), and because this is a surgeon-initiated subjective decision, the stage has often depended more on the surgeon than on the tumor. Figure 33-6 shows the North American strategy in COG study AHEP0731, which recommends tumor resection

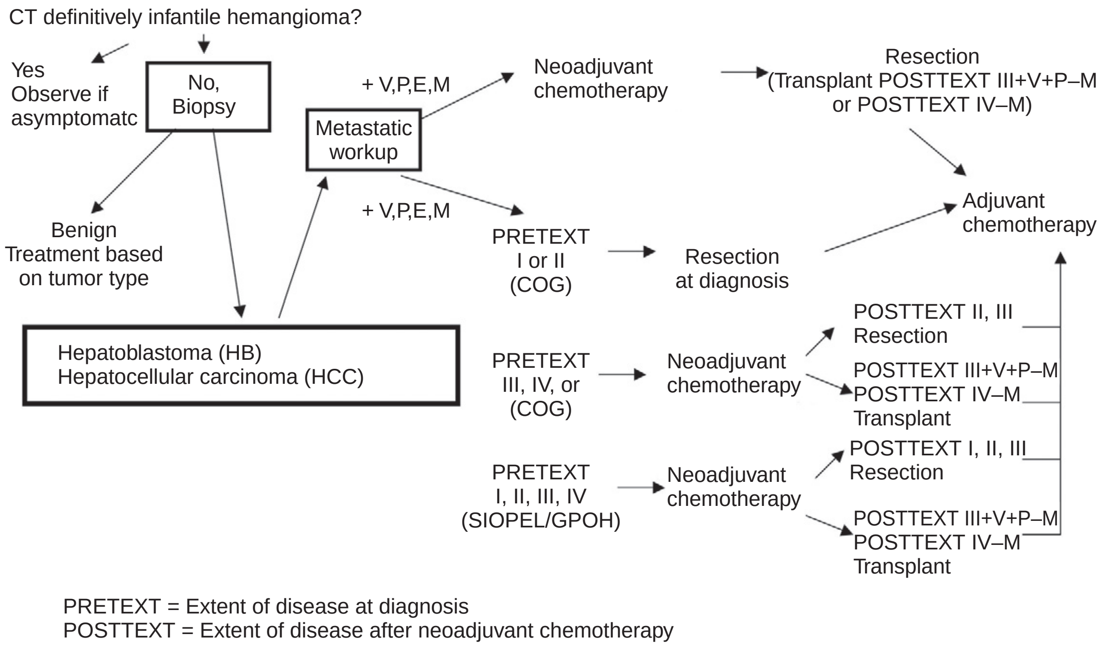


**FIGURE 33-6** Pediatric malignant liver tumor: simplified treatment algorithm. COG, Children's Oncology Group; CT, computed tomography; E, extrahepatic contiguous growth; GPOH, German Pediatric Oncology Hematology (study); M, metastasis; P, main portal or *both* portal branches involved; SIOPEL, International Society of Pediatric Oncology International Society of Pediatric Oncology (epithelial) liver tumor study group; V, vena cava or all three hepatic veins involved.

at diagnosis dictated by PRETEXT-defined surgical guidelines (PRETEXT I and II). Tumors can be resected by straightforward segmentectomy or lobectomy, and are resected at diagnosis. Following these guidelines, approximately one third of HB patients can successfully achieve a gross total resection of tumor at diagnosis, and among them it is possible to identify some that require minimal or no chemotherapy.[89,105] Although it has been debated, postsurgical complications do *not* appear to be more frequent with this approach in the modern era.[30,96,106,107] The potential to reduce cumulative chemotherapy exposure with upfront resection in PRETEXT I and II tumors is important given the ability of HB to develop resistance to standard chemotherapy.[32,82,84] Recent data on magnitude of AFP response actually suggest that the majority of chemotherapy tumor kill probably occurs in the first two cycles.[104]

The strategy in the German trials HB 89 and HB 94 was similar to that used in North America, that is, resection at diagnosis, when feasible, at the discretion of the operating surgeon. In a review of these studies, 30% of children with primary tumor resection had macroscopic or microscopic residual tumor.[31] Despite the larger number of advanced HB in the neoadjuvant chemotherapy group, an incomplete tumor resection was performed in only 18%. Based upon this statistically significant difference, GPOH adopted neoadjuvant chemotherapy for all patients in their latest trial, HB 99, and recommends against any surgical consideration of atypical, nonanatomic, or wedge resection.[18,98]

Surgical guidelines in the current COG trial, AHEP-0731 *do not* leave the decision about surgical resection at diagnosis up to the subjective discretion of the individual surgeon; objective resection guidelines are part of the protocol. PRETEXT is used to define which tumors should be resected at diagnosis (see Fig. 33-6). Resection at diagnosis is recommended for stage I/II only when segmentectomy or a facile, nonextended lobectomy will predictably yield a complete resection, that is, PRETEXT I or II tumors with at least 1 cm of clear margin anticipated upon review of diagnostic radiographic imaging. A POSTTEXT IIId tumor is a central tumor that may be best resected by mesohepatectomy in the hands of an experienced liver surgeon (Fig. 33-7). Transplantation is preferred in any tumor that invades the major vascular inflow (POSTTEXT +P) or outflow (POSTTEXT +V). If the PRETEXT (and POSTTEXT) suggests the need for major vascular reconstruction, which is sometimes called extreme resection (a resection performed in a patient who would otherwise meet criteria for liver transplantation) or liver transplantation, a referral for transplantation evaluation is advisable. Accuracy of PRETEXT is moderate (because of difficulty in differentiating tumor vessel compression from vessel ingrowth) with a slight tendency to overstage.[28] Nevertheless, good interobserver agreement has been reported, and comparing PRETEXT with POST-TEXT allows for an objective analysis of tumor response to chemotherapy.[39] The predictive value for survival using PRETEXT is excellent, and combining PRETEXT with traditional COG staging yields additional predictive value.[28,30]

*Postoperative* (adjuvant) chemotherapy is currently recommended by *all* study groups, for *all* patients with one small exception. Stage I pure fetal histology (PFH) in INT-0098 and COG P9645 received reduced or no chemotherapy[89,96,97] and has a 5-year event-free survival (EFS) and overall survival (OS) of 100% and 100%, respectively. Thus no chemotherapy is recommended for pure fetal histology patients resected at diagnosis in COG AHEP-0731. Cisplatin remains the backbone of the chemotherapy regimen, but the drug combinations differ somewhat between study groups. COG currently uses cisplatin/5-FU/vincristine (C5V) for low-risk tumors, C5V + doxorubicin for intermediate risk, and will investigate new agents (irinotecan) with upfront window

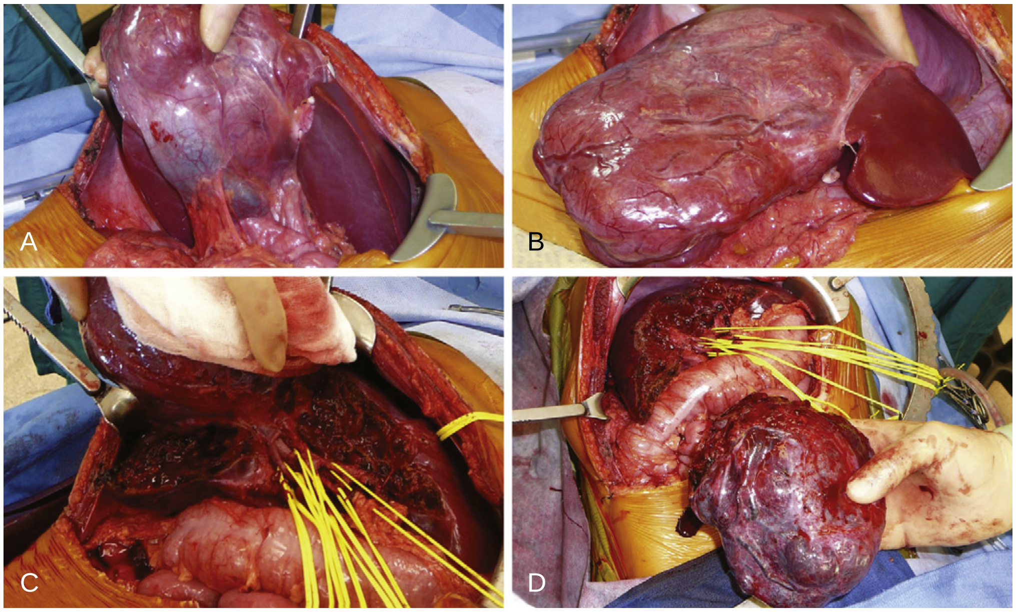


**FIGURE 33-7** Central PRETEXT IIId hepatoblastoma: resection with mesohepatectomy versus complete hepatectomy and transplantation, depends upon extent of macroscopic vessel involvement. **A,** Central hepatoblastoma involving left medial and right anterior sections (PRETEXT IIId). **B,** Resection with right or left trisegmentectomy would leave very little residual normal liver. **C,** Much of the normal liver can be saved by mesohepatectomy if the portal vessels are *not* encased and a good margin can be obtained. If tumor encases or invades the portal vessels, complete hepatectomy and transplantation is recommended. **D,** Frozen section shows negative margins.

therapy in high-risk tumors.[42] SIOPEL 3 compared cisplatin monotherapy with PLADO for standard risk[95] and used SUPERPLADO for high risk.[7] The current SIOPEL 4 high-risk study uses an intensified platinum regimen.[99] The recent GPOH trial HB-94 used IPA (ifosfamide/cisplatin/doxorubicin),[31] and the ongoing GPOH trial HB99 uses IPA for standard risk and carboplatin-VP-16 for high risk.[98] The recent Japanese trial JPLT-2 has used CITA (cisplatin/THP-Adriamycin [doxorubicin]) for standard risk and ITEC (ifosfamide/carboplatin/doxorubicin/etoposide) + HACE (hepatic artery chemoembolization) for high-risk patients.[108] Irinotecan, with or without doxorubicin, has been used in both North America and Europe for patients with relapse.[109,110]

In terms of overall survival rates, the results of the different study groups are generally comparable, projecting 3-year overall survival rates, regardless of the first therapeutic modality used, of 62% to 70% (Table 33-6).[7,31,95–100] The improved results in the high-risk group achieved in SIOPEL 3 highlight some important lessons learned over the past 2 decades. (1) With standard treatment, about 25% of patients who present with metastatic disease are ultimately cured, and alternative chemotherapy and surgical resection of pulmonary metastatic disease should be considered in patients who do not show an excellent early response to chemotherapy. (2) The presence of a positive microscopic margin may not portend a poor prognosis in patients who have had an excellent response to chemotherapy. (3) Liver transplantation or extreme resection (i.e., mesohepatectomy and major venous resection and reconstruction) should be considered in every child with unresectable HB (about 15% of cases).[9,10,102,111–113]

The current COG trial, AHEP-0731, is a risk-stratified study that seeks to diminish toxicity in low-risk patients, increase survival in intermediate-risk patients, and identify new agents(s) in high-risk patients.[107] Very-low-risk patients with pure fetal histology (PFH) hepatoblastoma resected at diagnosis receive no chemotherapy. Low-risk patients who have non-PFH histology resected at diagnosis receive two adjuvant cycles of cisplatin, 5-flouorouracil, and vincristine (C5V), a reduction from the standard four cycles of chemotherapy used in previous COG trials. For intermediate-risk patients with stage I SCU, stage II SCU, or any stage III hepatoblastoma the chemotherapy regimen will add doxorubicin to the C5V therapy (C5VD). High-risk patients with metastatic tumor or initial AFP less than 100 ng/mL will be treated with an upfront window of a novel agent (irinotecan) preceding the backbone therapy with C5VD.

### Liver Transplantation for Hepatoblastoma

In 1968, Starzl reported the first long-term survivor of liver transplantation, a child with hepatoma. From that time until the cluster of papers published by Al-Qabandi, Reyes, Pimpalwar, Molmenti, and Srivastin from 1999 to 2002,[114–118] most descriptions of the use of transplantation in hepatoblastoma were anecdotal case reports. Largely because of early negative experience with liver transplantation in the treatment of adult hepatocellular carcinoma, liver transplantation for the treatment of hepatic malignancy developed a reputation as a dreaded, last resort, heroic, and even potentially ethically inappropriate intervention. The biology of pediatric hepatoblastoma has proven to be very different from that of adult hepatocellular carcinoma, with cisplatin-based chemotherapy proven to be of significant value in a number of randomized trials. This availability of effective chemotherapy led credence to the bold statement by Reyes in his landmark paper in 2000 [115] that "in these children with unresectable tumors, the historical barrier of "unresectability" can be redefined with the concept of 'total liver resection' and salvage orthotopic liver transplantation (OLT)." Thus beginning about 2000, liver transplantation began to be offered to more and

**TABLE 33-6**

**Summary Results Recent Hepatoblastoma Cooperative Trials**

| *Study* | *Chemotherapy* | *No. of Patients* | *Outcomes* |
|---|---|---|---|
| INT0098 (CCSG, POG)[96] | C5V vs. CDDP/DOXO | Stage I/II: 50<br>Stage III: 83<br>Stage IV: 40 | 4-Year EFS/OS<br>Stage I/II: 88%/100% vs. 96%/96%<br>Stage III: 60%/68% vs. 68%/71%<br>Stage IV: 14%/33% vs. 37%/42% |
| P9645 (COG)[97] | C5V vs. CDDP/CARBO | Stage I/II: pending publication<br>Stage III: 38<br>Stage IV: 50 | 1-Year EFS*<br>Stage III/IV C5V: 51%; CDDP/CARBO: 37%<br>*Study closed early due to inferior results CDDP/CARBO arm |
| HB94 (GPOH)[31] | Stage I/II: IFOS/CDDP/DOXO<br>Stage III/IV: IFOS/CDDP/DOXO + VP/CARBO | Stage I: 27; II: 3; III: 25; IV: 14 | 4-Year EFS/OS<br>Stage I: 89%/96%; II: 100%/100%; III: 68%/76%; IV: 21%/36% |
| HB99 (GPOH)[98] | SR: IPA<br>HR: CARBO/VP16 | SR: 58<br>HR: 42 | 3-Year EFS/OS<br>SR: 90%/88%<br>HR: 52%/55% |
| SIOPEL 2[95] | SR: PLADO<br>HR: CDDP/CARBO/DOXO | PRETEXT: I: 6; II: 36; III: 25; IV: 21; Mets: 25 | 3-Year EFS/OS<br>SR: 73%/91%<br>HR: IV: 48%/61%<br>HR mets: 36%/44% |
| SIOPEL 3[7,99] | SR: CDDP vs. PLADO<br>HR: SUPERPLADO | SR: PRETEXT I: 18; II: 133; III: 104<br>HR: PRETEXT IV: 74; +VPE: 70; mets: 70; AFP $<$ 100: 12 | 3-Year EFS/OS<br>SR: CDDP 83%/95%; PLADO 85%/93%<br>HR: overall 65%/69%; mets 57%/63% |
| JPLT-1[100] | Stage I/II: CDDP (30)/THPA-DOXO<br>Stage III/IV: CDDP (60)/THPA-DOXO | Stage I: 9; II: 32; IIIa: 48; IIIb: 25; IV: 20 | 5-Year EFS/OS<br>Stage I: ?/100%; II: ?/76%; IIa: ?/50%; IIIb: ?/64%; IV: ?/77% |

C5V, cisplatin; CARBO, carboplatin; fluorouracil and vincristine; CCSG, Children's Cancer Study Group; CDDP, cisplatin; COG, Children's Oncology Group; DOXO, doxorubicin; EFS, event-free survival; GPOH, German Pediatric Oncology Hematology; JPLT, Japanese Pediatric Liver Tumor (study); IFOS, ifosfamide; HR, high risk; IPA, ifosfamide, cisplatin, Adriamycin; mets, metastatic disease; OS, overall survival; POG, Pediatric Oncology Group; PRETEXT, pretreatment extent (of tumor) staging system; SIOPEL, International Society of Pediatric Oncology (epithelial) liver tumor study group; SR, standard risk; SUPERPLADO, CDDP/CARBO/DOXO; THPA, THP-adriamycin; VP, etoposide; +VPE mets, *V*ena Cava, *P*ortal vein, *E*xtrahepatic metastatic disease.

more children as part of a planned treatment algorithm. With increased experience defining the optimal timing of transplantation, the outcomes with liver transplantation for hepatoblastoma have blossomed.

***Transplantation Outcomes for Hepatoblastoma*** In the past decade, more than a score of reports have appeared in the literature championing the potential role of liver transplantation in the treatment of unresectable pediatric hepatoblastoma (Table 33-7).[113–130] Transplantation, although potentially lifesaving, carries attendant consequences, including perioperative morbidity and mortality and the subsequent need for lifetime immunosuppression. The experience from Birmingham, United Kingdom illustrates contemporary experience, with 5-year disease-free survival of 100% when primary transplantation was performed in patients with a good response to chemotherapy, 60% after primary transplantation in patients with a poor response to chemotherapy, only 50% in patients with transplantation as a second option or "rescue transplantation," and 0% in patients not undergoing surgery.[116] In SIOPEL 1, overall survival at 10 years was 85% with a primary transplantation but only 40% for the children who underwent a rescue transplantation.[120] In a collaborative report of the world experience of liver transplantation for hepatoblastoma,[120] the overall survival rate at 6 years was 82% for 106 patients who received a primary transplantation, but only 30% for 41 patients who underwent a rescue transplantation.

***Indications and Contraindications for Transplantation in Hepatoblastoma*** The following criteria are currently used by COG and SIOPEL to select potential candidates for transplantation: (1) multifocal PRETEXT IV, multifocal tumor in all four liver sections at diagnosis; (2) unifocal PRETEXT IV, with neoadjuvant chemotherapy often these tumors will "downstage" to a POST-TEXT III and become amenable to conventional resection by trisegmentectomy; (3) POSTTEXT III+V, proximity of the tumor to the vena cava or all three major hepatic veins makes adequate tumor clearance without impaired venous outflow doubtful; (4) POSTTEXT III+P, proximity of the tumor to the portal venous bifurcation or both major branches of the portal vein makes adequate tumor clearance without impaired portal venous inflow doubtful; (5) Intrahepatic relapse or residual tumor after previous attempt at resection, known as rescue transplantation. Although these guidelines are very useful, some uncertainty and controversy remains regarding the management of multifocal tumors, patients with venous involvement who might be candidates for extreme resection, patients who present with pulmonary metastasis, and patients who are referred with relapse or residual tumor and require rescue transplantation.

***Transplantation for Multifocal Hepatoblastoma*** Both COG and SIOPEL currently recommend that all patients with multifocal PRETEXT IV tumors should undergo liver transplantation, even if one of the liver sections is apparently clear of tumor nodules after preoperative chemotherapy (Fig. 33-8). Microscopic foci of viable tumor are seen in explant livers despite the apparent radiographic disappearance of tumor nodules from these areas after preoperative chemotherapy.[131] In addition, multiple series have shown excellent results from primary transplantation and poor

**TABLE 33-7**
**Contemporary Outcomes Transplantation for Hepatoblastoma**

| | *No. of Patients* | *Survival (%)* | *Follow-up (years)* |
|---|---|---|---|
| Al-Qabandi et al, J Pediatr Surg, Birmingham, UK[114] | 8 | 75 | |
| Reyes et al, 2000, J Pediatr, Pittsburgh, Pa[115] | 12 | 83 | 0.1-15.4 |
| Pimpalwar et al, 2002, J Pediatr Surg, Birmingham, UK[116] | 12 | 83 | 0.1-9.2 |
| Molmlenti et al, 2002, Am J Transplant, Dallas, Tex[117] | 9 | 55 | 0.5-16 |
| Sinivasan et al, 2002, Transplantation, London, UK[118] | 13 | 85 | 0.1-9 |
| Chardon et al, 2002, Transplantation, Paris/Brussels[113] | 4 | 75 | 1.1-2 |
| Cillo et al, 2003, Transplant Proc, Padua, Italy[119] | 7 | 57 | 0.2-9 |
| Otte et al, 2004, Pediatr Blood Cancer,[120] | | | |
| SIOPEL 1 + "World Experience" | | | |
| Primary transplantation | 106 | 82 | |
| Rescue transplantation | 41 | 30 | |
| Tiao et al, 2005, J Pediatr, Cincinnati, Ohio[111] | 9 | 80 | |
| Mejia et al, 2005, Clin Transplant, San Antonio, Tex[121] | 10 | 70 | 3.7-18 |
| Kasahara et al, 2005, Am J Transplant, Kyoto[122] | 14 | 71 | 3.5 ± ? |
| Chen et al, 2006, J Pediatr Gastroent Nutr, St Louis[123] | 7 | 85 | 0.6-18 |
| Avila et al, 2006, Eur J Pediatr Surg, Madrid[124] | 11 | 82 | 1-14 |
| Austin et al, 2006, J Pediatr Surg, UNOS database[125] | 135 | 69 | |
| Cassas-Medley et al, 2007, J Pediatr Surg, Dupont, Del[126] | 8 | 75 | 0.6-4.4 |
| Beaunoyer et al, 2007, Pediatr Transplant, Stanford, Calif[127] | 15 | 86 | 3.3 ± 3.5 |
| Faraj et al, 2008, Liver Transplant, London, UK[128] | 25 | 78 | 0.9-14.9 |
| Browne et al, 2008, J Pediatr Surg, Chicago,[129] | 14 | 71 | 3.8 ± ? |
| Kalicinski et al, 2008, Ann Transplant, Warsaw[130] | 6 | 66 | |

SIOPEL, International Society of Pediatric Oncology (epithelial) liver tumor study group; UNOS, United Network for Organ Sharing.

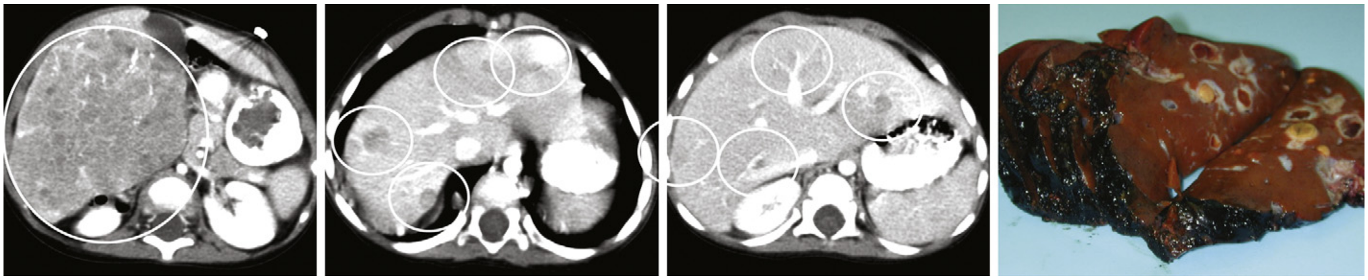

**FIGURE 33-8** PRETEXT IV multifocal hepatoblastoma. In the presence of extensive multifocal tumors, microscopic satellites should be assumed, and no distance of surgical margin can ensure complete surgical excision. Extensive multifocal tumors are best treated by complete hepatectomy and liver transplantation.

results from rescue transplantation.[116,120,124,126,129] In a recent series from Padova, predictors of failed conservative therapy included multifocality.[132]

***Major Venous Involvement: Transplantation versus Extreme Resection*** Aggressive resections, less than total hepatectomy, may be successful in select patients with tumor encroachment on the vena cava or main portal vein. Complex extensive resection, with vascular reconstruction if necessary, depends upon surgical expertise and a careful evaluation of the degree of vascular involvement and realistic ability to achieve complete, *and safe*, resection.[133,134] Poorly planned or executed operations risk excessive bleeding, inflow or outflow vascular obstruction, biliary leakage or stricture, cholangitis, and/or hepatic failure. Although most agree that extreme resection of tumors without liver transplantation will avoid the need for long-term immunosuppression,[102,113,132,133,135–137] outcomes with these techniques have not been rigorously reported. Current recommendations for referral of high-risk patients with hepatoblastoma to centers that have the ability to do an extreme resection, with liver transplantation as an immediately available safety net, should result in an improved ability to compare the outcomes of these two approaches.*

***Transplantation for Hepatoblastoma with Pulmonary Metastasis at Diagnosis*** An absolute contraindication to liver transplantation is persistent pulmonary metastases non-responsive to neoadjuvant chemotherapy and not amenable to surgical resection. Stable or progressive disease in the face of neoadjuvant chemotherapy is a relative contraindication to transplantation.[10,133] Lung metastases that disappear completely with chemotherapy, or with a combination of chemotherapy and surgical resection, do *not* pose a contraindication, yet the risk of post-transplantation pulmonary relapse is substantial, and therefore the use of liver transplantation for children with metastatic disease remains controversial.

* References 9,10,112,131,137,138

**TABLE 33-8**

**Liver Transplantation in Children with Hepatoblastoma and Pulmonary Metastasis at Diagnosis, Review of Literature (Meyers and Otte,[9] 2010)**

| *Pulmonary Metastasis at Diagnosis* | *No. of Patients* | *Post-transplantation Pulmonary Relapse* | *Alive without Evidence of Tumor* | *Died of Other Causes* |
|---|---|---|---|---|
| Lung lesions disappeared with chemotherapy | 24 | 9 (38%) | 14 (58%) | 1 (4%) |
| Pretransplantation pulmonary metastasectomy | 8 | 3 (38%) | 5 (62%) | |
| TOTAL | 32 | 12 (37%) | 19 (60%) | 1 (3%) |

Patients listed in table have been separately reported in the following series during the past 10 years: Perilongo, 2004[95]; Casanova, 2009[99]; Schnater, 2002[101]; Al-Qabandi et al, 1999[114]; Reyes et al, 2000[115]; Avila et al, 2006[124]; Cassas-Medley, 2007[126]; Superina et al, 1996[139]; Nathan 2009[140]; Otte, 2009.[141]

Table 33-8 shows the accumulated cases in the literature and presented at national and international meetings during the past 10 years.* Overall survival appears to be about 60% with no large difference in outcome when there is lung metastasis with complete radiographic resolution on chemotherapy versus pulmonary metastasectomy. Some centers do AFP imaging pretransplantation, PET-CT pretransplantation, median sternotomy with manual palpation of both lungs pretransplantation, and lobectomy rather than metastasectomy if the lung has more than four nodules in the same lobe.[142]

***Rescue Transplantation for Local Relapse Hepatoblastoma*** Multiple series have shown superior outcome after primary transplantation (about 80% overall survival) when compared with rescue transplantation (about 30% to 40% overall survival).[116,120,124,126,129] The basis for this is undoubtedly multifactorial, but two important reasons are (1) the likelihood of chemotherapy resistance in relapsed tumors and (2) the debilitated state of the patients when transplanted in the face of end-stage disease.

***Type of Allograft and Immunosuppression*** There is a trend to improved survival of children receiving a live-donor liver transplantation (LDLT).[120,121,128] When a living donor is available, pretransplantation chemotherapy can be scheduled optimally, with a rapid decision towards transplantation.[121] Whether living donor grafts might require less immunosuppression as suggested by Gras,[143] or whether alternative immunosuppression using rapamycin (sirolimus), a drug with both antineoplastic and immunosuppressive properties, will have any impact in children with hepatoblastoma remains to be seen. Many worry that the toxicity of chemotherapy might be potentiated by immunosuppression, but this has *not* been the experience at high-volume centers. With such a small number of patients in each of the individual series reported to date, it is not possible to make a clear recommendation at this time.

***Pediatric Liver Unresectable Tumor Observatory (PLUTO)*** SIOPEL, together with support from COG, GPOH, and the Study of Pediatric Liver Transplantation (SPLIT), has established a worldwide electronic registry for liver transplantation for childhood liver tumors (hepatoblastoma, hepatocellular carcinoma, and diffuse infantile hemangioma).[9,10,141,144] The link to obtain a password to register patients on this database can be accessed through the PLUTO Registry website: http://pluto.cineca.org/access.

* References 95, 99, 101, 114, 115, 124, 126, 139–141.

## New Agents and Treatment Modalities

***Hepatic Arterial Chemoembolization (HACE), Transarterial Chemoembolization (TACE)*** HACE and TACE are different acronyms for the same interventional radiologic procedure, also sometimes referred to as transcatheter arterial chemoembolization. This technique continues to be quite popular in China where recent experience in infants and children showed a mean tumor shrinkage of 59%, mean decrease in AFP of 60%, mean tumor necrosis in the surgical specimens of 87%.[145] Widespread use has been somewhat limited by toxicity, which includes fever, pain, nausea, vomiting, transient coagulopathy, and, most worrisome, pulmonary oil (Lipiodol) embolism.[145–147] Pulmonary oil embolism is infrequent, and although fatalities have been reported, the clinical course is usually self-limited oxygen desaturation for 24 to 48 hours and pulmonary infiltrate for about a week.[148] Chemotherapeutic cocktails have included various combinations of cisplatin, doxorubicin, doxorubicin-eluting beads, vincristine, pirarubicin, mitomycin, and Lipiodol, followed by gelatin foam particles or stainless steel coils, and radioactive microspheres.[131,145–148] There are scattered case reports of cure without the need for surgical resection,[149] although it is most often used not as a definitive treatment, but rather as palliation for large unresectable tumors in the presence of uncontrolled metastatic disease.[145]

***Ototoxicity*** Both SIOPEL and COG have put considerable effort into investigations trying to decrease the significant ototoxicity induced by the use of cisplatin-based chemotherapy in young patients, especially infants. The risk of cisplatin causing bilateral moderate to severe high-frequency hearing loss is significantly increased in children younger than 5 years of age.[150] The COG 9645 trial failed to reduce ototoxicity with the agent amifostine.[151] The recently opened SIOPEL 6 study will investigate sodium thiosulfate[152] as an agent to decrease the cisplatin-induced ototoxicity. The current COG trial, AHEP0731, attempts to reduce ototoxicity by limiting the extended use of cisplatin in the low-risk patients.

***Hepatoblastoma Risk Stratification and International Collaboration*** Current data suggest that pure fetal histology and PRETEXT I and II tumors have a favorable prognosis.[28,30,89] Risk factors that seem to portend a worse outcome include metastatic disease at diagnosis (COG Stage IV, PRETEXT +M), PRETEXT IV, AFP < 100 at diagnosis, small cell undifferentiated histology and possibly macrotrabecular and/or extensive multifocal histology.[18,30,90,153] In 2007, SIOPEL, GPOH, and COG decided to embark on a mutual project that

was called the *C*hildhood *H*epatic Tumors *I*nternational *C*ollaboration (CHIC). The complete databases of these groups are in the process of being united to address prognostic questions requiring increased statistical power. To identify these common data points for prognostication and risk stratification, data regarding prognostic factors (i.e., histology AFP, stage, multifocality, biological markers) can thus be studied in much larger patient groups in which the clinical outcome is known. These developments are the starting point of a new trans-Atlantic converging cooperation on a large intercontinental scale that will be of eventual benefit for children with liver tumors.

***New Agents, Tumor Relapse*** The prognosis for a patient with recurrent or progressive hepatoblastoma depends on many factors, including the site of recurrence, prior treatment, and individual patient considerations. It was recently shown that in patients who initially received only cisplatin/5-FU/vincristine cure may be possible with a multidrug relapse regimen including doxorubicin.[109] Surgical resection of pulmonary relapse is possible and has been reported to produce long-term cure, but does not carry as good a prognosis as resection of pulmonary metastatic lesions present at diagnosis that simply fail to completely resolve on chemotherapy.[154–156] If possible, isolated metastases should be resected completely in patients whose primary tumor is controlled.[138,142,157] Success with autologous peripheral blood stem cell transplantation with a double conditioning regimen has been reported in a child with pulmonary relapse after liver transplantation.[158] Irinotecan has been used in chemotherapy relapse regimens with some success.[159] In recurrent refractory disease, phase I and II clinical trials may be appropriate and should be considered. Multidrug chemotherapy resistance is a key factor for the poor outcome of relapsed HB. Novel gene-directed treatment approaches, such as adenovirus-mediated cytosine deaminase/5-fluorocystine suicide gene therapy, may offer hope for treatment of these chemotherapy-resistant tumors in the future.[82,83] Information on current COG trials can be found at www.childrensoncologygroup.org.

## HEPATOCELLULAR CARCINOMA

### Epidemiology, Biology, and Genetics

In Western countries, hepatocellular carcinoma occurs approximately half as often as hepatoblastoma (HB) or in 23% of all primary pediatric liver tumor cases, most often in school-age children and adolescents. Although described previously, it was not until 1967 that childhood HCC was identified by Ishak and Glunz[3] as an entity to be distinguished from HB. In 1974, Exelby and colleagues[5] analyzed the clinical course of childhood HCC and found an overall dismal outcome.

HCC occurs predominantly in the setting of underlying liver disease and cirrhosis. Compared with adults, in children cirrhosis is less commonly part of the antecedent process, while congenital or acquired disorders of the liver, such as metabolic disease, are common.[17] Table 33-9 shows the conditions that are associated with HCC in children.[43,66,160–175] Patients with tyrosinemia seem to be a particularly high risk and should be vigilantly screened with serial AFP and imaging.[174] In East Asia and Africa, HCC is more common than HB because of the widespread prevalence of hepatitis B and C.[43] In Taiwan, where HCC is most often seen in carriers of the hepatitis B virus, vaccination programs targeted against hepatitis have led to a significant decrease in the incidence of HCC.[42] In contrast to hepatitis B, the cirrhosis and the subsequent development of HCC in the hepatitis C population usually takes several decades to develop.[176] The genetic syndromes associated with HCC are shown in Table 33-3.[54,55,62–68]

**TABLE 33-9**
**Conditions Associated with Hepatocellular Carcinoma in Children**

| |
|---|
| Alpha-1 antitrypsin deficiency[160] |
| Anomalous abdominal venous drainage[161] |
| Alagille syndrome[162] |
| Biliary atresia[163] |
| Congenital hepatic fibrosis[164] |
| Familial polyposis/Gardner syndrome[165] |
| Focal nodular hyperplasia[166] |
| Hemochromatosis[167] |
| Hepatic adenoma[168] |
| Hepatitis B and C[43] |
| Glycogen storage disease (type I and III)[169] |
| Methotrexate therapy[166] |
| Neurofibromatosis[66] |
| Oral contraceptives[170] |
| Parenteral nutrition–associated liver disease (PNALD); total parenteral nutrition (TPN) cholestatic liver failure[171] |
| Progressive familial intrahepatic cholestasis (PFIC)[172,173] |
| Tyrosinemia[174] |
| Wilms' tumor/Bloom syndrome[175] |

### Pathology

In the pediatric age group, more than two thirds of HCC occur in children older than 10 years of age, but only 0.5% to 1% of all HCC manifest before 20 years of age, and very few HCCs are diagnosed in children less than 5 years old. About 20% to 35% of children with HCC have underlying chronic liver disease. It is still disputed whether classical (adult-type) HCC in the pediatric age group is the same or a different disease with respect to HCC in adult patients. It is currently suggested that HCC forms a tumor family, consisting of adult-type HCC and its variants, fibrolamellar HCC, and a novel entity occurring in older children and young adolescents, transitional liver cell tumor (TLCT).[92]

HCC presents grossly as solitary or multiple (multifocal) lesions. Solitary tumors display four main growth patterns, that is, expanding (or pushing) mass lesions, pedunculated (or hanging) lesions, invading tumors with poor delineation, and multifocal tumors resembling metastatic disease. These growth patterns exert a considerable influence on the surgical resectability of the tumors. The color of the cut surfaces of HCCs depends, apart from bleeding and necrosis, on differentiation features of the tumor cells, for instance bile synthesis and accumulation.

The microscopic features of pediatric classical HCC are similar to or the same as those in adult patients. Many tumors exhibit a trabecular growth pattern with intervening sinusoid-like vascular channels and a reduced reticulin network. Regarding grading, Edmondson and Steiner developed a system comprising a scale of I to IV.[177]

***Fibrolamellar Hepatocellular Carcinoma (FL-HCC)*** This tumor usually arises in noncirrhotic livers of adolescents or young adult patients and is encountered more frequently in Western countries.[178] Overall, FL-HCC accounts for less than 10% of all HCCs. Recent data show that FL-HCC has biological features similar to that of adult-type HCC. FL-HCC shows vascular invasion in up to 35% of cases, frequently metastasizes into locoregional lymph nodes (about 50% of cases), and tends to show unusual spreading patterns, including intraperitoneal spread. FL-HCC is typically a solitary lesion that has a predilection for the left liver lobe (two thirds; unusual for hepatic primary tumors). It reveals well-defined margins and a central scar in 70%. The cut surface often shows a firm, tan to brown tissue with radiating septa, sometimes closely resembling focal nodular hyperplasia. The leading cell is a large and polygonal, hepatocyte-like cell with a granular cytoplasm of large vesicular nuclei. These cells form strands embedded in the typical fibrosclerotic stroma that may form a central stellate scar. A considerable proportion of the tumor cells contain large, ground glass–like inclusions, the so-called pale bodies, which are helpful in bioptic diagnosis. Periodic acid–Schiff (PAS)-positive globular inclusions in part contain alpha-1-antitrypsin and other glycoproteins. Typically, cells of FL-HCC show marked immunostaining for cytokeratin 7.[92]

***Transitional Liver Cell Tumor (TLCT)*** Transitional liver cell tumor is a recently identified liver neoplasm that occurs in older children and young adolescents. The term transitional had been proposed to denote a putative intermediate position of the tumor cells between hepatoblasts and more mature hepatocyte-like cells. TLCT are highly aggressive lesions that have a treatment response pattern clearly different from hepatoblastoma.[179] The usual presentation is that of a large or very large solitary hepatic tumor (mostly in the right liver lobe), commonly associated with very high serum AFP levels. Grossly, the tumors display an expanding growth pattern and sometimes exhibit a large central necrosis. Histologically, the tumor cells vary between HCC-type cells and cells found in hepatoblastoma, sometimes with formation of multinuclear giant cells. The lesions markedly express beta-catenin, typically in a mixed nuclear and cytoplasmic pattern.[180]

### PRETEXT and Staging

Children's Oncology Group staging for hepatocellular carcinoma does not use risk stratification and simply follows the traditional COG stage I, II, III, and IV shown in Table 33-5. Nevertheless, discussions with colleagues describing the extent of tumor involvement of the liver are based upon PRETEXT to aid in making key decisions about surgical resectability.

### Treatment Strategies

Hepatocellular carcinoma is relatively chemotherapy resistant and therefore carries a poor prognosis with a dismal rate of cure.[181,182] Complete surgical resection or hepatectomy and transplantation for tumor localized to the liver is often the only hope. Unfortunately, HCC is most often advanced at diagnosis, and cure is rarely possible in the setting of metastatic disease. Even with aggressive attempts at surgical resection, tumor relapse is common and tumor-free survival rates of not more than 25% to 30% can be achieved. These mostly depend on the extent of disease, and the main prognostic factor for childhood HCC is resectability. The first multicenter clinical trials on pediatric liver tumors were conducted in North America by the Children's Cancer Study Group (CCSG) and POG, some of which included HCC in addition to HB.[181] These studies confirmed the poor response of HCC to chemotherapy and radiation and the dismal rate of cure in the majority of patients.

The North American cooperative study (INT-0098) as well as SIOPEL 1[181,182] used pre-operative chemotherapy in an attempt to increase surgical resectability for children and adolescents with HCC, because this is the foundation for curative therapy of liver tumors. Of the 46 patients entered onto INT-0098, only 8 had completely resected tumors (stage I) at study entry, 25 had unresectable tumors (stage III), and 13 presented with metastatic disease (stage IV). Patients were randomized to receive cisplatin with either doxorubicin or 5-fluorouracil and vincristine. No differences were seen in response or survival rates between the two treatment regimens. Seven of the 8 stage I patients (88%) with complete tumor excision at time of diagnosis, followed by adjuvant cisplatin-based chemotherapy, survived. This is a significant improvement when compared with only 12 of 33 patients (36%) treated before the consistent use of adjuvant chemotherapy. This result suggests that adjuvant chemotherapy may be of benefit for patients with completely resected HCC. However, because one third of these initially resected patients have fared well without any additional chemotherapy, the question of the necessity for adjuvant chemotherapy will only be answered in a randomized trial. In contrast, outcome was uniformly poor for patients with advanced-stage disease. The 5-year event-free survival for stage III and IV patients was 23% and 10%, respectively (Table 33-10).

Hepatocellular carcinoma patients have been treated in three consecutive studies of the German Society for Pediatric Oncology and Hematology (see Table 33-10).[26] In the first study, HB89, neoadjuvant and adjuvant chemotherapy consisted of conventionally dosed ifosfamide, cisplatin, and doxorubicin (IPA), which did not show any substantial benefit.[26] Of the registered 12 patients, only 4 with resectable tumor survived. In the second study (HB94), patients with nonresectable HCC received conventionally dosed carboplatin and etoposide in addition to IPA, which seemed to produce at least short-term benefit.[26] Of the registered 25 patients, 9 had locally unresectable and 11 metastatic HCC. Three of the 9 and 1 of the 11 patients survived free of disease in addition to 4 of 5 patients with resectable tumor (total 8 of 25 = 32%).

Results of SIOPEL 1, 2, and 3 are shown in Table 33-10.[182,183] Only 2 of the 39 patients entered onto the SIOPEL-1 study underwent complete resection of the tumor at diagnosis, followed by chemotherapy, while the remaining 37 patients had preoperative chemotherapy with cisplatin and doxorubicin. Metastases were identified in 31% of the patients, and extrahepatic tumor extension, vascular invasion, or both in 39%. Although partial tumor response to chemotherapy was observed in 49% (18 of 37) of the patients, complete tumor resection was achieved in only 36% (14 of 39) of the patients. Outcomes of patients on this study were also unsatisfactory, with a 5-year event-free survival of 17%. All long-term survivors had complete surgical excision of their tumor. Twenty-one patients were enrolled on the subsequent

**TABLE 33-10**

**Summary Results Hepatocellular Carcinoma Cooperative Trials**

| *Study* | *Chemotherapy* | *No. of Patients* | *Outcomes* |
|---|---|---|---|
| INT0098 (CCSG, POG)[181] | CDDP/DOXO | Stage I: 8<br>Stage II: 0<br>Stage III: 25<br>Stage IV: 13 | 5-Year EFS/OS<br>Stage I/II: 88%/88%;<br>III: 8%/23%;<br>IV: 19%/34% |
| HB89 (GPOH)[26] | CDDP/DOXO | Stage I/II/IIIa: 6<br>Stage IIIb, IV: 6 | 5-Year DFS<br>Stage I/II/IIIa: 50%; IIIb, IV: 17% |
| HB94 (GPOH)[26] | CDDP/DOXO | Stage: I/II/IIIa: 5<br>Stage IIIb, IV: 20 | 5-Year DFS<br>Stage I/II/IIIa: 60%; IIIb, IV: 25% |
| HB99 (GPOH)[26] | CDDP/DOXO | Stage: I/II/IIIa: 14<br>Stage IIIb, IV: 27 | 5-Year DFS<br>Stage I/II/IIIa: 71%; IIIb, IV: 15% |
| SIOPEL 1[182] | CDDP/DOXO | PRETEXT: I, 1; II, 14; III, 11; IV, 13, +VPEM, 8 | 5-Year EFS/OS<br>17%/28% |
| SIOPEL 2[182] | CDDP/DOXO | PRETEXT: I, 1; II, 3; III, 1; IV, 7; +VPEM, 5 | 5-Year EFS/OS<br>23%/23% |
| SIOPEL 3[183] | CDDP/DOXO | PRETEXT: I, 4; II, 22; III, 14; IV, 21; +VPEM, ? | 3-Year EFS/OS 10%/16% |

CARBO, carboplatin; CCSG, Children's Cancer Study Group; CDDP, cisplatin; DFS, disease-free survival; DOXO, doxorubicin; EFS, event-free survival; GPOH, German Pediatric Oncology Hematology (study); IFOS, ifosfamide; IPA, ifosfamide, cisplatin, Adriamycin; OS, overall survival; POG, Pediatric Oncology Group; PRETEXT, pretreatment extent (of tumor) staging system; SIOPEL, International Society of Pediatric Oncology (epithelial) liver tumor study group; VP, etoposide; +VPEM, *V*ena cava, *P*ortal vein, *E*xtrahepatic, *M*etastatic disease.

study SIOPEL 2. Data were available for 17 of these. One patient died 17 days after diagnosis from massive GI bleeding and never received treatment. Thirteen of the 16 treated patients received preoperative chemotherapy with cisplatin, carboplatin, and doxorubicin. Partial response to preoperative chemotherapy was observed in 6 of 13 cases (46%). Gross total tumor resection was achieved in 8 patients (47%), 3 at the time of diagnosis and 1 through liver transplantation. Nine tumors (53%) never became operable. One patient was lost to follow-up just before planned surgery. Four of the patients having resection of their tumors were alive at a median follow-up time of 53 months (range of 35 to 73 months). Twelve patients died because of progressive disease and one from surgical complications. The three-year overall survival for this study was 22%.

In comparing the results of these studies, the outcome for patients with HCC has shown no significant improvement, despite the progress in surgical techniques, chemotherapy delivery, and patient support. It seems obvious that a new treatment approach is needed to increase the rate of cure of childhood HCC.

In adults, fibrolamellar type of hepatocellular carcinoma has been traditionally associated with a higher resection rate and better survival when compared with the typical pathologic variant of HCC both in adolescents and young adults.[184,185] The higher resection rate for children and adolescents with the fibrolamellar variant of HCC was not supported by the studies reported by either Katzenstein[181] or Czauderna.[182] Patients with the fibrolamellar variant did not have a better outcome when compared with those with typical HCC, the 5-year event-free survival was 30% compared with 14%, respectively ($P = 0.18$), although the median survival was longer for patients with the fibrolamellar variant.

Given the poor response of HCC to chemotherapy and radiation, the mainstay of treatment is surgery. This means that, in contrast to hepatoblastoma, a primary radical tumor resection has to be attempted whenever possible using all available techniques in order to achieve this goal.[26] Therefore in school-age children and adolescents with a primary liver tumor the surgeon has to be prepared to perform highly sophisticated liver surgery after confirmation of the diagnosis by pathologic investigation of intraoperative frozen sections. Patients with the clinical constellation for advanced HCC should always be treated in consultation with a specialized center with experience in childhood liver surgery.

## Liver Transplantation for Hepatocellular Carcinoma in Children

***Outcomes, Indications, and Contraindications*** Published outcomes for liver transplantation in children with HCC are shown in Table 33-11.* The following guiding principles have been formulated by centers with particular expertise in pediatric liver transplantation. They are in a greater state of controversy and evolution than are the guidelines for HB. In most centers, the criteria for transplantation of multifocal and unifocal HCC are the same as for HB and do *not* follow adult limitations on size and number of nodules. Unlike HB, however, any history of pulmonary metastatic disease or extrahepatic disease is considered an absolute contraindication. Major vascular involvement, of the portal vein for example, is a relative contraindication depending upon the degree and severity of involvement.[142] It is important that consultation with a transplantation center with special expertise in pediatric liver surgery be considered early in the treatment to prevent delays and unwanted extended courses of chemotherapy while awaiting resection and transplantation.

***Response to Chemotherapy*** HCC tumor progression while on chemotherapy is a relative contraindication to transplantation, because occult extrahepatic micrometastatic disease is increasingly likely in this situation.

***Milan Criteria*** The Milan criteria, introduced by Mazzaferro in 1996, restrict transplantation in adults with HCC as follows: (1) single tumor diameter less than 5 cm; (2) not more than

* References 115, 124, 125, 127, 130, 139, 182, 186–194.

**TABLE 33-11**
**Literature, Transplantation for Pediatric Hepatocellular Carcinoma**

| | No. of Patients | Survival (%) | Tumor Recurrence | Small Incidental*† | Died Comp OLT† |
|---|---|---|---|---|---|
| ‡Olthoff et al, 1990, Arch Surg, UCLA[186] | 16 | 22 | 8/16 | – | 4/16 |
| ‡Penn et al, 1991, Surgery, Transplant Registry[187] | 429 | – | 158/429 | 31/429 | – |
| Tagge et al, 1992, J Pediatr Surg, Pittsburgh, Pa[188] | 9 | 44 | 3/9 | – | 1/9 |
| Yandza et al, 1993, Transplant Int, Paris[189] | 2 | 100 | – | – | – |
| Broughan et al, 1994, J Pediatr Surg, multicenter[190] | 4 | 75 | ¼ | 0 | 0 |
| Otte et al, 1996, Transplant Proc, Brussels[191] | 5 | 60 | 2/5 | 0 | 0 |
| Achilleos, et al 1996, J Pediatr Surg, Birmingham, UK[192] | 2 | 0 | ½ | ½ | ½ |
| Superina et al, 1996, J Pediatr Surg, Toronto[139] | 3 | 100 | 0/3 | 3/3 | 0 |
| Reyes et al, 2000, J Pediatr, Pittsburgh, Pa[115] | 19 | 63 | 6/19 | 7/19 | 2/12 |
| Tatekawa et al, 2001, J Pediatr Surg, Kyoto[193] | 2 | 100 | 0 | ½ | 0 |
| Czaudema et al, 2002, J Clin Oncol, SIOPEL 1[182] | 2 | – | – | ½ | – |
| Avila et al, 2006, Eur J Ped Surg, Madrid[124] | 1 | 100 | – | – | – |
| Austin et al, 2006, J Pediatr Surg, UNOS database[125] | | 41 | 63% | 12/41 | – |
| Beaunoyer et al, 2007, Pediatr Transplant, Stanford, Calif[127] | 10 | 83 | 1/10 | 4/10 | 2/10 |
| Kalicinski et al, 2008, Ann Transplant, Warsaw[130] | 8 | 75 | 1/8 | – | 1/8 |
| Ismail et al, 2009, Pediatr Transplant, Warsaw[194] | 11 | 72 | 1/11 | 3/11 | 2/11 |

*Most are patients with tyrosinemia, other metabolic liver disease, familial intrahepatic cholestasis, hepatitis, or biliary atresia.
†Died as a result of complications of orthoptic liver transplantation.
‡Did not separately analyze pediatric cohort.
Comp, complications; OLT, orthotopic liver transplantation; SIOPEL, International Society of Pediatric Oncology (epithelial) liver tumor study group; UCLA, University of California–Los Angeles; UNOS, United Network for Organ Sharing.

three foci of tumor, each one not exceeding 3 cm; (3) no angioinvasion; (4) no extrahepatic involvement. Since the introduction of these criteria, long-term recurrence-free survival after liver transplantation in adults with HCC improved from 30% to 75%.[195–198] The problem with the Milan criteria in children is that 50% to 70% of children present with large de novo tumors and a large tumor burden in otherwise healthy livers, *and the Milan criteria were developed in adults with small tumors and underlying cirrhotic liver disease.* In children, the number of nodules, as stipulated by the Milan criteria, is usually not considered a contraindication to transplantation as long as the disease is confined to the liver. Furthermore, de novo pediatric HCC often shows features on a continuum with pediatric HB, and these "transitional liver tumors" may have a more favorable biology.[92–200] In view of the lack of improvement in results of conventional treatment of pediatric HCC during the past 2 decades, most clinicians treating pediatric HCC do NOT recommend adherence to Milan criteria in children who present with large de novo tumors, no cirrhosis, and no evidence of extrahepatic disease.[201]

***Metastatic Disease*** Metastatic disease is considered an *absolute* contraindication to liver transplantation in HCC, and a very careful and thorough evaluation to exclude metastatic microdeposits is essential.

***Post-transplantation Chemotherapy*** Guidelines for post-transplantation immunosuppression in HCC are the same as with transplantation for HB with one possible difference. Many centers would consider post-transplantation adjuvant antiangiogenic therapy with sorafenib in HCC. Experience in the transplantation population of patients is limited, but in any patient considered to be at high risk for tumor relapse, options for possible antiangiogenic therapy should be discussed. Similarly, many centers have begun to experiment with rapamycin (sirolimus) as a post-transplantation immunosuppressant because of its antineoplastic, antiangiogenic properties.[203–205]

## New Agents and Treatment Modalities

***Antiangiogenesis, Sorafenib*** New treatment modalities including metronomic chemotherapy,[206] and adjuvant antiangiogenic therapy[207] are the target of investigation based upon some early promising results. Most promising has been the recent adult experience with sorafenib, an antiangiogenic tyrosine kinase inhibitor, where a survival advantage has clearly been shown in prospective trials of sorafenib in the treatment of HCC in adults with unresectable tumors.[202] Interestingly, this seems to be also the case in some preliminary investigation in childhood HCC.[208]

***Chemoembolization and Therasphere*s** Hepatic arterial chemoembolization (HACE) and transarterial chemoembolization (TACE) refers to the intra-arterial administration of chemotherapeutic and vascular occlusive agents (generally gelatin or Lipiodol) along with cytotoxic drugs. The drugs most frequently used for chemoembolization are doxorubicin, mitomycin, and cisplatin. Intra-arterial injection of cytotoxic agents results in higher local concentration of drugs with reduced systemic side effects, while the intra-arterial embolization causes ischemic necrosis of the tumor. This therapeutic strategy has been used in a small number of children and adolescents with recurrent HCC while awaiting the availability of a liver donor, or as adjuvant therapy in an attempt to facilitate tumor resection.[145,209] There are no large trials in children; however, in a study of adult HCC patients without liver failure or cirrhosis, although TACE successfully reduced tumor growth, it frequently caused acute liver failure and did not

improve survival.[210] A related approach that combines radiation therapy with angiographic embolization has been the intra-arterial injection of yttrium-90 radioactive microspheres, called Therasphers.[211]

***Portal Venous Embolization*** Portal venous embolization has been used in adults with liver disease to induce hypertrophy of the remaining liver remnant[212] and reported experimentally in children.[213] The portal venous branch on the side of the tumor is cannulated percutaneously, and polyvinyl alcohol and coils are inserted to induce portal vein occlusion under fluoroscopic control. This has a dual effect of alcohol thrombosis of the embolized tumor and compensatory hypertrophy of the unharmed opposite liver lobe, increasing the potential hepatic functional reserve in patients with cirrhosis and underlying liver dysfunction in preparation for hepatic resection.

***Percutaneous Ablative Therapies*** Ablative percutaneous methods of local control may be considered, especially in recurrent tumors. They include percutaneous radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and cryotherapy. Cryotherapy refers to cold injury produced by cryoprobe delivery of liquid nitrogen, and although once popular in adults, it has now fallen out of favor because of superior results achieved with RFA and PEI. In most cases, these treatment approaches are palliative and are suitable for smaller tumors only, generally below 3 cm to 4 cm maximum diameter. RFA provides slightly better tumor kill than PEI (90% vs. 80% complete tumor necrosis) with fewer sessions (mean of 1.2 vs. 4.8).[199] It is also associated with fewer side effects; thus in many centers, RFA is now preferred versus PEI; however, RFA is contraindicated in lesions located adjacent to the major biliary ducts or to bowel loops. Complications of these ablative techniques occur in about 8% to 9% of cases, mainly in the form of pain, fever, bleeding, tumor seeding, and gastrointestinal perforation.[214] Percutaneous ablation has not been well studied in children.

## Hepatic Sarcomas

Primary hepatic sarcomas are rare. Outcome depends primarily on tumor histology, sensitivity to chemotherapy and/or radiotherapy, and the ability to achieve complete tumor resection.[215]

### Biliary Rhabdomyosarcoma

The classic presentation of biliary rhabdomyosarcoma is in young children (average age 3½ years) with jaundice and abdominal pain, and it is often associated with distension, vomiting, and fever.[13] Histology is exclusively embryonal or botryoid, both histologic subtypes of rhabdomyosarcoma that are known to have a favorable prognosis. Because the tumor most often involves the central biliary tree and porta hepatis, the ability to achieve gross total resection is rare. Fortunately, the tumor is often sensitive to both chemotherapy and radiation, and long-term survival is seen in 60% to 70% of patients. Surgical intervention has two goals: to establish an accurate diagnosis and to determine the local-regional extent of disease. Although chemotherapy is generally effective at relief of the associated biliary obstruction, patients remain at risk for biliary sepsis until the obstruction abates.

### Rhabdoid Tumor

Although pediatric rhabdoid tumors are most common in the kidney and brain, they do occur at other sites, including the mediastinum and liver. When primary to the liver, rhabdoid tumor is difficult to distinguish from the small cell undifferentiated (SCU) variant of hepatoblastoma. Given the aggressive biological behavior and poor prognosis seen with the SCU variant of HB, it has been suggested that some tumors previously classified as HB-SCU may actually have been hepatic rhabdoid tumors. The differentiation of an HB-SCU from a rhabdoid tumor is challenging and is important in terms of research, but possibly clinically irrelevant at present because both are biologically aggressive with poor response to chemotherapy. Malignant rhabdoid tumor of the liver is a rare and aggressive tumor of toddlers and school-age children that may present with spontaneous rupture.[216,217] These rare tumors are often chemoresistant and fatal,[216] although a recent case report documents the potential for cure with multimodal therapy, including ifosfamide, vincristine, and actinomycin D.[217] As with all locally aggressive liver tumors that respond poorly to chemotherapy, the most important treatment goal is complete surgical excision.

### Undifferentiated Sarcomas

Undifferentiated (embryonal) sarcoma of the liver is a rare childhood hepatic tumor that has historically been considered an aggressive neoplasm with an unfavorable prognosis. These tumors may arise in a solitary liver cyst.[218] Survival has improved in recent multimodal approaches, designed for patients with soft tissue sarcomas at other sites, including conservative surgery at diagnosis, multiagent chemotherapy, and second-look operation in cases of residual disease. Using these techniques several small series have reported survival in up to 70% of children.[219–221]

### Angiosarcoma

Although rare, personal experience and multiple case reports in the literature support the potential for malignant transformation of an infantile hemangioma to angiosarcoma.[222,223] Histologic verification of malignancy may be difficult, and this rare entity must be suspected if the biological behavior of an infantile hemangioma shows unusual progression or recurrence after a period of relative quiescence. Relatively chemoresistant, prognosis is generally poor.

### Aggressive Hemangiomatous Tumors

***Locally Aggressive Infantile Hepatic Hemangioma*** Infantile hemangioma is the most common benign tumor of the liver in infancy[19] with striking variability of the three subtypes of infantile hemangioma: focal, multinodular, and diffuse. Many focal lesions are often discovered incidentally and are localized and small enough to be of little clinical significance. Symptoms seen with larger lesions may include abdominal distention, hepatomegaly, congestive heart failure, vomiting, anemia, thrombocytopenia and consumptive coagulopathy, jaundice secondary to biliary obstruction, and associated cutaneous or visceral hemangiomas.[11] Contrast-enhanced CT scan shows an area of diminished density, and after bolus injection of intravenous contrast, there is contrast enhancement from the periphery toward the center of the lesion. Further, after a short delay, there is complete isodense filling

of the lesion and liver. Magnetic resonance angiography (MRA) has been used in complex cases to identify atypical radiographic features that may portend a poor prognosis.[224] Unfavorable radiographic features include central varix with arteriovenous shunt, central necrosis or thrombosis, and diffuse hemangiomatous involvement of the liver with abdominal vascular compression.[224] Arterial angiography may be used in infants with refractory symptoms in whom either hepatic artery ligation or embolization is considered.

If a definitive diagnosis of simple infantile hepatic hemangioma can be made radiographically, management can be noninvasive because spontaneous regression occurs in most cases, especially focal tumors. The terminology is confusing, however, with different authors often using the terms hepatic hemangioma, infantile hepatic hemangioma, hepatic hemangioendothelioma, or kaposiform hemangioendothelioma interchangeably.[225] True kaposiform hemangioendothelioma with Kasabach-Merritt (as opposed to the high-output heart failure from intrahepatic shunts seen in diffuse infantile hemangioma), rarely, if ever, presents as a primary hepatic tumor.[226] Hemangioendotheliomas are occasionally primary to the retroperitoneum, where they can invade the liver and obstruct the porta hepatis, causing portal hypertension. These tumors are discussed in more detail in Chapter 125.

Sometimes a large rapidly growing infantile hepatic hemangioma can be life threatening with intractable high-output cardiac failure from intralesional arteriovenous shunting, intraperitoneal hemorrhage, respiratory distress as a result of pulmonary congestion, and massive hepatomegaly compressing abdominal vasculature and producing abdominal compartment syndrome (Fig. 33-9). Historically, the initial medical intervention for symptomatic tumors has been corticosteroids. Many other medical treatment options exist, although no single treatment has been shown to be universally effective. Congestive heart failure is treated with supportive care, digitalis, and diuretics. Anemia and coagulopathy are treated with corrective blood product replacement therapy. Both success and complete failure have been reported variously with many other treatments, including epsilon-aminocaproic acid, tranexamic acid, low-molecular-weight heparin, vincristine, cyclophosphamide, interferon-2-alpha, AGM-1470, and newer generation antiangiogenic drugs.[227–231] Recent studies have shown that the large tumors may produce antibodies to thyroid-stimulating hormone (TSH), and screening to rule out secondary hypothyroidism is recommended.[232,233] Most recently, propranolol has been shown to inhibit the growth of infantile hemangioma.[234] Although rare, malignant transformation to angiosarcoma has been reported, and close follow-up is recommended.[223,224,235,236]

In infants who fail medical management, symptomatic solitary tumors may be treated by excision, hepatic arterial ligation, or selective angiographic embolization.[237] Treatment algorithms may stratify treatment based upon whether or not the tumor is solitary, multifocal, or diffuse.[238,239] About 65% of tumors are solitary or unifocal with a survival of 86% and death usually not caused by the tumor but by a comorbidity.[19] Thirty-five percent of tumors are multifocal or diffuse, with a survival somewhere between 60% to 100%, with death usually secondary to cardiorespiratory compromise caused by tumors refractory to medical and interventional management.[19,237,238]

## Metastatic and Other Liver Tumors

***Metastatic Liver Tumors*** Unlike the large body of literature concerning liver resection for metastatic colorectal tumors in adults, there is little published data that addresses the treatment of metastatic tumors in the liver following from abdominal solid tumors in childhood. A recent series from a large metropolitan children's cancer center reported only 15 such patients during a 17-year period, including neuroblastoma (7), Wilms' tumor (3), osteogenic sarcoma (2), gastric epithelial (1), and desmoplastic small round cell tumor (2).[240] Eleven of the 15 patients died of progressive disease; 4 had a local recurrence. These results lead the authors to conclude that the overall prognosis in these patients remains poor, and the decision to perform hepatic metastasectomy should be made with caution. The treatment approach should not, however, be uniformly nihilistic, because not all liver lesions in children with abdominal solid tumors turn out to be metastatic disease. Both nodular regenerative hyperplasia and focal nodular hyperplasia have been reported to mimic hepatic metastasis in children[241]; definitive diagnosis requires biopsy and/or resection.

Occasionally, a pancreatoblastoma may present with extensive hepatic metastasis (Fig. 33-10). Despite the alarming radiographic appearance at diagnosis, this tumor was, in fact,

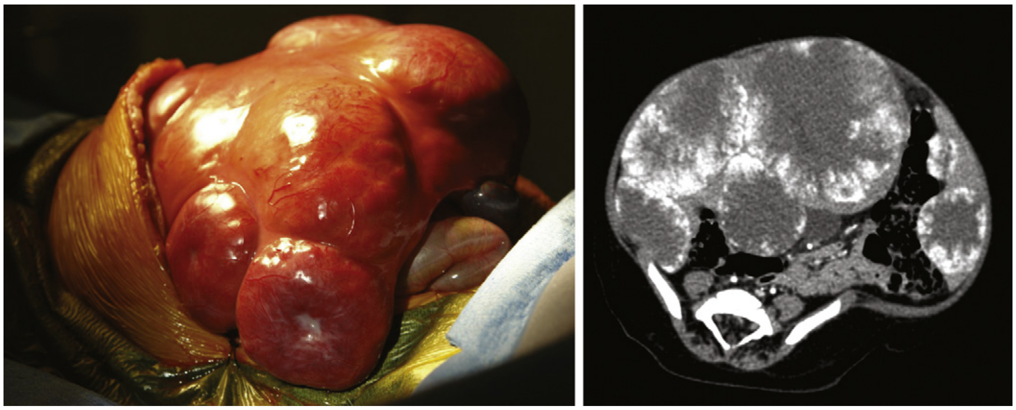

FIGURE 33-9 Symptomatic multifocal/diffuse infantile hepatic hemangioma. These tumors are benign but occasionally will be refractory to aggressive attempts at medical and percutaneous management. This tumor showed progressive growth despite chemotherapy and percutaneous embolization of largest nodules. The baby developed abdominal compartment syndrome and vena cava obstruction. Treated with temporizing abdominal decompressive laparotomy and, definitively, with hepatectomy and live-donor liver transplantation.

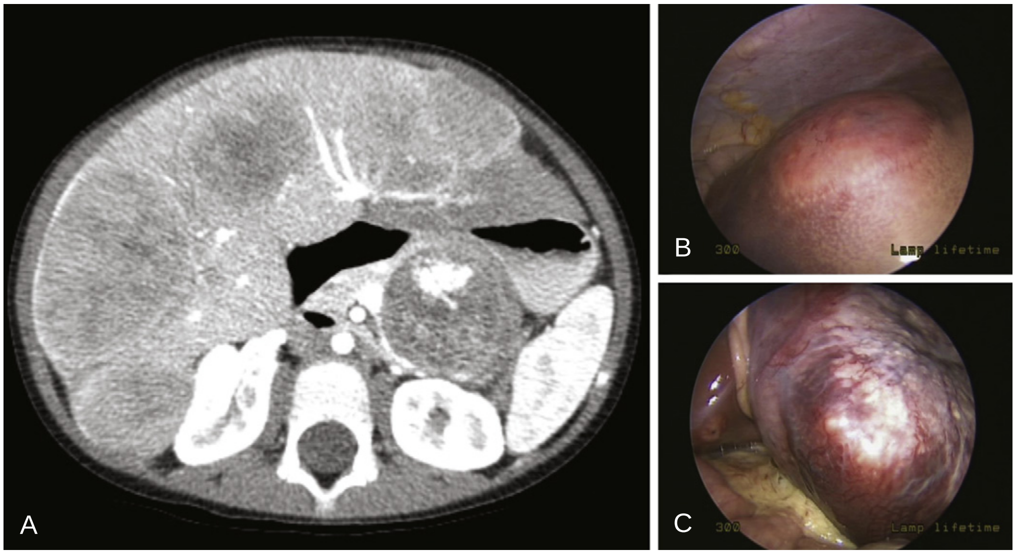


**FIGURE 33-10** Metastatic pancreatoblastoma. **A,** Infant with extensive metastatic tumor in the liver at diagnosis. **B** and **C,** Appearance at laparoscopic biopsy. Primary tumor is a pancreatoblastoma involving the body of the pancreas. Although the tumor metastases were extensive at diagnosis, they prove to be exquisitely chemosensitive with cisplatin/doxorubicin chemotherapy.

exquisitely chemosensitive, and the child did well after neoadjuvant chemotherapy, subtotal pancreatectomy, hepatectomy, and live-donor liver transplantation. Pancreatoblastomas are treated with multiagent chemotherapy analogous to hepatoblastoma and have a fair prognosis if chemosensitive.

### Liver Tumors as Secondary Malignancies

We recently saw a case of multiple lesions of focal nodular hyperplasia in the liver of a 10-year-old boy 9 years after treatment for stage IV neuroblastoma with double autologous stem cell transplantations. Given the history, we initially suspected metastatic neuroblastoma, but diagnostic laparoscopy and laparoscopic biopsy of multiple lesions showed focal nodular hyperplasia (FNH). Another case report of FNH in a child with a history of stage IV neuroblastoma showed foci of small cell undifferentiated hepatoblastoma in the resection specimen; so, very close follow-up is necessary if treatment of the FNH is nonoperative.[242] Liver tumors have been recognized as potential late effects and/or secondary malignancies in children who have previously undergone chemotherapy and radiation as toddlers.

### Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) may occasionally present as an abnormal liver mass in a newborn with coagulopathy. Predisposing factors include familial, herpes simplex virus, and severe combined immunodeficiency.[243] Diagnostic criteria according to HLH-2004 include fever, splenomegaly, bicytopenia, hypotriglyceridemia, hypofibrinogenemia, hemophagocytosis, low natural killer (NK) cell activity, hyperferritinemia, and high interleukin-2 (IL-2) receptor levels.[244] Treatment is with combination chemoimmunotherapy, including etoposide, dexamethasone, cyclosporine A, and anticipated mortality of about 40% is increased if the diagnosis or appropriate therapy is delayed.

### Langerhans' Cell Histiocytosis

Morphologic changes and clinical findings in Langerhans' cell histiocytosis (LCH) of the liver may resemble primary sclerosing cholangitis or a chronic nonsuppurative destructive cholangitis.[245] Therefore LCH is an important differential diagnosis of chronic destructive cholangitis with cholestatic liver disease, especially in children and young adults. Other involved organs include bone, pituitary, thyroid, and lungs.[246] The diagnosis can be verified by S-100 and CD-1a (antigen) immunohistochemistry. There have been rare reports of pediatric liver transplantation in toddlers with multisystem LCH, children who developed end-stage liver disease despite intensive chemotherapy.[247,248]

### Megakaryoblastic Leukemia

Rarely, congenital acute megakaryoblastic leukemia (AMKL) may present isolated to the liver, with ascites caused by massive infiltration of hepatic sinusoids by leukemic cells.[249] The bone marrow by microscopy and flow cytometry and the peripheral blood smear may not initially show the presence of blasts. Because the marrow fibrosis may not manifest until after the massive hepatic infiltration, it may initially be difficult to diagnose as leukemia. In most children with liver involvement the spleen, lymph nodes, and marrow will also be involved at diagnosis. But even in these cases, the diagnosis may be difficult both clinically and pathologically, and the hepatic and lymph node involvement is not uncommonly misinterpreted as solid tumor.[250]

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 34

# Pediatric Gastrointestinal Tumors

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Primary gastrointestinal (GI) tumors are uncommon in infants and children, and GI malignancies account for less than 2% of all cases of pediatric cancer.[1] The presentation and histopathology of pediatric GI tumors differ significantly from those seen in adults. Although rare, GI malignancy should be considered in any child with signs and symptoms of intestinal obstruction, intractable pain, alteration in bowel habits, or GI bleeding that are not attributable to other more common and established diagnosis. Symptoms often persist for several weeks and may progress to intestinal obstruction requiring emergency surgery.[1,2] Children with unexplained gastrointestinal symptoms require a detailed diagnostic evaluation.[3]

## Esophageal Smooth Muscle Tumors

Esophageal leiomyomas and leiomyosarcomas are rare in children, with fewer than two dozen patients accounting for all documented pediatric esophageal smooth muscle tumors. Although esophageal smooth muscle tumors are often solitary in adults, in children they are frequently multifocal, with a third involving the entire esophagus and 70% extending into the proximal stomach. Children typically present with esophageal obstruction and dysphagia, food regurgitation, and chest pain. Barium swallow findings mimic achalasia, and a biopsy is required for definitive diagnosis. Leiomyomas in children are occasionally associated with familial syndromes, such as familial leiomyoma and Alport syndrome. Extensive surgical resection is necessary in the majority of cases.[4,5]

## Esophageal and Gastric Adenocarcinoma

Esophageal and gastric cancer in children is extremely rare. Between 1988 and 1996 the Surveillance, Epidemiology, and End Results (SEER) database documented esophageal malignancy in only three patients between 10 and 19 years of age, and none younger than 10 years.[6,7]

The development of Barrett esophagus secondary to chronic gastroesophageal reflux disease (GERD) is a primary risk factor for the development of esophageal adenocarcinoma. Children with severe neurologic deficits, such as cerebral palsy, and those with congenital defects involving the esophagus, such as esophageal atresia and tracheoesophageal fistula, are at increased risk for development of Barrett esophagus.[8] The incidence of Barrett esophagus has been estimated to be 0.02% among children with severe GERD and associated risk factors. Nevertheless, adenocarcinoma of the esophagus has been documented in adolescents with long-standing GERD, and surveillance with upper endoscopy and multiple longitudinal biopsies is appropriate for those children who have the mucosal changes of Barrett esophagus.[9,10]

Barrett changes can also be seen in the retained cervical esophagus following esophageal replacement surgery. Postoperative care of these patients requires control of gastric pH and long-term surveillance endoscopy with biopsy of the retained upper esophageal segment. Esophageal replacement surgery for a patient with esophageal atresia can be performed with retention of the distal esophageal segment. This remnant can develop severe chronic esophagitis and Barrett changes requiring resection. Because Barrett esophagus is a premalignant condition, the distal segment of the esophagus should be removed at the time of esophageal replacement surgery.[11] Esophageal carcinomas may also occur in children after caustic esophageal injuries. Endoscopic evaluation with biopsies should be considered for patients with chemical injuries to monitor for the development of premalignant changes.[12]

Between 1975 and 2007, the SEER database reported a gastric cancer incidence of 9.25 per 100,000 individuals, with an age-adjusted incidence of 0.1% for patients younger than 24 years.[6,13] Despite the rarity of this entity, there are case reports of adenocarcinoma of the stomach in children as young as 2.5 years. The tumors can arise from any anatomic location in the stomach, with nonspecific symptoms including epigastric pain, weight loss, vomiting, anemia, and symptoms associated with esophageal achalasia. Surgical resection is the primary therapeutic modality; however, curative resection is rare and mortality rates are high for children with this tumor.[14–16]

# Gastrointestinal Stromal Tumors

## EPIDEMIOLOGY

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors whose classification is hindered by anecdotal reports, failure to distinguish between primary and secondary GISTs, and the mixing of benign and malignant tumors in the reports.[17] In addition, GISTs arising from various anatomic sites have been reported together, making prediction of their clinical behavior difficult.[18] The most common site is the stomach (50% to 70%), followed by the small intestine (20% to 30%), colon or rectum (10%), and esophagus (5%).[19]

## CLINICAL PRESENTATION

Patients with GIST tumors present with nonspecific symptoms, often generalized abdominal pain, dyspepsia, and occult GI bleeding. Iron-deficiency anemia should prompt an investigation to exclude a GI tract malignancy as the cause.[1] Less commonly, patients present with a palpable abdominal mass or intestinal obstruction.[20] Standard imaging studies may assist in the diagnosis (plain radiographs and computed tomography [CT]). Endoscopy can identify a tumor mass in the stomach, duodenum, or colon.[21]

## PATHOLOGY

GISTs are classified as mesenchymal tumors of the GI tract thought to originate from the intestinal cell of Cajal, an intestinal pacemaker cell.[22] Historically, smooth muscle tumors, such as leiomyomas and leiomyosarcomas, and neural tumors, such as nerve sheath tumors, have been categorized as GISTs. GISTs are now defined as cellular spindle cell, epithelioid, or occasional pleomorphic mesenchymal tumors that express the KIT (CD117, stem cell factor receptor) protein, as detected by immunohistochemistry. Additional cell type markers, such as CD34, smooth muscle actin, desmin, and S-100 protein, are also used to establish a diagnosis of GIST. These histologic and immunohistochemical features now distinguish GISTs from leiomyomas, leiomyosarcomas, neural tumors, and other tumors of smooth muscle origin.[23] Prognosis relies on traditional pathologic staging criteria, such as size, extent of tumor invasion into mucosa or surrounding organs, mitotic index, and nuclear pleomorphism. However, no single feature is consistently reliable in predicting outcome.[24]

Determining prognosis of pediatric patients with GIST tumors can be controversial. The usual criteria for assessing risk of malignancy (i.e., tumor size, mitotic activity, anatomic location) are not reliable in pediatric GIST. Children frequently present with multiple gastric nodules, making identification of a dominant mass difficult. Secondly, there exists a wide variation in proliferation index between patients and even among multiple tumors within the same patient. Furthermore, some pediatric patients develop GIST metastasis despite being classified as low risk by adult criteria, and others with low proliferation indices develop recurrent disease in perigastric nodal basins, the peritoneum, or liver.[25] Pediatric GIST is distinguished as a separate clinical, pathologic, and molecular subset with a predisposition for females, multifocal gastric tumors, and wild-type *KIT/PDGRA* genotype. This is in contrast to older-age, adult GIST and even GIST in young adults. All these factors must be considered when distinguishing benign from malignant pediatric gastric stromal tumors.[18,26]

## ASSOCIATED CONDITIONS

The Carney triad consists of a gastric leiomyosarcoma, functioning extraadrenal paraganglioma, and pulmonary chondroma. The gastric stromal tumors are usually located along the lesser curve or antrum and produce few symptoms; however, continued growth leading to mucosal ulceration, GI bleeding, and serosal involvement is common. Despite the possible development of additional gastric tumors in the remaining stomach, if feasible, partial gastrectomy is recommended as the initial operation, to avoid the complications of more extensive gastric resection, particularly in teenaged patients. Because the multifocal nature of the tumor can lead to local recurrence, regular follow-up is mandatory to assess for new gastric tumors. Adjuvant therapy has been unsuccessful in treating metastatic disease. Evaluation for adrenal tumors in patients with gastric stromal sarcomas and pulmonary chondromas should be considered, and a family history should be obtained from patients with the Carney triad. Recently, an autosomal dominant inheritance of paragangliomas and gastric GIST, called the Carney-Stratakis syndrome, has been identified, representing a separate condition affecting both males and females. Succinate dehydrogenase subunit gene mutations, typically associated with familial paragangliomas, have been implicated in the pathogenesis of Carney-Stratakis syndrome.[27–30]

An uncommon, histologically distinct subset of GIST, called a GI autonomic nerve tumor (GANT), has been described in children. Pediatric GANTs have a female prevalence and symptoms that may include anemia, abdominal pain, fullness, emesis, and a palpable abdominal mass. Although adult GANTs are found predominantly in the small intestine, pediatric GANT lesions are primarily gastric tumors. The majority of pediatric patients have localized disease at the time of diagnosis. Younger age, localized disease, gastric location, and small tumor size at diagnosis are associated with favorable prognosis. Immunocytochemical and ultrastructural evaluation is required to differentiate these tumors from GIST. Established pathologic criteria for malignancy are not well defined for the pediatric GANT because of the low incidence of these tumors. Surgical resection of the tumor is the treatment of choice, because there appears to be no definite role for chemotherapy or radiation.[10]

## TREATMENT

Complete surgical excision of GISTs, along with the pseudocapsule, is the treatment of choice. Achieving negative pathologic margins is frequently possible, because GISTs tend to hang from and do not diffusely infiltrate the structure from which they arise. Consequently, wedge resection of the stomach or segmental resection of the intestine provides adequate therapy; wide resection is not necessary.[17] In addition, because the status of microscopic margins does not appear to be important for survival, vital structures should not be sacrificed if gross tumor clearance has been attained. GIST rarely metastasizes to lymph nodes; so, lymphadenectomy is seldom warranted.[19]

The high rate of local and distant recurrence underscores the need for adjuvant therapy. GIST has traditionally been resistant to radiotherapy; however, imatinib mesylate, a selective KIT, PDGF-RA, PDGR-RB, and BCR-ABL tyrosine kinase inhibitor, has been successful as a first-line agent in treating advanced and metastatic GIST in adult patients. Imatinib blocks the constitutive activity of KIT receptor in GIST cells.[21] Recently, a mutation in the c-*KIT* gene on exon-11 associated with increased risk of recurrence and higher mortality was identified.[19] The efficacy of imatinib is related to GIST genotype, with *KIT* exon-11–mutated GISTs being more sensitive to imatinib than wild-type (WT) tumors. While imatinib mesylate has been effective adjuvant therapy for adult GISTs, pediatric GIST lesions are frequently less responsive. The lack of efficacy may result from pediatric GISTs being predominantly WT genotype and lacking the *KIT* mutations more commonly detected in adult GIST tumors.[31,32] Second-generation kinase inhibitors (i.e., sunitinib, nilotinib, sorafenib, and dasatinib) have demonstrated in vivo and in vitro efficacy in treatment of malignancy with *KIT* mutations.[33–36] Although investigations of adjuvant and neoadjuvant tyrosine kinase inhibitors are ongoing, surgical excision remains the initial option for pediatric GISTs. Adjuvant chemotherapy with imatinib and other agents may be used in cases of incomplete resection, tumor spillage, or other high-risk factors. For recurrent or metastatic GIST, a trial of a kinase inhibitor, followed by surgical resection, may be effective. Neoadjuvant tyrosine kinase inhibitor chemotherapy may similarly reduce unresectable GIST lesions making surgical resection possible. These therapies may decrease the incidence of postoperative GIST recurrence and spread, and thereby extend survival.[34,35]

### SURVIVAL

The long-term survival following surgical resection of pediatric GIST is difficult to determine, because most reports contain small numbers of children or include adults. Moreover, given recent changes in the recognition and pathologic identification of these tumors, many older series contain tumors that are actually not GISTs. Factors associated with long-term survival following surgical resection include small tumor size, low mitotic index, genotype, and gastric primary location.[20] Pediatric GISTs present with a higher incidence of metastasis than comparable adult gastric tumors. However, the biology of pediatric lesions appears more indolent than adult disease with significant long-term survival, despite the presence of metastatic disease and with or without effective adjuvant chemotherapy.[25]

## Intestinal Tumors

### MYOFIBROMATOSIS

Infantile myofibromatosis is a mesenchymal tumor that can arise in the skin, muscle, bone, subcutaneous tissue, or viscera. It is the most common fibrous tumor of infancy. Myofibromatosis presents with either solitary or generalized lesions, with or without visceral involvement. Most lesions spontaneously regress; however, extensive intestinal myofibromatosis is associated with significant morbidity and mortality.[37,38] Various chemotherapeutic interventions have demonstrated limited efficacy, significant treatment toxicity, and long-term morbidity. However, the combination of low-dose chemotherapy and long-term total parental nutrition for life-threatening infantile myofibromatosis can provide symptomatic relief and inhibit disease progression.[39,40]

### LYMPHOMA

Lymphoma is the most common small bowel malignancy in children, with high-grade non-Hodgkin lymphoma comprising 74% of these tumors. Burkitt lymphoma constitutes the most common histologic subtype. The majority of patients (50% to 93%) present with lymphoma localized to the distal small bowel, although tumor may occur anywhere from the stomach to the rectum.[41]

Patients may present with chronic GI distress, occult blood per rectum, hematochezia, and/or an abdominal mass. An acute worsening of symptoms may result in emergency surgery for treatment of ileocolic intussusception, with lymphoma creating the lead point (46%), acute appendicitis (22%), perforation (11%), or obstruction (8%). Higher mortality is associated with advanced disease stage, intestinal perforation, high-grade histology, and T-cell lymphomas.[42]

Surgical management depends on disease presentation, as well as extent of disease at presentation. Bulky disease is usually not completely resectable. Extensive resection of bulky retroperitoneal or mesenteric disease does not enhance survival; nevertheless, complete surgical resection (including bowel resection), if possible, significantly enhances the prognosis of patients with intestinal lymphoma, especially when included in a multimodality treatment approach. Tumor downstaging by complete resection allows for decreased duration and intensity of post-operative chemotherapy. When operating for a complication of intraperitoneal disease, the extent of the procedure should be limited to resolution of the complication and resection of sufficient tissue to ensure an accurate diagnosis. If limited disease is encountered, complete resection and an evaluation of mesenteric, perihepatic, and periaortic nodes should be undertaken to assess for regional metastatic spread. Two-year cumulative survival for intestinal B-cell lymphoma is 94% and 28% for intestinal T-cell lymphoma. The overall 5- and 10-year survival rates for all intestinal lymphoma patients treated with multimodality therapy (surgery, radiation, chemotherapy) are 52% and 44%, respectively. The corresponding disease-free survival rates are 43% and 38%, respectively.[43–48]

## Carcinoid Tumors

### EPIDEMIOLOGY

Carcinoid tumors originate from neuroendocrine cells within the GI tract. These neoplasms derive from GI epithelial and subepithelial endocrine progenitor cells that function as part of the amine precursor uptake and decarboxylation (APUD) system.[49] Carcinoids can also be found in the lungs, mediastinum, thymus, liver, pancreas, bronchus, ovaries, prostate, testes, and kidneys.[50] Pediatric carcinoid tumors typically occur in the GI tract—stomach, small intestine, appendix (most common), and rectum. Carcinoid tumors of the appendix occur with an estimated incidence of 1 case per million children per year, with a slight female predominance.[51–53]

### DIAGNOSIS

Carcinoid tumors are classified according to the location of origin in the primitive gut (foregut, midgut, and hindgut). Foregut tumors include carcinoids of the lung, bronchus, stomach, proximal duodenum, and pancreas. Midgut tumors arise from the distal duodenum, jejunum, ileum, and right colon, including the appendix. These account for 60% to 80% of all carcinoids in adults and children.[54–56] Hindgut tumors arise in the transverse and distal colon and rectum. Tumors can also arise from a Meckel diverticulum, enteric duplications, and the mesentery. Appendiceal carcinoids are the most common, with more than 70% of these tumors developing at the appendiceal tip. Pediatric carcinoid tumors are often discovered incidentally during an operation for presumed appendicitis or another unrelated diagnosis. Although clinical signs of acute appendicitis or gynecologic pathology may prompt exploration, true inflammatory changes of acute appendicitis are not often induced by the carcinoid, possibly because of the distal location of the tumor and absence of proximal luminal obstruction.[51,53,55]

The most serious complication of carcinoid tumors is a carcinoid crisis, which is most often associated with foregut tumors, larger tumors, and high serum/urine 5-hydroxyindoleacetic acid (5-HIAA) levels. Although pediatric carcinoids vary in size, carcinoid syndrome (flushing, diarrhea, abdominal pain, tachycardia, hypertension, hypotension, altered mental status, and coma) has not been typically associated with tumors confined to the appendix.[53,54] In contrast, pediatric patients with extra-appendiceal carcinoid tumors, such as in the lung or liver, are often symptomatic. Biologically active amines (serotonin, catecholamines, histamine) and metabolites (5-HIAA) are characteristically elevated in the plasma and urine of patients with symptomatic carcinoid tumors.[57] Patients with extra-appendiceal carcinoids frequently present with disseminated disease at the time of diagnosis and have a higher incidence of recurrent tumor following the initial diagnosis and resection.[58]

### TREATMENT

Tumor size at presentation dictates surgical decision making for carcinoid tumors of the appendix. For appendiceal carcinoid tumors less than 2 cm in diameter, surgical resection of the appendix and mesoappendix is considered curative. Long-term follow-up demonstrates minimal disease recurrence and a rare likelihood of metastatic disease.[51,52,58,59] Carcinoid tumors greater than 2 cm, those with cecal involvement, lymphatic invasion, lymph node involvement, mesoappendix infiltration, positive resection margins, goblet cell malignancy, or cellular pleomorphism with a high mitotic index require a more extensive resection (i.e., a right hemicolectomy with associated resection of the mesocolon).[55,60,61]

### SURVIVAL

Complete resection of localized appendiceal carcinoid tumors can result in cure, with greater than a 90% survival rate. Diminished disease-free and overall survival is associated with carcinoids larger than 2 cm, older age, positive lymph nodes, extra-appendiceal spread, distant metastatic disease, and tumors with atypical histologic features.[62]

## Colorectal Adenocarcinoma

Adenocarcinoma of the colon and rectum is the most common cancer of the GI tract, with approximately 142,570 new cases and 51,370 deaths in the United Sates in the past year. The lifetime risk of developing colorectal cancer in the general population is 1 in 19.[6] However, colorectal cancer in children is rare, with an estimated incidence of 0.3 to 1.5 cases per million.[63,64] Although reported as early as 9 months of age, the median age at diagnosis for pediatric cases is 15 to 19 years. Pediatric colorectal cancer accounts for 2% of malignancies in adolescents.[65–67]

Colorectal cancer differs greatly between adults and children. These differences include the presenting signs and symptoms, primary site of the tumor, pathologic findings, stage, and prognosis. Carcinoma of the colon is associated with several predisposing factors, including ionizing radiation (e.g., CT scan, therapeutic radiation treatments), polyposis syndromes, urinary diversion with previous ureterosigmoidostomy, and chronic parasitic infection. Various environmental factors, including herbicide exposure, may also be associated with tumor formation.[68]

## Polypoid Disease of the Gastrointestinal Tract

Polyps are common, occurring in 1% of all children, and are the most frequent source of rectal bleeding in the young child (2 to 5 years old). Most polyps are benign lesions and are either hamartomas or result from lymphoid hyperplasia. Some hamartomas, however, have the potential for dysplastic, adenomatous or neoplastic transformation because of germline mutations and somatic inactivation of *STK11, SMAD4, BMPR1A,* and *PTEN* genes.[68–71]

Isolated juvenile polyps (i.e., retention polyps, inflammatory polyps, cystic polyps) are considered hamartomas. They constitute 80% of polyps in children with 40% to 60% found in the rectosigmoid colon. If multiple (typically two to five polyps) they may be found in the proximal colon as well. They are one of the most common sources of GI bleeding in young children, but are rarely seen in adolescence. Colonoscopy of the entire colon is diagnostic and therapeutic if endoscopic removal is warranted.

Lymphoid polyps (lymphoid nodular hyperplasia) account for 15% of pediatric polyps and are submucosal lymphoid aggregates, specifically localized to distal small bowel, colon, and rectum (Peyer patches). Bleeding results from mucosal erosion and can usually be managed expectantly. Uncontrolled bleeding or irreducible intussusception requires surgical intervention.

*Juvenile polyposis coli syndrome* is transmitted in an autosomal dominant fashion. Affected individuals are at increased risk for colorectal malignancy with cumulative risk for cancer of nearly 50% to 70% by age 60 years.[63,64,72] A diagnosis of juvenile polyposis coli requires at least 5 polyps throughout the GI tract, or 1 polyp and a family history of juvenile polyposis. Most patients typically have 50 to 100 polyps including gastric and small bowel polyps. Higher numbers of polyps are associated with more severe symptoms, including chronic bleeding, anemia, hypoproteinemia, and failure to thrive.

These patients and their families require long-term endoscopic surveillance (semiannual panendoscopy) with subsequent total abdominal colectomy if mucosal dysplasia, persistent bleeding, or rapid increase in polyp number is detected. Depending on individual circumstance, there also appears to be a role for prophylactic total colectomy and rectal mucosectomy with an endorectal pull-through procedure.

*Diffuse juvenile polyposis of infancy* is a nearly universally fatal disease typically diagnosed within the first few months of life. Patients present with diarrhea, lower GI bleeding, intussusception, prolapse, obstruction, protein-wasting enteropathy, macrocephaly, and hypotonia. Despite involvement of the entire GI tract, bowel rest and total parenteral nutrition (TPN) permit selective surgical resection. However, survival beyond 2 years of age is rare.

*Diffuse juvenile polyposis* presents with hematochezia, abdominal pain, and prolapse from hamartomatous polyps in the colon and rectum in infancy to 5 years of age. Although hamartomas typically do not have premalignant potential, chronic polyp inflammation is thought to result in reactive hyperplasia that then progresses to dysplasia or adenomatous changes.

Several genetic disorders carry significant risk for the subsequent development of colon carcinoma and are characterized as polyposis syndromes. They include Gardner syndrome (adenomatous polyposis and soft tissue and bone tumors), Turcot syndrome (familial adenomatous polyps and central nervous system tumors), and familial polyposis coli. Both Gardner syndrome and familial polyposis are autosomal dominant disorders and are associated with adenomatous polyps in the colon and the small intestine. Because the entire surface of the colon can be carpeted with thousands of polyps, the ability to carry out effective surveillance and identify suspicious lesions is low. Recommendations for and the timing of colon resection are based on the likelihood of the development of malignancy. There is little question that colectomy is the appropriate treatment for patients with familial polyposis coli (familial adenomatous polyposis), Gardner syndrome, and Turcot syndrome.

*Peutz-Jeghers syndrome* is defined by polyposis of the intestinal tract and melanotic skin lesions. It is inherited as an autosomal dominant trait. Germline mutations in *LKB1, STK11,* and *ENG* genes may have a causative role in the pathogenesis of this syndrome.[73,74] Despite equal sex distribution, symptoms appear earlier in males. Brown and black melanotic spots occur in the rectum, around the mouth, lips, buccal mucosa, feet, nasal mucosa, and conjunctivae, typically presenting at puberty. Adolescents characteristically complain of frequent defecation, rectal bleeding, abdominal pain, vomiting, and may present with anemia or recurrent episodes of intussusception. Polyps are found in the small intestine (55%), stomach and duodenum (30%), and the colorectal bowel (15%). The risk of death because of cancer for those with Peutz-Jeghers syndrome is 50% by 60 years of age. There is a 13-fold increased risk of death because of GI cancer and a 9-fold increased risk for all other malignancies. Rapid growth, severe dysplasia, villous changes, or larger polyps (greater than 15 mm) may indicate GI malignancy and necessitate aggressive surgical intervention. However, repeated, extensive intestinal resections may result in short-bowel syndrome resulting from the multifocal and recurrent nature of these polyps.

*Gardner syndrome* patients present with adenomatous, rather than hamartoma polyposis, and extraintestinal lesions, including bone tumors (80%), sebaceous/inclusion cysts (35%), and desmoid tumors (18%). Bone lesions include cysts of the mandible, fibromas, and osteomas of the skull and face. These patients also may develop hypertrophy of the retinal pigmented epithelium. The syndrome is inherited in an autosomal dominant pattern. Various mutations of the adenomatous polyposis coli (*APC*) gene are associated with Gardner syndrome (*APC* polymorphism in exons 13 and 15), implicating this as a phenotypic variant of familial adenomatous polyposis (FAP). The intestinal polyps that characterize this syndrome have a 100% likelihood of undergoing malignant transformation.[75,76] Desmoids are fibroblastic tumors of the abdominal wall and mesentery that present as dysplasia or a malignant fibrosarcoma. They often become apparent after diagnosis of GI disease and carry a high mortality. Small desmoid tumors, if amenable to excision, have a 10% local recurrence. However, many desmoid lesions are unresectable at presentation. Slow-growing tumors can be treated with sulindac, tamoxifen, vinblastine, and methotrexate, while symptomatic, aggressive tumors require doxorubicin and dacarbazine or high-dose tamoxifen and radiation therapy.

*Turcot syndrome,* also considered a variant of FAP, is characterized by polyposis and brain tumors (e.g. gliomas, ependymomas). Carcinoma of the colon is prevalent in young adults. Chronic bloody diarrhea, hypoproteinemia, weight loss, anemia, malnutrition, bowel obstruction, and intussusception are common presenting symptoms. Medulloblastoma development is associated with *APC*-related mutations, while microsatellite gene instability (typical of hereditary nonpolyposis colon cancer) is associated with glioblastoma multiforme diagnosis.[77] *Cronkhite-Canada syndrome* is typified by multiple hamartomatous polyps in the stomach and colon. It is a variant of juvenile polyposis and is associated with early-onset skin hyperpigmentation, alopecia, and nail changes. Chronic diarrhea results in malabsorption, hypovitaminosis, hypoproteinemia, and fluid and electrolyte imbalance.

*Osler-Weber-Rendu syndrome* is characterized by childhood (less than 10 years of age) GI bleeding from cutaneous and hepatic telangiectases and vascular malformations in 50% of affected individuals. Telangiectases are found on the lips, oral and nasopharyngeal membranes, tongue, and perilingual areas. Lesions may also involve the brain, lungs, and liver. Within the GI tract, they occur commonly in the stomach and small bowel, causing significant recurrent GI bleeds throughout childhood. It is inherited in an autosomal dominant manner, and 80% of patients have a family history of the disease. With a high incidence of colon carcinoma or multiple juvenile colonic polyps, all Osler-Weber-Rendu patients with new-onset anemia or GI bleeding require lower GI tract evaluation.[78,79]

## Hereditary Associations

Although the majority of childhood colorectal carcinomas are not associated with hereditary factors, approximately 25% of childhood cases have some associated predisposing condition, that is, at least two first-degree relatives with colon cancer, genetic/polyposis syndromes (1%), inflammatory bowel disease (1%), and hereditary nonpolyposis syndromes (5%

to 6%). The progression toward tumor development may occur secondary to tumor suppressor gene mutation, loss of heterozygosity, or a mutational event.[80] Phenotypically normal colonic epithelium may develop hyperplasia as a result, then progress to adenoma formation, dysplasia, and finally, invasive carcinoma. Mutations associated with development of colon cancer may result from exposure to environmental influences or be the result of accumulated DNA transcription errors. Typical of these genetic changes are *APC* inactivation, *K-ras* activation, and *TP53* gene mutations.

*Familial adenomatous polyposis (FAP)* is inherited as an autosomal dominant trait that accounts for less than 1% of all colorectal cancer. A diagnosis of FAP requires greater than 5 colonic polyps, polyps throughout the GI tract, or polyps associated with a family history of juvenile polyposis. Extensive colonic polyposis (i.e., greater than 100 adenomatous polyps) is common, with some patients having thousands of polyps. Symptomatic patients often present with frequent bloody stools, anemia, and abdominal pain. Long-standing symptoms may signify the presence of a malignant lesion. Patients identified through family history should be assessed in early adolescence prior to the development of symptoms. All patients require early colonoscopic screening to determine the extent of polyposis and the possibility of malignancy. Colorectal carcinoma occurs by age 20 years in 7% of patients and by age 25 years in 15% of patients. Untreated FAP characteristically progresses to colorectal cancer by age 39 years. In contrast, gastric polyps seen with FAP are usually benign hamartomas. FAP patients are also at risk to develop desmoid tumors, congenital hypertrophy of retinal pigment epithelium, duodenal and periampullary adenocarcinomas, thyroid malignancy, and hepatoblastoma.[81,82]

The *APC* gene, a tumor suppressor gene on the long arm of chromosome 5, is known to contain a mutation in 80% to 90% of FAP patients. If a defective *APC* allele is inherited from one parent, a mutation acquired during childhood in the other *APC* gene results in the loss of function of the tumor suppressor gene product.[83] Inactivation of the *APC* alleles results in activation of subsequent signaling pathways leading to uncontrolled cell growth. Malignant progression from adenoma to dysplasia, then to malignancy, may occur. Site-specific *APC* gene mutations correlate with various FAP phenotypes and the development of associated tumors. Classic FAP is associated with central gene mutations, while a less aggressive, attenuated FAP presentation correlates with peripheral *APC* gene mutations. The development of malignancy is also associated with accumulation of other oncogene/tumor suppressor gene mutations, such as *K-ras* activation and *TP53* mutation, in otherwise quiescent adenomas.

Sulindac, a nonsteroidal anti-inflammatory drug (NSAID), and celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, have been used to reduce polyp numbers by induction of epithelial cell apoptosis. Despite the unique mechanism of action of these agents, they have not completely eliminated the risk of colorectal cancer in FAP patients.[84,85] FAP patients with few polyps are still at risk of early colorectal cancer. Resection is indicated even if extensive polyposis does not develop. Surgical options include total proctocolectomy with permanent ileostomy, total abdominal colectomy with ileorectal anastomosis, coloproctectomy with perseveration of the anal sphincter, coloproctectomy with ileoanal pull-through, and total colectomy with rectal mucosectomy and endorectal (J-pouch) pull-through. Each of these procedures has their proponents. Total colectomy with a rectal mucosectomy and endorectal pull-through has gained popularity in recent years. This procedure removes all "at-risk" colonic mucosa and laparoscopic techniques have been demonstrated to be practical, effective, and safe. Endorectal pull-through procedures typically incorporate a distal J-pouch ileal reservoir. Although straight ileal pull-through procedures initially have higher stool frequency, differences in stool frequency between straight pull-through and J-pouch patients have been reported by some authors to be negligible by 24 months. A number of patients treated with a J-pouch may require later treatment for intermittent pouchitis.[86,87] Total proctocolectomy with permanent ileostomy carries significant risk of postoperative urinary bladder atony, impotence, and retrograde ejaculation because of disruption of nervi erigentes during the pelvic dissection. More commonly used for adult colorectal pathology, this technique has limited utility for treatment of pediatric patients because of the psychological and physiologic impact of a permanent stoma.[88] Procedures involving the preservation of the distal rectum can result in the development of colorectal cancer. Forty-four percent of patients undergoing an ileorectal anastomosis require subsequent treatment for rectal polyps that develop in the remaining mucosa. The risk of rectal cancer in these patients is 10% at age 50 years and 29% by age 60 years. Polyps remaining or developing in preserved colorectal segment significantly increases the risk for subsequent cancer. Those with retained rectal mucosa at risk require annual flexible endoscopic surveillance of the pelvic pouch.[89–91] The significant long-term risk of rectal cancer in these patients makes this procedure unacceptable for treatment of FAP in the adolescent population.

*Hereditary nonpolyposis colon cancer (HNPCC)* has an autosomal dominant inheritance, is the most common hereditary colon cancer syndrome, and accounts for 2% to 3% of all colorectal cancers. It is characterized by early onset, multiple family members affected, and is 5 times more prevalent than familial polyposis–related colon cancer.[92] In contrast to familial adenomatous polyposis, HNPCC malignancy may develop in the absence of adenomatosis of the colon and rectum. Unlike sporadic colorectal tumors, HNPCC colorectal cancer usually develops in a proximal colon lesion and occurs at a younger age (approximately 45 years).

Disease may be limited to the colon in the Lynch syndrome I, where malignancies occur in the cecum and ascending colon more often than in other colorectal sites (70%). These tumors are characterized by poorly differentiated and mucin-producing lesions (i.e., signet cell). Lynch syndrome II is further defined by the development of synchronous and metachronous extracolonic cancers, such as carcinomas of the endometrium, uterus, ovary, stomach, small bowel, pancreas, hepatobiliary tract, brain, genitourinary system, and upper uroepithelial tract. They usually manifest in the second decade of life. HNPCC patients are categorized by the Amsterdam criteria: colorectal cancer in at least three relatives spanning two generations. One of these individuals is a first-degree relative of the other two and one of these individuals must have a diagnosis prior to age 50 years. Patients with the Lynch syndromes have a 50% to 70% lifetime risk of developing cancer and a threefold increased incidence of colorectal cancer compared with the general population.[93–96]

Hereditary nonpolyposis colon cancers, unlike FAP, do not have inherited defects in the *APC* gene. HNPCC tumors are characterized by mutations in genetic loci (*MSH2, MLH1, PMS1, PMS2,* and *GTBP*) resulting in defective DNA nucleotide mismatch recognition and repair. Greater than 90% of these mutations are in *MSH2* and *MLH1* genes on chromosome arms 2p and 3p, respectively. These genes are inherited in a dominant manner with 90% penetrance. Although benign adenomas appear with the same incidence in HNPCC patients as in the general population, DNA-repair–deficient HNPCC adenomas are more likely to grow and progress to invasive cancer than in the general population. As a result, a benign tumor may progress to cancer in as few as 3 to 5 years.[97]

Patients suspected of carrying *MSH2* and *MLH1* mutations may be tested for DNA mismatch-repair gene mutations. A total abdominal colectomy, rather than hemicolectomy or a segmental resection, is recommended, because the risk of recurrent colorectal cancer is 45% spanning 10 years. Patients who have undergone subtotal colectomy must undergo lifelong endoscopic evaluation of their remaining rectal segment. Subtotal colectomy with a rectal mucosectomy and endorectal pull-through has not been studied in this population. Patients who are poorly compliant with colonoscopic surveillance may be candidates for prophylactic colectomy. Asymptomatic HNPCC gene carriers may reduce their risk of invasive cancer through prophylactic colectomy or surveillance colonoscopy and polypectomy, starting with biannual colonoscopy at age 25 to 30 years and annually after age 40 years. All Lynch syndrome patients must undergo lifelong screening for extracolonic malignancies as well.[98,99]

## Other Associations

There is a strong association between long-term inflammatory bowel disease and the development of colon carcinoma. After the first 10 years with ulcerative colitis, the likelihood of cancer development increases from 1% to 2% per year.[100] Those with ulcerative colitis–associated carcinoma typically present with malignancy at a young age, have multifocal lesions, and have had a history of colitis involving the entire colon rather than isolated, left-sided disease. Crohn disease is an inflammatory bowel disease in which the risk for colon cancer is significantly greater (more than 20 times) than that in the general population.[101] Crohn-associated colon cancer may develop in an area of colon that appears grossly normal, making the diagnosis of malignancy more difficult than with ulcerative colitis. Routine surveillance contrast enema and colonoscopy are recommended for all patients with either ulcerative colitis or Crohn disease. Biopsies should be performed on suspicious areas as well as on random areas of the colon during the colonoscopy.[102]

Ureterosigmoidostomy performed for urinary diversion predisposes to the subsequent development of malignancy in the colonic segment used as a diversion conduit. Five percent of patients with ureterosigmoidostomy develop colon cancer, often at the site of ureteral implant. Chronic inflammation, possibly resulting from exposure to intermittently infected urine, has been shown to predispose to the development of colon cancer. Close follow-up and annual sigmoidoscopy is warranted for all patients following this type of urinary diversion, which is now infrequently used.

In the United States, approximately 600,000 abdominal and head CT studies are performed annually on children under 15 years of age. The risk of later malignancy related to diagnostic pediatric CT scan is directly proportional to the age of the child at the time of the study. It is estimated 500 of these individuals may ultimately die from a malignancy attributable to the CT irradiation received as a child. Secondary colorectal malignancies may also result from therapeutic radiation, especially if the abdomen was included in the field of primary irradiation. Radiation colitis and adenomatous polyps can develop years after radiation exposure and colonic adenocarcinoma decades later. Immunohistochemical studies suggest a radiation-induced *TP53* mutation may lead to the eventual development of colorectal cancer in these individuals.[67,103–105]

## Diagnosis

In children with colorectal tumors, presenting symptoms are nonspecific and include abdominal pain, nausea, and vomiting, and changes in bowel habits with the development of constipation, particularly with left-sided lesions. Physical findings include abdominal distention, tenderness, and a palpable mass. Many will have guaiac-positive stools. Lower GI (rectal) bleeding may be present in a third of patients and, as with adults, is more prevalent in those with cancer of the left colon and rectum. Significant weight loss affects 20% to 30% of patients.

The median length of time from onset of symptoms to presentation is often months; at least one report cited almost a year between the onset of symptoms and the diagnosis.[106] Diagnosis can be delayed if symptoms are repeatedly attributed to common pediatric conditions such as chronic gastroenteritis.[107] Delay in diagnosis may also be related to adolescents' tendency to minimize or hide embarrassing symptoms and the low index of suspicion of pediatricians for this rare entity. Rectal bleeding, commonly a sign of benign pathology, such as polyps or hemorrhoids, should also raise the suspicion of a colorectal malignancy. Delay in diagnosis contributes to the advanced stage of disease in many children. Most colonic lesions in adults are rectosigmoid in location and are identified by sigmoidoscopy. In contrast, childhood colorectal cancer is relatively evenly distributed throughout the colon, with one third of the tumors located in the right colon.[63,107] Colonoscopy, therefore, is required to obtain a biopsy for diagnosis.

## Sporadic Colorectal Carcinoma

Sporadic colon cancer in the young is an aggressive disease whose morphology and natural history differ from those of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, and adult colon cancer. The location, stage, and histologic type of pediatric colorectal tumors differ markedly than the same disease in adults. Primary colorectal tumors in children occur frequently in the right and transverse colon, as opposed to the predominant rectosigmoid distribution found in adults. Approximately 40% of adults with colon cancer have involvement of regional lymph nodes or have distant metastases (Dukes stage C or D lesions) at diagnosis. In children, more than 80% of tumors are Dukes stage C or

D at diagnosis.[63,64,106,107] In addition, more than half of the colorectal tumors in children are mucinous adenocarcinomas. The mucinous subtype has an aggressive course and is known to metastasize early. Both advanced stage of disease at presentation and the preponderance of mucinous subtype contributes to a poorer prognosis in children.[66] Accumulation of DNA base-pair mistakes resulting from defective mismatch repair processes (microsatellite instability) is an early step in the process leading to malignant transformation. Patients with colorectal cancer and high microsatellite instability are more likely to have multiple synchronous or metachronous colorectal cancers and are diagnosed at a younger age than those without microsatellite instability.[71,108] Microsatellite instability is not, however, associated with a family history of colorectal cancer or of phenotypic features.[81]

The utility of carcinoembryonic antigen (CEA) has been well established in adults with colon cancer; however, there is little evidence of similar utility in pediatric patients. CEA levels correlate with a change in tumor burden in only 60% of children with colorectal tumors. A number of children with Dukes stage C or D lesions have been shown to have normal antigen levels at the time of diagnosis.[107] In addition, CEA levels do not correlate well with long-term response to treatment in children and therefore should not be used as a definitive marker of recurrence.[64]

## Treatment

The primary treatment for colon cancer in children is surgical resection consisting of a wide excision of the involved colon, the mesentery, and the lymphatic drainage area. Unfortunately, resection for cure is possible in only 40% to 70% of pediatric patients because of advanced stage at diagnosis; these percentages are much lower than for adults. The ovaries and the omentum are common sites of metastasis. If resection for cure is performed, omentectomy, and in female patients, oophorectomy, is appropriate in patients identified with associated ovarian disease.[109]

No rigorously tested or widely accepted therapeutic protocols are available specifically for children with colorectal carcinoma. The use of adjuvant chemotherapy consisting of irinotecan, oxaliplatin, and leucovorin has been described in conjunction with 5-fluorouracil. The use of adjuvant chemotherapy, combined with second-look surgery in select cases, may improve survival.[3,68,107,110] As in adult rectal cancer, preoperative radiation therapy may convert unresectable rectal carcinoma to resectable tumors in selected patients. Although anecdotal case reports indicate these therapies can be beneficial, no data documents the utility of either chemotherapy or radiation therapy for cure or palliation; hence, prognosis and survival are most directly related to successful complete resection. The overall rate and duration of disease-free survival among children with colon carcinoma are low, with less than 30% of patients surviving 5 years. In patients who have resection for cure, predictors of survival include node involvement and histologic grade.

## Summary

The biology of pediatric colorectal carcinoma is different from colorectal malignancy in adults. The presentation, histologic type, stage, and prognosis differ sharply. Most cases of childhood colorectal cancer arise from previous adenomas. Children with syndrome-associated adenomas are at increased risk for colorectal carcinoma. This suggests that genetics play a greater role than previously thought, and fewer cases are truly sporadic. Understanding the molecular basis of colon carcinoma in children should facilitate the identification of patients at high risk and result in prophylactic intervention or earlier diagnosis and reduce mortality.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 35

# Diagnosis and Treatment of Rhabdomyosarcoma

Kevin P. Mollen and David A. Rodeberg

Historically, the mainstay of therapy for rhabdomyosarcoma (RMS) has been aggressive surgical resection, often including a significant amount of normal tissue along with the tumor.[1] As a result, operations were often disfiguring and outcomes disappointing, with survival rates from 7% to 70% depending on tumor location. It was not until chemotherapy was added to the RMS treatment algorithm in 1961 that outcomes began to improve. The addition of radiotherapy in 1965 to select patients further improved outcomes and decreased the need for aggressive radical operations. Recognition of the crucial contribution of multimodal therapy to the treatment of RMS led to the establishment of the Intergroup Rhabdomyosarcoma Study Group (IRSG) in 1972. The goal of the IRSG was to oversee the development of treatment protocols for RMS. Now called the Soft Tissue Sarcoma Committee of the Children's Oncology Group, this collaborative group has completed a number of cooperative group trials evaluating new drug combinations, chemotherapy dosing, imaging evaluation of tumors, radiotherapy, and surgical strategies for local tumor control and tumor biology.[2] During this time period, the overall 5-year survival rate of RMS has increased from 25% to 70% (Fig. 35-1).[3,4]

## Rhabdomyosarcoma Patient Demographics

Rhabdomyosarcoma is the most common type of soft tissue sarcoma diagnosed during the first 2 decades of life, accounting for 4.5% of all cases of childhood cancer.[5] It is the third most common extracranial solid tumor of childhood after Wilms' tumor and neuroblastoma. Age at presentation follows a bimodal distribution, with peak incidences between 2 and 6 years and again between 10 and 18 years of age.[6] This distribution reflects the incidences of the two major histologic subtypes of RMS. The incidence of embryonal RMS is highest at birth and extends through childhood before declining, while alveolar RMS peaks during childhood and adolescence.[7] Approximately 65% of all RMS cases occur in children younger than 6 years of age. Slightly more males (58.4%) are affected than females (41.6%), and whites have a higher incidence than African Americans (rate ratio 1.2).

## Rhabdomyosarcoma Tumor Biology

Rhabdomyosarcoma is a malignant tumor of mesenchymal origin.[5] RMS also falls under the greater category of small, blue, round-cell tumors of childhood that includes neuroblastoma, lymphoma, and primitive neuroectodermal tumors (PNET). The two major histologic subtypes of RMS are embryonal and alveolar. Embryonal RMS (ERMS) is the most common type of RMS, affecting two thirds of all patients with disease. ERMS can be further broken down into spindle-cell and botryoid subtypes. ERMS is typically composed of spindle-shaped cells with a rich stroma. In addition to occurring in younger patients, ERMS has a favorable survival rate of 60%. Tumors occur more frequently in the head and neck region as compared with the extremities. Spindle-cell histology is common in paratesticular lesions, whereas botryoid lesions are generally polypoid masses filling the lumen of hollow viscus, such as the vagina, bladder, and extrahepatic bile ducts. Alveolar RMS (ARMS) occurs in older children, and tumors are most commonly located on the trunk or extremities. These lesions are composed of small, round, densely packed cells arranged around spaces resembling pulmonary alveoli. However, this histologic classification of RMS may, in the near future, be supplanted by gene array analysis.[8] Prognosis is worse in ARMS than ERMS, with a 5-year survival rate of 54%. For all histologic types of RMS, outcome is heavily dependent on age at diagnosis, the primary anatomic site, extent of disease (tumor size, invasion, nodal status, metastatic disease), and the completeness of surgical excision. The Soft Tissue Sarcoma Committee is investigating the outcomes of patients by disease characteristics and tumor biology to refine risk-adapted therapy for the treatment of RMS.[2]

The exact nature of the pathogenesis of RMS is unclear; however, many hypotheses exist. It is largely thought that RMS arises as a consequence of regulatory disruption of skeletal muscle progenitor cell growth and differentiation.[9] Pathogenic roles have been suggested for the *MET* proto-oncogene, which is involved in migration of myogenic

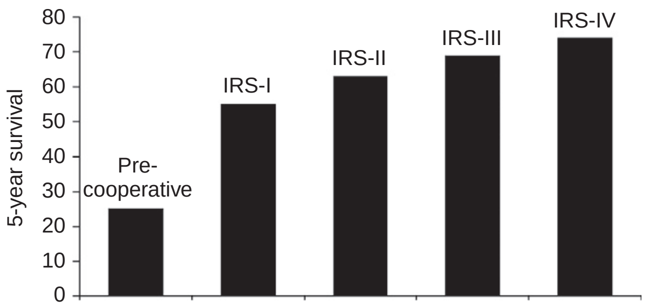


**FIGURE 35-1** Improvement in survival for RMS during the past 40 years.

precursor cells, and the *TP53* proto-oncogene, which is responsible for tumor suppression.[10,11] At the chromosomal level, ERMS is characterized by a loss of heterozygosity at the 11p15 locus, with a loss of maternal information and duplication of paternal genetic information. Within this locus lies the insulin growth factor II (IGF-II) gene.[12–14] Both ERMS and ARMS overproduce IGF-II, which has been shown to stimulate RMS tumor growth, suggesting that IGF-II plays a role in unregulated growth of these tumors.[15] Although the significance is unclear, ARMS is frequently tetraploid, whereas ERMS lesions are generally diploid. Translocations of the *FKHR* transcription factor gene from chromosome 13 with either the *PAX3* (chromosome 2) or *PAX7* (chromosome 1) transcription factor genes occur frequently in ARMS.[16–18] In these *PAX/FKHR* fusions, the DNA binding domain of *PAX* is combined with the regulatory domain of *FKHR*. This results in increased PAX activity leading to the de-differentiation and proliferation of myogenic cells. Understanding the role of these fusion proteins in tumor development may provide insight into treatment strategies and potential biomarkers for the diagnosis of RMS.[8] For example, it has been demonstrated that approximately 25% of ARMS tumors are translocation negative. By gene array analysis, these fusion negative ARMS tumors more closely resemble ERMS overall and have a similar prognosis to ERMS. It has therefore been proposed that tumors should be divided into *PAX/FKHR* fusion–positive and –negative tumors rather than the more ambiguous alveolar and embryonal histologies.

Although most cases of RMS occur sporadically, the disease is associated with familial syndromes, including Li-Fraumeni and neurofibromatosis I. Li-Fraumeni is an autosomal dominant disorder and is usually associated with a germline mutation of *TP53*. Patients with this syndrome present with RMS at an early age and have a family history of other carcinomas, especially premenopausal breast carcinoma.[19–22] Neurofibromatosis is an autosomal dominant genetic disorder characterized by optic gliomas, café-au-lait spots, and neurofibromas.[23] The association of RMS with Li-Fraumeni and neurofibromatosis appears to involve malignant transformation through the inactivation of the *TP53* tumor suppressor gene and hyperactivation of the *RAS* oncogene.[24,25] Nevoid basal cell carcinoma (Gorlin syndrome) is an autosomal dominant disorder caused by mutations in the *PTCH* tumor suppressor gene mapping to chromosome 9q22.3.[26] Animals with mutations in the *PTCH* gene have elevated levels of the tumor growth–promoting IGF-II and develop spontaneous RMS.[27,28] The association of mutations in the *PTCH* gene in human disease with spontaneous development of RMS is supported by the finding that up to 30% of sporadic cases of ERMS demonstrate molecular abnormalities at the 9q22.3 locus.[29,30] Autopsy findings suggest that one third of children with RMS also have congenital anomalies, suggesting that prenatal events may also contribute to tumor development.[31] Although no specific carcinogens have been identified, benzenediazonium sulfate has been shown to induce RMS in mice.[32] Maternal marijuana or cocaine use in pregnancy may be an environmental factor that contributes to the development of RMS.[33,34]

## Presentation of Rhabdomyosarcoma

Rhabdomyosarcoma typically presents as an asymptomatic mass found by the patient or the parents of younger children.[5] Specific symptoms vary based on the site of occurrence and extent of disease. These symptoms are generally related to mass effect or complications of the tumor. The most common sites of primary disease are the head and neck region, the genitourinary tract, and the extremities.

## Preoperative Workup

Patients with suspected RMS require a complete workup prior to surgical intervention.[5] Standard laboratory work, including complete blood counts (CBC), electrolytes, and renal function tests, liver function tests (LFTs), and urinalysis (UA) should be performed. In addition, imaging studies of the primary tumor should be performed with computer tomography (CT) or magnetic resonance imaging (MRI). CT is advantageous for the evaluation of bone erosion and abdominal adenopathy, whereas MRI provides better definition of the tumor and surrounding structures. MRI is preferable for limb, pelvic, and paraspinal lesions. Metastatic workup includes a bone marrow aspirate and bone scan, CT of the brain, lungs, and liver, and lumbar puncture for cerebrospinal fluid collection. Tumor imaging defines the proximity of tumors to vital structures and determines size. Both factors are important when determining if the tumor can be primarily resected or if neoadjuvant therapy is required to decrease tumor size and thereby decrease the morbidity of resection. It has been demonstrated that the size of the primary mass, as determined by pretreatment imaging, carries prognostic significance. Recent evidence would suggest that tumor volume and patient weight may be superior predictors of failure-free survival than tumor diameter and patient age in patients with intermediate-risk RMS.[35,36] Evaluation of regional and distant lymph nodes by clinical and radiographic means should be performed, because this is an important component of pretreatment staging.

Metabolic imaging using $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG PET) has become widely used in the adult population to determine the extent of disease in the setting of many cancers; however, there is limited experience in the pediatric population. Recent studies have suggested that FDG PET would be both a sensitive and specific tool in the clinical determination of the extent of disease in childhood sarcomas.[37–40] Further, when combined with CT, it may be more accurate than conventional imaging modalities in staging patients or re-staging patients at the time of recurrence.[41,42]

It is unclear what role FDG PET will have in the clinical evaluation of RMS, although there are several settings in which this imaging modality may improve our pretreatment staging and thus alter treatment for patients. FDG PET may enhance the evaluation of regional adenopathy versus traditional modalities. Similarly, FDG PET may offer improved detection of occult metastases, helping to differentiate them from normal structures. Finally, this modality may offer a guide to the diagnosis and treatment of recurrent disease. The diagnosis of a recurrence in a previously operated field is often difficult to obtain with conventional imaging methods. FDG PET/CT may offer an enhanced diagnostic tool and, more important, may offer tumor viability information which will guide further surgical therapy. One of the goals of ongoing trials will be to investigate the role of FDG PET in RMS.

## Pretreatment Clinical Staging

Staging of RMS is determined by the site of the primary tumor, primary tumor size, degree of tumor invasion, nodal status, and the presence or absence of metastases, and it is based solely on the preoperative workup of imaging and physical examination. This is expressed in a tumor-node-metastasis (TNM) classification system modified for the site of tumor origin (Fig. 35-2). Adequate pretreatment clinical staging requires a thorough physical examination and preoperative imaging. Several investigators have validated the modified TNM staging system as a reliable predictor of patient outcome.[43]

## Surgical Principles

### BIOPSY

Open biopsy of a mass suspected to be RMS should be performed to confirm the diagnosis. Care should be taken to obtain adequate specimens for pathologic, biological, and treatment protocol studies. For small lesions in areas that will be treated with chemotherapy and radiation or for metastatic disease, core needle biopsy may be appropriate for diagnosis.[44,45] Although less invasive than open biopsy, core needle biopsy obtains a smaller tissue sample, which increases sampling error and the number of inconclusive findings. This smaller volume of tissue may prevent the performance of adequate molecular biology studies. Image guidance with ultrasonography may increase the accuracy of sampling while helping to avoid inadvertent puncture of surrounding structures.[46] Clinical and radiographic positive lymph nodes should be confirmed pathologically. Open biopsy is recommended; however, fine-needle aspiration or core needle biopsy of lymph nodes may be performed at the discretion of the surgeon's judgment and pathologist's recommendations.[44,47] Sentinel

| Stage | Sites | T | Size | N |
|---|---|---|---|---|
| 1 | Orbit<br>Head and neck (excluding parameningeal)<br>GU nonbladder/ nonprostate | $T_1$ or $T_2$ | a or b | $N_0$ or $N_1$ or $N_x$ |
| 2 | Bladder/prostate, extremity, cranial parameningeal, other (includes trunk, retroperitoneum, etc.) | $T_1$ or $T_2$ | a | $N_0$ or $N_X$ |
| 3 | Bladder/prostate, extremity, cranial parameningeal, other (includes trunk, retroperitoneum, etc.) | $T_1$ or $T_2$ | a<br>b | $N_1$<br>$N_0$ or $N_1$ or $N_x$ |
| 4 | All | $T_1$ or $T_2$ | a or b | $N_0$ or $N_1$ |

| | | |
|---|---|---|
| Definitions: | Tumor T(site)$_1$– | Confirmed to anatomic site of origin<br>(a) <5 cm in diameter (b) >5 cm in diameter |
| | T(site)$_2$ | Extension and/or fixative to surrounding tissue<br>(a) <5 cm in diameter (b) >5 cm in diameter |
| | Regional nodes– | |
| | $N_0$ | Regional nodes not clinically involved |
| | $N_1$ | Regional nodes clinically involved by neoplasm |
| | $N_x$ | Clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation) |
| | Metastasis– | |
| | $M_0$ | No distant metastasis |
| | $M_1$ | Metastasis present |

FIGURE 35-2 TNM Pretreatment Staging Classification. Staging before treatment requires thorough clinical, laboratory, and imaging examinations. Biopsy is required to establish histologic diagnosis. Pretreatment tumor size is determined by external measurement or MRI or CT, depending on anatomic location. For less accessible primary sites, CT also will be used for lymph node assessment. Metastatic sites will require some form of imaging confirmation (but not histologic confirmation, except for bone marrow examination). CT, computed tomography; GU, genitourinary; MRI, magnetic resonance imaging.

node biopsy may offer a safe and less invasive means of lymph node evaluation for extremity and truncal lesions, although its role in RMS is yet to be determined but will soon become the focus of a clinical trial.[48–51]

## RESECTION OF THE MASS

Surgical biopsy of a primary lesion is often performed prior to a definitive surgical resection. If this is the case, pretreatment reexcision (PRE) is advisable. PRE is a wide reexcision of the previous operative site with adequate margins of normal tissue prior to the initiation of adjuvant therapy. PRE is most commonly performed on extremity and trunk lesions but should be considered the treatment of choice whenever technically feasible.[52]

The primary goal of surgical intervention is wide and complete resection of the primary tumor with a surrounding rim of normal tissue. A circumferential margin of 0.5 cm is considered adequate; however, there is minimal data to support this recommendation. Such a margin may be unobtainable, however, especially with head and neck tumors. Because of these limitations, adequate margins of uninvolved tissue are required unless excision would compromise adjacent organs, result in loss of function or poor cosmesis, or is not technically feasible. All margins should be marked and oriented at the operative field to enable precise evaluation of margins. If a narrow margin occurs, several separate biopsies of "normal" tissue around the resection margin should be obtained. These specimens should be marked and submitted separately for pathologic review. Communication between the pathologist and surgeon is mandatory to ensure that all margins are accurately examined. The surgeon should not bisect or cut the excised tumor into specimens prior to sending it to the pathologist. Any microscopic or gross tumor should be marked with small titanium clips in the tumor bed to aid radiotherapy simulation and subsequent reexcision. Published outcomes analyses have shown that a clear margin and no residual disease (group I) is superior to residual microscopic margins (group II) or gross residual disease (group III).[2,3,52–54] Tumors that are removed piecemeal are considered group II even if all gross tumor is removed.

## LYMPH NODE SAMPLING/DISSECTION

Lymph node status is an important part of pretreatment staging and therefore directly impacts risk-based treatment strategies in RMS. Regional lymph node disease (N-1) has been identified in ARMS as an independent poor prognostic factor in stage 3 patients.[2] Data from IRS-IV would suggest that N-1 disease in patients with ARMS is associated with tumor characteristics that carry a poor prognosis, such as older age, more invasive tumors ($T_2$), large tumor size (>5 cm), and unfavorable primary sites.[55] In addition, N-1 disease was present in 23% of all RMS patients, predominantly in primary tumor sites, such as perineum, retroperitoneum, extremity, bladder/prostate, parameningeal, and paratesticular. N-1 disease alters both failure-free survival (FFS) and overall survival (OS) for ARMS but not ERMS.[55] For patients with N-1, ARMS outcomes were more similar to patients with single-site metastatic disease than those with only local disease. However, for ERMS other prognostic factors, such as patient age, tumor invasion (T stage), site of primary tumor, and the presence of metastasis at initial presentation, were more important prognostic factors than N-1 disease. In addition, it has previously been shown that in patients with otherwise localized disease, such as an extremity, N-1 disease may be associated with an inferior outcome.[56,57] Clinical and radiographic positive nodes should therefore be biopsied to confirm tumor involvement, thus ensuring correct assessment of disease risk and assignment of optimal therapy. Lymph node removal has no therapeutic benefit, therefore prophylactic lymph node resection plays no role in therapy.[57] Therefore clinical and/or radiographic negative nodes do not require pathologic evaluation except in extremity tumors and for children older than 10 years of age with paratesticular tumors.[58,59] In both of these sites, the high incidence of nodal disease and false-negative imaging necessitates pathologic evaluation of regional nodal basins.

The use of sentinel node mapping to determine regional node status has proven to be beneficial in adult breast cancer and melanoma. For childhood RMS, sentinel node mapping is not yet the standard of care but may prove to be effective.[48] Sentinel node mapping has proven its utility in determining nodal status in pediatric skin and soft tissue malignancies and will likely become the standard of care for identifying the regional nodes involved with tumor.[60]

If regional nodes are positive then distant nodes should be harvested for pathologic evaluation. Tumor identified in these nodes would be considered metastatic disease and would therefore alter therapy using the current risk-based protocols. For upper extremity lesions, the distant nodes would be the ipsilateral supraclavicular (scalene) nodes. In the lower extremity, the distant nodes would include the iliac and/or paraaortic nodes. For paratesticular RMS, the ipsilateral paraaortic lymph nodes above the renal vein are considered distant nodes.[60]

## CLINICAL GROUP

The extent of residual disease after resection is one of the most important prognostic factors in RMS. For this reason, a clinical grouping system was developed in 1972 to stratify patients into groups that would more accurately reflect their prognosis and treatment options. Currently, patients are assigned to a clinical group based on the completeness of tumor excision and the evidence of tumor metastasis to the lymph nodes or distant organs after pathologic examination of surgical specimens (Fig. 35-3). This system differs from TNM staging in that determination of each patient's clinical group is based on the extent of the surgical resection instead of tumor size and site.

| Group | Criteria |
|---|---|
| I | Localized disease, completely resected<br>A. Confined to organ or muscle of origin<br>B. Infiltrating outside organ or muscle of origin: regional nodes not involved |
| II | Compromised or regional resection including:<br>A. Grossly resected tumors with microscopic residual tumor<br>B. Regional disease, completely resected, with nodes involved and/or tumor extension into an adjacent organ<br>C. Regional disease, with involved nodes, grossly resected, but with evidence of microscopic residual tumor |
| III | Incomplete resection or biopsy with gross residual disease remaining |
| IV | Distant metastases present at outset |

FIGURE 35-3 Clinical grouping for RMS patients.

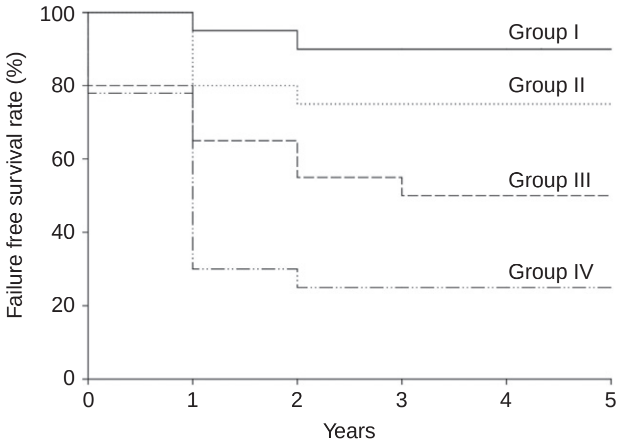


**FIGURE 35-4** Rhabdomyosarcoma survival based on completeness of surgical resection (clinical group).

Data from IRS-III and IRS-IV demonstrate that five-year failure-free survival rates vary according to clinical grouping and by histologic type (Fig. 35-4).[2] One criticism of clinical grouping is that variation of surgical techniques make comparisons of clinical grouping between different institutions problematic.[61] Nonetheless, this system offers a tremendous companion to preoperative staging in determining patient risk assessment and prognosis (Fig. 35-5).

### SECOND-LOOK OPERATIONS AND AGGRESSIVE RESECTION FOR RECURRENCE

After completing adjuvant therapy, patients with RMS are reimaged with CT or MRI. If residual tumor remains, or if the outcome of therapy remains in doubt, a second-look operation (SLO) may be considered. SLO can be performed to confirm clinical response, to evaluate pathologic response, and to remove residual tumor in order to improve local control.[62] As with the initial operation, the goal of SLO is complete resection of disease. Data from IRS-III suggested that SLO results in the reclassification of 75% of partial responders to complete responders after excision of residual tumors. These operations were most effective in extremity and truncal lesions.

In general, an aggressive surgical approach is used for recurrent RMS. Data would suggest that resection of recurrent RMS confers a 5-year survival of 37% compared with 8% survival in a group of patients without aggressive resection.[63] Given these results, SLO and aggressive resection for recurrence can be important tools for the treatment of RMS.

However, resection of residual masses after completion of adjuvant therapy may not be warranted. Associated morbidity of resection and the inability to achieve complete resection in some cases need to be considered. Further, it is not uncommon to find an absence of viable tumor tissue in resected samples.[63a] This brings into question the utility of aggressive re-resection and suggests that better means of detecting viable tumor is crucial. As discussed, PET/CT may provide the crucial information required to make these decisions.

## Chemotherapy

It was not until the 1960s that chemotherapy was recognized as an important adjunct to surgery in the treatment of RMS. Today, all patients with RMS receive some form of chemotherapy. Standard therapeutic regimens consist of a combination of vincristine, actinomycin-D, and cyclophosphamide (VAC). Although tremendous advances have been made in improving the outcomes of patients with isolated local and regional disease, little progress has been made in improving outcomes for advanced RMS tumors. The limiting factor has been an inability to improve significantly upon standard chemotherapeutic regimens. Dose intensification of vincristine and actinomycin-D is not possible because of their neurotoxic and hepatotoxic side effects. Studies evaluating dose intensification of cyclophosphamide found that although patients tolerate higher doses, outcomes of intermediate-risk tumors are not changed.[64] These findings have lead to the evaluation of new drug combinations and the development of risk-based treatment protocols.[65]

The combination of ifosfamide and etoposide was tested in a Phase II therapy window in IRS-IV. When combined with VAC, ifosfamide, and etoposide therapy resulted in a better 3-year survival rate, with less bone marrow toxicity when compared with the use of vincristine and melphalan with standard VAC regimens.[66] Other chemotherapeutic regimens being developed to treat advanced rhabdomyosarcoma have

| Risk group | Pretreatment stage* | Clinical group# | Site# | Histology |
|---|---|---|---|---|
| Low 1 | 1 or 2 | I or II | Favorable or unfavorable | EMB |
| | 1 | III | Orbit only | EMB |
| Low 2 | 1 | III | Favorable | EMB |
| | 3 | I or II | Unfavorable | EMB |
| Intermediate | 2 or 3 | III | Unfavorable | EMB |
| | 1–3 | I–III | Favorable or unfavorable | ALV |
| High | 4 | IV | Favorable or unfavorable | EMB |
| | 4 | IV | Favorable or unfavorable | ALV |

* Pretreatment stage dependent on site of disease
# Favorable sites: Orbit, genitourinary tract, biliary tract nonparameningeal head and neck

**FIGURE 35-5** Risk-based stratification of patients to guide degree of therapy and prognosis for RMS patients. ALV, alveolar; EMB, embryonal.

incorporated doxorubicin and the topoisomerase inhibitor irinotecan. Although used as a single agent, irinotecan is of little value, it may be a useful adjunct to current VAC regimens for the treatment of advanced RMS.[67–69] Another topoisomerase inhibitor, topotecan has shown some promise in patients with stage 4 disease when combined with cyclophosphamide.[70–72] However, alternating these drugs with standard VAC therapy has not shown any benefit in intermediate-risk patients.[73] Multiple drugs are currently being evaluated for the treatment of RMS in Phase I and II trials.

# Radiation Therapy

Radiotherapy is an important adjunct to therapy for many children diagnosed with RMS, offering improved local control and outcomes. Candidates for radiotherapy primarily include those with group II (microscopic residual disease) or group III (gross residual disease) disease. The impact of therapy is influenced by the location of the primary tumor and amount of local disease (tumor stage and clinical grouping) at the time radiotherapy is initiated.[74,75] Among patients with group II disease, low-dose radiation (40 Gy at 1.5 to 1.8 Gy/fraction) is associated with local tumor control rates of at least 90%.[76] For patients with group III disease, radiation doses are more commonly 50 Gy.[77] A randomized study within the IRS-IV protocol demonstrated that twice-daily irradiation at 110 cGY per dose, 6 to 8 hours apart (hyperfractionated schedule) for 5 days per week is feasible and safe. This schedule, however, is difficult to accomplish in small children who require twice-daily sedation for treatment. Unfortunately, the hyperfractionated schedule demonstrated no improvement in local control over conventional radiation therapy.[78]

Radiation therapy in very young children with RMS poses a unique therapeutic challenge. Concerns over the technical difficulties associated with external beam radiotherapy in young children and late side effects of therapy have led to the evaluation of strategies that reduce the total burden of therapy without sacrificing local control. Modern techniques, such as intensity modulated radiation therapy (IMRT) and proton beams, may improve outcome without compromising long-term function.[79,80] Ongoing studies continue to evaluate the dose of radiation necessary for local control of the tumor.

# Assessment of Response to Treatment

Although European RMS trials have incorporated the use of conventional radiologic modalities to evaluate the response to induction therapy and help tailor subsequent therapy, this has not been employed in the United States. IRS-IV data demonstrated no predictive value of radiographic response after 8 weeks of induction therapy.[81] Further, radiographic evidence of a complete response to therapy in group III RMS was not associated with a reduction in disease recurrence and death.[63a] Clearly, the significance of persistent radiographic masses in patients treated for RMS is unknown. Conventional imaging modalities offer no information about the biology of these masses and are unable to differentiate between active tumors and scar. It is possible that FDG PET may offer useful clinical information in patients treated or partially treated for RMS.

## SPECIFIC ANATOMIC SITES

Rhabdomyosarcomas are unique among solid tumors in that they may occur in many different areas of the body. Tumors in different parts of the body may behave differently than those in other areas. In addition, some areas of the body offer unique obstacles to surgical resection. As such, some specific anatomic sites of tumor occurrence will be discussed separately.

### Head and Neck (Superficial Nonparameningeal)

Approximately 35% of RMS arises in the head and neck region. Of these tumors, 75% occur in the orbits. Other sites include the buccal, oropharyngeal, laryngeal, or parotid areas.[3] The histologic variant of RMS correlates to some extent with the location of the orbital tumor. ERMS and differentiated types more commonly arise in the superior nasal quadrants, whereas ARMS generally originate within the inferior orbit.[83] For all head and neck RMS, biopsy is required for the confirmation of diagnosis. Resection may be limited by the inability to obtain an adequate margin, and therefore the success of resection is heavily dependent on location.[84–86] Lymph nodes are rarely involved in childhood head and neck RMS; however, clinically or radiographically positive nodes must be biopsied.[87] Outcomes correlate strongly with tumor location. Orbital RMS carries the best prognosis and is least likely to extend to the meninges. These tumors generally present earlier in the course of disease. Tumors arising in nonorbital parameningeal locations have a high likelihood of meningeal extension. If meningeal extension occurs after chemotherapy and radiation therapy, the outcome is often fatal.[88]

### Parameningeal Sites

Parameningeal RMS includes tumors arising in the middle ear/mastoid, nasal cavity, parapharyngeal space, paranasal sinuses, or the pterygopalatine/infratemporal fossa region. These tumors are considered high risk because of their propensity to cause cranial nerve palsy, bony erosion of the cranial base, and intracranial extension.[89] Wide local excision is recommended but is often not feasible because of the location of the tumors. Craniofacial resection for tumors of the nasal areas, paranasal sinuses, temporal fossa, and other deep sites are reserved for expert surgical teams. The recognition of poor outcomes associated with meningeal extension has lead to a propensity for early radiation therapy of primary tumors and adjuvant chemotherapy.[87] For patients with unresected tumors and/or lymph node-positive disease, the use of three-drug chemotherapy regimens (including an alkylating agent) plus local or regional radiation may be beneficial. The optimal dosing and timing of radiation are not yet determined.[84]

### Trunk

Accounting for only 4% to 7% of tumors, RMS of the trunk is associated with a poor prognosis. Symptoms for RMS of the trunk often occur late in the progression of disease, which leads to late diagnoses. Complete surgical resection is difficult, particularly when the pleura and peritoneum are involved. In

addition, resections are frequently morbid and associated with poor cosmetic outcomes. Resection may necessitate major chest wall or abdominal wall reconstruction with prosthetic materials or with flaps.[90,91] Indicators of poor prognosis include advanced stage at presentation, alveolar histology, recurrence disease, tumor size greater than 5 cm, lymph node involvement, and the inability to undergo gross total resection.[92,93]

### Abdominal Wall

Abdominal wall RMS generally presents as a painless, firm mass. Many abdominal wall primaries can be removed completely at presentation or following neoadjuvant chemotherapy. However, tumors arising from the interior abdominal wall may not be noticed until significant tumor progression has occurred, thus rendering resection much more challenging. Tumor excision should include full-thickness resection of the abdominal wall, including the skin and peritoneum with a margin of normal tissue. Reconstruction of the abdominal wall can be performed with mesh or myocutaneous muscle flaps in an attempt to preserve function and cosmesis after resection. Data would suggest that localized tumors of the abdominal wall can be resected with good outcomes and that younger children with abdominal wall RMS fare better than adolescents, possibly because of a higher proportion of unfavorable histology in the older group of children.[94] If the size or location prevents adequate excision, neoadjuvant chemotherapy should be initiated to reduce tumor size and facilitate subsequent resection.

### Chest Wall

The differential diagnosis for malignant chest wall masses includes Ewing sarcoma, primitive neuroectodermal tumors (PNET), and RMS. Diagnostic biopsies are performed in the long axis of the tumor, parallel to the ribs. Wide local excision of chest wall lesions with a 2-cm margin, including the previous biopsy site, involved chest wall muscles and involved ribs, as well as wedge excision of any involved underlying lung, is recommended. Thoracoscopy performed at the time of resection may be helpful in determining the extent of pleural involvement and tumor extension to the underlying lung. Chest wall reconstruction can be performed using a number of techniques employing prosthetic mesh, myocutaneous flaps, and titanium ribs. Chest wall lesions have a worse prognosis than other trunk lesions, with a 1.8-year survival rate of only 42%.[90] Although radiotherapy may be beneficial for local control of tumor, this option is associated with significant morbidity, including pulmonary fibrosis, decreased lung capacity, restrictive defects from altered development of the thoracic cavity, and scoliosis.[95] There is also no proven survival benefit.

### Biliary Tract

Classically, patients with biliary RMS present at a young age (average age 3.5 years) with jaundice and abdominal pain, often associated with abdominal distension, vomiting, and fever. Workup reveals a significant direct hyperbilirubinemia and a mild elevation of hepatic transaminases. Gross total resection of biliary tract RMS is rarely possible and is often unnecessary because of good outcomes with chemotherapy and radiation. Currently, open biopsy is the only definitive role of surgery in the treatment of biliary RMS, although this is controversial. The histology of these tumors is often the botryoid variant of embryonal RMS, which carries a good overall prognosis.[96] Biliary obstruction can be relieved by stenting, but external biliary drains should be avoided because of infectious complications. Overall, outcomes are good unless distant metastases are present at the time of diagnosis.[97,98]

### Paraspinal Sites

Paraspinal RMS is rare (3.3% of all RMS) and carries a poor prognosis. These tumors tend to spread along anatomic structures, such as neurovascular bundles and fascial sheaths, occasionally causing spinal cord compression. Complete excision of paraspinal lesions is often difficult to perform because of large tumor size at presentation and proximity to the vertebral column and spinal canal.[92,99] Recurrence rates for paraspinal RMS are high (55%) with the majority of these occurring at distant locations. The lung is the most common site of distant metastasis followed by the central nervous system.[99]

### Retroperitoneum/Pelvis

Like paraspinal tumors, retroperitoneal/pelvic lesions are often discovered at an advanced stage and thus generally carry a poor prognosis. These tumors can envelop vital structures, making complete surgical resection challenging. Neoadjuvant chemotherapy may play a role in tumors that cannot be safely resected at the time of diagnosis. With the exception of group IV metastatic disease, aggressive resection is recommended and has been shown to offer improvement in survival.[100] Group IV patients with embryonal histology and those who present at less than 10 years of age may also undergo surgical debulking.[101] It has been demonstrated that excising greater than half of the tumor before chemotherapy resulted in improved rates of failure-free survival when compared with patients who did not undergo debulking.[102] This is the *only* setting in which surgical debulking of RMS has shown any benefit.

### Perineal/Perianal Sites

Perineal tumors are rare and usually present at an advanced stage. Characteristics associated with improved survival include a primary tumor size less than 5 cm, less advanced clinical group and stage, negative lymph node status, and age less than 10 years of age. Interestingly, histology does not affect overall outcome for these tumors. Resection of these tumors can be challenging because of proximity to the urethra and anorectum. At resection, particular care should be taken to preserve continence. If anorectal obstruction exists, a temporary colostomy may be necessary. Patients presenting in clinical group I had 100% overall survival at 5 years compared with 25% for group IV patients.[103]

### Extremities

Rhabdomyosarcoma of the extremities accounts for 20% of all new diagnoses. The majority of these tumors have alveolar histology and thus a poor prognosis. The cure rate for children with extremity RMS has, however, improved steadily from 47% in IRS-I to 74% in IRS-III.[104,105] As with many types of RMS, complete gross resection at initial surgical intervention is the most important predictor of failure-free survival. The primary goal of local tumor control in extremity tumors is limb-sparing complete resection. Amputation is rarely necessary for tumor excision. Positive regional lymph nodes are

found in 20% to 40% of patients and are associated with decreased overall survival (46% survival rate for node-positive patients compared with 80% survival for node-negative patients). Seventeen percent of IRS-IV patients with clinically negative nodes were found to have microscopic nodal disease on biopsy. In light of this, surgical evaluation of lymph nodes is necessary to accurately stage children with extremity RMS, even in the absence of clinically positive nodes.[60] Currently, axillary sampling is recommended for upper extremity lesions, and femoral triangle sampling is recommended for lower-extremity lesions. Sentinel lymph node mapping may be a useful adjunct in the setting of extremity RMS. If regional nodes are involved, then x-ray therapy (XRT) fields are adjusted to incorporate regional lymph node basins. This approach is associated with decreasing rates of local and regional recurrence.[57] In-transit nodal involvement at the time of diagnosis, present in 4% of IRS-IV patients, has also been identified as a factor contributing to regional treatment failure. This may be evaluated by MRI, or possibly FDG PET, at the time of diagnosis. Radiation therapy (RT) should be used at regional lymph node sites in these patients.[106]

### Genitourinary Sites: Bladder/Prostate

Rhabdomyosarcoma of the bladder or prostate typically presents with urinary obstructive symptoms. These lesions are typically of embryonal histology (73%). The major goal of surgery is complete tumor resection with bladder salvage. This can be achieved in 50% to 60% of patients.[107,108] Partial cystectomy has resulted in similar survival rates and improved bladder function compared with more aggressive resections.[109,110] Bladder dome tumors frequently can be completely resected, whereas more distal bladder lesions frequently require ureteral reimplantation or bladder augmentation. Prostatic tumors require prostatectomy, often combined with an attempt at bladder salvage with or without ureteral reconstruction.[53] Continent urinary diversion may be necessary if tumors are unresectable or have a poor response to medical therapy. Lymph nodes are involved in up to 20% of cases. Therefore during biopsy or resection, iliac and para-aortic nodes should be sampled, as well as any other clinically involved nodes. An analysis of patients with bladder or prostate RMS in IRS-IV revealed that 70% of these tumors arose from the bladder with an overall 6-year survival of 82%.[111] Of these patients, 55 retained their bladder without relapse, but only 36 had normal bladder function. Urodynamic studies have been used to evaluate bladder function after treatment.[112]

### Genitourinary Sites: Vulva/Vagina/Uterus

Traditionally, females with primary tumors of the genital tract underwent aggressive resection followed by chemotherapy with or without radiation.[113–115] Newer treatment approaches rely more heavily on neoadjuvant chemotherapy to reduce tumor size and minimize the extent of resection in an attempt to preserve organ function. Primary tumors of the vagina are about 5 times more common than cervical tumors. The vast majority of these tumors are classic embryonal or are of the botryoid subtype. This may account for the more favorable prognosis that these tumors display.[116] These tumors respond well to chemotherapy, with impressive tumor regression that often precludes the need for radical operations such as pelvic exenteration. Vaginectomy and hysterectomy are performed only for persistent or recurrent disease. Primary uterine tumors require resection with preservation of the distal vagina and ovaries if they do not respond to chemotherapy. Oophorectomy is only indicated in the setting of direct tumor involvement. For those patients presenting with nonembryonal RMS of the female genital tract, more intensive chemotherapeutic regimens are recommended to reduce the risk of recurrence. Prognosis for this tumor site with only locoregional disease is excellent, with an estimated 5-year survival of 87%.[117]

### Paratesticular Sites

Paratesticular RMS generally presents as a painless scrotal mass. Histology is generally favorable, with most tumors showing the spindle-cell subvariant of embryonal histology. Survival rates are greater than 90% for patients presenting with group I or II disease.[118,119] Radical orchiectomy via an inguinal approach with resection of the spermatic cord to the level of the internal ring is the standard of care. Open biopsy should be avoided, because the flow of lymphatics in this region facilitates spread of the disease. If a transscrotal biopsy/resection has been performed, subsequent resection of the hemiscrotum is required. If unprotected spillage of tumor cells occurs during tumor resection, these patients are considered clinical group IIa regardless of the completeness of resection.[120] The incidence of nodal metastatic disease for paratesticular RMS is 26% to 43%.[121,122] Unfortunately, studies have demonstrated that CT is a poor means of evaluating lymph node positivity in the retroperitoneum.[123] In addition, patients older than 10 years of age or those with enlarged nodes have a much higher incidence of node positivity.[59] Those patients should therefore undergo an ipsilateral retroperitoneal nodal resection. Suprarenal nodes should be evaluated, because positive nodes in this area place a patient in group IV with disseminated metastatic disease.

## Metastatic Disease

Rhabdomyosarcoma metastasizes both through hematogenous and lymphatic routes. Children with metastatic RMS have very poor survival rates. For the IRS studies I through III, children with metastatic disease had a 5-year disease-free survival of 20%, 27%, and 32%, respectively, in each of the successive studies. Recently studies have employed the use of upfront "window studies" to address potential chemotherapeutic regimens that would improve the disease-free survival period when given to patients with newly diagnosed metastatic RMS. One such study evaluated the combination of ifosfamide and doxorubicin for the treatment of children with metastatic disease who are less than 10 years of age, have embryonal histology, and lack nodal, bone, or bone marrow involvement. This treatment strategy increased 5-year failure-free survival to 28% and 5-year overall survival to 34%.[68] Despite these improvements, more intensive research into chemotherapeutic regimens for group IV disease should be investigated to improve overall outcome.

## Prognosis

The prognosis of patients with RMS is dependent on many factors. Favorable prognostic factors include embryonal/botryoid histology, primary tumor sites in the orbit and

nonparameningeal head/neck region and genitourinary nonbladder/prostate regions, a lack of distant metastases at diagnosis, complete gross removal of tumor at the time of diagnosis, tumor size less than or equal to 5 cm, and age less than 10 years at the time of diagnosis.[77] Clinical grouping was identified as one of the most important predictors of failed treatment and tumor relapse.[2,77] These factors become important in the designation of treatment groups for risk-based therapy.

For group II patients, Smith and colleagues performed a retrospective review of patients enrolled in IRS-I through IRS-IV to determine the risk factors for relapse. Those patients in group II at highest risk for treatment failure had alveolar/undifferentiated histology, unfavorable primary sites, regional disease with residual tumor after gross resection and node involvement, or were treated with early therapeutic regimens (IRS-I or IRS-II). Current therapy for patients with group II tumors results in 85% survival long term, indicating that risk-based therapeutic strategies have assisted with failure-free survival.[124]

Patients with group III disease have incomplete resection or biopsy only prior to chemotherapy and irradiation. Wharam and colleagues determined that predictors of failure-free survival in group III include tumor size less than 5 cm, primary sites of orbit and bladder/prostate, and TNM staging equivalent to $T_1/N_0N_x$ tumors in stage I or stage II. Since radiotherapy is important for local control of group III disease, the incidence of local failure was stratified by radiotherapy dosing (<42.5 vs. 42.5 to 47.5 vs. > 47.5 Gy) and was not significantly different among these dose ranges.[125]

Approximately 15% of patients with RMS present with metastases (group IV) at the time of diagnosis.[104] Patients in group IV have poor outcomes despite aggressive multimodality treatments, with only 25% expected to be free of disease 3 years after diagnosis.[104,105] A review of prognostic factors and outcomes for children and adolescents with metastatic RMS in IRS-IV found that 3-year overall survival and failure-free survival was improved if there were two or fewer metastatic sites and the histology of the tumor was embryonal. Compared with patients without metastatic disease, group IV patients in the IRS-IV study were more likely to be older (median age 7 years vs. 5 years), had a higher incidence of alveolar histology (46% vs. 22%), had tumors that were more invasive ($T_2$: 91% vs. 49%) and larger (>5 cm: 82% vs. 51%), a higher incidence of lymph node involvement ($N_1$: 57% vs. 16%), and had a greater proportion of extremity and truncal/retroperitoneal primary sites (48% vs. 25%). This study concluded that not all children with metastatic RMS have uniformly poor prognoses, suggesting that therapy should be tailored according to these factors.[126]

Future clinical trials and a better understanding of the molecular biology driving RMS tumor behavior may assist with customized clinical therapies that will improve outcome and failure-free survival in patients diagnosed with RMS.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 36

# Other Soft Tissue Tumors

Andrea Hayes-Jordan

## Nonrhabdomyosarcoma Soft Tissue Sarcoma in Children: Background and Overview

Approximately 8% of childhood malignancies are soft tissue sarcomas. Half of these are nonrhabdomyosarcoma soft tissue sarcomas (NRSTSs). There are more than 50 histologic types, and genetic patterns are poorly understood. When surgical resection is feasible, ≈60% of patients are expected to achieve long-term survival with or without radiation therapy.[1] Patient outcome is largely based on age, the presence of metastasis at diagnosis, and size and depth of the lesion. Here we focus on the most common primary histologic types and differences in presentation and surgical treatment of childhood NRSTS and other common pediatric soft tissue tumors.

The treatment for children and adolescents with NRSTS has not previously been standardized, nor have there been any pediatric cooperative group trials as for rhabdomyosarcoma (RMS). Because there are many histologic subtypes of NRSTS, standardization of treatment is difficult. The first risk-based prospective trial of NRSTS in children and adolescents will complete enrollment soon, with results anticipated in 2013. In this trial, patients with NRSTS are treated as low, intermediate, or high risk based on criteria previously ascertained in a thorough review of 121 patients by Spunt.[2,3] In patients with surgically resected NRSTS, univariate analysis revealed clear risk factors. Positive surgical margins ($P = 0.004$), tumor size greater than or equal to 5 cm ($P < 0.001$), invasiveness ($P = 0.002$), high grade ($P = 0.028$), and intra-abdominal primary site ($P = 0.055$) had a negative impact on event-free survival (EFS). Multivariate analysis confirmed all of these risk factors, except for invasiveness. Local recurrence was predicted by intra-abdominal primary site ($P = 0.028$), positive surgical margins ($P = 0.003$), and the omission of radiation therapy ($P = 0.043$). As expected, the biology of the tumor, assessed by tumor size greater than 5 cm, invasiveness, and high grade, predicted distant recurrences. Children and adolescents with initially unresectable NRSTSs are a subgroup with pediatric NRSTSs that is particularly high risk. These are large tumors, greater than 5 cm, which involve critical neurovascular structures of the extremity, trunk, abdomen, or pelvis. In these patients, the 5-year estimated overall survival and EFS were 56% and 33%, respectively, and postrelapse survival was poor, 19% despite multimodality therapy.[4]

In addition to the tumor being unresectable, age is a prognostic indicator in pediatric NRSTS. Patients less than 1 year of age have an excellent prognosis, whereas the adolescents and young adults have the worse prognosis compared with younger patients or older adults.[2] A 34-year review of patients treated at St. Jude Children's Research Hospital (SJCRH) revealed the overall 5-year survival estimate for children less than 1 year of age was 92% compared with 36% in those 15 to 21 years of age. Patients between 1 and 15 years of age had an intermediate survival of approximately 60%. Survival after relapse was poor in all age groups less than 18 years, except those less than 1 year of age. The 5-year estimate of postrelapse survival in patients less than 1 year of age was 80% compared with the 15- to 25-years cohort in which survival was 21%. The type of chemotherapy used in these patients was variable; surgical excision was generally completed for lesions less than or equal to 5 cm, and for most patients, incisional biopsy was performed for lesions greater than 5 cm, followed by chemotherapy, reexcision, and radiation therapy or amputation.[5]

### INFANTILE FIBROSARCOMA

Patients in the study above who were less than 1 year of age had infantile fibrosarcoma (IF). This is a very rare form of NRSTS that occurs primarily during the first year of life, but can appear up to year 4. IF presents as a rapidly growing mass in the trunk or extremities. It can erode bone and usually reaches a large size.

Most cases of IF have a specific translocation t(12;15)(p13;q25)[6–8] leading to fusion of *ETV6 (TEL)*, a member of the ETS family of transcription factors, on chromosome 12p13, and *NTRK3 (TRKC)*, which encodes a tyrosine kinase receptor for neurotropin-3[9,10] on chromosome 15q25. Other cytogenetic abnormalities include trisomy 11; random gains of chromosomes 8, 11, 17, and 20[11]; deletion of the long arm of chromosome 17[12]; and a t(12;13) translocation.[13] The helix-loop-helix dimerization domain of *ETV6* fuses to the protein tyrosine kinase domain of *NTRK3*. The fusion protein results in ligand-independent chimeric protein tyrosine kinase activity with autophosphorylation. This leads to constitutive

activation of Ras-MAPK and P13K-AKT pathways through insulin receptor substrate-1, which is tyrosine-phosphorylated,[14–16] and through the activation of c-*Src*.[17] The fusion protein also associates with TGF-beta II receptor, which can be oncogenic by leading to inhibition of TGF-beta receptor signals that mediate tumor suppression.[18]

Identical genetic findings have been reported in the cellular variant of congenital mesoblastic nephroma, a microscopically similar tumor of the kidney,[19,20] and in secretory carcinoma of the breast[21] and acute myeloid leukemia,[22] implying oncogenesis by lineage-independent activation of kinase-related signaling pathways.

### SYNOVIAL SARCOMA

Synovial sarcoma (SS) and malignant peripheral nerve sheath tumor (MPNST) are the most common pediatric NRSTSs. SS is characterized by a very specific fusion gene 18[t(X;18) (p11.2;g11.2)]. Its etiology is unknown.[23] In evaluating the three largest reviews of pediatric SS, common principles are evident. For children 0 to 16 years old and tumors less than 5 cm in size, overall 5-year survival (OS) is 71% to 88%. In this group, the addition of chemotherapy did not improve survival. In patients 17 to 30 years old, the addition of chemotherapy does improve metastasis-free survival. In patients with SS tumors greater than 5 cm that are deep and invasive and without metastasis, OS is 50% to 75%, and chemotherapy responsiveness is 50% to 60%.[24] It is clear that for SS survival does not depend on surgical margins but depends on size (>5 cm) and local invasiveness. Brecht and colleagues found event-free survival was 92% and 56%, respectively, when SS tumors were less than or equal to 5 cm or greater than 5 cm.[24] Figure 36-1 shows the leg of a child with synovial sarcoma that was not responsive to chemotherapy and required resection down to the periosteum of the tibia. Radiotherapy does have a role in this disease and is recommended after marginal resection or before anticipated marginal resection, such as the one pictured.[23]

### MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

Malignant peripheral nerve sheath tumor (MPNST), also called schwannoma or neurofibrosarcoma, usually arises in proximity to nerve sheaths. MPNST develops in a preexisting neurofibroma in approximately 40% of patients, particularly those with neurofibromatosis type 1 (NF-1).[25] In a review of 171 patients the 5-year OS and progression-free survival was 51% and 37%, respectively. Multivariate analysis revealed absence of NF-1 and tumor invasiveness to be poor prognostic variables. The overall response of the patients who received neoadjuvant chemotherapy was 45%. Some partial responses were seen in patients with initial unresectable disease, because of neurovascular involvement.[25] Neoadjuvant radiotherapy failed to maintain or achieve local control in 45% of patients (26 of 58). Neither chemotherapy nor radiotherapy produced any statistically significant difference in outcome. This article concluded by stating "…complete surgical resection is the mainstay of successful treatment."[25] In another much smaller series, the same patterns in outcome were seen.[26]

## Surgical Approach and Presentation of Nonrhabdomyosarcoma Soft Tissue Sarcoma

Unlike rhabdomyosarcomas, NRSTSs are relatively chemoinsensitive. In the above pediatric studies and in adult multi-institutional studies, the impact of chemotherapy on outcome is minimal. In large American Joint Commission on Cancer (AJCC) stage 3 tumors, overall survival was no different whether or not chemotherapy was added to surgery and also if neoadjuvant or adjuvant radiation therapy was added.[27] Complete surgical excision provides the best outcome. Patients usually present with a painless mass, sometimes identified after a recent episode of trauma. Pediatric patients who have an extremity or trunk mass that is greater than 5 cm, should have a magnetic resonance imaging (MRI) examination, followed by core needle or open biopsy. If NRSTS is identified and no mutilating limb-sparing surgical excision is feasible, resection should be completed. If margins are microscopically positive, postoperative radiotherapy should be given in high-grade tumors and tumors larger than 5 cm. Low-grade tumors that are less than 5 cm can be reexcised or just watched closely. If surgical excision is not feasible without amputation or severe morbidity, whether less than or greater than 5 cm, preoperative chemotherapy and radiotherapy should be administered. If surgical excision is feasible, but R1 resection is anticipated, the type of radiotherapy, whether

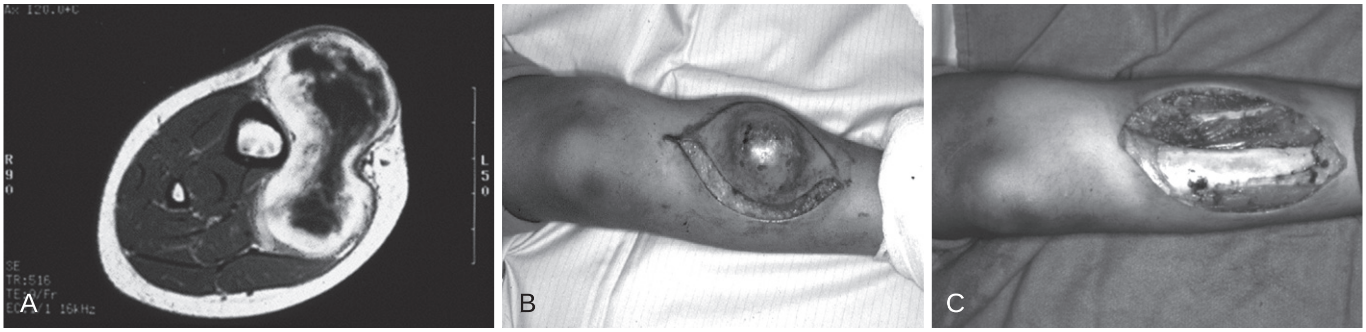


**FIGURE 36-1** **A-C**, Magnetic resonance (MR) image of a child with synovial sarcoma abutting the tibia. Neoadjuvant chemotherapy was not successful in reducing the size of the tumor. Marginal resection with postoperative radiation or brachytherapy is a preferred alternative to amputation.

preoperative or postoperative brachytherapy, proton beam therapy, or external beam therapy, should be discussed with the radiation oncologist, with the goal in pediatric extremity tumors to avoid the growth plate in younger patients who are still growing. In tumors less than 5 cm, complete surgical excision with negative microscopic margins is the goal. In the case of unexpected malignant pathology, primary reexcision is recommended. For all NRSTSs, negative microscopic margins should be achieved; however, there is no consistent reliable evidence to establish the appropriate width of the margins.

NRSTSs are graded histologically to help predict outcome. Grade 1 is any NRSTS with low malignant potential, such as infantile fibrosarcoma, with mitotic activity less than 5 mitoses per high-powered field (HPF). NRSTSs with tumor necrosis less than 15% and mitotic activity of 5 to 10 mitoses per HPF are graded 2, and specific histologic subtypes with known aggressive behavior and/or any sarcoma with tumor necrosis of more than 15% or mitotic activity of more than 10 mitoses per HPF are graded 3.[28]

Cytotoxic chemotherapy (Adriamycin, ifosfamide, vincristine, dactinomycin, etc.), will be effective, at best, in 45% to 50% of patients from the evidence we have to date.[4] (This does not include targeted therapy, because there are not yet sufficient data to analyze at this time.) Very close observation by imaging is warranted if neoadjuvant chemotherapy is chosen, because an increase in tumor size may preclude limb-sparing, nonmutilating surgery, and an abdominal or pelvic tumor may become unresectable.

Sentinel lymph node biopsy, although recommended for rhabdomyosarcoma to evaluate normal-appearing lymph nodes, is only recommended in histologic subtypes of NRSTS that have high risk of lymph node metastasis. These include epithelioid sarcoma and clear cell sarcoma, which have an approximate incidence of lymph node metastasis of up to 30%. Synovial sarcoma metastasizes to the lymph nodes about 15% of the time.

Computed tomography (CT) scan of the chest is a necessary part of the workup to exclude lung metastasis. Lung metastasis occurs in approximately 30% of patients with NRSTS. Because NRSTSs are relatively chemoinsensitive, surgical resection of lung metastasis is recommended. Thoracotomy is the recommended approach in order to palpate the lung for any tumors that may have been missed on imaging.

## Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is a malignant neoplasm in the soft tissue sarcoma family that arises from the peritoneal surface of the abdomen and pelvis. No more than 200 cases have been reported worldwide since the disease was first described in 1989 by Gerald and Rosai[29] and Ordonez.[30] The tumor is most prevalent in young white males.[29–30] Presenting symptoms include abdominal pain, constipation, and abdominal distension with ascites. Overall survival is approximately 30% to 55% despite chemotherapy, radiotherapy, and aggressive surgical resection.[31,32] Because most DSRCT patients present with multiple abdominal tumor implants (Fig. 36-2), microscopic tumor cells can be left behind, despite the complete resection of dozens to hundreds of tumors. The most widely accepted standard of care for DSRCTwas multimodality therapy with the P6 regimen: cyclophosphamide, doxorubicin, and vincristine, alternating with ifosfamide and etoposide for seven total courses,[31] followed by aggressive debulking surgery to remove all visible disease.[32] It is clear that without complete resection of all visible disease survival is poor.[32] Hyperthermic intraperitoneal chemotherapy (HIPEC) is a new therapeutic modality recently used in children; its results are promising, but studies are ongoing. Hyperthermia and chemotherapy have synergistic cytotoxicity that is of value in the treatment of microscopic disease in adult carcinomas. HIPEC has been applied successfully in adults with extensive peritoneal disease, commonly observed with mesothelioma, appendiceal, colon, and gastric carcinoma.[33–37] A recent publication shows that DSRCT can now be treated safely with aggressive cytoreductive surgery followed by (HIPEC) in children.[38] The study included 23 pediatric adolescent and young adult patients with DSRCT. HIPEC was compared with standard chemotherapy, radiation therapy, and surgical debulking. The patients were mostly males (96%). The age of the HIPEC patients ranged from 5 to 25 years of age. Complete resection (CR0) to less than 1.0-cm tumor size was achieved in all 8 patients who underwent HIPEC. Operative times ranged from 7 to 16 hours. Figure 36-3 shows the setup used in the operating room to deliver HIPEC. In the pediatric patients, the estimated 12-month disease-free survival (DFS) rate was 53% for the HIPEC group, compared with 14% for the non-HIPEC group. Median 3-year survival in this small group of patients was 29% with chemotherapy and radiotherapy alone, compared with 71% in the HIPEC with cytoreductive surgery group. The severe morbidities that occurred were partial bowel obstruction managed nonoperatively, prolonged ileus/gastroparesis, transient renal insufficiency, and one patient developed cardiomyopathy secondary to resection of more than 3 kg of tumor, causing release of tumor necrosis factor. HIPEC is an option in treating this rare tumor.[38]

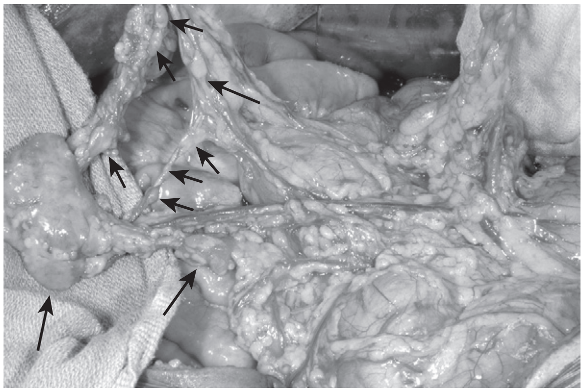

**FIGURE 36-2** Desmoplastic small round cell tumor in the omentum of a 5-year-old boy after six cycles of chemotherapy. Peritoneal disease has similar appearance. This child had 402 nodules removed at this operation.

## Desmoid Tumors

Desmoid tumors are very different than DSRCT. These are intermediate-grade sarcoma-type tumors that are locally very aggressive and can be fatal, but usually do not metastasize. Desmoid fibromatosis is a mesenchymal neoplasm. It is encountered

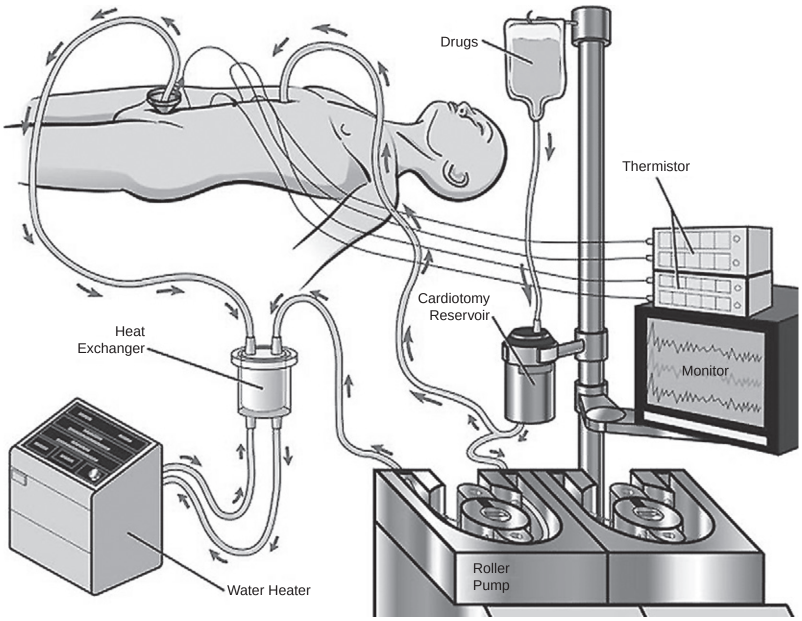


**FIGURE 36-3** Setup for hyperthermic intraperitoneal chemotherapy (HIPEC) therapy for children with "sarcomatosis" after cytoreductive surgery.

in two settings—within the context of familial adenomatous polyposis (FAP) and sporadically.[39] Here we focus on the sporadic group. Desmoid tumors can arise in any body site and are much more common in women. Surgery has been the therapeutic mainstay, but radiotherapy plays an important role in treatment as do systemic therapies, such as the tamoxifen and sulindac combination and nonsteriodal anti-inflammatory drugs (NSAIDs).[40–46] Desmoids have a very unique course in that they can recur locally and can be more aggressive or regress spontaneously. However, they have no capacity for metastasis.[39] Resecting recurrent tumors can be potentially mutilating. Some large retrospective studies[42,47,48] demonstrated that microscopically positive (or grossly positive) margins were predictive of increased frequency of local recurrence on retrospective multivariate analysis, although radiation improved outcome in one study. Other studies[40,49–51] have failed to demonstrate an effect of microscopic margin on recurrence. Some of these differences may result from the mixture of disease sites, pattern of application of adjuvant radiotherapy, and selection of patients treated by surgical approach. In the end, surgical therapy must be tailored to what is achievable in terms of margins with preservation of functional status for the individual patient.[39] Incomplete resection or positive microscopic margins in desmoid tumors should be treated with adjuvant radiotherapy. Figure 36-4 provides a helpful algorithm to follow.

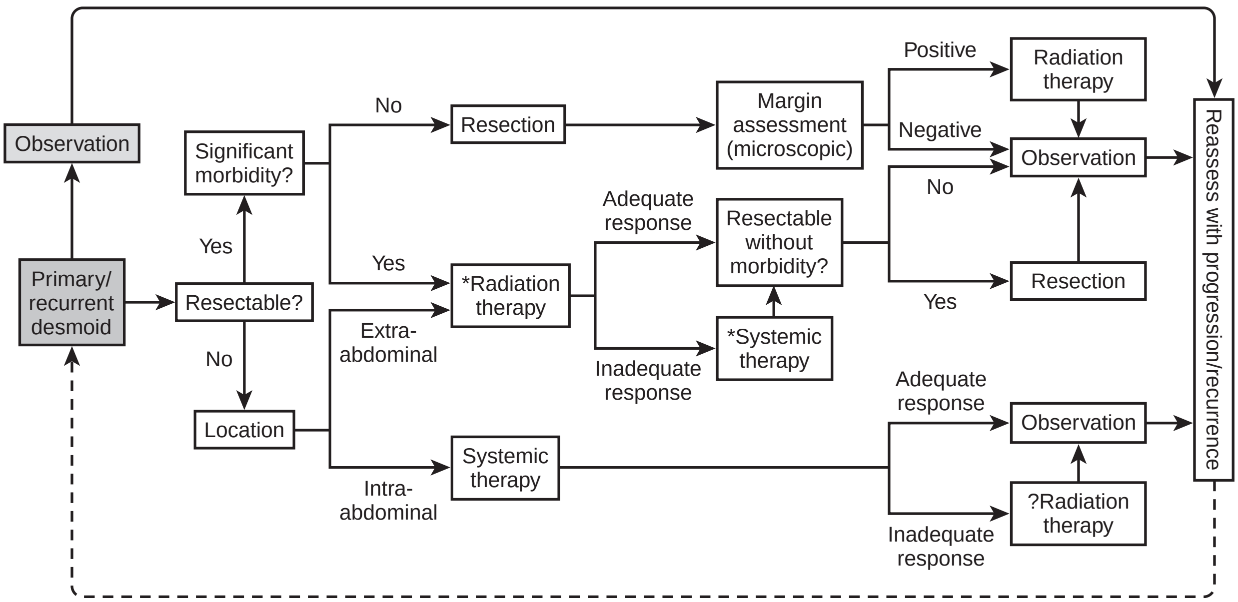


**FIGURE 36-4** General treatment protocol for desmoid tumors at the University of Texas M.D. Anderson Cancer Center. The route of initial observation for certain cases, to avoid overtreatment advocated by some, is depicted in *gray*. Given the propensity for progression on treatment and local recurrence, all treatment pathways ultimately end in observation. *Radiation therapy can be preceded, and even precluded, by systemic therapy in certain cases of initially unresectable extraabdominal desmoid tumors.

## Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a relatively common soft tissue tumor. Its peak age is in young adulthood, but it is frequently present in children and at birth. DFSP occurs primarily on the trunk and extremities. It can present as a plaque on the skin or in a more diffuse multinodular pattern.[52,53] The latter is more common in children. Pigmented dermatofibrosarcoma, giant cell fibroblastoma, and fibrosarcoma can arise in DFSP.[54,55]

Dermatofibrosarcoma protuberans has a reciprocal translocation, t(17;22)(q22;q13.1), resulting in fusion of the genes *COL1A* (encoding the alpha 1 chain of collagen type 1, a heterotrimer) on 17q21-22 and *PDGFB1* (encoding the beta chain of platelet-derived growth factor, a homodimer) at 22q13.[55,56] The same fusion is also seen in supernumerary ring chromosomes derived from t(17;22),[57] which are found in adult cases of dermatofibrosarcoma. Fusion gene transcripts can be detected by reverse transcriptase–polymerase chain reaction (RT-PCR).[53,58] This is not usually required for diagnosis but might be useful in guiding therapy, especially for superficial fibrosarcomas.

Dermatofibrosarcoma protuberans has a high local recurrence rate, especially if incompletely excised, and can metastasize in 5% of cases, usually after multiple local recurrences. Therefore complete excision with negative margins is crucial, and 2- to 3-cm margins are recommended. However, in areas such as the head and neck, lesser margins are acceptable.

Platelet-derived growth factor receptor (PDGFR) is a receptor tyrosine kinase, which in dermatofibrosarcoma protuberans is constitutively activated by autocrine or paracrine mechanisms as a result of overproduction of its ligand platelet-derived growth factor-beta (PDGFB),[59] leading to cellular proliferation.[60] This has suggested the use of the tyrosine kinase inhibitors imatinib[61] and, more recently, sunitinib or sorafenib in locally advanced or metastatic disease,[62–63] but fibrosarcomatous variants without the translocation do not respond[64,65] so that genetic analysis is indicated before targeted therapy. In the only multicenter Phase 2 study published to date, imatinib was found to be effective preoperative therapy in 36% of patients ($n = 25$) by reducing tumor size by an average of 20%. Response was measured by physical exam, ultrasonography, and MRI. Decrease in average diameter by 1 cm on physical exam, 1 cm by ultrasonography, and 2 cm by MRI were observed, respectively. In 21 of 25 patients, the fusion gene *COL1A1-PDGFB* was detected. Therefore when DFSP is located in places where a decrease in size provides a significant advantage in wound closure, neoadjuvant imatinib is a viable option.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 37

# Teratomas and Other Germ Cell Tumors

Frederick J. Rescorla

Pediatric germ cell tumors are rare tumors that are unique due to their varied clinical presentation and locations. Approximately 20% of pediatric germ cell tumors are malignant, and they represent 1% to 3% of all malignant tumors in childhood and adolescence.[1,2] Three features distinguish these childhood tumors from many other malignancies as well as their counterparts: In children, the extragonadal tumor site is more common than the gonadal site, whereas in adults, only 10% are at extragonadal sites; yolk sac tumor is the predominant malignant histology, and a serum marker (alpha fetoprotein, AFP) exists to follow response to therapy and monitor for recurrent disease; and the introduction of modern chemotherapy with cisplatin and bleomycin significantly increased survival for affected children and has allowed neoadjuvant therapy with vital organ preservation in initially unresectable cases.

Abnormal or arrested migration of primordial germ cells results in deposition of cells in the sacrococcygeal region, retroperitoneum, mediastinum, and pineal gland of the brain, resulting in the potential of extragonadal germ cell tumors at these sites. Whereas in adults 90% of germ cell tumors are at gonadal locations, in childhood, the extragonadal site is more common until puberty, at which time the gonadal sites are more common. The totipotential nature of these cells results in a wide variety of histologic patterns, and in addition, one quarter of pediatric tumors have more than one histologic component.[2] The management of these tumors is dependent upon complete surgical resection at diagnosis or after neoadjuvant therapy, accurate and thorough histologic examination, and selective use of chemotherapy. Prior to the late 1970s, the survival of advanced-stage tumors was dismal; however, Einhorn's introduction of cisplatin, vinblastine, and bleomycin for disseminated testicular cancer in 1977 changed the treatment of all germ cell tumors with dramatic results.[3] Subsequent studies validated the use of chemotherapy in a neoadjuvant fashion, thus allowing vital organ preservation in advanced cases with frequent massive tumor shrinkage. The role of the surgeon in determining resectability and performing a proper staging operation is vital.

Current therapy within the Children's Oncology Group (COG) is risk based: with surgery alone for stage 1 testes and ovary tumors and all immature teratomas, with anticipated survival of 95% to 100%; surgery and chemotherapy for all remaining gonadal tumors (except stage IV ovary) and low-stage (I-II) extragonadal, with anticipated survival of 90% to 100%; and surgery and intensive chemotherapy for high-risk (stage III-IV) extragonadal and stage IV ovary, with survival between 75% and 90%, depending on site and stage.

## Embryology and Classification

Primordial germ cells arise near the allantois of the embryonic yolk sac endoderm and are evident at the fourth fetal week. They migrate along the midline dorsal mesentery to the genital ridge, arriving by the end of the sixth fetal week. The migration of the germ cells appears to be mediated by the c-KIT receptor and stem cell factor; the latter is expressed in increasing levels from the yolk sac to the genital ridge.[4,5] Arrested migration is presumed to account for the extragonadal locations in the normal path of the germ cells (retroperitoneum), whereas aberrant migration results in cells at other extragonadal sites (pineal, sacrococcygeal).

### CLASSIFICATION

Teilum[6] proposed the germ cell origin of gonadal tumors, and the pathway of differentiation is listed in Figure 37-1. Seminoma (or dysgerminoma) is a primitive germ cell tumor that lacks the ability for further differentiation. It is unusual in childhood and occurs most frequently in the mediastinum, pineal gland, and at the gonadal sites during the adolescent years. Embryonal carcinoma is composed of cells capable of further differentiation into embryonic or extraembryonic tumors. Teratomas are the most common germ cell tumor and are composed of elements from one or more of the embryonic germ layers and contain tissue foreign to the anatomic site of origin.[7,8]

Mature and immature teratomas are considered benign lesions. It is, however, imperative to have a thorough and accurate pathologic review, because 25% of germ cell tumors in childhood are mixed tumors with more than one histologic

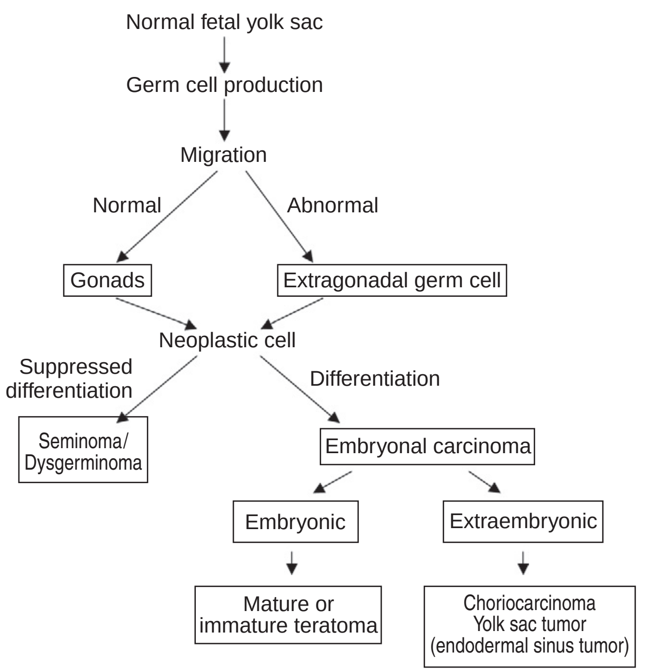


**FIGURE 37-1** Classification system for development of germ cell tumors.

component.[2] Certain sites are more likely to have mixed tumor histology, with ovary (46%) and mediastinal (61%) the most common.[9,10] Mature teratomas contain well-differentiated tissue, whereas immature teratomas contain neuroectoderm and are graded between 1 and 3 based on the number of low-power fields of primitive neuroepithelium.[11] There has been debate about the treatment of immature teratomas. Many adult reports of ovarian tumors have considered grade 3 lesions malignant, and these patients have been treated with chemotherapy. A review of childhood immature teratomas demonstrated an association between high-grade immaturity and the presence of microscopic foci of endodermal sinus tumor,[12] with malignant foci observed in 83% of grade 3 immature teratomas as the only risk factor for recurrence.[13]

Yolk sac tumors (endodermal sinus) and choriocarcinoma are well-differentiated, highly malignant tumors. Yolk sac is the more common histology in childhood and occurs primarily in the sacrococcygeal region, ovary, and prepubertal testes.

# Genetics and Risk Factors

Germ cell tumors demonstrate a bimodal age distribution with peaks at 2 and 20 years of age. Pediatric germ cell tumors differ in several aspects from their adult counterparts. Pediatric yolk sac tumors are more likely to have DNA ploidy, whereas adolescent and adult germ cell tumors are usually aneuploid.[14] In children younger than 4 years of age, the primary malignant germ cell tumor is yolk sac, and these are diploid or tetraploid; the teratomas are diploid with normal karyotypes and are benign.[15–17] Childhood yolk sac tumors have also demonstrated deletion of chromosomes 1p and 6q in 50% of specimens.[18] In addition, a smaller percentage demonstrates amplification of c-*MYC*. The isochromosome i (12p), which is identified in most pubertal or postpubertal testes tumors, is not observed in prepubertal tumors. Gains of 12p have been noted in malignant ovarian germ cell tumors but not in ovarian immature teratomas.[19]

The presence of intersex disorders is a known risk factor for gonadoblastoma, an in-situ germ cell tumor with the ability to differentiate into dysgerminoma, immature teratoma, yolk sac tumor, or choriocarcinoma.[20] One risk group includes testosterone deficiency, androgen insensitivity syndromes, and 5-alpha-reductase deficiency, which are androgen-deficient males. The presence of any portion of a Y chromosome is considered a risk factor in these children.[21] Risk of malignancy in androgen insensitivity is 3.6% at age 20 and 22% at age 30[22]; in view of this, gonadectomy usually in adolescence, is recommended. Gonadal dysgenesis is associated with a risk of malignancy of 10% at age 20 and 19% at age 30.

Undescended testes have an increased risk of malignancy, with the rate highest for intraabdominal testes. Approximately 0.4% of all males have undescended testes, however, it is observed in 3.5 to 12% of the testicular cancer population.[23] One study noted that although intraabdominal testes only account for 14% of undescended testes, they account for nearly 50% of tumors in the undescended testes group. The effect of orchiopexy on the risk of testes cancer is not known, and 20% of the tumors in patients with undescended testis occur in the descended testis.[24] Seminomas occur in a higher percentage of undescended testes (60%) compared with the descended testes tumors (30% to 40%),[25] and one study observed that orchiopexy decreases the incidence of seminoma.[26] The early identification of these children is important, because a recent report noted a 2-year-old boy with a large yolk sac tumor in an intraabdominal testis with lymph node involvement.[27] Surgery and chemotherapy yielded a successful outcome.

# Risk-Based Therapy

The survival of patients with advanced-stage germ cell tumors was poor prior to the introduction of modern chemotherapy, with most survivors having had low-stage surgically excised tumors. Surgery and chemotherapy consisting of vincristine, actinomycin, cyclophosphamide, and doxorubicin was the primary therapy in the 1960s and 1970s.[28] In 1975, Samuels and colleagues[29] introduced bleomycin with vinblastine for advanced-stage testicular tumors, and in 1977, Einhorn and Donohue[3] reported success with cisplatin, vinblastine, and bleomycin in disseminated testicular cancer. This therapy dramatically transformed the treatment of germ cell tumors. Even after the introduction of cisplatin-based regimens, the early results in children were poor. A report from the Children's Cancer Group (CCG) of children treated between 1978 and 1984, using cisplatin and bleomycin alternating with other agents (cyclophosphamide, dactinomycin, and doxorubicin), reported 4-year survival and event-free survival (EFS) of 54% and 49%, respectively, with ovarian tumors higher at 67% and 63%, respectively, and extragonadal tumors at 48% and 42%, respectively.[30] The lower survival in the early study may have been due to the inclusion of less effective chemotherapy that lengthened the intervals between the courses of the more effective cisplatin and bleomycin.

The subsequent CCG/Pediatric Oncology Group (POG) intergroup studies conducted between 1990 and 1996 used only cisplatin, etoposide, and bleomycin (PEB). The overall 6-year survival was 95.7% for stage I and II ovarian and

testes and 88.9% for stage III-IV gonadal and stage I-IV extragonadal.[31–33] The higher-risk group (stage III-IV gonadal and stage I-IV extragonadal) were stratified to either standard or high-dose cisplatin, and the overall survival was not different between the groups, but the toxicity was higher with the high-dose cisplatin, and it has therefore not been incorporated in the current study.

Based on these past studies, the current COG protocol for malignant germ cell tumors is risk based (Fig. 37-2). The overall goal is to maintain the excellent survival from the past intergroup study while decreasing the toxicity of the chemotherapy. Mature teratoma is considered to be a benign lesion, and these tumors are not entered on the current protocol. Immature teratomas at all sites are treated with surgery and observation. The 3-year survival for immature teratomas on the last study was 93% among 73 patients with immature teratoma, and four of the five recurrences were salvaged with platinum-based chemotherapy.[13,34] Stage I ovarian and testes tumors are treated with surgery and observation, although this portion of the protocol is currently suspended (see Ovary section). Stage II-III ovary and stage II-IV testes currently receive three cycles of PEB administered during 3 days compared with four cycles during 5 days on the prior study, thus resulting in significantly less total chemotherapy. Higher-risk tumors (stage IV ovary and stage III-IV extragonadal), are currently not a part of a protocol but would received PEB.

# Testes

## CLINICAL PRESENTATION AND INITIAL EVALUATION

Testicular germ cell tumors in children are one of the rarer germ cell tumor types, with an incidence of 0.5 to 2.0 per 100,000.[35] The bimodal age distribution of testes tumors, with a small peak in the first 3 years of life and a much larger peak in young adults, suggests a difference in the tumors of these age groups. The malignant germ cell tumors in the younger group are predominantly yolk sac tumors, whereas most adolescent and adult testes tumors are seminomas and mixed tumors. Several other factors provide evidence of differences between pediatric and adult testes tumors. Intratubular germ cell neoplasia (ITGCN), which is a carcinoma in situ, is commonly identified in adults with malignant germ cell tumors but does not occur in association with prepubertal yolk sac tumor. Adult testes tumors usually have a chromosomal gain of the short arm of chromosome 12p (isochromosome 12p), whereas this is not seen in prepubertal yolk sac tumors.

Testicular tumors are rare in boys prior to puberty, and during this time non–germ cell Sertoli tumors and paratesticular rhabdomyosarcomas are more common, whereas germ cell tumors predominate in pubertal and adult males. Paratesticular neuroblastoma has also been reported arising from an embryonic adrenal rest along the spermatic cord.[36,37] Although it is difficult to determine the incidence of malignancy in prepubertal testes tumors, several reports would suggest that it is less common than in adults. In one large series,[38] 74% of all tumors were benign, with teratoma accounting for 48% and yolk sac tumors only 5%. This has affected the initial surgical evaluation of these children in order to avoid unnecessary radical orchiectomy.

| | |
|---|---|
| **Low risk** | |
| Stage 1 ovary | |
| Stage 1 testes | Surgery alone |
| Immature teratoma | COG, AGCT 0132 |
| **Intermediate risk** | |
| Stage II–III ovary | |
| Stage II–IV testes | Surgery and |
| | Chemo-PEB x 3 |
| Stage I–II extragonadal | COG, AGCT 132 |
| **High risk** | |
| Stage III–IV extragonadal | Surgery and |
| Stage IV ovary | PEB |

FIGURE 37-2 Low- and intermediate-risk–based scheme for pediatric germ cell tumors. Children's Oncology Group AGCT 0132, opened November 2003.

Most testicular tumors present as a painless scrotal mass. In the intergroup CCG/POG study (1990 to 1996)[31] of malignant testes tumors, 76% of the stage 1 boys presented with a testicular mass and 17% with generalized scrotal swelling. The preoperative diagnosis was tumor in 79%, hydrocele in 11%, hernia in 3%, and acute scrotum or torsion in 3%.

Preoperative workup includes a thorough physical examination, looking for signs of androgenization as well as metastatic disease. Metastatic disease is relatively uncommon in prepubertal testes cancer, but if present, is usually in the retroperitoneum or chest. Testicular ultrasonography is useful to identify extratesticular lesions and may be useful to identify or raise the suspicion of a teratoma. Benign testes tumors tend to be well circumscribed with sharp borders and decreased blood flow on Doppler studies.[39] Preoperative AFP levels should be obtained, and this level was elevated in 98% of the children with malignant tumors in the most recent study.[31] If the preoperative diagnosis is a testicular malignancy (elevated AFP), it is reasonable to obtain an abdominal computed tomography (CT) scan, because the presence of enlarged nodes after an inguinal exploration can be due to either a reactive or malignant process.

## OPERATIVE MANAGEMENT

The standard approach consists of an inguinal incision, with initial control of the vessels at the level of the internal inguinal ring with subsequent mobilization of the testes. A preoperative elevation of AFP indicates the presence of yolk sac tumor and thus precludes consideration of testes-sparing surgery, and a radical orchiectomy is performed with ligation of the cord at the internal ring. If the AFP is normal, there is a much greater chance that the mass represents a benign lesion, and in these instances, the field can be draped off and the tunica opened. Enucleation is often possible, leaving a large amount of residual normal testes.[40] If frozen section analysis reveals a benign lesion, the tunica is closed, and if malignant, an orchiectomy is completed. Unfortunately, this is not always possible, and in a recent review from the U.K. Children's Cancer Group, 48 of 53 boys with mature or immature teratoma had radical orchiectomy.[41] There were no recurrences in the five treated with enucleation. Bilateral testes-sparing surgery

| Stage | Extent of disease |
|---|---|
| I | Limited to testis (testes), completely resected by high inguinal orchiectomy; no clinical, radiographic or histologic evidence of disease beyond the testes. |
| II | Transscrotal biopsy; microscopic disease in scrotum or high in spermatic cord (<5 cm from proximal end). Tumor markers fail to normalize or decrease with an appropriate half-life. |
| III | Retroperitoneal lymph node involvement, but no visceral or extraabdominal involvement. Lymph nodes > 4 cm by CT; or > 2 cm and < 4 cm with biopsy proof. |
| IV | Distant metastases, including liver. |

**FIGURE 37-3** Current Children's Oncology Group staging system for childhood testes cancer.

has been reported for testes teratoma.[42] A more recent report noted no atrophy or recurrence with enucleation in a large group of benign testes tumors.[43]

## POSTSURGICAL TREATMENT

Testicular teratomas are benign lesions and are treated with enucleation, if possible, and then postoperative observation. Testicular immature teratomas are also benign germ cell tumors, and surgery alone (enucleation if possible) is definitive treatment. Higher-grade immature teratomas are, however, associated with yolk sac tumors. In a (CCG/POG) review, grade 1 and 2 immature teratomas were not associated with yolk sac tumors, whereas 2 of 3 grade 3 lesions were associated with yolk sac tumors.[13]

Yolk sac tumor is the primary malignant prepubertal testes cancer. The current staging is noted in Fig. 37-3. The role of surgery alone for stage I testes tumors was reported in the 1980s[44] and confirmed in an initial small series.[45] The U.K. Children's Cancer Study Group[46] and the Testicular Tumor Registry of the Section of Urology of the American Academy of Pediatrics,[47] in larger series (73 and 181 children, respectively), confirmed the safety of surgery alone for stage I malignant testes tumors.

The intergroup trial of testes cancer (CCG/POG; 1990–1996)[31] confirmed the excellent outcome with stage 1 testes tumors treated with surgery alone (Table 37-1). This study of 63 boys (median age 16 months) reported AFP elevation in 98%. In patients with the preoperative diagnosis of tumor, the surgical guidelines were followed in 84% of boys but were followed in only 27% with a nontumor diagnosis. Although overall adherence to surgical guidelines did not affect outcome, scrotal violation was associated with a 75% recurrence rate compared with 15.5% in those without scrotal violation. All recurrences were successfully treated with surgery and chemotherapy.

Stage 2 boys on the CCG/POG study included only 17 patients, and 11 were stage II because of a transcrotal procedure.[32] Survival was excellent (see Table 37-1) with surgery and chemotherapy. Higher-stage 3 and 4 boys received surgery and were then randomized to standard or high-dose cisplatin, both with etoposide and bleomycin.[33] Sixteen were recurrences from stage 1 disease (median age 3.1 years), and the rest were newly diagnosed and much older (median age 16 years). Despite the advanced disease, outcome was

**TABLE 37-1**
**Survival for Testes Cancer, POG/CCG 9048/8891; 9049/8882, 1990-1996**

| *Stage* | N | *Treatment* | *6-Year EFS (%)* | *6-Year Survival (%)* |
|---|---|---|---|---|
| I | 63 S | 78.5 | 100 | |
| II | 17 | S + PEB × 4 | 100 | 100 |
| III | 17 | S + HDP/EB vs. PEB | 94.1 | 100 |
| IV | 43 | S + HDP/EB vs. PEB | 88.3 | 90.6 |

CCG, Children's Cancer Group; EB, etoposide and bleomycin chemotherapy; EFS, event-free survival; HDP, high-dose platinum chemotherapy; PEB, platinum, etoposide, and bleomycin chemotherapy; POG, Pediatric Oncology Group; S, surgery.

excellent (see Table 37-1). The toxicity with high-dose cisplatin was significant without added benefit, and it has therefore been eliminated from current protocols.

The current protocol of the Children's Oncology Group is designed to reduce the total dose and days of chemotherapy (Fig. 37-2). As noted in the staging, if the retroperitoneal nodes are greater than 4 cm in size, it is assumed to be due to tumor, whereas nodes between 2 and 4 cm require biopsy to confirm status. There is no role for retroperitoneal lymph node dissection in prepubertal yolk sac tumors at diagnosis and simple biopsy is adequate.

# Ovary

## CLINICAL PRESENTATION AND EVALUATION

Ovarian tumors are the most common site for germ cell tumors in children and adolescents. Eighty to 90% percent of all ovarian masses are benign (epithelial cyst, mature teratoma), often with predominant cystic components.[10,48] Presenting symptoms often include pain and gradual onset of lower abdominal fullness. Approximately 10% present with an acute abdomen secondary to torsion or tumor rupture.[10] Of all girls presenting with ovarian torsion, only 1.8% to 3% are malignant tumors; however, 33% are benign tumors, including teratoma and cystadenoma.[48]

In nonacute cases, preoperative evaluation should include assessment of AFP and beta-HCG, as well as ultrasonography and usually abdominal and pelvic CT scan. Unfortunately, reliable tumor markers are absent in many tumors. Germinoma is present in one third of malignant tumors, and they have normal markers or mild elevation of beta-HCG, and embryonal carcinomas have normal markers.[2] Benign lesions are primarily cystic, and a 2% risk of malignancy in cystic lesions is frequently quoted based on adult series.[49–51] This, however, is also unreliable, because in the recent intergroup study from the Children's Oncology Group (COG), 57% of malignant tumors had cystic components.[10] A recent study attempting to identify risk factors noted that markers were elevated in only 54% of malignant tumors. The best predictors were a mass with solid characteristics and a mass greater than 8 cm in diameter.[52] They also noted as, in other series, that girls between 1 and 8 years have the greatest incidence of malignancy. In view of these observations, great care should be taken to perform a proper staging operation with lesions with solid components.

1. Collect ascites or peritoneal washings for cytology
2. Examine peritoneal surface and liver; excise suspicious lesions
3. Unilateral oophorectomy
4. Examine contralateral ovary and biopsy if suspicious lesion
5. Examine omentum and remove if adherent or involved
6. Inspection of retroperitoneal lymph nodes, biopsy of enlarged nodes

**FIGURE 37-4** Operative procedure for malignant ovarian germ cell tumor.

**Stage I:** Limited to ovary (ovaries) peritoneal washings negative; tumor markers normal after appropriate half-life decline (AFP 5 days, HCG 16 hours).

**Stage II:** Microscopic residual; peritoneal washings negative for malignant cells, tumor markers positive or negative.

**Stage III:** Lymph node involvement; gross residual or biopsy only; contiguous visceral involvement (omentum, intestine, bladder); peritoneal washings positive for malignant cells; tumor markers positive or negative.

**Stage IV:** Distant metastases, including liver.

**FIGURE 37-5** Children's Oncology Group ovarian staging system. AFP, alpha fetoprotein; HCG, human chorionic gonadotropin.

The staging procedure endorsed by COG is listed in Figure 37-4 and the current staging system in Figure 37-5. The importance of an accurate and complete staging procedure and accurate pathologic evaluation cannot be overemphasized. The recent COG intergroup study of 131 girls reported positive ascites/peritoneal fluid in 23 of 100 girls, and 5 of these would have otherwise been stage I tumors.[10] This is particularly relevant, because the current low- and intermediate-risk COG study manages stage I girls with surgery alone.

The survival rates of children in the most recent intergroup study is listed in Table 37-2. The current therapy for ovarian malignant tumors is noted in Figure 37-2. In the most recent study,[33] the results for stage IV ovarian tumors did not allow them to be included in the current low- and intermediate-risk COG study (AGCT 0132) using reduced chemotherapy.

Some tumors are noted with invasion into surrounding structures, and in these cases, recommendations are for initial biopsy, neoadjuvant chemotherapy, and delayed resection. Bilateral ovarian tumors were observed in 8% of girls on the recent study, and 4 of the 11 contralateral tumors were benign teratomas. The current recommendation for bilateral tumors is to attempt ovarian preservation, if possible, on the least involved side, attempting to find a plane of demarcation between the tumor and normal ovarian tissue. The larger tumor should be removed and sent for frozen section. If the first side is malignant and the contralateral side is greater than 10 cm, it should also be removed.

The treatment algorithm for malignant ovarian tumors is surgery and observation for stage I and surgery and chemotherapy for higher-stage tumors (see Fig. 37-2). The surgery-only arm was based on a German and French series of a total of 39 girls with stage I tumors treated with surgery alone who experience a 67% EFS with salvage of 12 of 13 recurrences with chemotherapy for an overall survival of 97.4%.[53,54] The CCG/POG intergroup study noted excellent results in girls with stage I immature teratoma, with microscopic yolk sac tumor

**TABLE 37-2**
**Event-free Survival (EFS) and Survival in Pediatric Ovarian Germ Cell Tumors, POG/COG Intergroup Study 1990-1996**

| *Stage* | N | *Treatment* | *6-Year EFS (%)* | *6-Year Survival (%)* |
|---|---|---|---|---|
| I | 41 | S + PEB | 95 | 95.1 |
| II | 16 | S + PEB | 87.5 | 93.8 |
| III | 58 | S + HDP/EB vs. PEB | 96.6 | 97.3 |
| IV | 16 | S + HDP/EB vs. PEB | 86.7 | 93.3 |

CCG, Children's Cancer Group; EB, etoposide and bleomycin chemotherapy; HDP, high-dose cisplatin chemotherapy; PEB, cisplatin, etoposide, and bleomycin chemotherapy; POG, Pediatric Oncology Group; S, surgery.

treated with surgery alone as well as stage I girls treated with surgery and PEB.[55] The current low-risk arm of the study has been closed because of a higher than expected recurrence rate in stage I ovarian tumors. These girls had a less than 70% three-year EFS, thus leading to suspension of the trial; however, with salvage chemotherapy, they have an overall survival of over 95%.[56]

Laparoscopy has been widely used for ovarian cystic disease, and the application of this for malignant procedures has been controversial. The primary concern is adequate completion of the staging procedure (potential understaging) and avoidance of intraperitoneal spill or tumor rupture, which could upstage a stage I to a stage II tumor. The COG germ cell committee and others[10,57] recommend laparotomy for known malignancy; however, this is difficult to determine preoperatively, although preoperative elevated markers and a large solid mass are very suggestive of malignancy. A recent French study suggested that size greater than 7.5 cm or predominately solid components predicted malignancy and thus required laparotomy.[57]

Most primarily cystic lesions, some of which are large, are benign, and a laparoscopic approach is appropriate. One option to avoid spill is to either excise the cyst, as a cystectomy or oophorectomy, and then place it in a retrieval bag, which is then delivered out of the umbilical opening, allowing decompression of the cyst while in the bag without spill and then removal of the bag and cyst. A second option is to glue a bag to the cyst through a small laparotomy, using one of the adhesives, such as cyanoacrylate, as described by Shozu and colleagues.[58] The cyst is incised by cutting through the center of the bag–cyst interface, allowing removal of the fluid without spill, and the decompressed cyst is then delivered from the abdominal cavity. The cyst can then be separated from the normal ovary as a cystectomy, or if not possible or if there is concern for malignancy, an oophorectomy.

# Sacrococcygeal Tumors

## CLINICAL PRESENTATION AND INITIAL EVALUATION

Tumors of the sacrococcygeal region, referred to as sacrococcygeal teratomas (SCTs) in most reports, generally present in two distinct fashions: neonates with large predominantly external lesions, which are detected in utero or at birth and are rarely malignant (Fig. 37-6); and older infants and children

who present with primarily hidden pelvic tumors with a much higher rate of malignancy (Fig. 37-7). Sacrococcygeal teratomas are the most common extragonadal tumor in neonates, accounting for up to 70% of all teratomas in childhood. A 3 to 4:1 female to male ratio is generally reported.[59] Newborns typically present with a mass protruding from the sacral region, and many are detected with prenatal ultrasonography. Abdominal delivery should be considered if the external mass is greater than 5 cm, to avoid dystocia and rupture.[60] In-utero shunting can lead to fetal hydrops, which is associated with high mortality. Adzick and colleagues[61] performed the first successful fetal resection in a fetus that developed placentomegaly and polyhydramnios and, at 25 weeks, underwent

FIGURE 37-6 A newborn with a large ruptured sacrococcygeal teratoma.

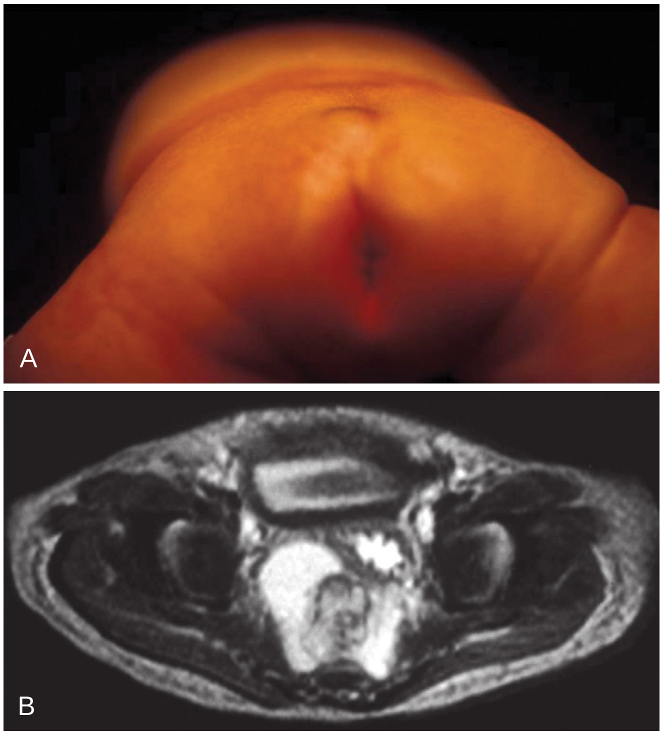


FIGURE 37-7 **A,** Three-month-old boy with a small external mass noted since birth. **B,** Underlying presacral mass noted on magnetic resonance imaging.

fetal resection of a 400-g immature teratoma. After delivery at 29 weeks, the child underwent exploration, with no residual tumor identified.

Makin and colleagues[62] reported a 77% survival among 41 antenatally diagnosed SCTs but noted survival of 50% in those undergoing fetal interventions and survival of only 14% if the intervention was for hydrops. Intervention included nonresection procedures, such as cyst drainage, laser ablation, or alcohol sclerosis. Another study of prenatally detected lesions noted the highest survival (100%) in lesions less than 10 cm with predominantly cystic tumors, whereas survival was only 48% in tumors greater than 10 cm and in those with increased vascularity, vascular steal syndrome, or rapid growth.[63] This is a difficult group, and the University of California San Francisco experience with fetal resection noted a survival of 20%.[64]

Older infants and children typically present with symptoms related to compression of the bladder or rectum. If a mass has been noted at birth and left in place, an increased rate of malignancy has been noted.[65] AFP levels, which can be normally elevated in newborns, should be obtained and then followed to ensure that they return to normal by 9 months of age. An association of the triad of presacral teratoma, anal stenosis, and sacral defects was first reported by Ashcraft and Holder, who also confirmed the autosomal dominant nature of the condition.[66] Currarino proposed that adhesions between the endoderm and ectoderm form, causing a split notochord that results in this association, and the triad now bears his name.[67]

## CLASSIFICATION AND ASSOCIATION WITH MALIGNANCY

Altman and colleagues[68] developed the classification system of SCTs based on a survey of the Surgical Section of the American Academy of Pediatrics (Fig. 37-8). In this study, the malignancy rate increased with the more hidden (type III and IV) lesions. This survey also noted the low rate of malignancy in neonates and young infants ($\leq$2 months of age, 7% girls and 10% boys have malignant tumors) and the higher rates in older infants and children ($\geq$2 months of age, 48% girls and 67% boys have malignant tumors). Several subsequent studies have confirmed this and noted malignancy rates as high as 90%.[65,69]

## SURGICAL MANAGEMENT

In neonates presenting with large external masses, the degree of pelvic and abdominal involvement should be assessed preoperatively with either ultrasonography, CT, or magnetic resonance imaging (MRI), and these studies may also offer a clue as to the characteristics of the vascular supply. An open or laparoscopic abdominal exploration may be required to mobilize the pelvic portion and to divide the middle sacral artery.

The neonatal type I and II lesions can usually be approached with the child in the prone position (Fig. 37-9). Removal of the coccyx is an essential step, because Gross and colleagues[70] reported a 37% recurrence rate if it was not removed. In view of the anterior displacement caused by the large mass, the rectum is often brought back to a more posterior location at the time of closure. Fishman and colleagues[71] described a buttocks contouring closure bringing

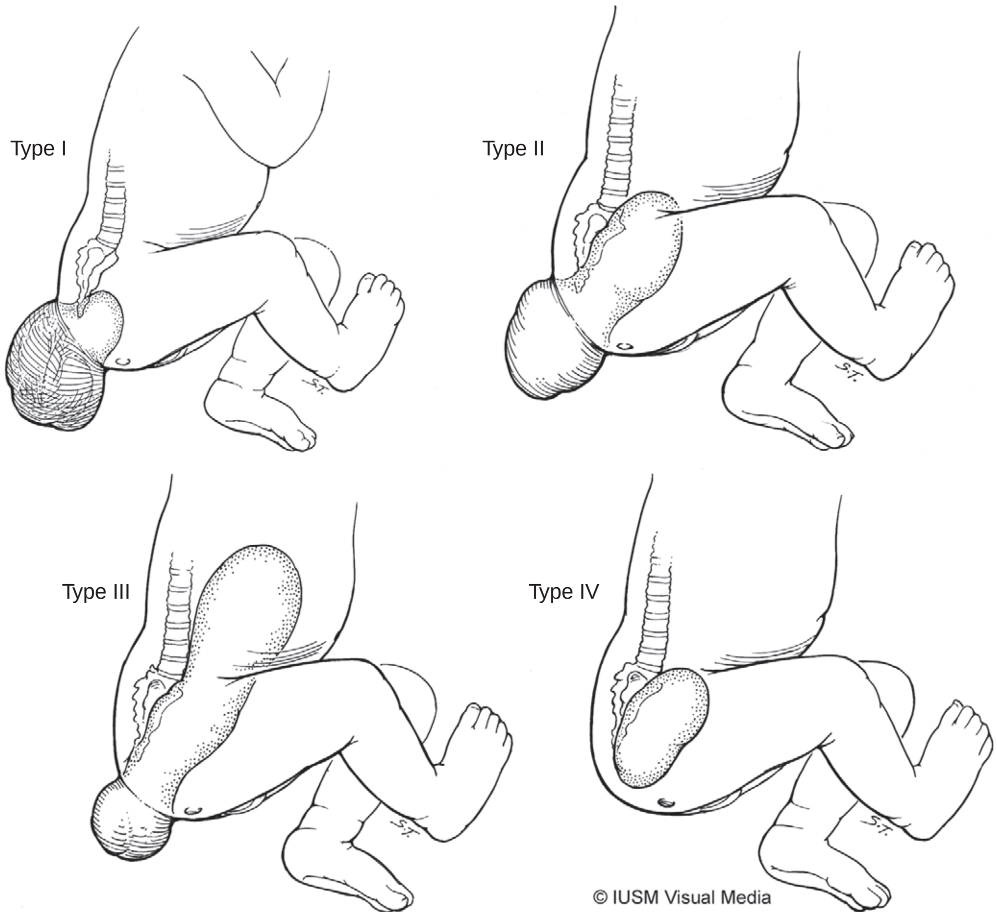


**FIGURE 37-8** Classification of sacrococcygeal teratomas based on Altman's study: Type I (46.7% of reported cases) predominantly external, type II (34.7%) external with intrapelvic extension, type III (8.8%) visible externally but predominantly pelvic and abdominal, type IV (9.8%) entirely presacral. (Adapted from Altman RP, Randolph JG, Lilly JR: Sacrococcygeal teratoma: American Academy of Pediatric Surgical Section Survey—1973. J Pediatr Surg 1974;9:389-398.)

the ventral portion of the lateral flaps to a more central posterior location, thus resulting in a transverse posterior incision and two vertical incisions in the midportion of each buttock. The operative approach in older infants and children is similar; however, due to the presence of malignancy in many of these cases with invasion of adjacent structures or massive size, initial resection is not possible, and an initial biopsy followed by neoadjuvant chemotherapy is the best mode of management (Fig. 37-10). In the CCG/POG Intergroup study, there was no survival difference between initial and delayed rejections, supporting surgical delay in these cases.[72]

## POSTOPERATIVE MANAGEMENT

The staging system for extragonadal tumors is noted in Figure 37-11. Most neonatal tumors are mature or immature teratomas that can be managed by surgery and postoperative observation. Recurrent tumors are noted in 10% to 20% of initially benign tumors, and 50% of these are malignant recurrences.[65,73] The recurrence may be due to a sampling error of the original tumor, incomplete resection of a malignant focus, or transformation of a small benign remnant into a malignant lesion. The large size of the neonatal tumors and frequent cystic components can often result in rupture during resection. Follow-up of these neonates should include serial AFP levels to ensure return to normal by 9 months of age and rectal examination every 3 months until 3 years of age, because the latest reported recurrence has been at 33 months.[65]

The management of the older infants with malignant tumors has been influenced by the chemosensitive nature of these yolk sac tumors. In the intergroup study of 74 infants and children (median age 21 months; 62 girls, 12 boys), 59% had metastatic disease at diagnosis, and the initial procedure was biopsy in 45 patients and resection in 29 patients.[72] All patients received chemotherapy, and postchemotherapy resection was accomplished in all but three patients. Definitive resection required a sacral approach in 63% and a combined abdominal-sacral approach in 35%. The 4-year EFS and survival was 84 ± 6% and 90 ± 4%, respectively, with no significant difference noted between timing of resection or presence of metastatic disease. In view of these results, it is strongly recommended to avoid resection of normal structures at initial exploration.

Long-term follow-up of the newborns and older children is necessary, because neuropathic bladder or bowel abnormalities have been reported in 35% to 41% of survivors.[74,75] A recent report from the U.K. Children's Cancer Group noted that 10 of 95 survivors of sacrococcygeal tumors had a neuropathic bladder, and two had leg weakness.[41] In a large survey of

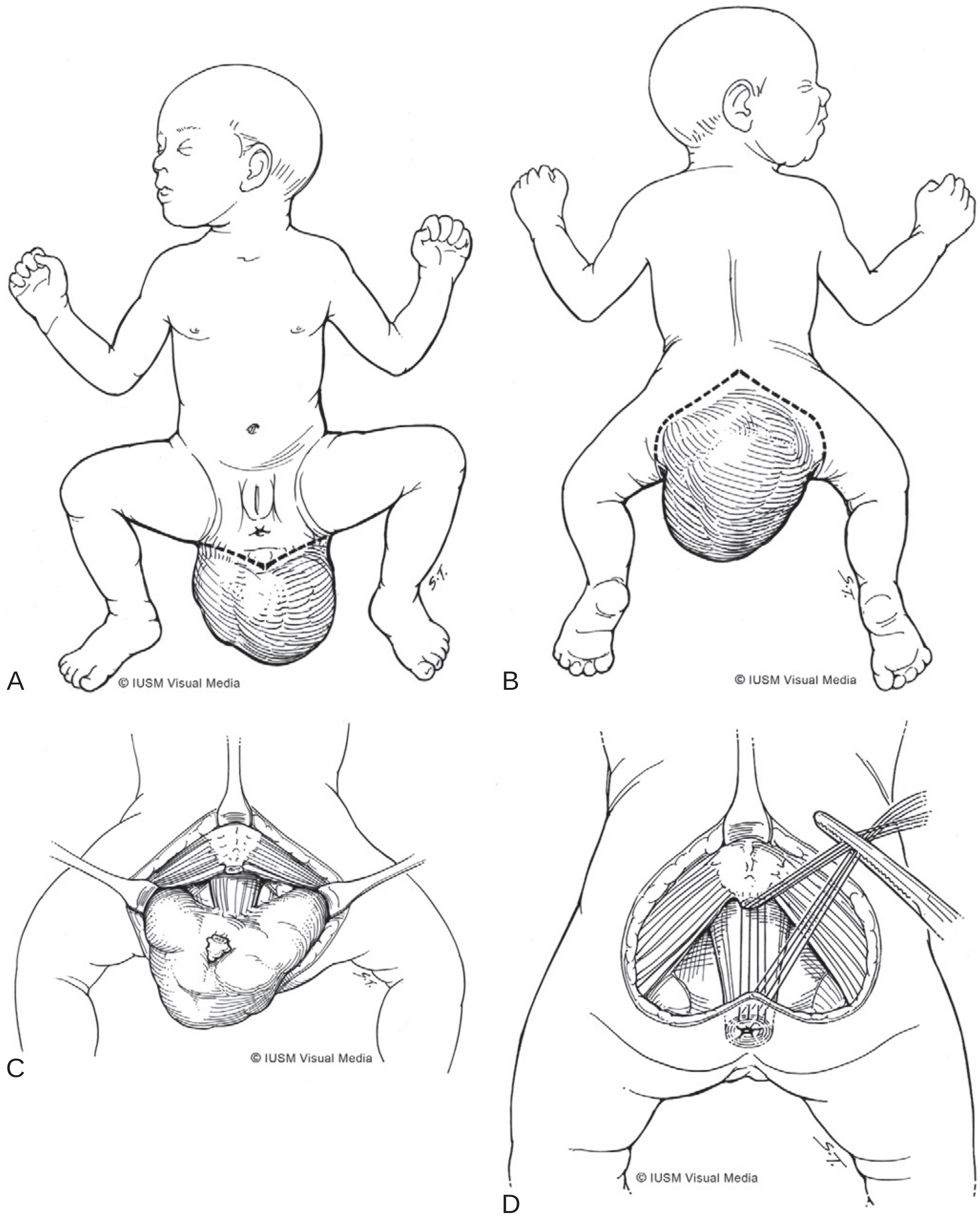


**FIGURE 37-9** **A** and **B,** Operative excision of sacrococcygeal teratoma in a neonate with an inverted-V incision. **C** and **D,** The tumor along with the coccyx is excised with careful preservation of the rectum.

79 patients from the Netherlands, 9.2% reported involuntary bowel movements, 13.2% suffered from soiling, 16% had constipation, and 30% reported difficulty with urinary control,[76] with all of these correlating with decline in their quality of life. Interestingly, the Altman classification of the tumor did not correlate with the occurrence of these long-term complications.

## Mediastinal Germ Cell Tumors

Mediastinal tumors are relatively common in childhood and adolescence and are more common in boys than girls. Germ cell tumors compromise approximately 6% to 18% of mediastinal tumors,[77] and of these, 86% are benign.[78] Mediastinal germ cell tumors are typically located in the anterior mediastinum. Younger children present predominantly with respiratory symptoms. The most common symptoms during adolescence include chest pain, precocious puberty, or facial fullness related to superior vena caval obstruction. Klinefelter's syndrome is also observed in the adolescent group as are hematologic malignancies. The histology of the malignant mediastinal germ cell tumors is more heterogeneous than other sites. In the intergroup study of 38 children, yolk sac was seen in boys less than 5 years of age and in all girls; the older boys had mixed malignant tumors in greater than 50%.[9] Reflective of this, the AFP was elevated in 29 cases and beta-HCG in 16 cases.

Anterior mediastinal tumors pose significant anesthetic risks because of airway compression and may affect the anesthetic from compression as well as the weight of the tumor,

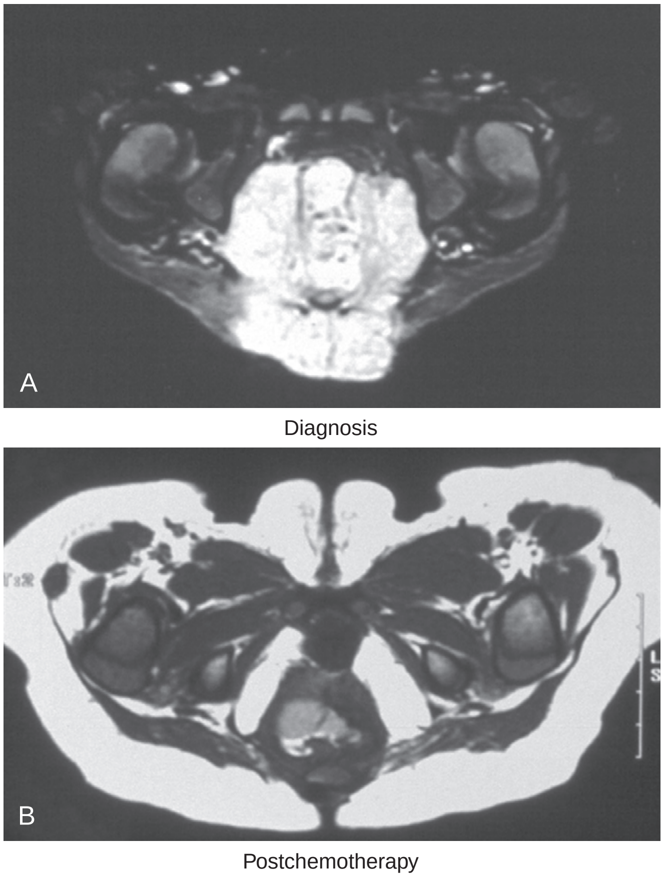


**FIGURE 37-10** **A,** Appearance of a large unresectable malignant yolk sac tumor treated with biopsy and neoadjuvant chemotherapy. **B,** Residual postchemotherapy tumor.

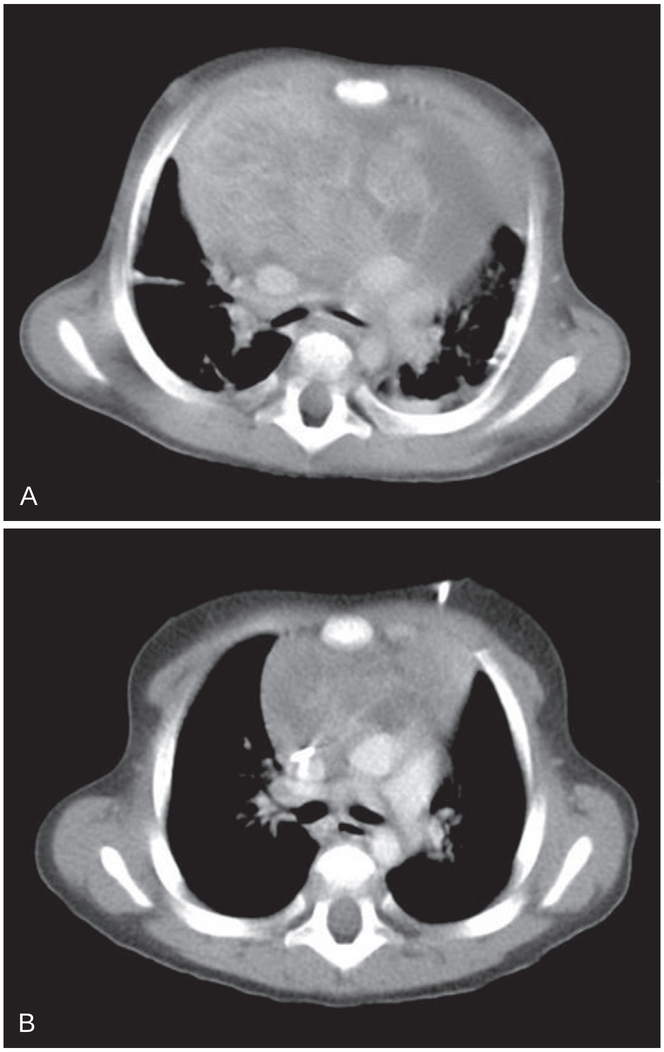


**FIGURE 37-12** **A,** Appearance of a large mediastinal mass causing tracheal compression and cardiac displacement. **B,** Appearance after neoadjuvant chemotherapy.

leading to further compression with loss of spontaneous ventilation. An early report suggested increased risk of respiratory collapse upon induction of anesthesia if the trachea was compressed by one third of the cross-sectional area.[79] Shamberger and colleagues,[80] added pulmonary function tests and observed that general anesthesia was well tolerated if both the tracheal area and the peak expiratory flow rate were greater than 50% of predicted. Alternatives to general anesthesia for diagnostic procedures in children in these situations include aspiration of pleural fluid and needle biopsy or open biopsy under local anesthesia. Open biopsy can be performed using an anterior thoracotomy (Chamberlin procedure) with excision of a segment of costal cartilage.[81]

**Extragonadal germ cell tumors:**

| Stage | Extent of disease |
|---|---|
| I | Complete resection at any site, coccygectomy for sacrococcygeal site, negative tumor margins. |
| II | Microscopic residual: lymph nodes negative. |
| III | Lymph node involvement with metastatic disease. Gross residual or biopsy only; retroperitoneal nodes negative or positive. |
| IV | Distant metastases, including liver. |

**FIGURE 37-11** Staging system for extragonadal germ cell tumors.

In the intergroup study ($N = 38$) 14 children underwent initial resection, with 12 survivors.[9] Twenty-two patients underwent biopsy followed by neoadjuvant chemotherapy and subsequent resection in 18, with 13 survivors. The size of the mass was reduced by a mean of 57% in 12 of the patients and was stable or increased in 6 (Fig. 37-12). Four patients had no further surgery, because of complete radiographic resolution in 1, progressive disease in 1, and death from toxicity in 2. Eight of 10 image-guided biopsies were successful. Of 31 resections, 20 were by median sternotomy and 11 by thoracotomy. Excision was frequently reported as difficult because of adherence to the major arteries and veins as well as the phrenic and vagus nerves and the lung and thymus. The overall survival was 71%, which is higher than the historical series but lower than survivals reported for the other extragonadal sites. The outcome was superior

in the patients with yolk sac tumors, and all of the tumor deaths were noted in adolescent boys with mixed germ cell tumors.

## Abdominal and Retroperitoneal Germ Cell Tumors

Retroperitoneal and abdominal germ cell tumors account for approximately 4% of germ cell tumors in children. Most present in infancy, although several have been indentified antenatally.[82] Eighty percent were less than 5 years of age in the recent intergroup (CCG/POG) study.[83] Mass and pain are the most common presenting symptoms, but fever, weight loss, constipation, and acute abdomen are also reported. An unusual group within this cohort are the infants with choriocarcinoma, which are thought to be primary placental tumors with metastases to the fetal liver. The beta-HCG production can lead to precocious puberty, and these infants usually present with hepatomegaly and anemia in the first 7 months of life.

Most retroperitoneal germ cell tumors are mature and immature teratomas; reports have noted malignancy rates between 0% and 24%, with the highest percentage occurring in infants.[82,84–87] The histologic pattern of the malignant tumors is most commonly pure yolk sac (63%), but also includes choriocarcinoma and mixed tumors. In the intergroup study,[83] 19 of 24 of the malignant tumors had elevated AFP, indicating yolk sac components were present but also illustrating the difficulty of determining malignancy preoperatively. Prior to attempting resection, a search for metastatic disease is appropriate, because nearly 90% of those with malignancy have stage III or IV disease at presentation.[83]

Primary resection should be attempted if preoperative imaging suggests lack of contiguous organ involvement or metastatic disease. Unfortunately, the benign tumors can also encase blood vessels, and the hazardous nature of these operations was demonstrated by two recent reports about several major vascular, biliary, and intestinal injuries.[82,86] In the intergroup study of 25 children, only 5 underwent initial resection, 13 had resection after chemotherapy and biopsy, or there was partial resection in 7.[83] Of note, 4 had no residual tumor after chemotherapy. The outcome with modern chemotherapy has dramatically improved the outcomes of children with these lesions from a historical survival of less than 20%[59] to current 6-year EFS of $82.8 \pm 10.9\%$ and overall survival of $87.6 \pm 9.3\%$.[83] There are other rare abdominal sites that may present later in life, and yolk sac tumors of the pelvis and uterus have been reported in adult patients.[88–90]

## Genital (Vaginal) Germ Cell Tumors

Genital lesions are rare and most commonly involve the vagina in girls. Although early reports of surgery alone reported survival rates of 50%, survival has improved with the addition of platinum-based adjuvant chemotherapy.[91,92] Vaginal lesions generally occur in girls less than 3 years of age who usually present with vaginal bleeding. A mass is typically identified within and often protruding from the vagina and uterus, and the actual site of origin may be difficult to ascertain. The CCG/POG report of 13 genital lesions (12 vaginal, 1 penile) confirmed the efficacy of platinum-based chemotherapy administered in a neoadjuvant fashion, with ultimate preservation of the vagina in 10 of 12 girls.[93] This is best accomplished by initial biopsy, followed by chemotherapy, and subsequent excision of the residual tumor, with the goal of partial vaginectomy. Although there is no role for initial total vaginectomy or hysterectomy, this rarely may be required in chemoresistant cases.

## Cervicofacial Teratomas

This rare site accounts for 5% to 6% of teratomas, which generally present in the neonatal period with large tumors. Most are mature or immature teratomas, but up to 20% are malignant.[94] A review of 20 neonates noted that 35% presented with airway obstruction.[94] A more recent report of seven giant fetal cervical teratomas observed that four developed hydrops (two died, one aborted), with one undergoing fetal resection.[95] Three neonates without hydrops underwent ex utero intrapartum treatment (EXIT) with intubation, tracheostomy, and resection on placental support in one each. If there is no evidence of hydrops, these can be followed to term. If the fetus is sufficiently mature ($\geq$28 weeks) and hydrops is present, the fetus can undergo delivery; however, if the gestational age is less than 28 weeks, fetal resection should be considered.[95]

## Gastric Teratomas

Tumors at this location generally present within the first few months of life with abdominal distention, bleeding, or symptoms of gastric outlet obstruction because of the gastric mass.[96] We have seen older children present with pain and obstructive symptoms as a primary cystic component has enlarged. These tumors occur primarily in males, and there are no reported malignancies at this site. Resection with primary closure of the stomach is the treatment of choice.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 38

# Hodgkin Lymphoma and Non-Hodgkin Lymphoma

Peter F. Ehrlich

## Hodgkin Lymphoma

Hodgkin lymphoma (HL) is one of the few cancers that affect both adults and children with a wide spectrum of histopathologic and clinical presentations. Unlike many other cancers, the adult and pediatric forms have similar biology and natural history. Pediatric HL accounts for 12% of all HL cases and represents 6% of all childhood cancers. Cure rates for pediatric HL are excellent, approaching 90% to 95% (Fig. 38-1).[1,2] Despite these excellent rates of cure, treatment can result in significant short-term and long-term morbidity. The aims of current therapeutic trials are to maintain or improve on outcomes while reducing short-term and long-term complications of therapy.[3]

Hodgkin lymphoma is named after Thomas Hodgkin, a British pathologist, who in 1832 described the disease in a paper titled *On Some Morbid Appearances of the Absorbent Glands and Spleen.*[4] One hundred and fifty years later, with the advent of microscopic histology, Sternberg (1898) and Reed (1902) described the distinctive multinucleated giant cell with the prominent nucleoli that are characteristic of Hodgkin disease (HD) (Fig. 38-2). They showed that these cells, now referred to as Reed-Sternberg cells, are derived from germinal center B cells.[5,6] Radiotherapy was the first reported "curative" treatment for HL in the 1930s.[7] In 1950, Peters published the first long-term series of survivors (20 years) treated with radiotherapy.[8] Single-agent chemotherapy (nitrogen mustard) was used to treat HL in 1946, and multiagent treatment with MOPP (Mustargen [mechlorethamine], Oncovin [vincristine], procarbazine, prednisone) was reported in 1967.[9,10] In the 1960s, the staging laparotomy was increasingly used to identify sites of involvement and for research purposes.[11] In the 1980s, oncologists began to appreciate the long-term morbidity of the chemotherapy and radiotherapy regimens used to treat patients with HL. Thus multimodality therapy designed to maintain outcomes while reducing toxicity were initiated. Currently, biologically based therapies, both immunotherapy and small molecules, are being investigated for use as primary and relapse therapy.

### INCIDENCE AND EPIDEMIOLOGY

Hodgkin lymphoma accounts for 6% of all pediatric malignancies, with an incidence of about 6 cases per 1 million, with a bimodal distribution with peaks in adolescence (15 to 19 years) and after age 55 years. HL is exceedingly rare in children less than 5 years of age.[12] Epidemiologic studies identify three forms of HL: two that involve the pediatric population and one in adults. Childhood HL is found in children less than 14 years old and accounts for 10% to 12% of cases; adolescent young adults (AYA) HL is defined as occurring in those 15 to 35 years of age and accounts for greater than 50% of the cases. It is the most commonly diagnosed cancer among adolescents 15 to 19 years of age. Older adults HL occurs in those older than 55 years of age and comprises 35% of the cases.[13]

Childhood HL is more common in males, and the histology is more likely to be mixed cellularity or nodular lymphocyte predominant. Risk factors include increasing family size, lower socioeconomic status, and exposure to the Epstein-Barr virus (EBV).[14–17] The EBV viral infection appears to precede tumor cell expansion, and EBV may act alone or in conjunction with other carcinogens.

The AYA form has no gender predilection, and the most common form is nodular sclerosis. Risk factors include higher socioeconomic status, early birth order, smaller family size, and EBV. In the AYA forms, it is hypothesized that EBV exposure is delayed (as opposed to the childhood form), suggesting that delayed exposure to EBV or some other unidentified common infectious agent may be a risk factor for AYA HL.[16–19]

Hodgkin lymphoma is derived from a single transformed B cell that has undergone monoclonal expansion. Classic cells include Reed-Sternberg, lymphocytic, and histiocytic cells. There are also many cytokine-producing and cytokine-responding cells that are responsible for the nonspecific signs and symptoms seen with this tumor. Immune system dysfunction is hypothesized to be one of the primary causes for Hodgkin lymphoma. In the childhood form, it is thought to result from immune immaturity, whereas in the adult form, it is thought to result from immune dysregulation. Support for this hypothesis is found in diseases with altered immune states in which an increased incidence of HL is seen, including

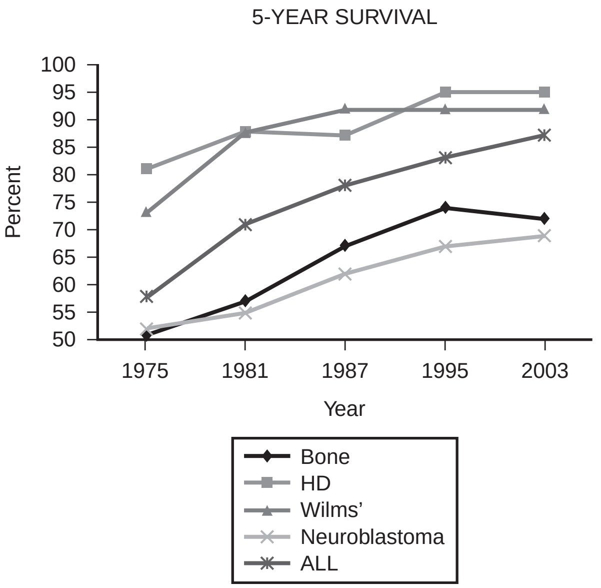


**FIGURE 38-1** Graph shows survival statistics of different pediatric cancers from 1975 to 2003.

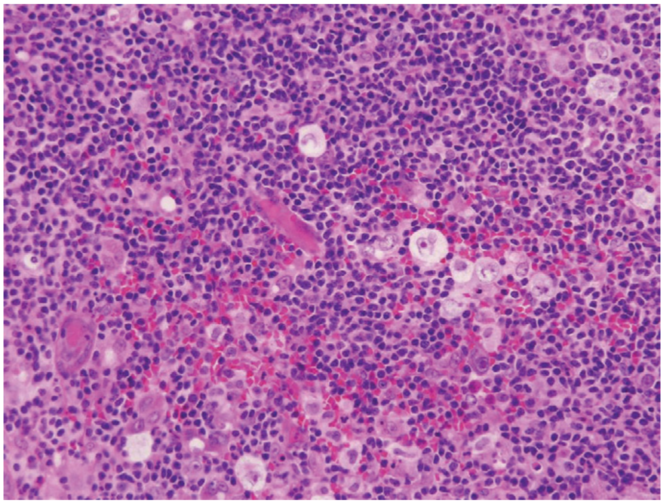

**FIGURE 38-2** High-power hematoxylin and eosin–stained slide of a patient with nodular sclerosis Hodgkin lymphoma with typical Reed-Sternberg cells.

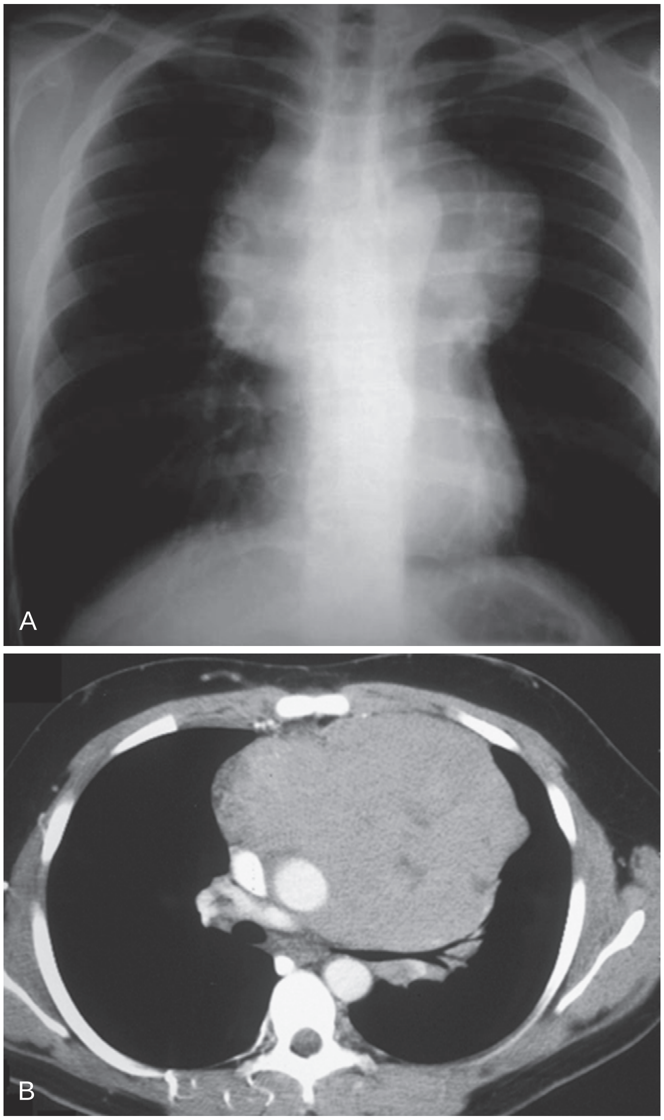


**FIGURE 38-3** **A,** Chest radiograph demonstrating a large anterior mediastinal mass. **B,** Computed tomography scan demonstrating a large anterior mediastinal mass.

patients with human immunodeficiency viral infection, other acquired immunodeficiency states (post–solid organ or hematopoietic stem cell transplantation), and autoimmune disorders or a family history of autoimmune disorders.[20–24]

## CLINICAL PRESENTATION

Hodgkin lymphoma must be considered in any child with lymphadenopathy. Involved nodes are described as firm, nodular, and painless. Children and adolescents most frequently present with cervical and or supraclavicular lymphadenopathy (80%). Patients presenting primarily with enlarged axillary nodes (25% of all cases) or inguinal nodes (5%) are far less common. Associated mediastinal disease is found in up to 75% of adolescents and 33% of children.[13,25–27] Mediastinal involvement must be assessed prior to any operative intervention; involvement may be extensive and produce major complications upon the induction of anesthesia (Fig. 38-3) Patient's may also present with B symptoms, including fever greater than 38° C, soaking night sweats, and weight loss of 10% or more. These symptoms are not specific to HL and can occur in non-Hodgkin lymphoma. The presence or absence of B symptoms, which occur in up to a third of children, has prognostic significance and is reflected in the staging of HL.[13,25] Respiratory symptoms may also result from large mediastinal masses, including dyspnea on exertion or orthopnea. Itching or pruritus is a frequent finding but is nonspecific.[28]

## DIAGNOSIS

A full history and physical examination focusing on nodal areas and the abdomen should be performed. At present there is no specific laboratory test for HL. An excisional biopsy of a suspicious lymph node should be the initial step to diagnosis

**TABLE 38-1**
**Hodgkin Lymphoma Staging: Ann Arbor Classification with Cotswolds Modification**

| | |
|---|---|
| Stage 1 | Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer ring) or involvement of a single extralymphatic site |
| Stage II | Involvement of two or more lymph node regions on the same side of the diaphragm |
| Stage III III1 III2 | Indicates that the cancer has spread to both sides of the diaphragm, including one organ or area near the lymph nodes or the spleen<br>With or without involvement of splenic, hilar, celiac, or portal nodes With involvement of paraaortic, iliac, and mesenteric nodes |
| Stage IV | Indicates that the cancer has spread to both sides of the diaphragm, including one organ or area near the lymph nodes or the spleen |

Modifiers:
*A* or *B:* The absence of constitutional (B-type) symptoms is denoted by adding an "A" to the stage; the presence is denoted by adding a "B" to the stage.
*E:* Used if the disease is "extranodal" (not in the lymph nodes) or has spread from lymph nodes to adjacent tissue.
*X:* Used if the largest deposit is greater than 10 cm large (bulky disease), or whether the mediastinum is wider than one third of the chest on a chest x-ray.
*S:* Used if the disease has spread to the spleen.
The nature of the staging is (occasionally) expressed with:
*CS:* Clinical stage as obtained by doctor's examinations and tests.
*PS*: Pathologic stage as obtained by exploratory laparotomy (surgery performed through an abdominal incision) with splenectomy (surgical removal of the spleen). Note: Exploratory laparotomy has fallen out of favor for lymphoma staging.

of Hodgkin lymphoma. Prior to surgery, a chest radiograph must be obtained to assess the presence of mediastinal disease. If a mediastinal mass is detected, a computed tomography (CT) scan of the chest is mandated to assess the tracheal area, and pulmonary function tests further define the extent of respiratory impairment. In some cases, the procedure may need to be performed under local anesthesia because of the size of the mediastinal mass and the resultant respiratory compromise (see Fig. 38-3). Minimally invasive techniques have been used to biopsy mediastinal masses, if no suspicious extrathoracic lymph nodes are available for biopsy. Care must be taken when using a thoracoscopic or laparoscopic technique to ensure that adequate specimens are obtained. A report from the Children's Oncology Group Hodgkin's Lymphoma Committee demonstrated that up to 50% of mediastinal cases required a second diagnostic biopsy when a thoracoscopic biopsy was performed.[29] thoracoscopic biopsy should also be avoided in children with respiratory compromise.

## HISTOPATHOLOGY

Reed-Sternberg cells are the pathognomonic cells of HD (see Fig. 38-2). The classification systems for HL have evolved over time from the Rye classification to the Ann Arbor Classification and the Cotswolds modification (Table 38-1).[30–32] The current World Health Organization classification system separates HL into two broad categories: classical and lymphocyte predominant. Classical has four subtypes: lymphocyte depleted, nodular sclerosing, mixed cellularity, and classical lymphocyte rich. Classical HL accounts for 90% of all cases. For children, nodular sclerosis is the most common subtype, accounting for 65% of cases. Immunohistochemical studies define a common immunophenotype for classical Hodgkin, characterized by CD15-positive and CD30-positive Reed-Sternberg cells (Fig. 38-4). Classical HL expresses CD30, a marker of activated B-lymphoid and T-lymphoid cells, in almost all cases.[25,28,30] About 87% of classical Hodgkin lymphomas express CD15, the carbohydrate X hapten. Classical Hodgkin lymphoma rarely expresses CD45, also known as common leukocyte antigen, which is expressed by nearly all non-Hodgkin lymphomas and can serve as a useful differential marker between HL and non-Hodgkin lymphoma.

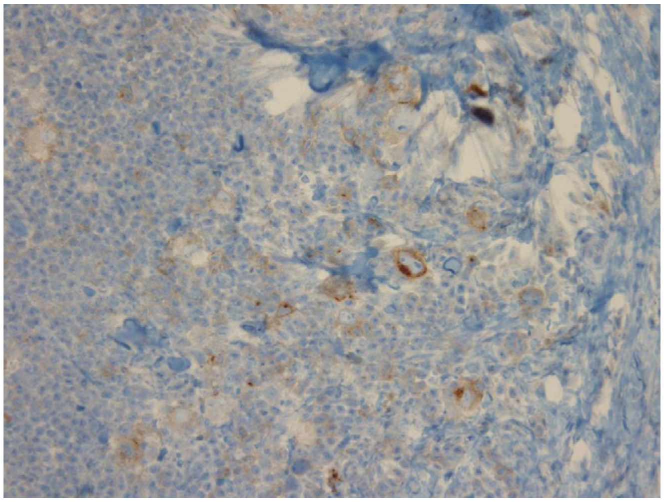
**FIGURE 38-4** CD30-positive staining for Reed-Sternberg cells in a patient with Hodgkin lymphoma.

The lymphocyte predominant (LPHD) subtype accounts for 10% of all cases and is characterized by lymphocytic and histiocytic (L&H) cells that express markers not typically seen in the classical subtype (Fig. 38-5). These cells are also known as "popcorn cells" and are CD20 positive. Other B-cell immunomarkers found in LPHD include CD79a, CD75, epithelial membrane antigen, and CD45. The lymphocyte predominant subtype historically carries the best prognosis. However, since the development of highly effective multiagent and multidisciplinary treatment regimens, all histologic subtypes have become responsive to therapy.

## STAGING

Staging has both clinical and pathologic features. The Ann Arbor staging system and its Cotswolds modification remain the standard for adult and pediatric HL (see Table 38-1).[30,33,34] The original Ann Arbor staging system developed in 1974 was based principally upon the use of staging laparotomy and lymphangiogram, both of which have been abandoned.

Clinical staging requires a complete history and physical examination. Basic tests should include a complete blood cell count with differential, lactate dehydrogenase, alkaline phosphatase, erythrocyte sedimentation rate, or C-reactive protein (CRP), baseline hepatic and renal function tests, and electrolytes. Radiographic studies include a chest radiograph and a computed tomography (CT) scan of the neck, chest, abdomen, and pelvis. Chest radiographs often reveal the presence of a mediastinal mass, and the ratio of its maximal diameter to that of the thoracic cavity on a posteroanterior view is important prognostically. A mass with a ratio greater than 1:3 places

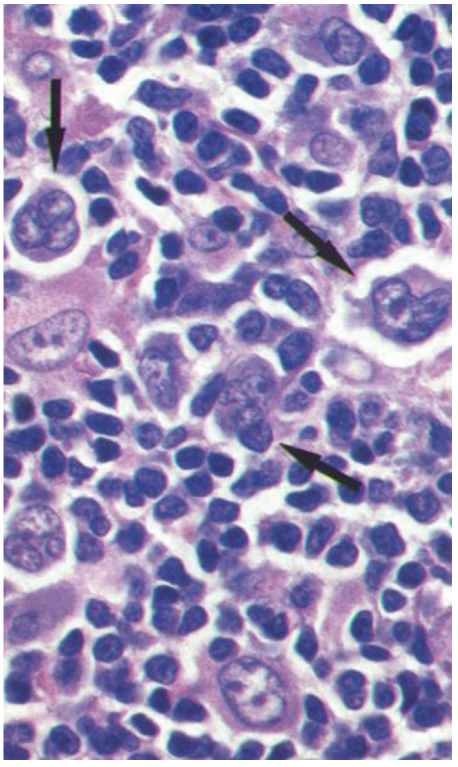

**FIGURE 38-5** High-power hematoxylin and eosin–stained slide of a patient with lymphocyte predominant Hodgkin lymphoma demonstrating classical "popcorn" cells as defined by the arrows.

the patient in the subcategory of bulky mediastinal disease associated with a worse prognosis. Bone marrow biopsy is reserved for those patients with B symptoms or stage III-IV disease. (18F)-2 fluoro-D-2-deoxyglucose positron emission tomography (FDG PET) is replacing gallium scans, and recent studies have assessed the ability of PET scans to replace CT scans and as possible prognostic indicators for response to therapy.[25,28,35–37] Magnetic resonance imaging (MRI) provides a more accurate evaluation of disease in the abdomen compared with CT, with better visualization of fat-encased retroperitoneal nodes, but whether or not this provides clinically significant information has yet to be established.

## TREATMENT

### Risk Classification

Children and adolescents with HL are divided into three risk categories—low-, intermediate-, and high-risk disease—based on clinical and pathologic staging data, histology, stage at presentation, presence or absence of B symptoms, number of involved sites, and/or presence of bulky disease (>10 cm). The exact definitions of each stage will often change between studies and clinical trial consortiums, such as the Children's Oncology Group (COG).[34] In general, *low-risk* disease is defined as classical Hodgkin lymphoma patients, with clinical stage I or II disease showing no B symptoms or bulky nodal involvement and disease in fewer than three nodal regions. *Intermediate-risk* disease includes stage I, II, and sometimes IIIA disease with criteria that vary from trial to trial.[26,30] Some trials have included B symptoms, bulky disease, a large number of involved nodal regions, and extranodal involvement of disease. *High-risk* patients are those with stage IIIB and IVA/B disease.[38–40] LPHD is considered a low-risk disease but is often separated from the classical HL studies.

### Surgery

The role of surgery in the initial diagnosis and staging for HL has been reduced. With the wide application of chemotherapy in all stages of HL, surgical staging has become irrelevant, because the additional information it provides does not alter treatment.[41,42] The surgeon's primary role is to obtain tissue for diagnosis. Biopsies should be taken from the most easily accessible site, and adequate tissue must be obtained and sent fresh to pathology for immunohistochemistry, immunophenotyping, cytogenetics, and flow cytometry. Fine-needle aspiration is generally discouraged, because it is inaccurate and inadequate tissue is obtained to properly stage and classify the patient. Thoracoscopic biopsy or a Chamberlain procedure can be used for diagnosis in patients with only mediastinal involvement. Retroperitoneal lymphadenopathy is often accessible through laparoscopic biopsy. However, thoracoscopic and laparoscopic, as well as core needle biopsies, have a higher incidence of misdiagnosis and can require multiple procedures to obtain an adequate sample.[29] The second role for surgery is to provide central venous access for chemotherapy. Bilateral oophoropexies are also performed in girls who will receive abdominal radiotherapy.

### Chemotherapy and Radiation Therapy

Chemotherapy and radiotherapy (RT) are the mainstay treatments of HL. Although the outcomes for children with HL have improved dramatically, the short-term and long-term toxicity of therapy has been substanial.[43,44] Therefore recent and current therapeutic protocols for HL have focused on maintaining excellent outcomes but reducing toxicity. Ideal chemotherapy regimens use drugs that are individually effective with different mechanisms of action and toxicities, to allow for a maximal dose. The first widespread successful regimen was MOPP (Mustargen, oncovin, procarbazine, and prednisone). In a long-term study of 188 patients from the National Cancer Institute, who were treated with MOPP, the complete remission rate was 89%, and 54% of patients remained disease free at 10 years.[45] In this study, 95% of patients had stage III or IV disease, and 89% had B symptoms. ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine) was the second regimen used in the treatment of HD.[46] It was developed for the treatment of patients failing MOPP therapy and contains individually effective drugs with nonoverlapping toxicities.

Historically, radiation therapy was based on the concept of contiguous lymph node basin involvement.[47] The whole nodal region was included as defined by Kaplan and Rosenberg, sometimes additionally covering uninvolved adjacent lymph node region(s), extended field radiotherapy (EFRT).[47] However, radiation therapy is one of the major contributors to early and late toxicity in children with HL. Similar to chemotherapy, treatment has evolved, however, to reduce the radiation necessary. EFRT has been supplanted by involved field radiation therapy (IFRT). Over time, improvements in equipment and targeting have reduced the exposure of uninvolved areas. These practices aim to reduce salivary gland and oral cavity morbidity and to optimally spare the heart from irradiation. A further reduction of RT volume to cover just the nodal

tissue involved by disease, without any attempt to include whole nodal region(s), is termed involved node radiation therapy (INRT).[48] Relapses in patients treated with chemotherapy alone occur primarily in the initially involved lymph nodes.[49] Using FDG PET analysis of residual disease and advances in radiation planning, it is possible now to confine the radiation to the initially involved nodal tissues rather than the whole nodal chain. The hope is that a reduction in irradiation volume will result in a lower incidence of late complications. This goal may be particularly important in young females with anterior mediastinal disease, where exclusion of the hilar and subcarinal nodes from the radiation field would lead to significant reductions in radiation dose to the breasts. This is important because the most common malignancy following treatment for HL is breast cancer. In addition, children have been shown to be particularly susceptible to thyroid toxicity following RT, and the transition to INRT may potentially exclude the thyroid from the treated volume for many patients with supradiaphragmatic HL. Preliminary data reported from British Columbia in Canada indicated no increase in relapses with INRT compared with IFRT or EFRT using a current multiagent chemotherapy regimen.[50]

### Therapy for Low-Risk Disease

Optimal therapy for low-risk Hodgkin disease in children and adolescents continues to evolve. Protocols using chemotherapy followed by low-dose radiation therapy have achieved cure rates of greater than 90% for patients with low-risk Hodgkin disease and represent the standard of care for children and adolescents with Hodgkin disease. Several multi-institutional trials demonstrate that children and adolescents with low-risk HL can be effectively treated with two to four cycles of chemotherapy followed by 15- to 25-Gy IFRT, with series reporting 90% or better event-free survival (EFS), with overall survival (OS) greater than 95%.[51–54] The most recent COG low-risk HL study used a response-based chemotherapy regimen of AP-PC (Adriamycin [doxorubicin], vincristine, prednisone, and cyclophosphamide) with or without IFRT. After three cycles, those with complete response do not receive IFRT. IFRT consists of 21 GY in 14 fractions of 1.50 Gy per day for 14 sessions.[37] This study closed in the fall of 2010.

### Therapy for Intermediate-Risk Disease

Intermediate-risk trials for HL have documented the need for adjuvant radiotherapy in most patients.[54–56] In a German trial, patients who completely responded to induction therapy had radiation therapy omitted, but their event-free survival was lower than expected.[40] In the CCG 5942 trial, intermediate-risk children with complete response were randomized to receive either IFRT or no further treatment.[54] Three-year EFS was 82% with OS of 93%, but the patients who received IFRT had three-year EFS of 88%. Both these studies support the need for IFRT with most intermediate HL patients. The current intermediate-risk COG trial is a randomized trial to see if early complete responders can have a dose reduction of both chemotherapy and radiation therapy without a decrease in their EFS. Induction chemotherapy consists of ABVE-PC (Adriamycin [doxorubicin], bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) for two cycles. It is a double randomized response–based protocol with both IFRT and chemotherapy intensifications following induction.[36] This study closed in the fall of 2010.

### Therapy for High-Risk Disease

Patients with high-risk tumors require both intensification of chemotherapy and radiation therapy. The German (GPOH) HD-DAL 90 protocol treated high-risk patients with two or four cycles of COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) plus 20- to 35-Gy IFRT. Five-year EFS in high-risk groups was 93% and 86%, respectively.[53] The EFS in the high-risk groups was comparable to that seen in the low-risk group. The Children's Cancer Group (CCG) 5942 protocol treated those with high-risk disease with two courses of intensive multiagent chemotherapy with cytarabine/etoposide, COPP/ABV, and cyclophosphamide, vincristine, doxorubicin, and methylprednisolone/prednisone with granulocyte colony–stimulating factor support. Complete responders were randomly assigned to 21-Gy IFRT or no further therapy. Three-year EFS rates in intermediate- and high-risk patients receiving IFRT were 88% and 91%, respectively.[54] In both the GOPH HD-95 and CCG 5942 trials, the benefit of IFRT in reducing relapse rates was most pronounced among high-risk patients. The most recent studies suggest that outcome of patients with high-risk factors can be improved with intensification of chemotherapy and lowering RT based on response. Pediatric Oncology Group (POG) 9425 study reported 2-year EFS for intermediate- and high-risk disease in a response-based paradigm. In this study, 63% of patients received 9 weeks of chemotherapy and 21 Gy of IFRT because of good response, whereas the others received more intensive therapy.[56] The most current COG high-risk study recently opened. This is a nonrandomized response-based protocol. Induction therapy is with ABVE-PC, and patients will be divided into rapid early responders and slow early responders. Response will be determined by PET scan, and further chemotherapy and radiotherapy targets are based on the PET scan.[57]

### Therapy for Lymphocyte-Predominant Hodgkin Disease

Lymphocyte-predominant Hodgkin disease (LPHD) is recognized as a distinct clinical-pathologic entity, with a favorable outcome, but also associated with a higher risk of late relapse and subsequent development of non-Hodgkin lymphoma (NHL). LPHD comprises up to 10% of cases in adult and pediatric series. Most patients with LPHD reported in the literature have been treated similarly to patients with classical HD, using chemotherapy, RT, or combined modality treatment.[3,58] However, treatment by surgical resection alone has been reported in adult and pediatric patients. The outcomes suggest that patients with low-stage disease may be effectively treated with surgery alone, particularly considering the toxicity of treatment.[59–61] In 2007, European researchers reported 100% survival in 58 LPHD patients treated initially with surgery alone; 50 had a complete response (CR) and received no adjuvant therapy.[62] In this group, 14 (28%) recurred, but 73% required no other therapy at 43 months follow-up. A recently completed COG protocol treated patients with stage I single node disease with surgery only. Results have not been published.[35]

### Novel Therapy

Novel therapies are being investigated for children with HD at diagnosis and relapse. These include rituximab (an anti-CD20 monoclonal antibody) and small molecule agents, such as

bortezomib, a reversible proteosome inhibitor that leads to the blockage of NF-kappa beta being explored in HD. Other agents include histone deacetylase inhibitors, such as MGCD0103; however, none of these agents are being incorporated in standard therapies.[3]

### Treatment Toxicities

Toxicities of treatment include decreased stature, cardiopulmonary dysfunction, thyroid disease, infertility, second malignancies, impaired psychosocial functioning, and decreases in health-related quality of life.[28]

***Growth Problems*** Full-dose (35- to 44-Gy) RT produces bone and soft tissue hypoplasia in prepubertal children. For patients treated with mantle fields, this manifests as spinal and clavicular shortening and underdevelopment of the soft tissues in the neck.

***Cardiopulmonary Dysfunction*** Long-term survivors of HL treated with full-dose RT have an increased risk of atherosclerotic heart disease, valvular dysfunction, and pericardial disease.[62–64] A study reported a 45-fold mortality risk from acute myocardial infarction in children treated before the age of 20 years with more than 30 Gy of mediastinal radiation.[65] Heart disease and valvular disease tends to occur late—8 to 10 years after therapy. Lower doses and cardiac shielding reduce this risk. Pericarditis can occur, especially if the tumor involved the pericardium. Anthracyclines, such as doxorubicin, cause dose-dependent myocardial heart failure and coronary artery disease.[66] In children, a cumulative dose of 300 $mg/m^2$ of doxorubicin increases heart failure rate by 11-fold at 15 years after therapy.[67,68] Contemporary chemotherapy regimens delivering 250 $mg/m^2$ doxorubicin with low-dose IFRT appear to be associated with minimal early cardiac toxicity.[69] Bleomycin results in both short-term and long-term lung toxicity with impaired diffusion capacity and restrictive lung disease.[70] RT can also produce breast hypoplasia and contribute to the pulmonary fibrosis.

***Thyroid*** Hypothyroidism, hyperthyroidism, as well as benign and malignant thyroid nodules have been recognized as problems occurring in long-term survivors of HL.[71,72] In the Childhood Cancer Survivor Study, 34% of 1,791 5-year survivors of HL treated between 1970 and 1986 reported thyroid abnormalities.[72] Thyroid nodules appear late in the follow-up, often 10 or more years after completion of therapy. The relative risk (RR) is 18.3 (confidence interval, 11.4 to 27.6) compared with the general population. Children receiving neck RT also appear to be at greater risk of hypothyroidism than adults.[71]

***Infertility*** Sterility/infertility is a significant risk of alkylating agents, most commonly cyclophosphamide and/or procarbazine.[73] Males in the German GPOH studies receive etoposide in place of procarbazine, because testicular germinal function is more sensitive to alkylating agents than is ovarian function, and current COG protocols limit alkylating agents to doses compatible with preservation of fertility.[35–37,57] Gonadal failure is also a result of pelvic RT. In boys, doses greater than 3 Gy can produce irreversible azospermia.[74] Low-dose IFRT to iliac or inguinal lymph nodes may impair fertility among females if the direct or scattered dose to the ovaries exceeds 2 to 3 Gy. Oophoropexy can help limit the adverse effects of radiation therapy. Also reported in females is a high risk of prematurity and premature menopause.[75]

***Second Cancers (SC)*** The risk of second cancers is significantly increased in the long-term survivors of HL treated with full-dose RT.[76–80] The Late Effects Study Group estimated the 30-year cumulative incidence of SC to be 26.3% among survivors diagnosed before age 16. The two most frequent cancers are breast cancer (20% risk at 45 years of age), followed by thyroid carcinoma (36-fold increased rate).[80] Exposure to alkylating agents, particularly in conjunction with extended-field RT, is associated with an increased risk of leukemia. Leukemias tend to arise 2 to 10 years after therapy. The risk of SC after modern treatment is not yet known, because reduction in exposure to alkylating agents and the use of low-dose IFRT became standard practice within the last 15 to 20 years. The transition from extended-field RT to IFRT significantly reduces the radiation dose to breast and lung tissue.[81] It is thought that modern IFRT should lead to lower SC rates than have been documented in the past.

## Non-Hodgkin Lymphoma

Non-Hodgkin lymphomas (NHLs) comprise a heterogeneous group of tumors that has a constantly evolving classification system. The current World Health Organization (WHO) pathologic classification identifies almost 60 unique subtypes based on morphologic, immunophenotypic, and genetic differences, as well as clinical behavior (Table 38-2). NHL can be broadly divided based on the cell of origin (B cell or T cell) or on clinical behavior (indolent, aggressive, or highly aggressive). There are distinct differences between adult and pediatric NHL, with a strong bias toward precursor B-lymphoblastic and T-lymphoblastic lymphoma, anaplastic large cell lymphoma, and Burkitt lymphoma in childhood.

Indolent lymphomas are slowly progressive but incurable diseases, with a median survival time of 8 to 10 years. Aggressive lymphomas, such as Burkitt and Burkitt-like lymphomas, are rapidly progressive at presentation but curable in 70% to 90% of patients, with outcome strongly dependent on clinical and biological features (as identified by current molecular and immunologic approaches) at presentation.

### INCIDENCE EPIDEMIOLOGY AND CLASSIFICATION

There are 750 to 800 new cases of non-Hodgkin lymphoma each year in the United States.[82] Non-Hodgkin lymphoma (NHL) accounts for 7% of cancer in children and adolescents, with an incidence of 10 per 1 million population annually in the United States.[83] NHL is rare at less than 5 years of age, with an incidence of 2.8 per million cases but increases dramatically after age 20. NHL is more common in males (1.1 to 1.4:1), with a higher frequency in whites than in blacks or Asians. Certain NHL types cluster according to race, for example, the natural killer (NK) T-cell lymphomas are most frequently encountered in Asian populations. A family history of a hematologic malignancy produces an increased risk, but it is not NHL-disease specific.[82]

DNA and RNA viruses are thought to play an important role in the pathogenesis of NHL.[17,82] The Epstein-Barr virus (EBV)

**TABLE 38-2**
**World Health Organization and Clinical Classification of Selected Subtypes of Non-Hodgkin Lymphoma**

| | **Clinical Behavior** | | |
|---|---|---|---|
| ***WHO Pathologic Category*** | ***Indolent*** | ***Aggressive*** | ***Highly Aggressive*** |
| Mature B-cell neoplasms | Follicular lymphoma | Diffuse large B-cell lymphoma, NOS | Burkitt lymphoma |
| | Chronic lymphocytic leukemia/small lymphocytic lymphoma | Primary mediastinal large B-cell lymphoma | |
| | Hairy cell leukemia | Mantle cell lymphoma | |
| | Extranodal marginal zone lymphoma | | |
| | Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia | | |
| | Splenic B-cell marginal zone lymphoma | | |
| Mature T-cell and NK-cell neoplasms | Mycosis fungoides | Hepatosplenic T-cell lymphoma | |
| | Sézary syndrome | Peripheral T-cell lymphoma, NOS | |
| | | Angioimmunoblastic T-cell lymphoma | |
| | | Anaplastic large cell lymphoma, ALK+ type | |
| | | Anaplastic large cell lymphoma, ALK− type | |

Adapted from Jaffe E, Harris NL, Stein H, et al: Introduction and overview of the classification of lymphoid neoplasms. In Swerdlow SH, Campo E, Harris NL, et al (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC Press, 2008, p 158-166.
ALK, anaplastic lymphoma kinase; NK, natural killer; NOS, not otherwise specified; WHO, World Health Organization.

is the most prominent. EBV was first detected in cultured African Burkitt lymphoma cells and is known to be present in greater than 90% of such cases. EBV is important as a trigger for lymphoproliferations/lymphomas occurring in congenital immunodeficiencies, iatrogenically immunosuppressed organ transplant recipients, patients receiving maintenance chemotherapy, and patients receiving combined immunosuppressive therapy for collagen disorders.[84] EBV is also found in HL (mostly the mixed cellularity type), and patients who have had infectious mononucleosis are at increased risk of HL. Other viruses implicated in the pathogenesis of NHL include the retrovirus human lymphotropic virus type 1 (HTLV-1), with adult T-cell lymphoma and human herpesvirus 8 (HHV-8) as a cause of primary effusion lymphoma, a rare type of large cell lymphoma confined to serous-lined body cavities, which occurs with highest frequency in the HIV-positive population. Bacterial overgrowth can also promote the occurrence of a lymphoma. In gastric lymphoma of mucosa-associated lymphoid tissue (MALT) type, *Helicobacter pylori* infection has been shown to be necessary for the development and early proliferation of the lymphoma.[85]

NHLs in children are typically high grade.[86] Ninety percent are from three main groups. These are (1) mature B-cell NHL, which includes Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL), or diffuse large B-cell lymphoma (DLBCL); (2) lymphoblastic lymphoma (LL); or (3) anaplastic large T-cell lymphoma (ALCL). The other 10% are similar to types seen in adults, such as MALT and mature T-cell natural killer (NK) cell lymphoma (see Table 38-2). NHL subtypes have different cell lineages and cell cycle kinetics with different propensities to invade the bone marrow and central nervous system.[87]

## CLINICAL PRESENTATION AND STAGING

Similar to HL, NHL must be considered in any child with lymphadenopathy. However, most children with B-cell lymphoma present with a palpable abdominal tumor or a mediastinal tumor.[88,89] Frequently, the lymphoma presents as a mass in the right iliac fossa and can be confused with appendicitis or an appendiceal abscess. Children may also present with intussusception bleeding, ascites, or a bowel perforation.

As with HL, the presence of mediastinal disease must be assessed, because these masses can be exceedingly large and result in significant morbidity or mortality (see Fig. 38-3). Superior vena cava syndrome and respiratory distress are more common in patients with NHL. In these cases, immediate treatment with corticosteroids with or without cyclophosphamide or radiation may be required. The concern in these situations is that the treatment will make it difficult to establish the pathologic diagnosis. However, there is some thought that treatment for up to 48 hours is beneficial and unlikely to obscure subsequent pathologic diagnosis, but if there is significant resolution of the mass, the tissue may be necrotic.[90] Many children with NHL will present with advanced-stage disease, including bone marrow involvement and malignant pleural or pericardial effusions. Pleural fluid and pericardial fluid often require drainage; cytologic examination of the fluid can be diagnostic.[90] Patients may also present with B symptoms. The presence or absence of B symptoms has prognostic significance and is reflected in the staging of these lymphomas. B symptoms occur in up to one third of children with NHL.[13,25] In NHL, the proper diagnosis allows for classification to the distinct biological subgroups. Specimens should be sent fresh to pathology. Regular histopathology, cytology, immunopathology, cytogenetics using fluorescence in situ hybridization (FISH, to look for chromosomal translocation), polymerase chain reaction (PCR), and growth patterns all are needed to properly classify a case of NHL.[91,92]

### Staging

Staging laparotomy is not performed in non-Hodgkin lymphoma, because all patients require systemic chemotherapy. However, patients may require surgical intervention because of abdominal complications, such as intussusception or bleeding or to obtain diagnostic tissue. In some cases, the disease is localized and a total resection can be performed, in others the

**TABLE 38-3**
**St. Jude's Murphy Staging System for Non-Hodgkin Lymphoma**

| Stage | Description |
|---|---|
| I | A single extranodal tumor or single anatomic nodal area with exclusion of mediastinum and abdomen |
| II | A single extranodal tumor with regional nodal Involvement greater than or equal to two involved nodal regions or localized involvement of extranodal disease on the same side of diaphragm<br>A primary gastrointestinal tract tumor that is completely resected |
| III | Greater than or equal to two nodal or extranodal tumors on opposite sides of the diaphragm<br>Any primary intrathoracic tumor<br>Unresectable primary intraabdominal disease<br>Any paraspinal or epidural disease |
| IV | Involvement of central nervous system and/or bone marrow |

disease is extensive with involvement of the mesenteric root and retroperitoneum.

Although no staging system is entirely satisfactory, the most widely used staging system for NHL is the St. Jude's Murphy system (Table 38-3).[93] The Children's Oncology Group divides NHL into two categories: limited and extensive. Limited disease corresponds to stages I and II in the St. Jude's system, and extensive correlates with stages III and IV.

## NHL SUBTYPES IN CHILDREN AND ADOLESCENTS

A detailed review of all the different types of NHL is beyond the scope of this chapter. The most common subtypes of NHL, accounting for 90% of cases found in children, are presented.

### Mature B-cell NHL: Burkitt Lymphoma, Burkitt-Like Lymphoma, and Diffuse Large B-Cell Lymphoma

B cells originate in the bone marrow from totipotential stem cells that differentiate through many intermediate cell types to eventually become antibody-producing plasma cells (Fig. 38-6). Malignant transformation can occur at any point along the path of differentiation. The clinicopathologic subtypes of NHL are determined by the stage of differentiation at which malignant transformation occurs. Because of their appearance by light microscopy, tumors in this category are also called small, noncleaved cell lymphomas. Because B cells develop in the bone marrow and then migrate to secondary lymphoid organs (lymph nodes, spleen, Peyer patches, liver), one would expect clinical localization of the developing neoplasm in those anatomic sites. Alternatively, B-cell lymphoma should not occur in the anterior mediastinum in the region of the thymus, because normal B cells are not thymic dependent. Usually, but not always, this anatomic distribution is consistent with clinical observations.

***Burkitt Lymphoma and Burkitt-Like Lymphoma*** BL was first described in 1958 in Uganda by a surgeon who observed rapidly enlarging tumors involving the jaw in children.[94] BL and BLL account for about 40% of childhood NHLs (Fig. 38-7).[86] There are three variants of BL: endemic, sporadic, and immunodeficiency related. In the United States, BL most frequently occurs in the abdomen; in western equatorial Africa, it usually arises in the mandible, but abdominal lymphoma is also noted in up to 20% of these patients. BL can also be found in the central nervous system and bone marrow. BL of the anterior mediastinum is extremely rare.[95,96] The gold standard for the diagnosis of BL is c-*MYC* rearrangement.[97] This is based on a characteristic chromosomal translocation, usually involving chromosomes 8 and 14, that was discovered in BL in 1976.[98] In 80% of the translocations, this involves the locus at 14q32, in 15% of cases it is 2p11, and in 5% it is 22q11. BL is the most rapidly growing tumor in

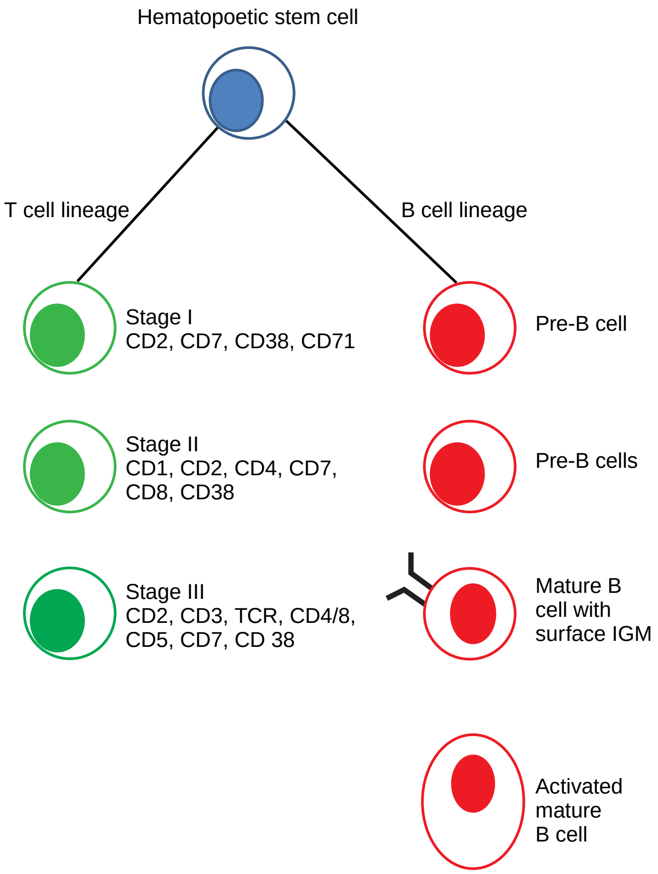


**FIGURE 38-6** A schematic of B-cell and T-cell lineages.

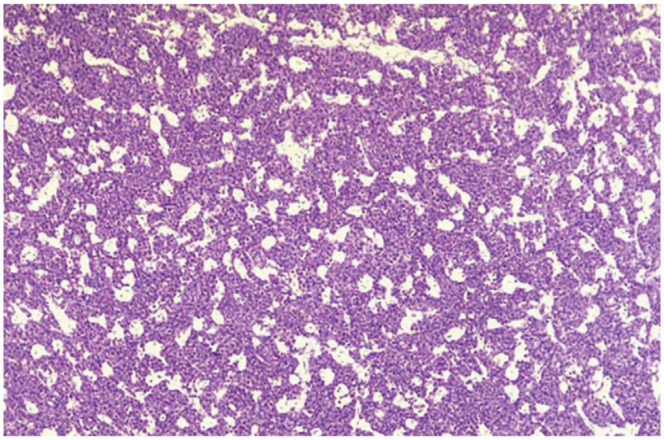

**FIGURE 38-7** A low-power hematoxylin and eosin–stained slide of a patient with Burkitt lymphoma. Shows the typical "starry sky" appearance of the tumor.

children, with a doubling time of approximately 24 hours. The rate of cell death or apoptosis is also high, with the dead cells being taken up by pale histiocytic cells within the tumor that punctuate the low-power view, giving a “starry sky” appearance (see Fig. 38-7).[97] BL cells are mature B-cells that are positive for CD19, CD20, CD22, and CD79a and have a monotypic surface IgM.[99] BLL is an aggressive highly proliferative variant with features that overlap classical BL and DLBCL; BLL is treated by BL regimens.[97] The distinction between BL and BLL is controversial. Because of the rapid growth seen in BL and BLL, when the disease is suspected, the pediatric surgeons are often asked to intervene immediately so that treatment can begin.

***Diffuse Large B-Cell Lymphoma*** DLBCL accounts for 10% of pediatric lymphomas. It is less common in young children and becomes frequent in adolescents. DLBCL is derived from transformed mature B cells of the peripheral lymphoid organs.[100] DLBCL tumors have cells that are 4 to 5 times the size of small lymphocytes. In adults, there is a genetic signature; however, in children this is not the case. The tumors do express c-*MYC*–like BL as well as genes from the NF kappa-beta pathway, but there is no specific marker of DLBCL.[101] The tumors express CD19, CD20, CD22, and CD79a. The three most common morphologic variants are centroblastic, immunoblastic, and anaplastic. Gene expression profiling has identified two subtypes: germinal center B-cell–like (GC) and activated B-cell (ABC). The most common subtype, GC, has a more favorable outcome. A progressively enlarging mass is the most common mode of presentation. Symptoms are based on tumor location. About 20% of pediatric DLBCL present as a mediastinal mass, but the tumors can occur anywhere. Increased lactate dehydrogenase (LDH), pleura effusions, and ascites are less frequently observed than in other NHL. The bone marrow (BM) and the central nervous system (CNS) are rarely involved.[87]

### T-Cell Tumors

***Lymphoblastic Lymphoma*** Lymphoblastic lymphomas (LL) make up approximately 30% of childhood NHL.[12,82,83,86] In pediatric patients with LL, 75% will have a T-cell immunophenotype. The remaining LL patients have a precursor B-cell phenotype more commonly presenting as disease localized in skin and bone rather than T-cell LL. Some oncologists and pathologists feel LL is acute lymphoblastic leukemia in an extramedullarly site. Whether the LL is a T cell or B cell does not affect prognosis. LL tumors have a precursor lymphoblast phenotype (TdT [terminal deoxynucleotidyl] positive) and express T-cell markers, including CD7 or CD5.[12,102.] Although there is no genetic signature, T-cell rearrangements are common, as well as several cytogenetic and molecular changes.[12,103,104] Because thymic residence is a necessary part of T-cell development, most lymphomas presenting in the anterior mediastinum originate from the T-cell lineage. Fifty percent to 70 percent of patients with lymphoblastic lymphoma (T cell) present with an intrathoracic tumor. Abdominal involvement is uncommon and, when observed, usually includes hepatosplenomegaly. Bone marrow infiltration is common in this situation, making the distinction from acute lymphoblastic leukemia difficult. In these cases, survival may be better after treatment with a lymphoblastic leukemia–type regimen. Pleural effusions are often observed, and patients may complain of dyspnea, chest pain, or dysphagia. Superior vena cava syndrome with facial, chest, and upper extremity edema and dilated cutaneous veins over the upper torso and shoulders, or airway compression with severe dyspnea or orthopnea (or both) can also occur. The central nervous system is rarely involved at diagnosis.

***Anaplastic Large T-Cell Lymphoma*** ALCL is a mature T-cell cancer and accounts for 10% of NHL in children. Morphologically, ALCL are characterized by large cells with big cytoplasms and horseshoe- or kidney-shaped nuclei called hallmark cells.[105] More than 90% of ALCL cases are CD30-positive (Ki- antigen) and have the translocation t(2;5)(p23;q35). This results in production of a fusion protein NPM/ALK, although variant *ALK* translocations have been reported.[106] The WHO divides ALCL into systemic (ALK+ and ALK−) and cutaneous lymphomas. ALK− is predominantly found in adults with a poorer prognosis, with OS of 45%. ALK+ prognosis is good, with an 80% OS.[107–109] The cutaneous form is extremely rare in children and only accounts for 1.7% of ALCL; its OS is 90%. Clinically, ALCL has a broad range of presentations, including involvement of lymph nodes and a variety of extranodal sites, particularly skin and bone. Involvement of the CNS and bone marrow is uncommon. As opposed to other pediatric NHL, ALCL is often associated with B symptoms (e.g., fever and weight loss), and a prolonged waxing and waning course can complicate and often delay diagnosis.

***Post-Transplant Lymphoproliferative Disorders*** The 2% to 4% risk of developing cancer after solid organ transplantation (SOT) is about 5- to 10-fold greater than that of the general population. The risk correlates with the intensity and cumulative exposure to immunosuppression.[110] The lowest frequency seen is in renal transplant recipients (1%), and the highest is in heart-lung or liver-bowel allografts (5%). EBV seronegativity at time of transplant and young age at transplant are the two greatest risk factors for subsequent PTLD. In children, post-transplant lymphoproliferative disorders (PTLDs) may occur early, because of their risk for a primary EBV infection.[111] Many of the tumors exhibit an EBV-induced monoclonal or, more rarely, polyclonal B-cell or T-cell proliferation as a consequence of immune suppression.[112] The diagnosis can be difficult and patients tend to present with nonspecific findings, such as episodic and unexplained fever, weight loss, and fatigue. A high index of suspicion is needed to diagnose PTLD. The tumors can occur both within and outside the allograph, including lymphoid tissue, gastrointestinal (GI) tract, lung, and liver. Involvement of the GI tract may present with vomiting, diarrhea, bleeding, intussusception, or obstruction. Perforation may occur at presentation or immediately following initiation of therapy in the presence of transmural necrosis of the lesion.

## TREATMENT AND OUTCOMES

### Chemotherapy for Non-Hodgkin Lymphoma

Non-Hodgkin lymphomas in childhood are in most cases disseminated at diagnosis. Chemotherapy is the primary treatment modality. Each regimen is divided into phases of induction, consolidation, reintensification, and maintenance.

Historically, only 20% to 30% of patients with non-Hodgkin lymphoma survived for 5 years until the pioneering work of Wollner and colleagues in 1975, when the $LSA_2$-$L_2$ (cyclophosphamide, vincristine, methotrexate, daunorubicin, prednisone, cytarabine, thioguanine, asparaginase, carmustine, hydroxyurea) regimen, adapted from the treatment of acute lymphoblastic leukemia, resulted in a 73% salvage rate.[113,114] At the same time, Ziegler and colleagues reported similar success with treatment of these patients using the COMP (cyclophosphamide, Oncovin [vincristine], methotrexate, prednisone) regimen.[115,116] A third important NHL treatment regimen is the Berlin-Frankfurt-Münster (BFM). This is a similar regimen to $LSA_2$-$L_2$.The main difference is the earlier application of L-Asp and high-dose methotrexate (MTX) in the BFM regimen.

The results of the Children's Cancer Group (CCG) randomized trial CCG-551 is considered one of the main studies to alter therapy for NHL in children. It compared $LSA_2$-$L_2$ with COMP. This study stratified treatment modalities by biological subgroups. The three main findings were (1) different chemotherapy regimens exert different effects in different NHL subtypes, (2) differences in treatment efficacy are seen mainly in advanced-stage disease, and (3) in advanced-stage disease, the differences in treatment efficacy are more pronounced in patients with LBL (i.e., patients receiving $LSA_2$-$L_2$ had fewer relapses) and BL (i.e., patients receiving COMP did better), while event-free survival (EFS) rates were not significantly different between treatment regimens in patients with large cell lymphoma.[117] A Pediatric Oncology Group trial further helped with the stratification issue by demonstrating that even in patients with localized disease, different strategies had different effects in histologic subgroups.[118] Despite the different disease process, stages, and stratification, most treatment regimens are based on one of the three regimens described previously with adjustment made for stage, histology, and phases of therapy. For example, LBL protocols are continual exposure to cytostatic agents over a long period of time; BL/BLL and DLBCL are treated with rapid repeated short, dose-intense chemotherapy courses. ALCL have a completely different strategy.[90]

## Surgery

Initial surgical management includes incisional biopsy for diagnosis, followed by intense, multiagent chemotherapy, except for small, easily resectable lesions.[119] Resection of massive retroperitoneal or mediastinal masses is not indicated. In abdominal BL, the extent of disease is a more significant predictive variable than is completeness of surgical resection. The surgical committee of the Children's Cancer Group (CCG) evaluated the role of surgical therapy in 68 patients with non-Hodgkin lymphoma in the CCG-551 study.[60] Tumor burden was the most important prognostic factor. However, in disease that can be completely resected, it may improve EFS and prevent complications such as bowel perforation. In the setting of localized disease, data do support a role for complete resection.[120–122]

## Radiation Therapy

In the treatment of localized non-Hodgkin lymphoma, radiation therapy has been shown to add toxicity with no therapeutic benefit. Several studies continue to show that radiotherapy has a limited role (stage I disease) in the treatment of NHL.[123] Radiation is used for CNS disease with limited effects and is controversial.[124]

## Burkitt Lymphoma and Burkitt-Like Lymphoma and Diffuse Large B-Cell Lymphoma

Most BL and BLL regimens are derived from the $LSA_2$-$L_2$ or BFM regimens with the use of methotrexate (MTX) for CNS disease. Rituximab is currently being studied in clinical trials, because it has shown good results in adult NHL. Because of its high proliferation rate, BL therapy uses cytotoxic drug concentrations over a period and drugs with different mechanisms of action with nonoverlapping toxicities that is sufficient to affect as many lymphoma cells as possible during the active cell cycle, using either fractionated administration or continuous infusion.[125] Treatments use high-dose intensity and short treatment intervals. Although these regimens are effective, they are toxic even with use of granulocyte colony–stimulating factor (G-CSF), because up to 3% can die from treatment complications.[126,127] One particular threat is acute tumor cell lysis syndrome (ATLS). Depending on the size of the tumor, the acute lysis of many tumor cells places a tremendous metabolic load on the kidneys, composed of phosphates, potassium, purines, and protein. Patients may present with elevated serum uric acid, lactate, and potassium levels. This syndrome may be further aggravated during the initial massive cell lysis caused by chemotherapy. ATLS can result in hyperuricemic nephropathy and renal shutdown. Patients with localized resected tumors have nearly 100% EFS with two 5-day therapy courses. Recent trials report overall survival rates of 98%, 90%, and 86% in stage I/II, III, and IV disease, respectively.[128] DCLC also has excellent outcomes when treated on BL and BLL protocols with event-free survival reaching 97%.

## Lymphoblastic Lymphoma

Event-free survival for children with LL ranges from 60% to 90%, with 5-year survival, with lower stages reaching 90%.[129–132] Most current treatments are based on one of two protocols: the $LSA_2$-$L_2$ protocol (cyclophosphamide, vincristine, methotrexate, daunorubicin, prednisone, cytarabine, thioguanine, asparaginase, carmustine, hydroxyurea) or the BFM group strategy. Each uses similar drugs divided into phases of induction, consolidation, reintensification, and maintenance. The main differences between the protocols are earlier application of L-Asp and high-dose MTX in the BFM regimen. Treatment intensity is stratified according to stages I and II versus stages III and IV. Children with stage I/II are rare and achieve EFS rates higher than 90% with reduced-intensity (omission of reintensification in the BFM protocol) and full-length maintenance therapy. Most relapses occur early. Radiation is used for CNS disease with limited effects and is controversial.[124]

A current COG study is looking at the benefit of high-dose MTX with added cyclophosphamide and anthracycline during induction with the regimen from the BFM-95. The study is still open and accruing patients.

## Anaplastic Large Cell Lymphoma

ALCL uses different treatment for local and systemic disease. Patients with localized disease show the best results with pulsed multiagent chemotherapy similar to the regimen used

in mature B-cell NHL reporting overall survival of 93%. Children and adolescents with disseminated ALCL have a poorer survival of 60% to 75%. It is unclear which strategy is best for the treatment of disseminated ALCL. COG is testing the replacement of vincristine with vinblastine in the maintenance phase of the APO regimen (doxorubicin, vincristine, and prednisone.)

## TOXICITIES

The long-term toxicity profile for patients with NHL is very similar to HL. Acutely, the NHL regimens, because of their intensity, tend to be more toxic as described previously.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 39

# Ovarian Tumors

Daniel Von Allmen and Mary E. Fallat

## Ovarian Tumors Incidence

Primary cysts and tumors of the ovaries are uncommon in children. The majority of these masses are not malignant.[1] Gynecologic malignant conditions account for approximately 2% of all types of cancer in children, and 60% to 70% of these lesions arise in the ovary.[2] The North American Association of Central Cancer Registries released data from 1992 to 1997 regarding more than 1.6 million women and children diagnosed with cancer.[3] This report revealed that 1.2% of ovarian cancer cases occurred in females between birth and age 19 years.[3] Lindfors[4] analyzed several large series of ovarian tumors in children and estimated that the annual incidence of combined benign and malignant lesions was 2.6 cases per 100,000 girls younger than 15 years. Using the Surveillance, Epidemiology, and End Results (SEER) registry, 1,037 pediatric patients with malignant ovarian tumors were identified.[5] The age-adjusted incidence of malignant ovarian tumors in those less than 9 years was 0.102 versus 1.072 per 100,000 in those aged 10 to 19 years old. Malignancy is very rare in children less than 5 years old. The predominant pathology was germ cell tumors in all age groups (77.4%) and 61.7% of tumors occurred in patients 15 to 19 years old. The concept that the highest incidence of malignant conditions occurs in the youngest patients has been reassessed. Newer diagnostic imaging techniques have increased the detection of all gonadal masses, and the frequency of ovarian cancer has decreased.

## Epidemiology

A few syndromes or diseases are associated with ovarian pathology. The Peutz-Jeghers syndrome is associated with granulosa cell tumors, ovarian cystadenomas, and sex cord–stromal tumors with annular tubules.[6] Juvenile granulosa and Sertoli-Leydig cell tumors are detected with Ollier disease (multiple enchondromatosis)[7] and juvenile granulosa cell tumors and fibrosarcoma with Maffucci syndrome (enchondromatosis and hemangiomas).[8,9] Sclerosing stromal tumors are associated with the Chédiak-Higashi syndrome (oculocutaneous albinism, pyogenic infections, and leukocyte granule abnormalities that result in deficient phagocytosis).[10] The presence of ovarian cysts had been noted in various dysmorphic syndromes, including those with craniofacial, laryngeal, and digital malformations.[11] The McCune-Albright syndrome (triad of café-au-lait macules, polyostotic fibrous dysplasia, and autonomous endocrine hyperactivity) is generally characterized by gonadotropin-independent sexual precocity resulting from recurrent ovarian follicle formation and cyclic estradiol secretion.[12] Fibromas are associated with the basal cell nevus syndrome.[13]

Nulliparity and increased education are associated with a greater risk of the development of ovarian cancer.[14] Women who have never used oral contraceptives have a greater risk than women who have used them, and hormone replacement therapy slightly increases the risk.[15] Other potential but more controversial risk factors include exposure to ovulation-inducing drugs without successful pregnancy and diets high in meat and animal fats, dairy products, and lactose. The risk is not uniform across histotypes for most of these factors. Prior tubal ligation and hysterectomy may reduce the risk of epithelial ovarian cancer.[16–18] More recent reports suggest that higher body mass index (BMI) may predict a higher risk of ovarian malignancy in women presenting with adnexal masses, and avoidance of obesity and smoking seem protective against development of benign serous and mucinous epithelial ovarian tumors.[19,20] Late age at menarche, earlier age at menopause, the use of vitamin E supplements, and fish consumption tend to be associated with a decreased risk of some histologic subtypes. Occupational physical activity seems protective against all histotypes.[16]

Approximately 5% to 10% of women with breast and ovarian cancer have a genetic predisposition. High percentages of hereditary breast and ovarian cancers arise from mutations in the tumor suppressor genes *BRCA1* and *BRCA2*. Approximately 70% of familial ovarian cancer cases are caused by *BRCA1* mutations and 20% by *BRCA2*. These mutations are inherited in an autosomal dominant fashion. If a woman is a carrier of one of these gene mutations, she has a lifetime risk of developing ovarian cancer as high as 60%.[21,17] Genetic testing of adolescents is controversial.[22] Kodish[23] formulated the argument that physicians should respect the “rule of earliest onset” and defer testing until the age when the onset of disease becomes possible. An alternative view proposed by Elger and Harding[24] is that some mature adolescents may obtain significant psychological relief from knowing their mutation status and may be capable of using this information for reproductive and health decisions. In most cases, surgical intervention is not indicated until age 35 years or older or completion of childbearing. The use of oral contraceptives

has been shown to reduce the risk of ovarian cancer in the general population. Whether the use of these agents in young women with *BRCA* mutations is beneficial remains to be determined.[17]

# Clinical Presentation

The clinical presentation is variable and does not differentiate a benign from a malignant tumor. Abdominal pain is the most common symptom.[22,25] With cysts and other nonneoplastic conditions, the pain can be acute in onset, with a crescendo pattern of severity because of torsion, rupture, or hemorrhage. The clinical picture may mimic appendicitis. A more chronic, insidious pattern of pain, increasing girth, and marked distention over several weeks to months may occur. Secondary symptoms include anorexia, nausea, vomiting, and urinary frequency and urgency. A palpable abdominal mass with or without tenderness is the most frequent finding on physical examination and is detected in more than half of patients with ovarian tumors.[22] These tumors are usually mobile and palpable above the pelvic brim. Bimanual palpation between the lower abdomen and rectum may be helpful in detecting smaller lesions. Vaginal examination is usually reserved for sexually active patients, although vaginal inspection is of value in all patients. An increasing number of ovarian lesions are discovered incidentally by abdominal radiographs or ultrasonography (US) done for other reasons.

Both neoplastic and nonneoplastic ovarian lesions demonstrate endocrine activity in approximately 10% of cases.[13] Ovarian cysts of the simple, follicular, or luteal type may secrete estrogen and can cause precocious isosexual development. The lesions usually function autonomously, and the girls have suppressed gonadotropin concentrations. As a result, they can be distinguished from patients with central precocious puberty (with accelerated skeletal maturation) or premature thelarche (isolated breast development) by estrogen withdrawal and vaginal bleeding after cyst involution or removal. Precocious pseudopuberty may occur because of the production of human chorionic gonadotropin in girls with germ cell tumors, including dysgerminomas, yolk sac tumors (YSTs), and choriocarcinomas. Ovarian tumors most commonly associated with precocious puberty include the sex cord–stromal tumors, such as juvenile granulosa cell tumors or some Sertoli-Leydig cell tumors, which cause elevated levels of circulating estrogen. In the Grumbach syndrome, hypothyroidism presents with precocious puberty and bilateral ovarian cystic masses that resolve with thyroid replacement therapy.

Virilization resulting from androgen excess can occur with Sertoli-Leydig cell tumors, and masculinization is occasionally seen in older girls with dysgerminomas that contain syncytial trophoblastic giant cells. Yolk sac tumors, steroid cell tumors, and polycystic ovaries can be associated with virilization.

# Diagnosis

## LABORATORY TESTS

Many ovarian neoplasms are associated with the secretion of specific tumor markers or hormones. These are outlined in Tables 39-1 and 39-2 and are discussed further in the sections on individual tumors.

**TABLE 39-1**
**Ovarian Tumor Markers**

| | *CA 125* | *AFP* | *hCG* | *Inhibin* |
|---|---|---|---|---|
| **Germ Cell Tumors** | | | | |
| Dysgerminoma | +/− | − | +/− | − |
| Yolk sac tumor* | +/− | + | − | − |
| Choriocarcinoma | +/− | − | + | − |
| Embryonal carcinoma | +/− | +/− | +/− | − |
| Immature teratoma | +/− | +/− | − | − |
| Mixed germ cell tumor | +/− | +/− | +/− | − |
| **Epithelial-Stromal Tumors** | | | | |
| Serous carcinoma | + | − | − | − |
| Mucinous carcinoma | +/− | − | − | + |
| Endometrioid carcinoma | + | − | − | + |
| **Sex Cord–Stromal Tumors** | | | | |
| Granulosa cell tumor | +/− | − | − | + |
| Thecoma-fibroma | +/− | − | − | + |
| Sertoli-Leydig cell tumor | +/− | +/− | − | + |

*Endodermal sinus tumor
Comments: CA 125 levels may be slightly elevated in any of the ovarian tumors. LDH levels are useful for staging and risk assessment in germ cell tumors.
AFP, alpha fetoprotein; CA 125, cancer antigen; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.
Table courtesy Dr. Robert Debski, Assistant Professor of Pediatrics and Pathology, University of Louisville.

### Tumor Markers

Germ cell tumors are associated with various biologic markers that are useful in identifying and managing this group of tumors.[26] Protein markers, including alpha fetoprotein (AFP), beta-human chorionic gonadotropin (beta-hCG), and lactate dehydrogenase (LDH), are the most readily available. They are measured with serum assays or immunohistochemical staining of paraffin-fixed or frozen tumor.

### Alpha Fetoprotein

Because the fetal yolk sac is the source of AFP early in human embryogenesis, elevations of the marker occur with yolk sac tumors.[27] This is also true with hepatoblastoma, hepatocellular carcinoma, and teratocarcinoma.[28] The elevation reflects the presence of fetal tissue from which normal progenitor cells arise. There is wide variability in normal levels of AFP from birth through the first year of life,[29] and AFP is significantly elevated in premature and normal newborns. Its usefulness in the diagnosis of yolk sac tumor or embryonal carcinoma in the first month of life is limited. Its value in tumor identification begins when the AFP level is significantly elevated over the normal range at any particular age. The normal serum half-life of AFP is 5 to 7 days. Its decline after removal of an AFP-producing tumor signifies a response to treatment. The goal of any treatment is to return AFP to normal levels. Tumor recurrence is marked by a sudden elevation of the AFP level.

### Beta-Human Chorionic Gonadotropin

Beta-hCG is a glycoprotein produced by placental syncytiotrophoblasts. It comprises two subunits, alpha and beta; the latter can be reliably assayed.[30] Beta-hCG elevation in a patient with a germ cell tumor suggests the presence of syncytiotrophoblasts, as seen in seminoma, dysgerminoma, choriocarcinoma,

**TABLE 39-2**
**Ovarian Tumors and Hormones**

| *Histologic Subtype* | *Estradiol* | *Testosterone* | *Urinary 17-ketosteroid* | *Gonadotropin* | *MIS* |
|---|---|---|---|---|---|
| Ovarian cyst | | | | | |
| Simple | ↑ | | | | |
| Follicular | ↑ | | | | |
| Luteal | ↑ | | | | |
| Sex cord–stromal | | | | | |
| Juvenile granulosa | ↑ | ↑‡ | | ↓ | ↑§ |
| Sertoli-Leydig | ↑* | ↑† | | ↓ | |
| Luteinized thecomas | ↑ | ↑‡ | | | |
| Sex cord tumors with annular tubules | ↑ | | | | |
| Steroid cell tumor | | ↑ | ↑ | ↓ | |
| Gonadoblastoma | ↑‡ | ↑ | ↑ | ↓ | |
| Choriocarcinoma | ↑ | | | ↑ | |

*Functioning Sertoli cells predominate.
†Functioning Leydig cells predominate, biologic marker for disease behavior.
‡Indicates rarer variants of the tumor.
§May be useful tumor marker for diagnosis and follow-up.
MIS, Müllerian inhibiting substance.

and, occasionally, embryonal carcinoma.[31] Elevations greater than 100 ng/mL are unusual and suggest the diagnosis of choriocarcinoma.[32] Unlike the much longer half-life of AFP, the beta subunit has a half-life of 20 to 30 hours.[32] Its rapid disappearance implies complete removal of a tumor.

### Serum Lactate Dehydrogenase

Serum LDH is a nonspecific marker that is widely distributed in human tissues and is therefore of limited value in establishing tumor type or response to treatment. However, elevated LDH may indicate increased cell turnover and has been used as a nonspecific indicator of malignancy.[33] It is most useful as a prognostic marker for lymphoid tumors and neuroblastoma. The gene for this isoenzyme is located on 12p, and nonrandom structural changes in chromosome 12 have been seen in all histologic subtypes of germ cell tumors, particularly dysgerminoma.

### CA 125

CA 125 is the best available marker for epithelial ovarian cancer, although it lacks sensitivity for stage I disease and specificity for early ovarian cancer. Levels greater than 35 U/mL may indicate malignant or borderline ovarian tumors. However, levels are also occasionally raised in some benign conditions, including endometriosis, uterine myomas, acute and chronic salpingitis, and pelvic inflammatory disease.[34] One small series showed a low sensitivity and specificity of CA 125 for detection of epithelial ovarian malignancy in premenarchal girls.[35]

## VALUE OF FROZEN SECTION FOR INTRAOPERATIVE DIAGNOSIS

Benign, borderline, and malignant lesions have been identified within the same surgical specimen, suggesting evolution from dysplasia to cancer in some cases, although frequency and speed of this process remain unknown. A quantitative systematic review performed to estimate the diagnostic accuracy of frozen sections compared with paraffin sections, including specimens from 3,659 women aged 1 to 95 years concluded that diagnostic accuracy rates were high for both malignant and benign tumors but low in borderline tumors.[36] This has relevance because a fertility-sparing approach can be used in borderline tumors, but surgeons confronted with this potential diagnosis during surgery should also use a standard approach for staging (discussed later in this chapter), because determination of extent of disease has implications for future treatment and prognosis.[36]

## IMMUNOHISTOCHEMISTRY

Immunohistochemistry (IHC) has had a major impact in recent years as an aid to diagnosis in ovarian neoplasia. From a practical standpoint, the time-honored approaches, including gross and microscopic features, thorough sampling, and consideration of patient age and presence or absence of coexisting endometriosis, still take precedence. In general, IHC panels should include markers which are expected to be positive (and negative) in the various tumors in the differential diagnosis. Virtually no antibody is specific for any given tumor, and unexpected positive and negative immunoreactions may occasionally occur. In ovarian pathology, IHC seems to be most valuable in the evaluation of tumors with follicles or other patterns that bring a sex cord–stromal tumor into the differential. The two most useful markers are alpha inhibin and calretinin. Calretinin is a slightly more sensitive marker of ovarian sex cord–stromal tumors as a group, but alpha inhibin, produced by granulosa cells, is a more specific marker, because most other ovarian neoplasms are negative.[37,38]

## CANCER GENETICS

Ovarian germ cell tumors are associated with sex chromosome abnormalities. Although a few case studies suggest otherwise, a large study examining 456 first- or second-degree female relatives of 78 patients with ovarian germ cell tumors did not identify an increased risk for occurrence.[39] Some abnormal karyotypes are associated with abnormal gonads that are predisposed to the development of germ cell tumors.

The application of new cytogenetic technologies has increased our understanding of the genetics and molecular mechanisms involved in the development of germ cell tumors. Nonrandom changes in molecular structure have commonly been reported in chromosomes 1 and 12, as well as in others.[40–42] For example, the chromosomal aberration of trisomy 12 has been identified in many stromal tumors.[43] An isochromosome is a chromosome in which both arms are derived from one of the two arms by breakage at the centromere and subsequent duplication. Isochromosome 12p [i(12p)] has been identified in all types of germ cell tumors,[44–47] including testicular germ cell tumors in men.[46] The presence of three or more copies of i(12p) has been associated with treatment failure.[41] Nonrandom endodermal sinus tumors in children involve the deletion of segments of chromosome 1p and 6q. Deletion of the terminal portion of 1p has been identified in other tumors, indicating that it may be a locus of one or more tumor suppressor genes not yet characterized. Endodermal sinus tumors in children may show cytogenetic differences from adults with no evidence of i(12p), but with deletions involving 1p, 3q, and 6q.[48] The c-*MYC* oncogene has been found in a few endodermal sinus tumors, and the current Children's Oncology Group protocol will begin to correlate amplification with survival and response to therapy.[49] Further studies are required to determine the significance of these findings. Many germ cell tumors in children express P-glycoprotein, a membrane-bound protein that can decrease the response to chemotherapy; this may explain why these tumors are frequently resistant to treatment.[50]

### Role of Tumor Markers in the Incidentally Identified Ovarian Mass

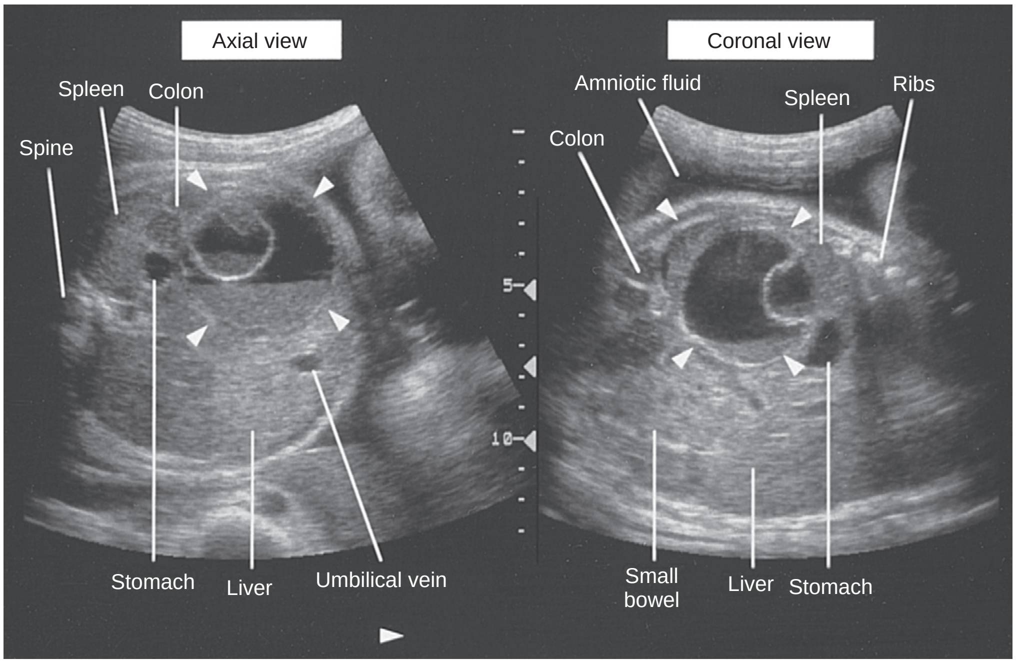
If a mixed cystic and solid ovarian mass is discovered incidentally on an imaging study, a preoperative AFP, beta-HCG, and CA-125 assay should be done. If normal, the mass should be removed with ovarian sparing, if possible. If any of these are elevated, a chest CT should be included in the evaluation to look for metastatic disease. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), estradiol and lactate dehydrogenase (LDH) serum levels should be added to the preoperative testing if there are signs of precocious puberty.[51]

## IMAGING TECHNIQUES

Various radiographic studies play an important role in the clinical evaluation of pediatric ovarian lesions. Prenatal US can usually differentiate ovarian lesions from intestinal duplication, hydronephrosis, duodenal atresia, choledochal cyst, urachal remnants, hydrometrocolpos, and intestinal obstruction (Fig. 39-1). Mesenteric and omental cysts are more difficult to distinguish from simple ovarian cysts, because the ovary is an abdominal rather than a pelvic organ in an infant.

US is the diagnostic study of choice for the initial evaluation of potential ovarian pathology in all age groups. Adequate urinary bladder distention is mandatory to displace gas-filled intestinal loops out of the pelvis and to ensure adequate sound wave transmission through the ovaries. Ovarian volume changes with age from less than 0.7 $cm^3$ in girls younger than 2 years to 1.8 to 5.7 $cm^3$ in postpubertal patients.[52] Morphologic characteristics also change. In children younger than 8 years, the ovaries are generally solid, ovoid structures with a homogeneous echogenic texture. During and after puberty, the ultrasonographic spectrum of the gonad undergoes cystic changes that parallel ovulatory follicle activity in the organ. Ovarian cysts are generally anechoic, thin-walled masses with through transmission. With torsion, fluid debris or septation may be present.[53] Most benign tumors are complex masses that are hypoechoic with peripheral echogenic mural nodules, which may exhibit acoustic shadowing. Malignant tumors are

A




B

**FIGURE 39-1** **A** and **B,** Two views of an ultrasonogram of a fetus in the third trimester. A large, complex ovarian cyst containing fluid debris, internal septation, and solid components can be seen (*arrowheads*). An ovarian neoplasm was identified during surgery after birth. (Courtesy Gary A. Thieme, MD, Prenatal Diagnosis Center, University of Colorado School of Medicine.)

often larger in diameter and appear as complex soft tissue masses with ill-defined, irregular borders and central necrosis, thick septations, or papillary projections on US. Doppler color-flow imaging and transvaginal US are also valuable in postpubertal patients to determine morphologic characteristics of ovarian lesions.[54,55] When vessels are located in the central, septal, or papillary projections, together with a diffuse vascular arrangement, the tumors are likely to be malignant.[56] Other discriminating factors include the presence and nature of solid components and free intraperitoneal fluid. Based on the premise that angiogenesis is a neoplastic marker for malignancy, newer methods of ultrasonography using high-resolution color Doppler with extended flow (e-flow) have resulted in better discrimination of malignancy because of higher sensitivity in detection of blood flow in minute vessels.[57]

Computed tomography (CT) and magnetic resonance imaging (MRI) are useful when the origin of the pelvic mass cannot be established by US or when assessment of the full extent of a noncystic lesion is necessary. The characteristic finding of a benign tumor on CT is a fluid-filled mass with fat and calcifications.[58] Focal solid components arising from the tumor wall are common (Fig. 39-2). Malignant lesions are large and predominantly solid with occasional cystic areas as well as fine or coarse calcifications. Direct extension of tumors to adjacent pelvic structures or to the liver and lungs can also be demonstrated by CT, which provides more accurate staging of disease than US. Adnexal torsion in association with any tumor has a distinct appearance on CT, which is demonstrated by dynamic scanning after the administration of contrast medium. The appearance is generally characterized by lack of enhancement of mural nodules, which indicates interruption of blood flow, and demonstration of thick, engorged blood vessels that drape around the tumor and indicate markedly congested veins distal to the site of torsion.

MRI is well suited for imaging pelvic lesions, because it is not influenced by extensive subcutaneous fat and offers superb soft tissue contrast resolution.[59] The technique is especially valuable in determining whether a mass is ovarian or uterine in origin, and it contributes to the characterization of adnexal masses based on criteria suggestive of benignity (fatty components, shading on T2-weighted images) or malignancy (vegetations or solid portions within cystic masses).[60] MRI accuracy can reach 91%. The long imaging times required may cause peristalsis and respiratory motion to obscure peritoneal and intestinal surfaces, and sedation may be needed in small children. Ovarian torsion with hemorrhagic infarction can be detected on MRI by the finding of a high-intensity rim at the periphery of the mass on the T1-weighted image.[61]

Positron-emission tomography (PET) scanning is a newer modality that may play a role in the differentiation of malignant from borderline ovarian tumors.[62] PET and PET-CT have a potential role in evaluating patients for recurrent ovarian cancer, particularly those with negative CT or MRI findings and rising tumor marker levels. Fused PET-CT scans obtained with combined scanners can help localize pathologic activity and differentiate this activity from physiologic radiotracer uptake.[63]

## Disease Classification and Staging

Ovarian lesions are generally divided into nonneoplastic and neoplastic entities; the former category includes functioning cysts, and the latter includes benign and malignant tumors. The clinical system presented here is modified from the most recent version of the World Health Organization's proposal for

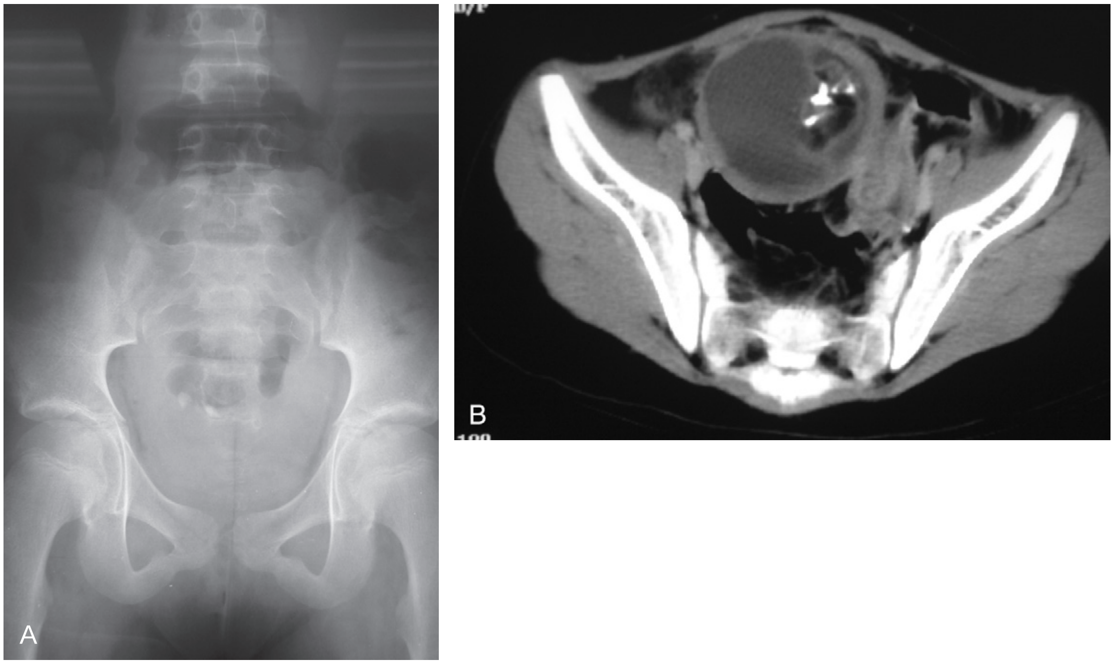



FIGURE 39-2 **A,** Plain abdominal radiograph of a 16-year-old girl with a unilateral ovarian teratoma; the pelvic mass contains toothlike calcifications. **B,** Computed tomography scan of a large, calcified abdominal mass. The mass has a large cystic component, with solid, thickened walls that are eccentric in appearance. The tumor was a thin-walled fibrous cyst with extensive hemorrhagic infarction throughout the entire cyst wall. Histology was consistent with a benign cystic teratoma.

**TABLE 39-3**
**World Health Organization Histologic Classification of Nonneoplastic Ovarian Lesions**

000 Ectopic pregnancy
D27 Benign neoplasm of ovary
E28 Ovarian dysfunction
 E28.2 Polycystic ovarian syndrome
N70-77 Pelvic inflammatory disease
N80 Endometriosis
N83 Noninflammatory disorders of ovary, fallopian tube, and broad ligament
 N83.0 Follicular cyst of ovary
 N83.1 Corpus luteum cyst
 N83.2 Other and unspecified ovarian cysts (simple cyst)
 N83.8 Other noninflammatory disorders of ovary, fallopian tube and broad ligament

From WHO International Classification of Diseases (ICD), 2007. Available at http://www.who.int/classifications/icd/en/. Accessed June 6, 2010. WHO International Statistical Classification of Diseases and Related Health Problems, revision 10, 2007.

the international histologic classification of diseases and its adaptation for oncology (Tables 39-3 and 39-4).[64–66] Nonneoplastic and neoplastic lesions may arise from surface epithelium, germ cell components, or support stroma. Neoplastic lesions are listed based on the tissue of origin.

Proper management of ovarian neoplasms requires accurate staging of the initial extent of disease. In malignant cases, recent advances in therapy have resulted in increased survival rates and preservation of fertility. Surgical staging with histologic confirmation must be done to supplement the clinical assessment of disease status. Precise staging is based on clinical examination, surgical exploration, tissue histology, and fluid cytology. In the United States, staging of epithelial ovarian cancer is performed at the time of surgery using the International Federation of Gynecology and Obstetrics (FIGO) staging system of 1988 (which was evaluated and not changed in 2009) (Table 39-5).[67,68] This system is ideal, because it accurately correlates clinical findings with survival in a continuum. However, the FIGO staging protocol does not describe the thoroughness of the lymphadenectomy required for ovarian cancer staging, and it has been suggested that the number of lymph nodes obtained at surgery has prognostic and clinical significance.[68]

Because ovarian neoplasms are relatively uncommon, evaluation and treatment protocols developed from multi-institutional collaborative studies have been valuable. Stromal and germ cell tumors have been assessed in studies from the Children's Cancer Group (CCG), the Pediatric Oncology Group (POG), and the Gynecologic Oncology Group (GOG).[49,69–71] In children, the intergroup POG 9048/9049 and CCG 8882/8891 studies used a system that incorporated both surgical and pathologic findings.[70] This concept has been preserved by the Children's Oncology Group (COG) (Table 39-6). Uniform surgical guidelines that incorporate standard approaches to these lesions have been formulated, although the approach to ovarian neoplasms has become more conservative with time.[72,73] Preoperative assessment should try to exclude obvious malignancy by the collection of serum tumor markers and carefully performed pelvic US to determine whether the ovarian mass is complex in nature.

**TABLE 39-4**
**World Health Organization Classification of Tumors of the Ovary**

1. Surface epithelial–stromal tumors
   1.1. Serous tumors
   1.2. Mucinous tumors
   1.3. Endometrioid tumors
   1.4. Clear cell tumors
   1.5. Transitional cell tumors
   1.6. Squamous cell tumors
   1.7. Mixed epithelial tumors
   1.8. Undifferentiated and unclassified tumors
2. Sex cord–stromal tumors
   2.1. Granulosa–stromal cell tumors
      2.1.1. Granulosa cell tumor group
         2.1.1.1. Adult
         2.1.1.2. Juvenile
      2.1.2. Tumors in thecoma-fibroma group
   2.2. Sertoli–stromal cell tumors
   2.3. Sex cord–stromal tumors of mixed or unclassified cell types
      2.3.1. Sex cord tumor with annular tubules
      2.3.2. Gynandroblastoma
   2.4. Steroid cell tumors
3. Germ cell tumors
   3.1. Primitive germ cell tumors
      3.1.1. Dysgerminoma
      3.1.2. Yolk sac tumor (endodermal sinus tumor)
      3.1.3. Embryonal carcinoma
      3.1.4. Polyembryoma
      3.1.5. Nongestational choriocarcinoma
      3.1.6. Mixed germ cell tumors (specify components)
   3.2. Biphasic or triphasic teratomas
      3.2.1. Immature
      3.2.2. Mature
   3.3. Monodermal teratomas
4. Germ cell sex cord–stromal tumors
   4.1. Gonadoblastoma
   4.2. Mixed germ cell–sex cord–stromal tumor of nongonadoblastoma type
5. Tumors of rete ovarii
6. Miscellaneous tumors
   6.1. Small cell carcinomas, hypercalcemic type
   6.2. Gestational choriocarcinomas
   6.3. Soft tissue tumors not specific to ovary
7. Tumorlike conditions
8. Lymphoid and hematopoietic tumors
9. Secondary tumors

(From International Classification of Diseases for Oncology, ed 3 (ICD-O-3). Creation date: 1976; last date change: 2000.

Elevated tumor markers and a complex mass on US strongly suggest a malignancy, and an abdominal and pelvic CT scan should be obtained. For potentially malignant lesions, an adequate abdominal incision is used, and violation of the tumor capsule is avoided. Alternatively, if tumor markers are negative and the mass is thought to be benign (e.g., a mature cystic teratoma) a laparoscopic approach can be considered.

Initial resection in pediatric patients should virtually always be conservative. Pelvic washings, unilateral ovarian cystectomy, intraoperative frozen section, and careful visual

**TABLE 39-5**
**Staging of Carcinoma of the Ovary: International Federation of Gynecology and Obstetrics (FIGO)**

| Stage | Extent of Disease |
|---|---|
| | Primary tumor cannot be assessed |
| 0 | No evidence of primary tumor |
| I | Tumor confined to ovaries |
| IA | Tumor limited to one ovary, capsule intact |
| | No tumor on ovarian surface |
| | No malignant cells in ascites or peritoneal washings |
| IB | Tumor limited to both ovaries, capsule intact |
| | No tumor on ovarian surface |
| | No malignant cells in ascites or peritoneal washings |
| IC | Tumor limited to one or both ovaries, with any of the following: |
| | capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings |
| II | Tumor involves one or both ovaries with pelvic extension |
| IIA | Extension to or implants on uterus or tubes or both |
| | No malignant cells in ascites or peritoneal washings |
| IIB | Extension to other pelvic organs |
| | No malignant cells in ascites or peritoneal washings |
| IIC | IIA or IIB with positive malignant cells in ascites or peritoneal washings |
| III | Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis or regional lymph nodes metastasis |
| IIIA | Microscopic peritoneal metastasis beyond the pelvis |
| IIIB | Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension |
| IIIC | Peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension or regional lymph nodes metastasis |
| IV | Distant metastasis beyond the peritoneal cavity |

**TABLE 39-6**
**Clinicopathologic Staging of Ovarian Germ Cell Tumors: Children's Oncology Group (COG)**

| Stage | Extent of Disease |
|---|---|
| I | Limited to ovary (peritoneal evaluation should be negative); no clinical, radiographic, or histologic evidence of disease beyond the ovaries (Note: The presence of gliomatosis peritonei does not change stage I disease to a higher stage.) |
| II | Microscopic residual; peritoneal evaluation negative (Note: The presence of gliomatosis peritonei does not change stage II disease to a higher stage.) |
| III | Lymph node involvement (metastatic nodule); gross residual or biopsy only; contiguous visceral involvement (omentum, intestine, bladder); peritoneal evaluation positive for malignancy |
| IV | Distant metastases, including liver |

inspection of the contralateral ovary are appropriate in the initial management of benign lesions or tumors of low malignant potential. Pelvic washings are part of the staging system for ovarian tumors and should be performed immediately on entry into the abdomen (by either laparoscopy or laparotomy) in an attempt to avoid contamination in the event of intraoperative tumor rupture. Because the final pathology will not be known until either frozen section or histologic evaluation of paraffin-embedded tissue, peritoneal washings should be performed in all patients with complex adnexal masses in case of an unsuspected malignancy. If there is no evidence of free fluid upon entering the abdomen, lactated Ringer solution can be used to irrigate the pelvis and paracolic gutters, then aspirated and sent as washings.

Malignant germ cell and stromal tumors are almost never bilateral in early-stage disease; so, unilateral salpingo-oophorectomy with a staging procedure is adequate first-line management. Excellent responses have been reported with chemotherapy, even in children with extensive tumors, and maintenance of childbearing capability is possible with this approach. In bilateral or more advanced disease, the current success of in vitro fertilization techniques has prompted the consideration of uterus-sparing procedures during the initial operation.[74,75] The expected biologic behavior of the tumor and its response to adjuvant therapy generally dictate the ultimate extent of surgery required. The value of laparoscopic examination in the assessment of pelvic disease is well established, because it will allow identification and management of ovarian masses as well as identification of nonovarian lesions.[76,77] The American Association of Gynecologic Laparoscopists reviewed more than 13,000 procedures performed for persistent ovarian masses.[78] Stage I ovarian cancer was detected in 0.4% of cases. Although these results are encouraging in adult women, there is concern about the difficulty of establishing the true nature of an ovarian tumor by gross examination in children, because experience with such an evaluation is so infrequent. Nevertheless, techniques are being established to avoid tumor spillage that may expand the use of this method. Experienced surgeons have performed more extensive staging procedures and lymph node dissections using the laparoscope.[79] Studies evaluating the laparoscopic approach have been retrospective and suggested that staging is safe, feasible, and a valid alternative, but there has been no prospective trial to date comparing the laparoscopic to open approach.[68]

# Treatment

## NONNEOPLASTIC OVARIAN TUMORS

Ovarian cysts are known to arise from mature follicles. Fetal FSH, LH, estrogens (maternal, placental, and fetal), and placental hCG all stimulate the ovarian follicle, and mature follicles can be found in more than half of newborn ovaries.[80] A postnatal decrease in hormonal stimulation often leads to a self-limited process. Autopsy studies of prepubertal girls have documented active follicular growth at all ages and in normal oocytes, granulosa cells, and cysts in various stages of involution.[81,82] By convention, physiologic follicles are differentiated from pathologic ovarian cysts on the basis of size, and any lesion larger than 2 cm in diameter is no longer considered a mature follicle.

Nonneoplastic cysts are benign and generally asymptomatic. Although surgical intervention is rarely indicated, these lesions occasionally have clinical manifestations, based on size or associated functional activity, that warrant differentiation from true ovarian neoplasms. When an operation is necessary, a conservative approach should be undertaken with the goal of ovarian preservation.

### Follicular Cysts

Follicular cysts represent about half of nonneoplastic ovarian lesions. They are unilateral, unilocular, and histologically benign and often have a thin, yellowish, clear liquid content. Cohen and associates[83] detected cysts in 84% of all imaged ovaries in 77 patients from birth to 24 months of age. The prevalence was similar in each 3-month age bracket. Parallel findings were noted in premenarchal girls between 2 and 12 years of age,[84] with a generally equal distribution across the age spectrum. Occasionally, ovarian cysts persist and enlarge and are capable of secreting estrogen, thereby leading to precocious isosexual development.[85]

The size of an ovarian lesion has been a major factor in determining clinical management.[80] Simple cysts, regardless of size, are more likely to regress. Larger cysts (>5 cm) have a greater risk of torsion. Larger cysts in children have a greater association with sexual precocity. Complex cysts may already have torsed or may be neoplastic. Complex cysts should be resected, rather than observed, in prepubertal children. Complex cysts in adolescents are most often due to hemorrhage into a functional cyst and can be managed conservatively with symptom control. Operation is indicated for persistent cysts or persistent symptoms despite conservative management.

Ovarian cysts noted in the prenatal period can be expected to spontaneously regress during the first year of life, and in utero therapy is seldom justified.[86,87] Cysts that develop in utero are most often lined by luteinized cells, whereas those in older children are more often lined by granulosa cells.[32] These lesions may occasionally be complicated by torsion, intestinal obstruction, or perforation and cyst rupture.[80,88] Bagolan and colleagues[89] and Giorlandino and colleagues[90] confirmed that echogenic cysts with fluid debris, retracting clot, or septation were associated with torsion and hemorrhage. In newborns, torsion is often a prenatal event, and viable ovarian tissue may not be identified, even with the most expeditious neonatal surgical intervention (Fig. 39-3). Most authors now advocate increasingly conservative measures for neonatal ovarian lesions.[80] Small, asymptomatic cysts are generally observed for regression with serial US. Cysts 5 cm in diameter or larger and those with a long adnexal pedicle are more likely to undergo torsion and may be excised with ovarian preservation or aspirated.[91] However, in one randomized study of postmenarchal patients, cysts greater than 5 cm in diameter and those with a complex appearance on imaging studies were followed for a short time with serial pelvic US. High regression rates were seen with those followed expectantly.[35] Although practitioners often reflexively prescribe oral contraceptive pills (OCPs), hormonal therapy has not been shown to improve the regression rates of ovarian cysts compared with those followed expectently.[92] Exploratory laparotomy or laparoscopy has been recommended for patients with cysts that do not resolve or increase in size within 2 to 3 months[92] and for cysts associated with acute or severe chronic abdominal pain or intra-abdominal complications.

FIGURE 39-3 This newborn female infant had a prenatal diagnosis of an intra-abdominal cystic mass. Postnatal imaging showed a low-attenuation cystic structure with a curvilinear calcification along one wall. Laparotomy disclosed a torsed ovarian cyst and ovary, attached by only a small residual stalk. The fallopian tube was preserved. Pathology showed a thin-walled cyst containing dystrophic calcifications.

In prepubertal children, the occurrence of acute symptoms and endocrine activity are more problematic. Surgical intervention is recommended for any cyst that increases in size or fails to regress on follow-up US or if there is evidence of a neoplasm on imaging studies.

As many as 75% of girls with juvenile hypothyroidism have large multicystic ovaries and may show varying degrees of sexual precocity and/or galactorrhea resulting from increased secretion of pituitary gonadotropins and prolactin.[93] Multiple follicular cysts should be distinguished from polycystic ovary syndrome, which is the most common cause of delayed puberty and heavy anovulatory bleeding in adolescent females.[94]

In nonneoplastic ovarian cysts, surgical preservation of as much normal ovarian tissue as possible is a high priority.[95] A plane of dissection can usually be established between the normal gonadal tissue and the cyst after injecting saline with a fine-bore needle beneath the visceral peritoneum. If the surgical manipulation necessary to completely remove the lesion would threaten significant viable ovarian tissue, the cyst should be unroofed and debulked, and the cyst wall excised to the extent possible, while protecting the ovary. Unilateral oophorectomy is indicated only if there is a reasonable certainty that no viable gonadal tissue can be salvaged. The ipsilateral fallopian tube should be spared, because fertilization is still possible from the contralateral normal ovary.

### Corpus Luteum Cysts

True functioning corpus luteum cysts develop only in adolescents who are actively ovulating. Although these cysts may be bilateral and become quite large, they usually regress spontaneously with the cyclic decline in serum progesterone. The gross appearance of the external surface is often bright yellow, although it may take on a hemorrhagic appearance when filled with bloody fluid. The cyst lining is composed of luteinized granulosa and theca cells and is capable of actively producing estrogen and progesterone. These cysts may cause acute pelvic pain if they rupture or undergo torsion. Failure of the corpus luteum to involute may cause menstrual irregularity and dysfunctional uterine bleeding. Surgical goals for corpus luteum cysts parallel those for other follicular lesions. Surgical intervention is indicated in the presence of cyst accident or persistence, demonstrated by repeat pelvic US performed 4 to 6 weeks after the initial assessment. Hasson[96] was able to treat 17 of 19 patients who had corpus luteum cysts with laparoscopic aspiration, fenestration, or cyst wall excision. Clinical symptoms resolved in all but one patient. Cyst recurrence was rare.

### Parovarian Cysts

Parovarian cysts are usually small and rarely symptomatic. They do not arise from ovarian tissue but are usually considered with this group of lesions because of their proximity to the gonad. These cysts originate from the epoophoron and are located in the leaves of the mesosalpinx. Parovarian cysts cannot be distinguished from ovarian follicular cysts using any radiographic imaging technique. During an operation, their gross features are virtually identical to those of follicular lesions, but they can usually be accurately distinguished because of their anatomic position. When surgical treatment is required, both standard open and minimally invasive techniques have been used.[96,97] Large parovarian cysts (>3 cm) should be completely enucleated from the mesosalpinx in such a way that the fallopian tube and ovary are not damaged.[98] Those less than 3 cm may be treated with puncture and bipolar coagulation of the cyst wall.[98]

### Endometriosis

Endometriosis is a disorder in which the endometrial glands and stroma are implanted on the peritoneal surfaces of extrauterine sites. The proposed mechanisms for the pathogenesis of this disease include menstrual flow obstruction with retrograde menstruation, mechanical transplantation and implantation of endometrial elements, and coelomic metaplasia.[99–101] The interval between the onset of menarche and the diagnosis of endometriosis may be as short as 1 month, and the incidence of disease in teenage girls may be far higher than previously anticipated or described.[102] Extensive disease and the presence of endometriomas is uncommon in children and young adolescents unless it is associated with an obstructive müllerian anomaly.[103] An endometrioma or endometrioid cyst may occur in the ovary and can be diagnosed by ultrasonography. Endometrioid *cysts* are filled with dark, reddish-brown blood and may range in size from 0.75 to 8 inches. Several surgical treatments are available for endometriomas, including simple puncture, ablation, removal of the cyst wall, or drainage and medical therapy, followed by later removal. Complete removal is the procedure of choice to decrease recurrence of disease. The revised American Fertility Society classification of endometriosis is widely accepted as the staging system for the disease and was developed as a prognostic tool for patients with infertility.[104] For patients with pelvic pain and a suspected diagnosis of endometriosis, medical therapy with nonsteroidal antiinflammatory drugs or oral contraceptives should be considered. Both medications act to suppress prostaglandins, which are known to be important in the pathophysiology of dysmenorrhea. These drugs along with gonadotropin hormone antagonists, used for a 6-month period, are the most commonly used medications.

## NEOPLASTIC OVARIAN TUMORS

Most neoplastic ovarian tumors develop from cell lines derived from one of three sources: the germinal epithelium covering the urogenital ridge, the underlying stromal elements of the urogenital ridge, or the germ cells that arise from the yolk sac. Cells from each of these lineages may develop into an ovarian neoplasm by de-differentiation, proliferation, and eventually malignant transformation.[105] Malignant ovarian tumors probably arise from their benign counterparts because of either direct or indirect hormonal stimulation.[106] Histologic and biologically intermediate forms between benign and malignant epithelial lesions have been identified and designate tumors of low malignant potential.

Age influences the relative frequency of the various types of ovarian neoplasms. In adults, most tumors are derived from the epithelial line and adenocarcinomas predominate. In children, germ cell tumors are most common and represent approximately 60% to 77% of cases.[105] Epithelial lesions account for approximately 15% of tumors in the younger age group.[95,107] Although germ cell tumors predominate in each age group, the peak incidence of sex cord–stromal tumors occurs in the first 4 years of life, and epithelial tumors are more common in older teenagers. Neoplasms that are rare in children include endometrioid and clear cell tumors (which are usually malignant); Brenner tumors, which are usually benign; disseminated malignant lymphoma; and metastatic lesions to the ovary.

### Surface Epithelial-Stromal Tumors

Epithelial tumors account for 70% of all ovarian neoplasms, but they are much less common in children. In most series, they account for approximately 15% of all surgically resected ovarian masses.[108] Norris and Jensen[109] reported that 67 of 353 ovarian tumors (19%) in children were epithelial in origin and 12% were malignant. The tumors are usually serous or mucinous.[13] Twenty percent of serous tumors are bilateral, and very few are malignant.[13,110] Mucinous tumors are usually unilateral, and 10% are malignant.[13] Deprest and colleagues[111] calculated a 16% malignancy rate for ovarian epithelial neoplasms derived from a collected series that reported more than 1700 pediatric patients with various types of ovarian tumors. Ovarian carcinoma is different in children than in adults. The proportion of mucinous tumors in children was 40% compared with 12% in adults, and 30% were of borderline malignant potential compared with the adult rate of fewer than 10% for these more favorable lesions. As previously discussed, serum CA 125 is a useful tumor marker in malignant epithelial ovarian tumors.[68] However, in premenopausal patients, it may also be raised in several benign gynecologic conditions, including endometriosis, pelvic inflammatory disease, fibroids, and pregnancy.

Proper staging of epithelial tumors is important and differs from the staging algorithm used in pediatric germ cell tumors, which are far more common. Epithelial tumors are staged using the adult FIGO system (see Table 39-5).[67,68] Stage IA tumors may be treated with unilateral salpingo-oophorectomy. The opposite ovary should be examined externally and a biopsy should be taken of any surface abnormalities. Most young patients with stage IB tumors (tumors limited to both ovaries) may be adequately treated by bilateral gonadectomy, but the uterus should be preserved to allow future fertilization.[74,112] In ovarian cancer of a more advanced stage, maximum cytoreduction is important and has been associated with an improved outcome.[113] Total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy and resection of as much gross intraperitoneal disease as possible is necessary. Systemic chemotherapy after appropriate surgery has been beneficial in cases of advanced ovarian carcinoma. Combinations of cisplatin, cyclophosphamide, and paclitaxel are standard agents, while newer biologic therapies hold some promise to improve the overall poor outcome in advanced-stage disease.[114]

Fortunately, advanced-stage disease is uncommon in pediatric patients as tumor stage is the most important prognostic factor.[68]

### Tumors of Low Malignant Potential

Ovarian epithelial tumors of low malignant potential or borderline ovarian tumors (BOTs) differ from epithelial cancer in two major ways: They occur in younger patients, and they have a better prognosis than ovarian cancer. They have been described for all subtypes of ovarian cancer.[111] The serous and mucinous tumors are by far the most common and resemble their benign counterparts. These borderline tumors are differentiated from standard adenocarcinoma in that they lack stromal invasion by neoplastic epithelial elements (Fig. 39-4). Up to 50% of these tumors are bilateral, and they demonstrate a characteristic indolent clinical course. However, recurrences may occur as long as 10 to 15 years after surgery for the primary tumor, and they may be in the form of invasive cancer.[115,116]

In adults, 91% of borderline mucinous tumors present with stage I disease and have a 5-year survival rate of 98%. Serous tumors have a similar outcome. The extensive review of Massad and colleagues[117] noted an overall survival of 98% for stage I tumors, 94% for stage II, and 79% for stages III and IV. In children, Morris and colleagues[118] noted that 75% of the cases presented with stage I disease, and overall survival was 100%. The combined 10-year survival rate for all stages was 73%. In a more recent adolescent study, 26/28 cases were stage I, two cases were stage II, and all patients were alive at 5 years.[116]

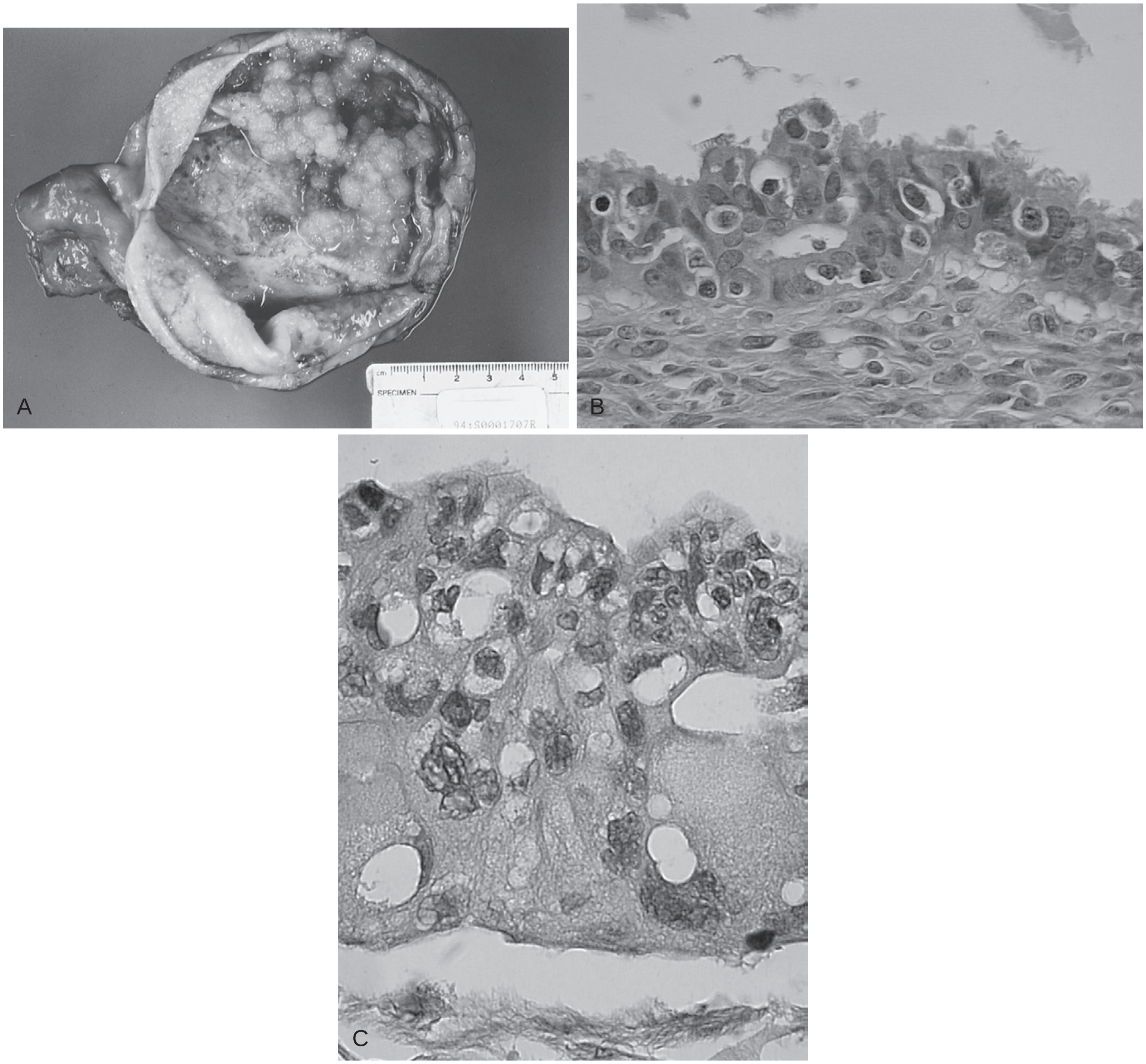



**FIGURE 39-4** **A,** Ovarian tumor from a 17-year-old girl with massive bilateral ovarian lesions. The opened specimen shows a cavity filled with clear fluid, and the wall is lined by numerous nodules and papillary protuberances. **B,** Histologic section of the lesion shows serous papillary tumor of low malignant potential (hematoxylin-eosin stain). **C,** Higher-power photomicrograph of a section of the lesion shows mucinous tumor of low malignant potential (hematoxylin-eosin stain).

Surgery is the primary method of therapy. Unilateral salpingo-oophorectomy is adequate for all low-stage tumors and has been standard treatment; however, some studies have shown that ovarian cystectomy can be performed in young patients with careful follow-up.[119] These patients require close follow-up with pelvic exams, CA 125 assay, and ultrasonography every 3 to 6 months, because patients managed with ovarian cystectomy have a higher risk of recurrence than those managed more aggressively.[120] Morice and colleagues have demonstrated this to be 36.3%, 15.1%, and 5.7% after cystectomy, oophorectomy, and hysterectomy/bilateral oophorectomy, respectively.[119] Despite the difference in recurrence risk, there was no demonstrated impact on overall survival, because all patients were salvaged with further surgery. Conservative treatment should therefore be considered in young patients who wish to preserve their fertility and will comply with routine follow-up.[121]

Bilateral tumors will require bilateral oophorocystectomy or salpingo-oophorectomy. Uterine-sparing procedures are probably not appropriate for advanced-stage disease. The pathologic features that identify poor prognosis are being sought,[115] but currently there are no clear candidates. At present, surgery remains the most effective therapy for these patients with the place of adjuvant therapy yet to be established.[122] No individual treatment strategy has led to consistently superior outcomes, but the favorable biology of this tumor minimizes the importance of the limited clinical benefit from adjuvant therapy.

## Sex Cord–Stromal Tumors

Sex cord–stromal tumors probably arise from uncommitted mesenchymal stem cells that reside below the surface epithelium of the urogenital ridge.[123,124] This totipotential tissue may differentiate into several different cell lines, including granulosa-theca cells in the ovary and the Leydig-Sertoli cells in the testicular interstitium. Sex cord–stromal tumors are referred to as functioning ovarian tumors, because they produce systemic hormonal effects. They account for 5.7% to 17% of malignant tumors in series of ovarian neoplasms in children.[5] Before 9 years of age, most sex cord–stromal tumors are feminizing, and after 9 years of age, there is a predominance of virilizing neoplasms.[32]

***Granulosa-Theca Cell Tumors*** Granulosa-stromal cell tumors are the most common type of sex cord–stromal neoplasms, and the most common type of functioning ovarian neoplasm. The juvenile granulosa cell tumor is a specific subclassification of these lesions; 44% of these occur in the first decade of life and 97% are seen by 30 years of age.[125] Isosexual pseudoprecocious puberty is the presenting sign in the majority of premenarchal girls who have this tumor (Fig. 39-5).[123] Most patients have elevated serum and urinary estrogen levels, whereas gonadotropin levels are low. This profile assists in differentiating children with these tumors from those with true sexual precocity, gonadotropin-secreting lesions, or feminizing adrenal tumors. The peptide hormones

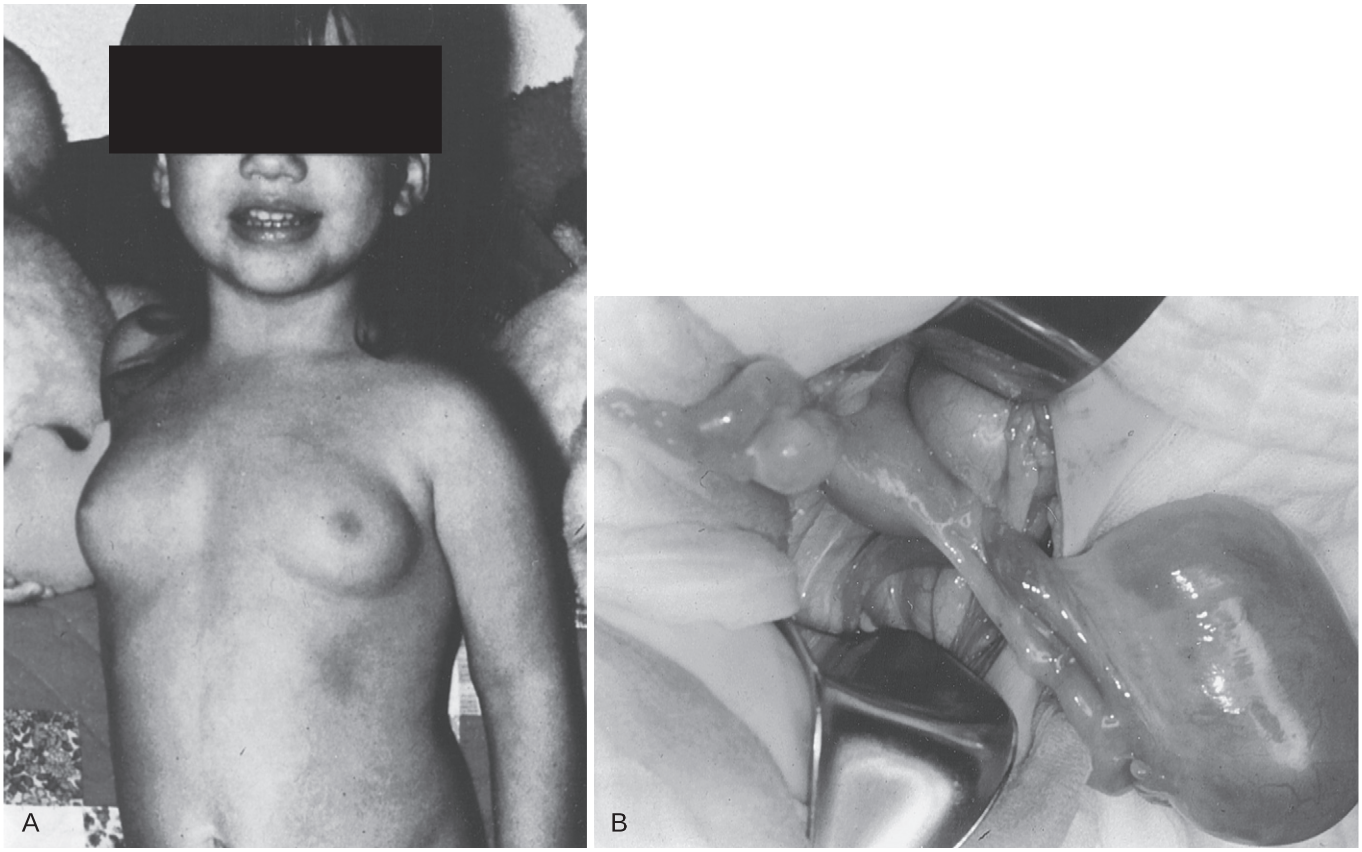



**FIGURE 39-5** **A,** Three-year-old girl demonstrating isosexual pseudoprecocious puberty. **B,** Surgery revealed a benign juvenile granulosa cell tumor. Unilateral salpingo-oophorectomy was performed to remove the tumor.

inhibin and antimüllerian hormone are produced by ovarian granulosa cells and may be useful tumor markers for diagnosis and follow-up of granulosa cell tumors.[126]

Clinical findings include premature thelarche, vaginal discharge or bleeding, labial enlargement, development of pubic or axillary hair, increased somatic growth, and advanced bone age. Clitoral enlargement is a rare manifestation of virilization and tumor androgen production. Postpubertal girls may present with an abdominal mass, relatively nonspecific symptoms of abdominal pain, or increased girth. Amenorrhea and other menstrual irregularities may occur.

In addition to differences in clinical presentation, juvenile granulosa cell tumors demonstrate a pattern of histologic features and biologic behavior that are very distinct from the adult counterpart. The juvenile variety is usually a relatively large lesion that averages 12.5 cm in diameter.[127] At laparotomy, it appears as a yellow-tan or gray solid neoplasm with cystic areas that often contain hemorrhagic fluid. In contrast to the adult tumors, the juvenile type has abundant eosinophilic or luteinized cytoplasm with atypical nuclei and a higher mitotic rate. Deoxyribonucleic acid (DNA) content and cell cycle kinetics analyzed by flow cytometry do not necessarily correlate with the prognosis in children as they often do in adults.[128]

Although the adult form is generally an indolent, slow-growing lesion of relatively low malignant potential, the biologic behavior of the juvenile tumor is more aggressive and correlates well with tumor size, disease stage, presence of rupture, and degree of nuclear atypia and mitotic activity. The lesion was unilateral in 122 of 125 cases reviewed by Young and colleagues.[129] If the adult tumor recurs, it is usually more than 5 years after diagnosis. Malignant granulosa cell tumors in young patients tend to recur much more quickly.

Granulosa cell tumors are staged similarly to other ovarian lesions (see Table 39-5). In children, these tumors are associated with a favorable prognosis, because more than 90% of affected children present with stage I disease. In a German series, 69% of patients were less than 10 years of age, and 82% of patients less than 5 years of age presented with endocrine symptoms. Survival of FIGO stage IA patients was 100%, stage IC was 76%, and stage II/III was 67%. Platinum-based chemotherapy is recommended for tumors of stage IC and above.[93]

***Fibromas and Thecomas*** Fibromas and thecomas account for 14% of sex cord–stromal tumors in pediatric patients.[13] Although they are extremely uncommon in females younger than 20 years of age, fibromas are usually associated with the basal cell nevus syndrome and are frequently bilateral, multicentric, and calcified. Most ovarian thecomas occur in menopausal women; however, two variants of this lesion have been reported in the second decade of life. Calcified thecomas invariably cause amenorrhea or other menstrual irregularities and hirsutism.[130] If these tumors contain a substantial number of lutein cells, they are appropriately called luteinized thecomas and can occur in younger girls associated with androgenic manifestations.

On gross examination, fibromas are firm, solid masses with a whorled, trabeculated appearance on cross section. The lipid content of thecomas imparts a pale yellow to orange color on sectioning the tumor. These lesions are benign, and unilateral oophorectomy is adequate treatment. In the case of bilateral fibromas, all gross tumor tissue should be removed with particular attention to sparing normal-appearing ovarian tissue.[131] Tumor recurrence is rare and managed by reoperation. Virilizing symptoms usually resolve after resection of the tumor.

***Sclerosing Stromal Tumors*** Sclerosing stromal tumors have recently been recognized as distinct tumors that are separate from fibromas and thecomas. These tumors are seen in girls, with 30% of documented cases occurring in the first 2 decades of life. Estrogen secretion has occasionally been reported, whereas androgen manifestations are quite rare. The typical presentation includes the presence of a pelvic mass and pelvic pain in a young patient with a history of menstrual irregularity. This lesion has also been associated with the Chédiak-Higashi syndrome.[10]

Sclerosing stromal tumors are unilateral, usually larger than 5 cm in diameter, and benign. At laparotomy, these tumors are well-circumscribed, firm, whitish-yellow masses with clearly demarcated areas of edema and cyst formation. Histologically, the tumor is characterized by a pseudolobulated pattern with cellular foci clearly demarcated from the edematous and collagenized areas.[132] Gross tumor removal is generally adequate for treatment.

***Sertoli-Stromal Cell Tumors*** Sertoli-Leydig cell tumors account for less than 0.5% of all ovarian tumors but represent 10% of the sex cord–stromal neoplasms.[13] Although most of these tumors are masculinizing, some are nonfunctional or even associated with estrogenic effects. Therefore the older terms, *arrhenoblastoma* and *androblastoma* are no longer favored. One third of cases occur in patients younger than 20 years of age. These tumors are almost always unilateral and present as stage IA at diagnosis. Survival is excellent, with tumor-related deaths in only 5% of affected individuals.[32] Similar to granulosa cell tumors, the gross appearance of Sertoli-Leydig cell tumors varies widely, but these lesions are less often filled with hemorrhagic fluid and rarely have a unilocular thin-walled cystic appearance. Current classifications now recognize five histologic patterns based on the degree of differentiation and presence of heterologous, endodermal, or mesenchymal elements. Tumor stage and histologic appearance are important prognostic factors. Sertoli-Leydig cell tumors with heterologous elements are more common in younger patients and may be difficult to distinguish from immature teratomas.[32] There are two phases of the masculinizing effects of androgen overproduction. Initially, defeminization takes place with amenorrhea, breast atrophy, and loss of female body habitus. This may be followed or overlapped by masculinization characterized by hirsutism, clitoral hypertrophy, and deepening of the voice. In prepubertal girls, masculinization and accelerated somatic growth predominate. Postpubertal girls usually have menstrual irregularities, acne, body habitus masculinization, and hirsutism. The virilizing effects are caused by testosterone accumulation resulting from a deficiency in catabolizing enzymes. Gonadotropin levels are low, and excretion of urinary 17-ketosteroids and pregnanetriol is normal. Because the testosterone level is often directly related to tumor tissue volume, this hormone is a biologic marker for monitoring disease behavior.[133] Tumor markers most likely to be elevated are alpha fetoprotein (AFP) and CA 125.[134] LDH may be elevated or normal. The hormonal

profile of these lesions assists in differentiating them from exogenous androgen sources, adrenal tumors, true hermaphroditism, and polycystic ovaries. Similar to granulosa cell tumors, the Sertoli-Leydig cell lesions may be associated with multiple enchondromas caused by nonhereditary mesodermal dysplasia (Ollier disease).[124]

Surgical therapy should be conservative for patients with low-stage disease. Unilateral oophorectomy or adnexectomy is adequate for such disease and will preserve later childbearing capacity. If tumors are bilateral, poorly differentiated or have ruptured or demonstrate aggressive behavior, a more aggressive approach similar to that used for granulosa cell tumors is necessary. Oral contraceptives and gonadotropin-releasing hormone agonists may provide some ovarian protection both during and following chemotherapy.[135]

***Sex Cord Tumors with Annular Tubules*** Sex cord tumors with annular tubules (SCTAT) are rare but distinct variants of sex cord–stromal tumors. They have potential for bidirectional differentiation into granulosa or Sertoli cells.[13] These lesions are observed in patients with Peutz-Jeghers syndrome.[6] When associated with this syndrome, the lesions are small, multifocal, and usually bilateral. The tumors are often calcified and are invariably noted incidentally during autopsy or in an ovary removed for reasons unrelated to neoplasia. Although patients with these tumors occasionally have menstrual irregularities suggesting hyperestrogenism, surgical therapy is rarely indicated. When these tumors occur in the absence of Peutz-Jeghers syndrome, the clinical difference is significant. Such lesions occur in older patients with a mean age of 34 years, although cases have been reported in patients from 6 to 76 years of age. In the younger patients, the tumor is unilateral and almost always larger than 5 cm in diameter; 20% are malignant. Even with aggressive therapy, 50% of patients with these tumors die.[136]

***Steroid Cell Tumors*** Steroid cell tumor is the now preferred name for lesions previously called lipid cell tumors. This name is more appropriate because of the morphologic features of the tumor, its propensity to secrete steroid hormones, and because many such lesions contain little or no lipids. The group is subclassified into three major categories according to the cells of origin: (1) stromal luteoma is a small steroid cell tumor contained in the ovary arising from the stromal lutein cell; (2) Leydig cell tumor contains the classic intracytoplasmic Reinke crystals and arises from histologically similar precursor cells found in the ovarian hilus; (3) steroid cell tumors not otherwise specified account for approximately 60% of cases and typically occurs in younger patients.

The first and second categories of lesion are usually encountered in postmenopausal women and are only rarely reported in patients in the first 3 decades of life. Most of the cases in the third category and in prepubertal children have been associated with androgenic, heterosexual pseudoprecocity. The tumors are rarely estrogenic, but isosexual pseudoprecocious puberty has been reported.[137] The androgenic tumors show elevated testosterone and androstenedione levels, increased urinary 17-ketosteroid excretion, and decreased gonadotropin levels. In children, these lesions are virtually always benign and of a low stage. Unilateral salpingo-oophorectomy is adequate treatment, but close follow-up is essential. Most of the hormonal symptoms should progressively resolve after removal of the tumor, although younger children may develop true precocious puberty after resection, because chronic androgen exposure appears to induce an early maturation of the hypothalamus.[138]

### Germ Cell Tumors

The path of descent of the primordial germ cells is imperfect; as a result, some of the cells may occasionally miss their destination and be deposited anywhere along this migration route. Germ cells have been found in the pineal area of the brain, mediastinum, retroperitoneum, the sacrococcygeal area, and the ovary and testis. If malignant transformation occurs at any of these sites, a gonadal or extragonadal neoplasm will develop. Because these nests of cells are totipotential in nature, a wide variety of tumors are seen. The specific type of tumor depends on the degree of differentiation that has occurred. This has been characterized by Telium.[27] According to this schema, if no differentiation occurs, a germinoma develops; with differentiation, embryonal carcinomas occur; and with extraembryonic differentiation, these lesions become choriocarcinomas or endodermal sinus tumors. If embryonal differentiation occurs, then the teratoma or most mature of these tumors is seen.

Germ cell tumors are rare in children and adolescents, but when they occur, the gonad is the most frequent site. The ovary is the site of origin for 30% of all germ cell tumors in children.[139,140] Epithelial and stromal ovarian tumors prevail in adults; germ cell tumors predominate in children. Several large series of ovarian neoplasms report an incidence of germ cell tumors ranging from 67% to 77%.[5,141] This group of tumors develops from the same totipotential primordial germ cell, but each neoplasm has different behavioral characteristics, and will be presented individually and then as a group relative to overall management decisions.

***Germinoma*** The term *germinoma* is used to include a group of tumors with common histologic characteristics. It is the primary malignant tumor found in dysgenetic gonads. This tumor may be referred to as a seminoma if found in the testis, a dysgerminoma in the ovary, and a germinoma in an extragonadal site. Germinomas are believed to arise from the totipotential germ cells that were present at the undifferentiated stage of gonadal development.[142] Germinomas represent the most frequent ovarian malignant neoplasm seen both in children and adults.[32] They account for 26% to 31% of malignant ovarian tumors in children.[143,144]

Germinomas are most often seen in prepubertal girls and young women, with 44% of cases occurring before 20 years of age and 87% by 30 years of age.[145] The typical patient is genotypically and phenotypically normal. These often large tumors may reach massive proportions and lead to abdominal pain and symptoms of pelvic pressure, or symptoms related to obstruction of the gastrointestinal or urinary tract. Occasionally, girls with these tumors present with an acute abdomen as a result of torsion, rupture, or hemorrhage into the tumor. Ascites may be present. In pure dysgerminoma, LDH is elevated in 95% of patients, but other markers are negative. In the mixed form of these tumors, other markers may be positive, including neuro-specific enolase, beta-hCG, and CA 125, depending on which germ cell component is present.[146,147] Ovarian dysgerminomas may also be associated with a paraneoplastic syndrome causing hypercalcemia, which typically resolves with

removal of the tumor but may persist for several days.[148] On gross examination, these tumors appear bulky, encapsulated, solid, and yellowish in color (Fig. 39-6); they can be bilateral in 5% to 30% of cases.[142,149,150] Germinomas have a rather uniform microscopic appearance consisting of large, round cells that have vesicular nuclei and clear-to-eosinophilic cytoplasm. These cells resemble primordial germ cells. Lymphoid infiltrates may be present.

The management of germ cell tumors begins with surgical excision. Conservative surgery with a unilateral salpingo-oophorectomy, thorough inspection of the contralateral ovary with biopsy of suspicious lesions, and careful staging (as outlined in the section on surgical approach) is mandatory. Although these tumors are very radiosensitive, surgery alone is adequate treatment in stage I disease. In more advanced disease, radiation has been abandoned in favor of effective

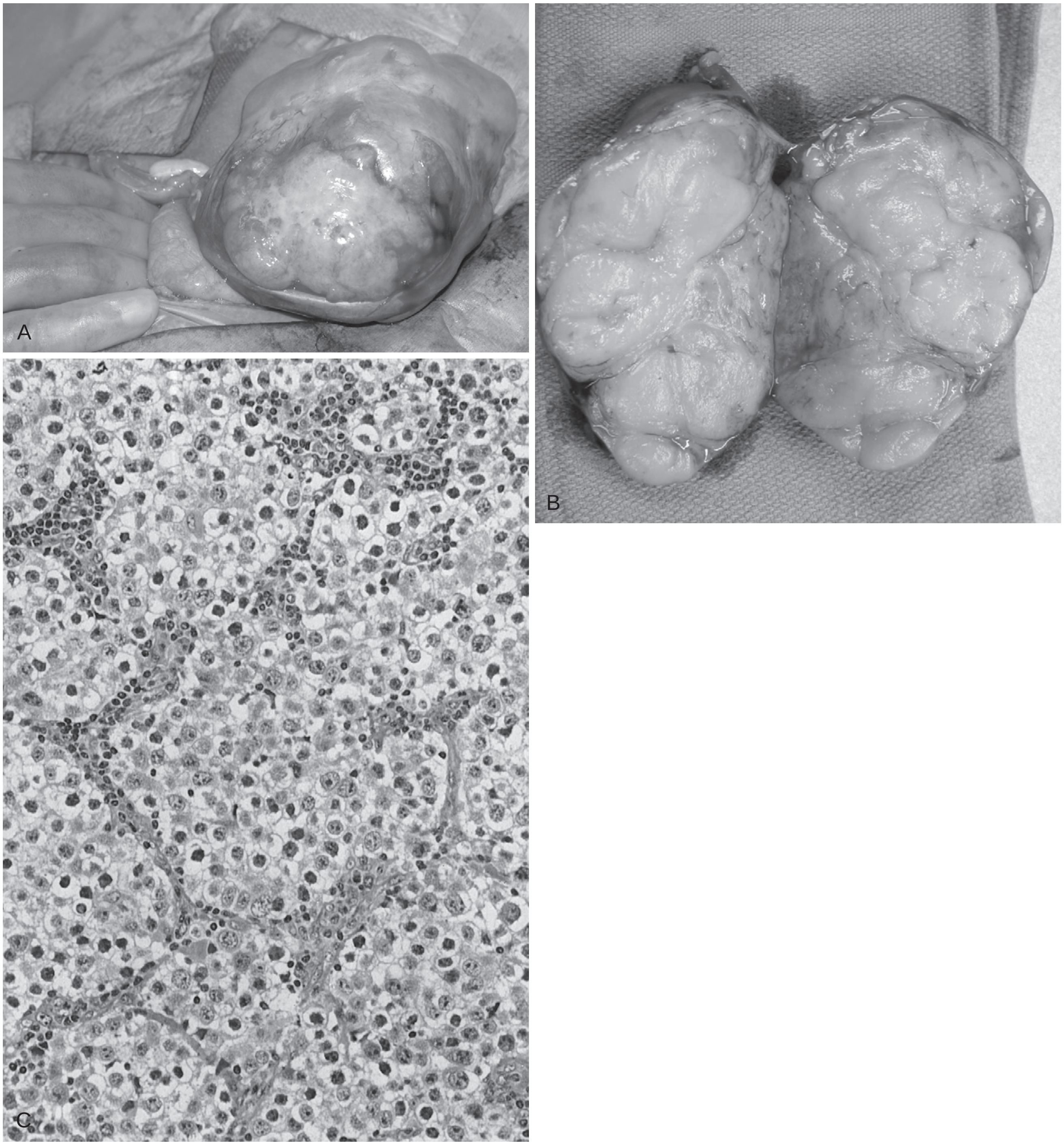


**FIGURE 39-6** **A,** This encapsulated mass from a 5-year-old girl with acute abdominal pain proved to be a dysgerminoma. The child's contralateral tube and ovary are seen to the left of the tumor. A small portion of the ipsilateral tube and uterus were in the surgical specimen but uninvolved with tumor. **B,** The cut surface of the tumor is characterized by lobules divided by thin, fibrous septae. **C,** Micrograph of a dysgerminoma demonstrating polygonal, clear tumor cells divided into small lobules by fibrous septae that contain scattered lymphocytes.

multiagent chemotherapeutic programs that include platinum, etoposide, and bleomycin, which is now standard therapy.[146,151,152]

***Endodermal Sinus Tumors*** Endodermal sinus or yolk sac tumors are aggressive malignant neoplasms that, either alone or as a component of a mixed germ cell tumor, are the second most common histologic subtype of malignant ovarian germ cell tumors in children and adolescents.[32,153] In neonates and young children the primary location of these tumors is in the sacrococcygeal area. In older children and adolescents, it is found most frequently in the ovary. The origin of this particular tumor has been debated, and many microscopic patterns of this tumor have now been described. Nogales suggested that this tumor originates from the primary yolk sac, a structure that develops very early in embryogenesis and consists of multipotential primitive endoderm.[154] This tissue is capable of differentiating epithelial somatic tissues as well as secondary yolk sac tissue (a terminal, temporary structure with limited differentiating capacity) and mesenchyme. Yolk sac tumors with pure endodermal sinus subtypes are less mature than the differentiated glandular or hepatoid subtypes.[155] Symptoms are generally present for less than a month and are related to the presence of an intra-abdominal mass. Sixty-three percent of patients present with abdominal pain and/or abdominal distention.[156] Elevation of the biologic marker AFP is the hallmark of this tumor.

The gross appearance of these tumors during surgery is pale yellow-tan and slimy, with foci of cystic areas and necrosis.[157] The tumors are soft and friable when handled. Most tumors show a distinct histologic subtype with differentiation toward vitelline or yolk sac structures.[158] Microscopically, the most common papillary pattern has the so-called endodermal sinus structures (Schiller-Duval bodies) or perivascular sheaths of cells. Most well-differentiated yolk sac tumors also contain extracellular and intracellular droplets that are resistant to periodic acid–Schiff diastase staining and positive for AFP.

***Embryonal Carcinomas*** A relatively uncommon isolated germ cell tumor is embryonal carcinoma, which may resemble an anaplastic carcinoma with extensive necrosis. Embryonal carcinoma is more often found in association with other germ cell tumors and is referred to as a mixed germ cell tumor. One subtype of this tumor, the polyembryoma, is capable of producing both AFP and beta-hCG, resulting in clinical endocrinopathies, including menstrual irregularities and isosexual precocious puberty. The histologic appearance is characterized by bodies that resemble tiny embryos.[159]

The workup and surgical approach to this tumor is similar to that for an endodermal sinus tumor. Isolated, unilateral disease is managed by unilateral salpingo-oophorectomy. Advanced local disease necessitates hysterectomy for local control along with multiagent chemotherapy.[160]

***Choriocarcinomas*** Choriocarcinomas are extremely rare in the pure form but may be present in mixed germ cell tumors as well. They are endocrinologically active, highly malignant germ cell tumors that occur in girls and women. Estrogen is produced both by the tumor and by the ovary itself in response to release of gonadotropin by the neoplastic chorionic tissue. The beta-hCG level is elevated, and AFP is normal. The clinical presentation is influenced by the age of the patient. In a review of 30 cases, Goswami reported a mean age of 13.9 years, with the predominant presenting symptom being abdominal pain. Ten cases occurred in prepubertal girls, three of whom developed isosexual precocious puberty, and in one case a mature teratoma was identified in the contralateral ovary.[161] These usually large, solid tumors generally adhere to surrounding tissues, and distant metastatic disease is associated with this tumor. Operative excision can be a formidable task, because the tumor may be friable, quite vascular, and often invades contiguous structures.[162] If the lesion is localized, surgery is limited to unilateral salpingo-oophorectomy. However, this rarely is the case, and a more extensive extirpative procedure is usually required that involves removing the tumor, the opposite ovary, the uterus, and as much metastatic tissue as possible.

These tumors appear grossly as nodular with a friable consistency. The tumor is purple with variegated areas of dark brown and yellow secondary to hemorrhage and necrosis. Microscopic evaluation of these tumors reveals cytotrophoblasts and syncytiotrophoblasts with evidence of extensive necrosis and hemorrhage. Metastatic implants are friable and have a similar gross and microscopic appearance as the primary lesion. Survival is based on stage at diagnosis and treatment. Platinum-based and methotrexate-based multiagent chemotherapy are described treatment regimens, and platinum-based (bleomycin, etoposide, and cisplatin) chemotherapy has improved survival. Goswami reports an 82% survival in patients treated with chemotherapy versus 28% in those treated with surgery alone.[161]

***Teratomas*** Teratomas are a group of neoplasms composed of tissue elements that are foreign to the organ or anatomic site in which they are found.[163] Classically, these tumors are defined as being composed of tissue derived from the three germ layers: ectoderm, mesoderm, and endoderm. All three germ layers do *not* have to be present in each tumor, but some embryonic tissues must be found in an abnormal location. These tissues show elements of disorganization as well as various levels of maturation. As such, teratomas are histologically classified as mature and immature tumors and those with monodermal components.[164,165] The development of a somatic malignancy within a teratoma is a rare event in childhood, and is thought to occur within differentiated teratomatous elements rather than from totipotent embryonal cells.[32]

**Mature Teratomas** Most teratomas in children are of the mature type. The majority of mature ovarian teratomas have entered, but have not completed meiosis, suggesting that they arise from germ cells arrested in meiosis I.[32] There is little or no tendency to malignant degeneration of preexisting benign elements or the coexistence of malignant cells in a benign teratoma.[107] In neonates, mature teratomas are found most commonly in the sacrococcygeal area followed by the head and neck.[146,164,166] The ovary becomes an important site later in childhood, especially during adolescence. Ovarian teratomas are predominantly cystic in nature.[107] Overall, benign cystic teratomas are the most common ovarian neoplasms in children[162] and can be bilateral in as many as 10% of patients.[107,165,167]

Symptoms of mature teratomas can be acute or chronic. Acute symptoms that mimic appendicitis are seen when torsion, hemorrhage, or rupture of the mass occurs. Gradual onset of symptoms may be related to the presence of an intra-abdominal adnexal mass, which may cause pressure on adjacent organs.[165] Rarely, a ruptured teratoma may lead to a chronic inflammatory

response with the development of a mass of intestine and omentum adhering to the anterior abdominal wall; this condition is associated with pelvic adenopathy, which mimics a malignant tumor.[168] On examination, findings are primarily related to the mass itself. These tumors are located in the abdomen in infants and young children. They are found in the pelvis of adolescents, although large tumors may be palpated in the abdomen, and there may be associated tenderness.

Plain abdominal radiographs demonstrate calcifications in up to 67% of cases.[169] Ultrasonography is a commonly used diagnostic test. The positive predictive ability of ultrasonography approaches 100% when two or more characteristic findings for mature cystic teratoma (MCT), such as shadowing echodensity and regionally bright echodensity, are present.[170] Magnetic resonance imaging has been reported to be more useful than CT scan in the diagnosis of mature cystic teratoma due to its ability to clearly define soft tissue components.[171]

Conservative ovarian surgery in childhood and adolescence is important for the development of normal puberty and future fertility. This must be balanced with complete removal of the mature cystic teratoma. Traditional management of children with mature cystic teratomas has been oophorectomy by laparotomy. However, laparoscopic removal, either by cystectomy or oophorectomy affords a safe alternative option when done by an experienced laparoscopist.[73] Campo and colleagues, in a randomized controlled trial, demonstrated that the use of an endobag in the removal a mature cystic teratoma at the time of laparoscopy decreased spillage from 46% to 3.7% of cases.[172] Aspiration of a giant predominantly cystic lesion in order to facilitate removal through a smaller incision runs the risk of upstaging the patient by spillage of the cyst contents if malignant components are identified. Techniques have been described to minimize this risk while allowing a less invasive approach to large cystic lesions.[173,174] Every effort should be made to spare the ovary when a teratoma is suspected based on radiographic findings and normal tumor markers. Very large or bilateral teratomas can be successfully enucleated in an attempt to preserve hormonal and reproductive functions (Fig. 39-7).[165,175,] If this is not possible, the gonad and tumor alone should be removed, leaving the ipsilateral fallopian tube in place.

Miliary, intraperitoneal glial implants (gliomatosis peritonei) are occasionally encountered in association with mature teratomas.[176] These implants are rarely suspected before surgery. They appear as white or gray nodules, usually 1 to 3 mm in diameter, and are usually confined to the omentum, pelvic peritoneum, or adjacent or adherent to the tumor itself. Several explanations have been offered for the development of these implants.[177] The most recent data using microsatellite DNA analysis suggest that the glial implants arise from subperitoneal cells, presumably pluripotent müllerian stem cells and not from the teratoma.[178,179] Implants can have a disturbing appearance and biopsy is necessary, but no specific treatment is indicated when they are well differentiated, and their presence does not change management of the primary tumor. However, if adjacent components are immature, the lesions may progress and require adjuvant therapy.

**Immature Teratomas** Immature teratomas are germ cell neoplasms that are composed of tissue derived from the three germ cell layers. These teratomas are clinically distinct from benign or malignant teratomas, because they also contain immature, neuroepithelial elements (see Fig. 39-7). Immature teratomas can coexist with the more mature solid or cystic benign teratomas or with malignant teratomas, in which case treatment is determined by the malignant component.[180] Immature teratomas are graded based on the relative quantity of immature elements and the presence and quantity of the neuroepithelial components. The grade of the primary tumor is significant and is one of the major determinants of the likelihood of recurrence following resection. Multiple grading systems have been proposed based on the system developed by Thurlbeck and Scully.[181] The criteria outlined by Gonazez-Crussi identified the percentage of incompletely differentiated (embryonal) elements in the tumor as follows: grade 0, 0%; grade I, less than 10%; grade II, 10% to 50%; grade III, greater than 50%.[163,182]

The treatment of immature teratomas has gone through an evolution from aggressive treatment with surgery followed by multidrug chemotherapy to conservative surgical approaches with no adjuvant therapy. In a study of 58 pure immature teratomas published in 1976 by Norris,[180] survival was 82% for patients with grade I tumors, 62% for grade II, and 30% for grade III. Based on this study, along with others, use of multiagent chemotherapy for grade III immature teratomas was advocated. The protocol for extracranial nontesticular germ cell tumors of the German Society for Pediatric Oncology and Hematology (GPOH), which was initiated in 1983, recommended adjuvant chemotherapy for grade II and III immature teratomas of all nontesticular sites.[183] Using this approach, the relapse rate was 13.3% for patients with mature and immature lesions. In a follow-up study from the German registry, immature lesions had a higher rate of recurrence than mature lesions when completely resected (8/78 vs. 3/104), as in the previous study, but the recurrence rate overall dropped from 13.3% to 9.5%. Complete resection was associated with a relapse rate of only 4.2% in both studies, and the malignant relapses were explained by microfoci of yolk sac tumor present in the primary tumor as shown retrospectively in single cases by reevaluation of the primarily resected teratoma.[184] The hypothesis that recurrent tumor stems from microfoci of malignant cells present in the original mass is supported by an intergroup study in the United States in which yolk sac tumor elements were detected in 29% of immature teratoma specimens (73 immature teratoma, 21 with YST-microfoci). It was suggested that the true incidence of such microfoci might be underestimated in these typically large masses, as a result of sampling errors.

The combined report from the Children's Oncology Group and the Pediatric Oncology Group in 1999 included 31 patients with pure immature teratomas of the ovary treated with surgery alone. Eighty-six percent of the tumors were grade I or II and the 3-year event-free survival (EFS) was 97.8%, with only one patient developing recurrent disease. That patient was salvaged with a combination of surgery and platinum, etoposide, and bleomycin. The authors advocate surgical excision alone, with close follow-up as appropriate therapy for all ovarian immature teratomas.[185] Based on the excellent survival and avoidance of the risks of chemotherapy, immature teratomas are treated in the United States with fertility-preserving surgery and observation without adjuvant chemotherapy.[185,186]

**Monodermal Teratomas** A monodermal teratoma refers to an ovarian tumor composed exclusively or almost exclusively of ectoderm or mesoderm or endoderm, for example, neuroectoderm.[187]

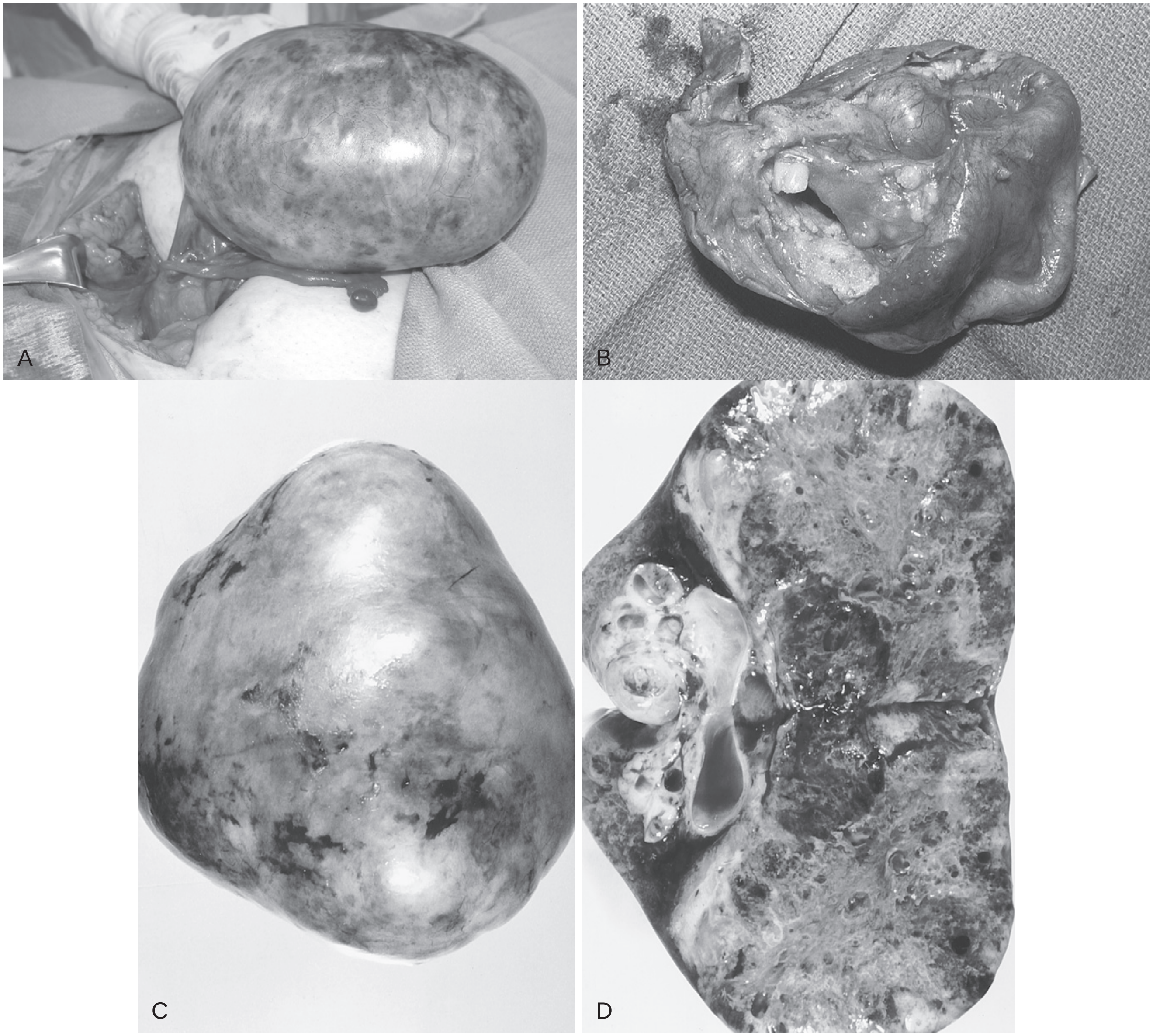



**FIGURE 39-7** **A,** Large ovarian dermoid tumor in a 14-year-old girl with acute severe abdominal pain upon awakening. The fallopian tube is seen below the tumor. **B,** Opened gross specimen of ovarian dermoid showing multiple tooth- and jawlike calcifications. **C,** Characteristic gross appearance of an immature teratoma in a 5-year-old girl who presented with a left ovarian mass. The tumor is a solid and cystic globoid mass with a smooth, shiny surface. **D,** Cut section of an immature teratoma shows a variegated, solid, cystic appearance with focal areas of hemorrhage.

## Gonadoblastomas

Gonadoblastoma, a tumor first described by Scully[188] in 1953, is relatively rare and occurs most commonly in patients with dysgenetic gonads. Most patients are virilized or nonvirilized phenotypic females. In the only large series reported, Scully[189] reviewed 74 cases and found that 89% were chromatin negative and the most common karyotype was 46XY or 45X/46XY. Troche, in a literature review of 140 cases of neoplasms arising in dysgenetic gonads, found that 80% also had these karyotypes.[190] Patients are usually older adolescents or in the third decade of life with a history of primary amenorrhea. Androgen production by the tumor causes virilization. When a workup for amenorrhea or virilization is undertaken, an abnormal karyotype with a Y chromosome or chromosome fragment can be found in as many as 90% of patients.[190] These often small tumors may then be identified during examination or exploration. They may also be found incidentally during excision of gonadal streaks or dysgenetic gonads.[191,192] These tumors become invasive early and gonadectomy is recommended as soon as 46XY gonadal dysgenesis is diagnosed.[18,190]

Gonadoblastomas are composed of germ cells and sex-cord derivatives that are similar to granulosa and Sertoli cells, although immunohistochemical and ultrastructural findings are more supportive of Sertoli-like differentiation.[193] Lutein or Leydig-like stromal cells occur in two thirds of cases and probably reflect a stromal reaction to gonadotropin stimulation.[193] These tumors are considered precursors to germ cell tumors in dysgenetic or streak gonads, because they may coexist with dysgerminomas and other germ cell tumors in more than half of the patients.[190] The tumor may be difficult to identify on gross examination because of overgrowth by the

malignant component and other changes, including calcification, fibrosis, or both. In fact, calcification may be the only remnant of the gonadoblastoma, and the presence of calcification in a dysgerminoma should raise the suspicion of an underlying gonadoblastoma. The malignant potential of this tumor is determined by the underlying malignant component and should be treated accordingly. The outcome for patients with these tumors may be improved, because abnormal sexual development prompts early evaluation of the patient and subsequent diagnosis of the tumor. The prognosis of nongerminomatous germ cell tumors has improved with the advent of bleomycin, etoposide, and cisplatin protocols, and survival rates of 70% to 90% have been reported.[32]

### Mixed Germ Cell Tumors

Germ cell tumors in children are often composed of more than one pure histologic type. Benign but questionably malignant tumors (i.e., immature teratomas) and frankly malignant tumors (germinomas, choriocarcinomas, endodermal sinus tumors, and embryonal carcinomas) may be present. Management of mixed tumors is geared toward the most malignant component of the mass.

## Surgical Guidelines for Ovarian Germ Cell Tumors

The goal of surgery is to completely evaluate the extent of disease, safely and completely resect the tumor, and spare all uninvolved reproductive organs. Preservation of reproductive potential is a high priority during surgery for ovarian lesions in children. Laparoscopic procedures are being increasingly performed for evaluation of pelvic masses, and there are now data to demonstrate that the benefits of a faster recovery time and shorter hospital stay seen in adults are also applicable to children.[73,194] If a suspected ovarian malignancy is detected at the time of laparoscopy, complete surgical staging and resection by conventional laparotomy is recommended. Benign lesions require only tumor resection by ovarian cystectomy or unilateral oophorectomy.

Benign tumors, frankly malignant tumors, and those with mixed histologic characteristics often cannot be distinguished based on gross appearance alone. If in doubt, staging is recommended, because treatment and prognosis of malignancies depend on accurate staging. The current intergroup COG protocol includes thorough inspection, palpation, and biopsy of any suspicious peritoneal and liver nodules (including the subphrenic spaces).[49] Both ovaries are inspected. If a tumor is found in an ovary and malignancy is suspected, it should be removed by unilateral oophorectomy if the fallopian tube is not involved. A salpingo-oophorectomy is indicated if the fallopian tube is involved. The contralateral ovary should be inspected, and nodules or suspicious areas should be biopsied. A contralateral salpingo-oophorectomy should be avoided unless malignancy is confirmed.

Staging procedures for malignancies differ somewhat for different cell types, which can result in inadequate staging of unsuspected epithelial tumors. Staging guidelines for germ cell tumors proposed by the Children's Oncology Group (see Table 39-6) include peritoneal fluid aspiration/washings, inspection of the omentum and contralateral ovary with biopsy of suspicious lesions, biopsy of clinically suspicious lymph nodes, and removal of the primary tumor. Epithelial tumors are staged by the FIGO system (see Table 39-5), which requires peritoneal biopsies, peritoneal washings/aspiration, omentectomy, removal of the primary tumor, and an ipsilateral lymph node dissection. The need for a lymph node dissection is not based on the gross appearance of the nodes, because up to 30% of clinically normal nodes can be positive for metastatic disease.

## Chemotherapy for Ovarian Germ Cell Tumors

Forty years ago, no effective therapy for germ cell tumors existed. Based on the early success of management of testicular germ cell tumors using multiagent platinum-based chemotherapy, ovarian tumor treatment evolved along similar lines. The addition of chemotherapy reduced the risk of recurrent disease for adult patients with completely resected ovarian germ cell tumors.[195] Current regimens for ovarian germ cell and sex cord–stromal tumors is platinum-based therapy, and the regimen of cisplatin, etoposide, and bleomycin (PEB) has become the preferred protocol. An 8-year study from the GOG that closed in 1992 evaluated PEB, and 91 of 93 patients were free of recurrent germ cell tumors, with a median follow-up of 38.6 months.[196]

Several chemotherapeutic regimens were also historically tried in children, and the best results were achieved with PEB.[197,198] In a pilot study, Pinkerton and colleagues[199] demonstrated the effectiveness of substituting cisplatin with carboplatin, a less toxic drug; carboplatin was then combined with bleomycin and etoposide. Eight of eight patients with ovarian germ cell tumors survived with this regimen. Using a platinum-based regimen, only 1 of 17 girls with resected ovarian nonseminomatous germ cell tumors in FIGO stage IA relapsed in an analysis of European trials by Gobel and colleagues.[200]

In 1991, the Children's Cancer Group (CCG) experience of 93 children with malignant germ cell tumors included 30 ovarian tumors.[151] By study design, immature teratomas and dysgerminomas were not included. Using a cisplatin-based regimen, the 4-year, event-free survival rate was 63%. Tumor size affected prognosis. If the tumor was larger than 16 cm in diameter, the outcome was worse. Patients in whom complete tumor resection could not be done during the original procedure were more likely to have subsequent adverse events than if the tumor was completely removed ($P = 0.08$). In 1994, Nair and colleagues[201] reported their findings in 107 children with germ cell tumors, including 43 girls with ovarian tumors. Of these, 22 received multiagent chemotherapy. A complete response was seen in 6 of 11 patients treated with platinum, vinblastine, and bleomycin, compared with 10 of 11 patients who completely responded to treatment with PEB (with etoposide replacing vinblastine). The risk for chemotherapy-related complications is low relative to the effectiveness of the PEB regimen and compared with prior regimens that included vinblastine.[202] Others have shown that the PEB regimen is superior to other chemotherapy regimens.[160]

Current efforts in the United States are geared toward reduction of therapy for low- and intermediate-risk tumors. A phase III study undertaken by the Children's Oncology

Group (COG-AGCT0132) stratified malignant germ cell tumors into three risk groups (low, intermediate, and high risk) defined by stage and primary site. Based on data from the POG 9048/CCG 8891 study, demonstrating that patients with stage I ovarian and extragonadal immature teratoma with malignant elements appeared to do well following complete surgical resection,[69] all patients with stage I ovarian tumors were categorized as low risk and were initially treated with surgery, followed by close observation and monitoring. That arm of the study has subsequently been amended to include stage I ovarian tumors in the intermediate-risk group because of a higher-than-expected failure rate with observation alone. Overall survival remains greater than 95%. The intermediate-risk group will consist of patients with stage I to III gonadal tumors. Such patients have been shown to have a 3-year EFS of about 90% with standard-dose PEB.[49,71] These patients will be treated with a modified standard PEB regimen, consisting of three cycles of compressed PEB every 21 days. Saxman and colleagues[203] reported that long-term survival was equivalent for men treated with germ cell cancer for three or four cycles of PEB. Patients who are partial responders (PR) may then have surgical resection of residual tumor. Therapy is discontinued upon pathologic complete response and normal markers, or continued for an additional three cycles in children who remain PR. High-risk patients, defined as those with stage IV disease, showed some improvement in survival with a high-dose platinum regimen that was offset by increased toxicity. Patients with recurring germ cell tumors may be salvaged using high-dose chemotherapy with autologous stem cell transplantation.

## Miscellaneous Tumors

Small cell carcinoma of the ovary is an extremely rare condition with a very poor prognosis.[204] These tumors are very aggressive and are the most common undifferentiated ovarian carcinoma in young patients. They have been encountered in patients from 9 to 44 years of age, with a mean age of 23 years.[205] Paraendocrine hypercalcemia occurs in two thirds of cases, but patients rarely have clinical manifestations of this abnormality. Serum parathormone levels are normal. Virtually all tumors are unilateral, although only 40% have been detected at stage 1A. Only one third of patients with stage 1A tumors survive long-term, and survival of patients with more widespread disease is rare.[13] Unilateral salpingo-oophorectomy has been associated with long-term survival in some patients with stage 1A tumors. Asynchronous appearance of tumor in a contralateral conserved ovary has been encountered, and bilateral adnexectomy may be a more appropriate surgical option. Despite various treatment modalities including resection, radiation therapy, and intensive chemotherapy, the average life expectancy remains low at 18 months.[205]

Primary ovarian sarcomas are a heterogenous group of aggressive tumors associated with poor survival. Most cases occur in older women; however, a recent review of 151 cases described 10 of 29 patients with rhabdomyosarcoma who were younger than 20 years of age.[206] These patients presented with nonspecific symptoms of abdominal discomfort or swelling with occasional urinary or gastrointestinal complaints secondary to mass effect. Accurate staging is critical. Hysterectomy with bilateral salpingo-oophorectomy and debulking of as much diseased intra-abdominal tissue as possible has been done. Radiation therapy was administered for residual pelvic disease, and several chemotherapeutic regimens have been used. In contrast to rhabdomyosarcomas arising at other sites, the outcome for patients with ovarian lesions has generally been poor, perhaps because of the advanced stage of disease at diagnosis. Nevertheless, the most recent chemotherapeutic regimens used in cooperative group studies have been highly effective, and it is reasonable to assume that more conservative surgical resection will provide adequate treatment for these rare tumors.

Stromal sarcomas and low-grade endometrial stromal sarcomas of the ovary have been occasionally reported in the second decade of life. These lesions are believed to arise from ovarian endometriosis, coelomic mesenchyme, or neometaplasia of stromal cells. Lesions are usually discovered because of nonspecific pelvic discomfort, although early infiltration into adjacent tissues may cause intestinal or ureteral obstruction. Tumor infiltration may not be grossly apparent, so initial surgical resection should be aggressive with total hysterectomy and bilateral salpingo-oophorectomy. Progesterone administration may provide effective adjunctive therapy, although this has to be continued indefinitely because stromal sarcomas have been reported to reappear and spread dramatically when the medication is stopped. Radiation therapy has been used for local residual disease, although recurrence is common. The role of chemotherapy for these tumors has not been defined.

Cases of genuine ovarian fibrosarcoma in children are extremely rare. Patients present with pelvic pain and a palpable mass. Fibrosarcoma has been associated with Maffucci syndrome.[8] Although the outcome has been uniformly poor in older patients, survival of younger patients who have undergone aggressive surgical resection, including hysterectomy and bilateral salpingo-oophorectomy, has been reported. Success with subsequent radiation or chemotherapy has not been reported.

Primary leiomyosarcoma of the ovary is extremely rare in children. These tumors may arise de novo from any of the smooth muscle sites in the ovary or may represent malignant degeneration of leiomyoma, a benign counterpart.[207] As with most of these rare tumors, presenting symptoms are nonspecific and discovery may occur in the advanced stage of disease. Aggressive surgical therapy is recommended, because no adjuvant therapy has proven to be effective.

## Secondary Tumors

Although secondary ovarian malignancy is rare, the ovaries are a potential metastatic site for a wide variety of childhood malignancies (Table 39-7).[127,208] Distinguishing primary neoplasms from secondary neoplasms is important to prevent inappropriate therapy or adverse sequelae. Metastatic spread to the ovary occurs through four main pathways: (1) hematogenous spread, (2) lymphatic spread, (3) transcoelomic dissemination with surface implantation, and (4) direct spread.[208] Recently described highly malignant tumors that have a predilection for the pelvic region are intra-abdominal desmoplastic small round cell tumors.[209]

Lymphoma can occur in the ovary in children either as a primary tumor or a manifestation of systemic disease. Most

**TABLE 39-7**

**Secondary (Metastatic) Tumors Occurring in the Ovary in Children**

| |
|---|
| Colorectal |
| Breast |
| Gastric carcinoma |
| Carcinoid tumors (liver, lung) |
| Malignant melanoma |
| Burkitt lymphoma |
| Rhabdomyosarcoma |
| Wilms' tumor |
| Neuroblastoma |
| Retinoblastoma |
| Ewing sarcoma |
| Rhabdoid tumor of the kidney |
| Medulloblastoma |
| Osteogenic sarcoma |
| Chondrosarcoma |
| Leukemia |

of the reported cases have been of the small, noncleaved cell type (Burkitt or non-Burkitt category), although T-cell non-Hodgkin lymphoma and anaplastic large cell lymphoma have also been reported.[210] Pais and colleagues[211] reviewed 23 cases of ovarian involvement in patients with relapsing leukemia. Abdominal pain was the most common symptom, and a mass could usually be palpated. Although most patients in whom leukemia treatment failed had systemic and not local disease, ultrasonography revealed a characteristic appearance and was effective in detecting ovarian involvement.[212] Survival was based on aggressive systemic multiagent chemotherapy and not on the degree of surgical resection of the ovarian lesion. Routine pelvic radiation therapy was of no benefit.

Reports have noted granulocytic sarcoma of the ovary occurring in patients with acute or relapsed acute myelogenous leukemia.[213] Although aggressive systemic chemotherapy is critical to survival, an ovarian mass should be investigated immediately to determine its nature (i.e., benign or malignant and exact cell type). In this instance, surgical resection of the ovary and any other involved gynecologic organs or pelvic tissue must be done. Radiation therapy has been used for residual disease in the pelvis. Although the ultimate outcome of granulocytic sarcomas is probably more related to effectiveness of chemotherapy, local measures of tumor control cannot be overlooked when this tumor is detected.

# Unclassified Benign Tumors

Although the ovary is highly vascularized, hemangiomas are extremely rare; a recent review found only 40 published cases.[214] Their occurrence is relatively evenly distributed between infancy and postmenopausal age groups. The lesions are usually quite small, asymptomatic, and discovered incidentally. Bilateral occurrence is rare, and the tumors are almost always cavernous. Benign-appearing ultrasonographic features have been described.[215] When the tumors are large, associated symptoms include abdominal pain, distention, and bloody ascites. Torsion or rupture may cause an acute surgical emergency. No malignant tumors of this type have been described, and oophorectomy or adnexectomy is curative if needed.

Primary ovarian leiomyomas are also extremely rare, although they have been reported in teenage girls.[216] Most reported cases are clinically silent; however, the lesion may be large enough to cause increased abdominal girth and pelvic pain. Tumor markers are normal, and imaging studies are generally unable to differentiate this benign solid tumor from a malignant process. Unilateral salpingo-oophorectomy is curative. The ovarian myxoma is a rare benign tumor characterized by conspicuous vascularity and mesenchymal proliferation that requires only a conservative surgical procedure.[217]

Struma ovarii is a benign variant of a germ cell tumor that typically occurs in older women but has been reported in teenagers. It is composed of more than 50% benign thyroid tissue, which is functional in 5% to 12% of cases. Rarely, the tumor contains malignant components and, in some cases, represents the patients' only functioning thyroid tissue. CA 125 levels may be elevated, but other markers are usually normal. Treatment is resection of the mass.[218] In another thyroid-related condition known as the Van Wyk and Grumbach syndrome, long-standing hypothyroidism can lead to large ovarian cysts. TSH levels are extremely high and several theories hypothesize a crossover hormonal effect on FSH or direct stimulation of the ovary by TSH. CA-125 and LDH levels may be elevated. The ovarian cysts resolve with thyroid replacement therapy.[219]

# Summary

The diagnosis and management of ovarian lesions in infants and children remains a challenge because of the wide variety of possible pathologies, some of which are extremely rare. Nonneoplastic lesions are being detected more commonly as imaging techniques continue to improve. Neoplastic lesions are more readily diagnosed and completely characterized with advances in biochemical, immunohistologic, and cytogenetic technology.

Because of the relative rarity of ovarian tumors in children, clinical approaches may be based on experience with similar adult lesions. However, it is critical to recognize the differences exhibited by the juvenile forms of many of these entities, which often present at a less advanced stage and have a more favorable natural history and response to therapy. Preservation of reproductive and endocrine function is of paramount importance in the treatment of ovarian lesions in infants and children. Careful observation or nonoperative therapies may be appropriate for many nonneoplastic conditions. Most benign neoplasms are adequately managed with conservative surgical approaches. Even frankly malignant tumors increasingly yield to multimodal therapy, which can include less radically ablative surgery and still result in long-term survival and possible preservation of fertility for young patients.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 40

# Testicular Tumors

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Historically, prepubertal malignant testicular tumors were managed using the same treatment protocols as their adult counterparts, with radical orchiectomy and retroperitoneal lymph node dissection (RPLND) weighing heavily in the treatment pathway.[1,2] However, with growing clinical evidence, it became clear that prepubertal tumors differed from the postpubertal population not only in presentation but differed in terms of clinical behavior, incidence, histologic diagnosis, and prognosis.[1–6] In recognition of the differences in this population of patients, the Prepubertal Testis Tumor Registry (PTTR) of the urologic section of the American Academy of Pediatrics was established in 1980 to better delineate the natural history of these lesions and to document their response to therapy.[1,2,4] Since its inception, several important features have emerged that have significantly altered the management of testicular tumors in the pediatric population. The management has been further clarified by a series of recent multicenter clinical trials of the most common malignant tumors of the prepubertal testis.[7–12]

The results of the PTTR confirmed that testicular tumors in children are rare, making up approximately 1% to 2% of all pediatric solid tumors, with an incidence of 0.5 to 2/100,000 among whites, while African-American males appear somewhat protected, with an incidence of 0.25/100,000.[1–3,13] Asian/Pacific Island males have a 1.4-fold increased risk of testicular tumors compared with whites.[14] In contrast to adult testicular cancer, which has experienced a marked increase in incidence, pediatric testicular tumor incidence has been stable during the past 30 years.[15] Testicular tumors are 10 times more frequent in the postpubertal cohort compared with boys younger than 12 years of age.[1] Furthermore, epidemiologic data from several sources suggest a bimodal distribution, with a small distinct peak in the first 3 years of life, followed by a large peak in adolescents (15 to 18 years).[2,3] The majority of testicular tumors in the postpubertal age group are malignant, with 90% to 95% demonstrating histologic features of either seminoma or mixed germ cells.[2,6] Initially, the PTTR reported that the yolk sac tumor (62%) was the most common prepubertal testicular tumor, with benign tumors occurring much less commonly.[1,2,13] However, a landmark paper by Metcalfe and colleagues[13] suggested that the PTTR registry and the Armed Forces Institute of Pathology American Tumor registry are subject to reporting bias, with overreporting of malignant tumors and failure to capture the benign tumors. In a series of articles that followed, 74% to 87% of tumors identified were benign, with teratoma making up 43% to 48%, while malignant yolk sac tumors constituted only 15%.[1,5,6,13] Recognition of this fact led to a marked reassessment of the management of testicular tumors in the prepubertal population.

## Risk Factors for Testicular Cancer

Although a number of risk factors have been proposed regarding the occurrence of testicular tumors, to date only a few may be considered as “established” based upon a sufficient level of evidence.[16] Other associations that have historically been considered important etiologically have since been refuted. Only four factors have sufficient evidence that links them “highly” with testicular cancer: (1) undescended testis (cryptorchidism), (2) contralateral testicular germ cell tumor (GCT), (3) familial testicular germ cell tumor, and (4) gonadal dysgenesis.[16,17] Associations that may be considered “likely” include infertility, twin-ship, and testicular atrophy. Clinical factors with equivocal/low association include scrotal trauma, inguinal hernia, mumps orchitis, testicular torsion, maternal estrogen exposure, and occupational exposure. Parameters that have historically drawn attention but have since been shown to be irrelevant include obesity, vasectomy, smoking, hydrocele, varicocele, alcohol, and circumcision.[16]

Cryptorchidism occurs in 2% to 5% of term infant males; however, by 12 months of age, this number is reduced to 1%.[18] To date, cryptorchidism is the only factor that has level I evidence linking it with testicular cancer. A meta-analysis of 20 case control studies showed a strong association between undescended testis (UDT) and testicular cancer, with an overall relative risk of 4.8.[16] Similarly, Walsh and colleagues[19] showed boys who underwent orchiopexy after 10 years of age had a 3.5-fold increased risk of testicular cancer, compared with those that had the procedure at an earlier age. In a population-based prospective observational study, Pettersson and colleagues followed 16,983 men treated for UDT for a mean period of $12.4 \pm 7.4$ years.[20] This study demonstrated two important findings. There was an increased risk of testicular cancer for the entire cohort (relative risk [RR] = 2.23) versus normal population figures, and the incidence of cancer was significantly higher (RR = 5.4) in those who were

treated after the age of 13 years.[20] The lowest incidence of cancer was seen in children who underwent orchiopexy before the age of 6 years (RR = 2.02). Orchiopexy before the age of 10 to 12 years results in a twofold to sixfold relative risk decrease in testicular cancer in children with unilateral UDT.[21] Because of the increased risk of malignancy, patients with UDT seen after age 10 may still be candidates for orchiopexy with close surveillance; however, consideration of testicular biopsy may be useful in directing therapy. The decision of timing for orchiopexy should include consideration not only of an effort to reduce the incidence of testicular cancer, but also a consideration of the possibility of spontaneous descent and the evidence regarding preservation of fertility. Canavese and colleagues demonstrated an inverse relationship between age at orchiopexy and total sperm counts and sperm motility, and they recommended orchiopexy during the first year of life.[22] Taking all factors into account, consideration should be given to orchiopexy in all children if complete descent has not occurred by 12 months of age.[21]

## Clinical Presentation

The most common presentation of a testicular tumor is a nontender scrotal mass, accounting for 50% to 85% of cases.[5,6,13,23] The presentations of children that were subsequently diagnosed with a prepubertal tumor have included trauma and persistent swelling (3%), hydrocele (10%), epididymitis (13%), incidental discovery during surgical repair of a congenital or acquired disorder (53%), testicular pain/torsion (21%), and bruising.[5,6,13,23] Tumors may also be diagnosed by ultrasonography during investigations for UDT or nonresolving acute hydroceles.

Physical examination should differentiate between those problems arising from the cord (varicocele, spermatocele, epididymitis) and those arising from the testicle (trauma, orchitis, tumor). There may be bruising or a hydrocele present that may confound the diagnosis, because both of these findings may coexist with a tumor. This is particularly true in cases where preceding trauma draws attention to the scrotal area. Careful evaluation of the child's pubertal status relative to their chronologic age is important, because stromal cell tumors may present with precocious puberty (Leydig cell) or gynecomastia (Sertoli cell).

## Diagnosis

In addition to a history and physical examination, all boys with testicular masses, and those with a tense hydrocele or with a suspicious examination, should undergo a scrotal ultrasound. Although preoperative ultrasound is highly sensitive for distinguishing intratesticular from extratesticular tumors, it has poor specificity to distinguish between benign and malignant lesions.[5,13,24] Tumor size (volume) on ultrasonography has not been shown to be indicative of benign or malignant tumors.[5] Sonographic features suggestive of benign tumors (epidermoid cyst) include intratesticular cystic lesions with a hypoechoic center, representing central keratinizing debris, and an outer hyperechoic rim. Features of a teratoma may include an entirely intratesticular cystic, septated mass with intervening solid components with calcifications (bone or psammoma bodies).[13] This contrasts with malignant lesions, which tend to be more solid in appearance. In cases where malignancy is suspected, computed tomography (CT) of the chest, abdomen, and pelvis should be obtained to exclude metastatic disease to the most common sites—lung and retroperitoneum.[2,4]

## Tumor Markers

Serum tumor markers are essential in the workup and postoperative monitoring of children with testicular tumors. Human chorionic gonadotropin (HCG) and α-fetoprotein (AFP) are important markers for certain malignant germ cell histologies.[2] AFP is secreted by yolk sac tumors in up to 90% of cases, and β-HCG is secreted by choriocarcinoma. HCG has a half-life of 24 hours, whereas AFP has a half-life of 5 days. In the prepubertal age group yolk sac tumors are the most common malignant histology, and AFP is very important, whereas HCG is rarely elevated. An important consideration is that AFP is normally very high in infancy, and remains elevated for up to 8 months, decreasing to adult levels around 1 year of age.[2,23] Older boys are more likely to have malignant germ cell tumors of mixed histology, and both AFP and HCG may be elevated. For those patients with elevated tumor markers at diagnosis, serial AFP and HCG should be monitored monthly in the first postoperative year, then every other month in the second year to follow current recommendations.[25] Patients presenting with precocious puberty and a testicular mass should prompt assessment of a urinary 17-ketosteroid, serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone. Unlike precocious puberty induced by a pituitary lesion, in which the LH, FSH, and testosterone are high, testicular tumors display a low LH and FSH and a high testosterone.

## Classification and Stage

Table 40-1 lists the histologic diagnoses for prepubertal testicular tumors from several institutions, and the diagnoses are compared with the 2002 AAP tumor registry.[1,13,26] This table demonstrates the reporting bias of the national tumor registry and the population-based distribution of all testicular tumors. Table 40-2 outlines the Children's Oncology Group (COG) testicular tumor staging system.[7]

### PRIMARY TESTICULAR TUMORS

#### Epithelial-Based Tumors

***Epidermoid Cysts*** The epidermoid cyst is a benign tumor, accounting for 2% to 14% of testicular tumors in the prepubertal population.[1,5,13] They are hormonally inactive and typically present as a smooth, firm intratesticular mass. The tumor consists of a cystic structure filled with keratinizing squamous epithelium, contributing to a characteristic ultrasound appearance: central hypoechoic mass, a surrounding echogenic rim, or a mixed internal echogenicity.[27,28] Epidermoid cysts are rare, making up only 1% of testicular tumors.

**TABLE 40-1**

**Differences in Distribution of Testicular Tumors Based on Tumor Histology among Study Sites**

| *Tumor Type* | *2002 Registry %* (N = *395)* | *Pohl %* *(N = 98)* | *Metcalfe %* (N = *51)* | *Ciftci %* (N = *51)* |
|---|---|---|---|---|
| **Benign** | | | | |
| Teratoma | 23 | 48 | 43 | 18 |
| Epidermoid cyst | 3 | 14 | 10 | 6 |
| Leydig cell | 1 | 4 | 0 | 6 |
| Sertoli cell | 3 | 3 | 4 | 0 |
| Juvenile granulosa cell | 3 | 5 | 0 | N/A |
| **Malignant** | | | | |
| Yolk sac | 62 | 15 | 8 | 45 |
| Mixed germ cell | 0 | 0 | 8 | 6 |
| Rhabdomyosarcoma | 4 | Excluded | 25 | 19 |
| Gonadoblastoma | 1 | 2 | 2 | 0 |

N/A, not available.

**TABLE 40-2**

**Staging of Testicular Malignant Germ Cell Tumors**

| **Testicular Stage** | |
|---|---|
| I | Limited to testis, completely resected by high inguinal orchiectomy; no clinical, radiologic, or histologic evidence of disease beyond the testis; tumor markers normal after resection |
| II | Transscrotal orchiectomy; microscopic disease in scrotum or high in spermatic cord; retroperitoneal node involvement (<2 cm) and/or increased tumor markers after resection |
| III | Gross residual disease, retroperitoneal lymph node involvement (>2 cm), or malignant cells in pleural or peritoneal fluid |
| IV | Distant metastases involving lung, liver, brain, bone, distant nodes, or other sites |

From Cushing B, Giller R, Cullen JW, et al: Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study—Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol 2004;22:2691-2700.

These cysts lack atypia and mitotic activity. Although some epidermoid cysts show loss of heterozygosity for certain chromosomal loci, there is currently debate as to whether they represent a true neoplasm.[29]

## Stromal Tumors

***Sex Cord-Stromal Tumors*** The stromal tumors consist of three subtypes: Leydig cell, Sertoli cell, and juvenile granulosa cell tumors. This group of tumors accounts for 8% to 11% of pediatric tumors.[1,13] The vast majority of stromal tumors are benign, compared with a 10% rate of malignancy in postpubertal males.

Leydig tumors and granulosa cell tumors are universally benign in children. Leydig cell tumors tend to present in boys 5 to 10 years of age and with precocious puberty.[2] The precocious puberty is a peripherally driven etiology; therefore, the hormone profile consists of a low luteinizing hormone (LH), low follicle-stimulating hormone (FSH), and elevated testosterone. Granulosa cell tumors are rare in children and occur almost exclusively in the first 6 months of life. Chromosomal anomalies of the Y chromosome are common, and granulosa cell tumors have occurred in association with ambiguous genitalia.[2] Because of the benign nature of both Leydig and granulosa cell tumors, both can be treated with either orchiectomy or tumor enucleation in the prepubertal population.[30]

Approximately 10% of adult Sertoli cell tumors are malignant, whereas malignancy is rare in prepubertal males. Review of the PTTR showed a median age of presentation of 6 months, with no cases of malignancy reported in children less than 5 years of age.[31] Therefore complete excision of the tumor is adequate treatment in infants and young children. Presently there are no histologic criteria to predict tumor behavior in older children; however, a full metastatic evaluation should be considered if there is microscopic invasion of the spermatic cord,[31] or worrisome findings, such as a large tumor, necrosis, vascular invasion, cellular atypia, or increased mitotic activity.[2] Large cell calcifying Sertoli cell tumors are histologically distinct tumors occurring in older children and adolescents. One third of these patients have an associated genetic syndrome or endocrinopathy, most commonly, Peutz-Jeghers and Carney syndromes (myxoma of the skin, soft tissue, heart or breast, lentigines of the face and lips, cutaneous nevi, pituitary adenoma, and schwannoma).[2] They have been universally benign in patients less than 25 years of age and may be treated with testis-sparing procedures. Bilateral or multifocal disease is present in 25% of cases, increasing the need for this approach.

## Germ Cell Tumors

***Teratoma*** Testicular teratoma is the most common germ cell tumor in prepubertal males according to recent literature.[1,5,6,13] These tumors are invariably benign, unlike the adult population, where 90% to 95%[6] of germ cell tumors are malignant.[32] Teratomas are typically pure; derived from ectoderm, mesoderm, and endoderm; have diploid DNA; and a normal 46 XY karyotype.[29,32] The tissue arrangement is often organized with a gross solid cystic appearance. Dermoid and epidermoid cysts analogous to the prepubertal teratomas occur in the postpubertal testis. The testicular dermoid, like the ovarian dermoid, contains hair within a cystic tumor, and microscopic replication of skin without cellular atypia or widespread mitotic activity. The adjacent testis has normal spermatogenesis.[29] The finding of pilosebaceous units in an epidermal surface, occasionally with a lipoid reaction resulting from leakage of oil from the sebaceous glands, is a prerequisite for diagnosis of a testicular dermoid.

***Yolk Sac Tumor*** The yolk sac tumor comprised approximately 60% of the tumors historically reported in the AAP registry.[2] However, recent population-based studies, including benign testicular tumors, now report the incidence of yolk sac tumors to be 8%[13] to 15%.[1] Most of the yolk sac tumors occur in boys less than 2 years of age, but they are rare in the first 6 months of life. This is important in differentiating this tumor from the juvenile granulosa cell tumor (see previous section).[32] The majority of patients (84.5%) identified in the PTTR presented with localized stage I disease.[33] Prepubertal patients are less likely than adults to have metastasis limited

to the retroperitoneum. In a review of the PTTR of the American Academy of Pediatrics, 15.5% of boys with yolk sac tumors presented with metastatic disease. The reported sites included retroperitoneum (27%), retroperitoneal and hematogenous spread (18.8%), chest (24%), lung and an additional hematogenous site (12%), scrotum (3%), and 2% were not documented.[33]

Elevated AFP levels in excess of age-adjusted levels in the context of a testicular mass should raise suspicion of a yolk sac tumor, and the child should be managed with a standard radical inguinal orchiectomy (see later).

Grossly, the tumor is a soft solid, white to grey, or pale yellow mass with cystic degeneration containing areas of necrosis and hemorrhage. Microscopically, the yolk sac tumor characteristically contains solid papillae with a connective tissue core containing a central vessel projecting into cystic spaces; these structures are referred to as Schiller-Duval bodies.[32] The tumor invariably stains positive for AFP and placenta-like alkaline phosphatase.

***Embryonal Carcinoma*** Embryonal carcinoma is a relatively common testicular germ cell tumor after puberty; 10% are pure embryonal tumors, and a substantial number of tumors will have a mixed embryonal component.[29] This tumor demonstrates distinctive sheets, glands, and papillary structures composed of primitive epithelial cells with crowded pleomorphic nuclei. In poorly differentiated tumors, positive immunostains for CD30 and OCT3 with a c-KIT–negative profile are helpful in confirming an embryonal carcinoma.[32] Embryonal carcinoma is treated with orchiectomy. Tumors composed of more than 80% embryonal cell carcinoma or with elevated preoperative AFP (>10,000 mg/mL), vessel invasion in the primary tumor, and tumors of stage T2 or greater are considered high risk and are treated with postoperative chemotherapy and close follow-up.[34]

***Gonadoblastoma*** Gonadoblastoma has classically been identified in patients with mixed gonadal dysgenesis (45,X/46,XY), and is likely related to the presence of the testis-specific protein-Y–encoded gene (TSPY).[35] The ectopic location of the testis adds to this risk. The most commonly encountered invasive tumor in the intersex gonad is the seminoma. The development of these invasive tumors is always preceded by the presence of an in situ neoplastic lesion—intratubular germ cell neoplasia unclassified (ITGNU) or gonadoblastoma.[35,36] ITGNU is commonly referred to as carcinoma in situ (CIS). Because gonadectomy is performed prophylactically in early childhood in patients with gonadal dysgenesis, most of the encountered germ cell tumors are benign or CIS lesions. The overall prevalence of germ cell tumors in dysgenetic gonads is 15%, which is much lower than the previously reported prevalence of 33%.[35] The tumor presents with virilization of a phenotypic female harboring an XY karyotype.[37]

Gonadoblastoma typically arises from an intraabdominal testis in a young patient with gonadal dysgenesis. It is usually small, bilateral in 30% of cases, malignant in 10%, and histologically resembles a seminoma. Available data suggest the gonad of origin to include dysgenetic testis in 20%, streak gonad in 26%, and an undifferentiated gonad in 54%.[36] Extension beyond the testis has not been reported. Management has traditionally involved bilateral gonadectomy because of the risk of degeneration into an invasive seminoma. However, the recognized role of testosterone in gender differentiation has led to a more conservative approach to the contralateral gonad, which may involve a contralateral orchiopexy to allow gender development, followed by annual scrotal examinations and ultrasonography after age 10 years until puberty. At puberty, testicular biopsy should be carried out to evaluate for CIS in the remaining testicle.[38] If no evidence of CIS is identified, annual follow-up with testicular ultrasonography until age 20 is recommended. If CIS is identified at puberty, orchiectomy should be considered.[38]

***Choriocarcinoma*** Choriocarcinoma is among the rarest of the gonadal germ cell tumors, representing 0.3% of testicular tumors.[29] These tumors elaborate β-HCG, and may be associated with a number of hormonal manifestations. These include precocious puberty from β-HCG–induced Leydig cell stimulation, gynecomastia, and hyperthyroidism because of the similarity of the β-HCG subunits to thyroid-stimulating hormone.[29] Testicular choriocarcinomas frequently have distant metastasis at the time of presentation rather than a scrotal mass. Histologically, they are composed of syncytiotrophoblastic cells with mononucleated cells around foci of hemorrhage. They stain positive for β-HCG and placental lactogen.[32]

### Rhabdomyosarcoma

Although technically a paratesticular tumor, rhabdomyosarcoma should be included in the differential diagnosis of scrotal tumors. It is the most frequent tumor of paratesticular origin, accounting for 4% to 25% of scrotal masses.[13] The tumor has a bimodal distribution, peaking between 3 to 4 months of age and 15 to 19 years of age. The infant tumor has a more indolent behavior than the tumor presenting in the adolescent age group (90% vs. 63% failure-free survival).[39] Despite its aggressive behavior, the prognosis of paratesticular rhabdomyosarcoma has improved dramatically from 10% to 77% overall survival with the introduction of vincristine, dactinomycin, and cyclophosphamide (VAC) chemotherapy.[39,40] The most common subtype is embryonal rhabdomyosarcoma, which accounts for 97% of paratesticular tumors.

The tumor consists of small round blue cells and presents as a scrotal mass in 80% of patients. Ultrasonography is highly effective in demonstrating its paratesticular location and distinguishing it from the tumors of testicular origin.[13] CT or MRI of the retroperitoneum should be performed prior to surgery for staging purposes. Thirty to 40 percent of boys will have micrometastasis to the retroperitoneum. The tumor should be resected by a radical inguinal orchiectomy. A retroperitoneal lymph node dissection (RPLND) is recommended for all patients 10 years of age or older for accurate staging, and in patients less than 10 years with radiologic evidence of retroperitoneal involvement.[39] A metastatic workup should include a chest CT, liver function tests, bone scan, and bone marrow biopsy.

## SECONDARY TESTICULAR TUMORS

Lymphoma and leukemia are the dominant secondary tumors of the testis. Acute lymphoblastic leukemia (ALL) is a common cause of a prepubertal testicular mass. Microscopic

involvement of the testis has been found at autopsy in 66% of patients with ALL.[32] Malignant lymphomas account for 5% of testicular tumors; 10% to 15% are bilateral at presentation.[32]

The management of leukemia and lymphoma are the same. The presence of a palpable mass in a patient with newly diagnosed leukemia/lymphoma should prompt a scrotal ultrasonography. This usually demonstrates a homogeneous hypoechoic mass. Current literature discourages testicular biopsy in patients prior to initiating chemotherapy, because there is no survival advantage.[41] In contrast, a patient with persistent or newly enlarged testis undergoing chemotherapy, particularly in leukemia, implies a relapse while on therapy. This should prompt a biopsy to direct subsequent therapy. This typically involves additional chemotherapy to eradicate residual disease in sanctuary sites and possible systemic residual disease and radiation to the affected testis.

In 25% of cases, testicular lymphoma is a manifestation of widespread systemic involvement, another 25% present with Ann Arbor stage II disease (involvement of lymph nodes below the diaphragm), and the remaining 50% have disease confined to the testis (Ann Arbor stage I).[32]

Metastasis to the testis in children is rare. The most frequent metastasis has been carcinoma from the prostate, colon, kidney, stomach, pancreas, and malignant melanoma in adults, while neuroblastoma and Wilms tumor predominate in children.[32] Most of these tumors have distinctive features that allow easy identification.

# Surgical Management

## TESTIS-SPARING SURGERY

In the last 2 decades, multiple reports have confirmed that many testicular tumors in the prepubertal population can be managed more conservatively than in adults, because the distribution of prepubertal tumors favors a benign histology. This realization has confirmed the safety and feasibility of testis-sparing surgery, especially when the lesion is evaluated preoperatively by ultrasonography and serum AFP and intraoperatively by frozen section analysis. Metcalfe and colleagues[13] have provided a practical treatment algorithm incorporating the common benign tumors for nonradical surgery (Fig. 40-1).

In general, before puberty, teratoma, gonadal stromal tumors (Leydig cell and Sertoli cell) and epidermoid cyst can be managed with a testis-sparing approach (Fig. 40-2). Postpubertal patients with teratoma or stromal tumors should be treated as adults, with radical orchiectomy because of their more malignant behavior.

Testis-sparing surgery is carried out through an inguinal incision. The cord is mobilized after opening the external oblique aponeurosis to the level of the internal ring. The cremasteric fibers are dissected from the cord structures to allow circumferential control of the cord. The cord should be occluded at the level of the internal ring with a noncrushing clamp. The testis is then delivered through the inguinal incision, and the wound is protected. The tunica vaginalis is opened directly over the mass, and an excisional biopsy of

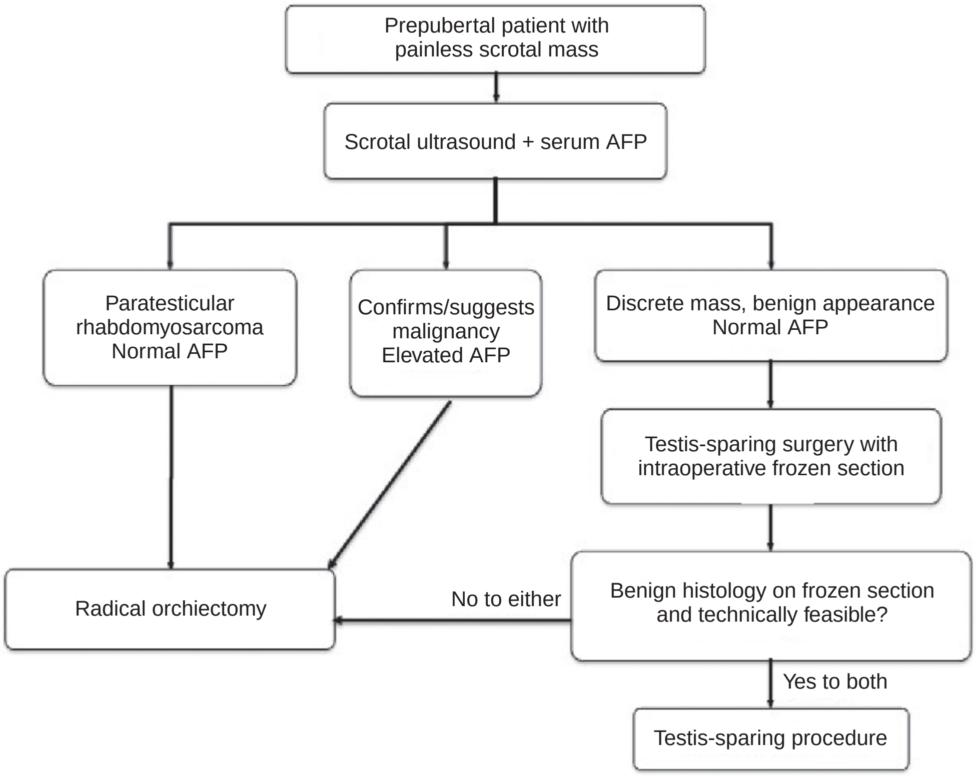


**FIGURE 40-1** Proposed treatment algorithm for prepubertal patients presenting with a painless scrotal mass. AFP, α-fetoprotein. (From Metcalfe PD, Farivar-Mohseni H, Farhat W, et al: Pediatric testicular tumors: Contemporary incidence and efficacy of testicular preserving surgery. J Urol 2003;170:2412-2415; discussion 2415-2416.)

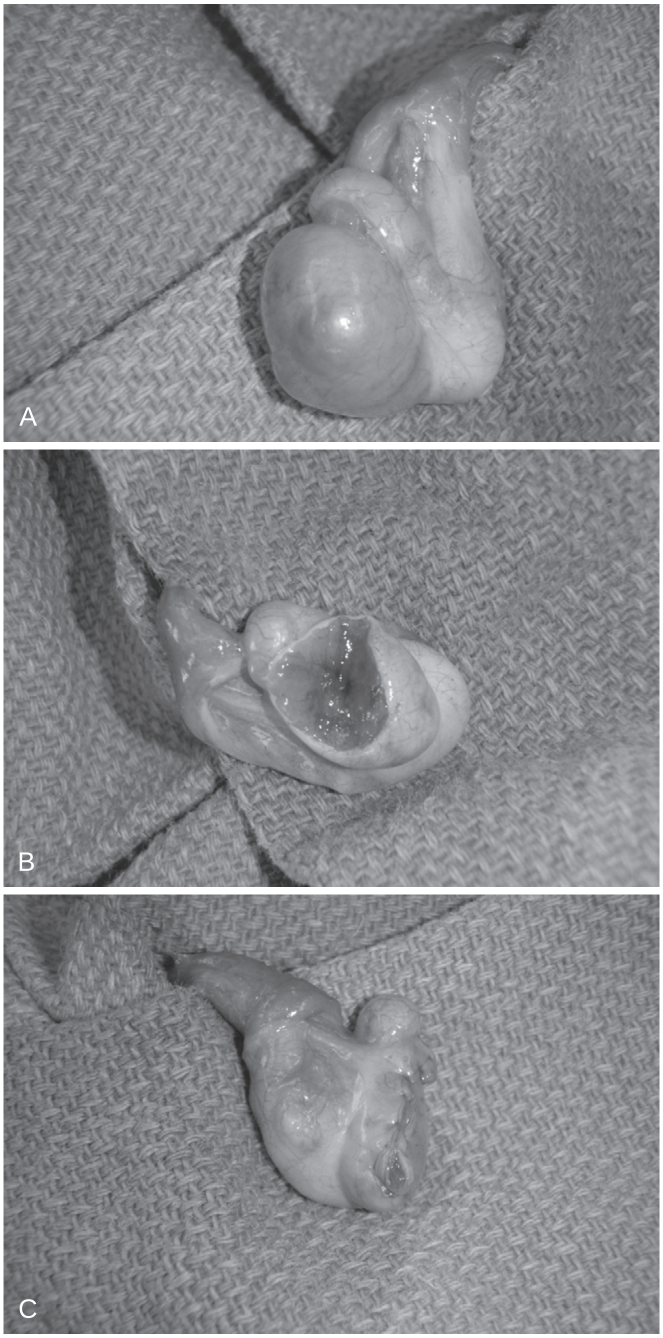


**FIGURE 40-2** **A,** Intraoperative photograph of a child with painless swelling of testicle. **B,** Wedge resection of epidermoid cyst. **C,** Suture closure of testicular capsule. (Courtesy Dr. P. Metcalfe, personal file.)

the mass is performed without violating the tumor capsule. Frozen section evaluation is obtained. Hemostasis is achieved with electrocautery. If a benign testicular tumor is diagnosed, the tunica vaginalis is closed with fine absorbable sutures (see Fig. 40-2), and the testis is replaced in the scrotum. Normal tissue adjacent to the tumor must be assessed by a pathologist to exclude pubertal changes. It is commonly assumed that the postpubertal testis with a tumor will behave in a similar fashion to the adult testis, although specific data are lacking. Adult testicular tumors are associated with intratubular germ cell neoplasia (ITGCN) in the surrounding parenchyma in more than 90% of cases. These cells are the precursors for germ cell tumors and are felt to represent a risk for recurrent neoplasia if the residual testicular parenchyma is left in situ. The progression through puberty evolves over a period of time and sequential histologic changes. The testes go through a maturation process starting from simple tubules without lumen and with interstitial Leydig cells in the neonate. The Leydig cells then regress and the tubules become more tortuous. As puberty begins, the Leydig cells become more prominent, and the basal germ cells begin to divide. There are multiple layers of spermatocytes and the tubule lumens form, followed by the appearance of mature sperm. The appearance of mature sperm or ITGCN would be indicative of completion of pubertal changes.

## RADICAL INGUINAL ORCHIECTOMY AND RETROPERITONEAL LYMPH NODE DISSECTION

A radical inguinal orchiectomy is performed through a standard inguinal incision, with clear demarcation of the external oblique aponeurosis and external ring and opening of the external ring back to the level of the internal ring. The cremasteric fibers are once again dissected from the cord, and the cord is fully mobilized from the inguinal canal, followed by vascular control at the internal ring. The cord is then clamped and divided at the level of the internal ring, after which the stump is suture ligated. After ligation, dissection proceeds distally with mobilization of the testis from the scrotum and division of the gubernaculum. If the tumor is too large to deliver through the scrotal canal, the incision may be carried onto the superior aspect of the scrotum.[42,43] Once the tumor is excised, the wound is closed in standard fashion.

Current pediatric testicular tumor protocols do not include a RPLND. Postchemotherapy masses are treated with local resection. Postpubertal patients will often be managed with adult protocols, although data regarding adolescents is lacking. The indications for and the extent of RPLND are a matter of some controversy even in adults. Prechemotherapy RPLND is no longer employed, and postchemotherapy RPLND is eliminated in some centers if residual disease is less than 1 cm in dimension by imaging.[44] In the event that a RPLND is required, a midline abdominal incision is made and a thorough laparotomy performed to identify retroperitoneal low-volume metastasis not appreciated on preoperative imaging. There is also controversy regarding the extent of dissection. Because of the morbidity of bilateral RPLND (40%), a variety of unilateral templates have been developed in addition to the concept of nerve-sparing dissection.[45,46] In low-stage disease, lymphatic spread is typically unilateral, and therefore a full bilateral RPLND is not used in some centers.[47] For the unilateral template, dissection for patients with right-sided disease involves removal of the lymphatics in the interaortocaval, precaval, and right paracaval distribution (Fig. 40-3, *A*).[43] For left-sided lesions, this includes the left paraortic and preaortic lymphatics (Fig. 40-3, *B*). This dissection strategy is important, because it preserves the contralateral sympathetics important for emission and ejaculation.[48] Preservation of efferent sympathetic fibers maintains emission and ejaculation rates at 99%.[48] The finding of viable tumor outside of the template distribution has led to the recommendation for bilateral dissection

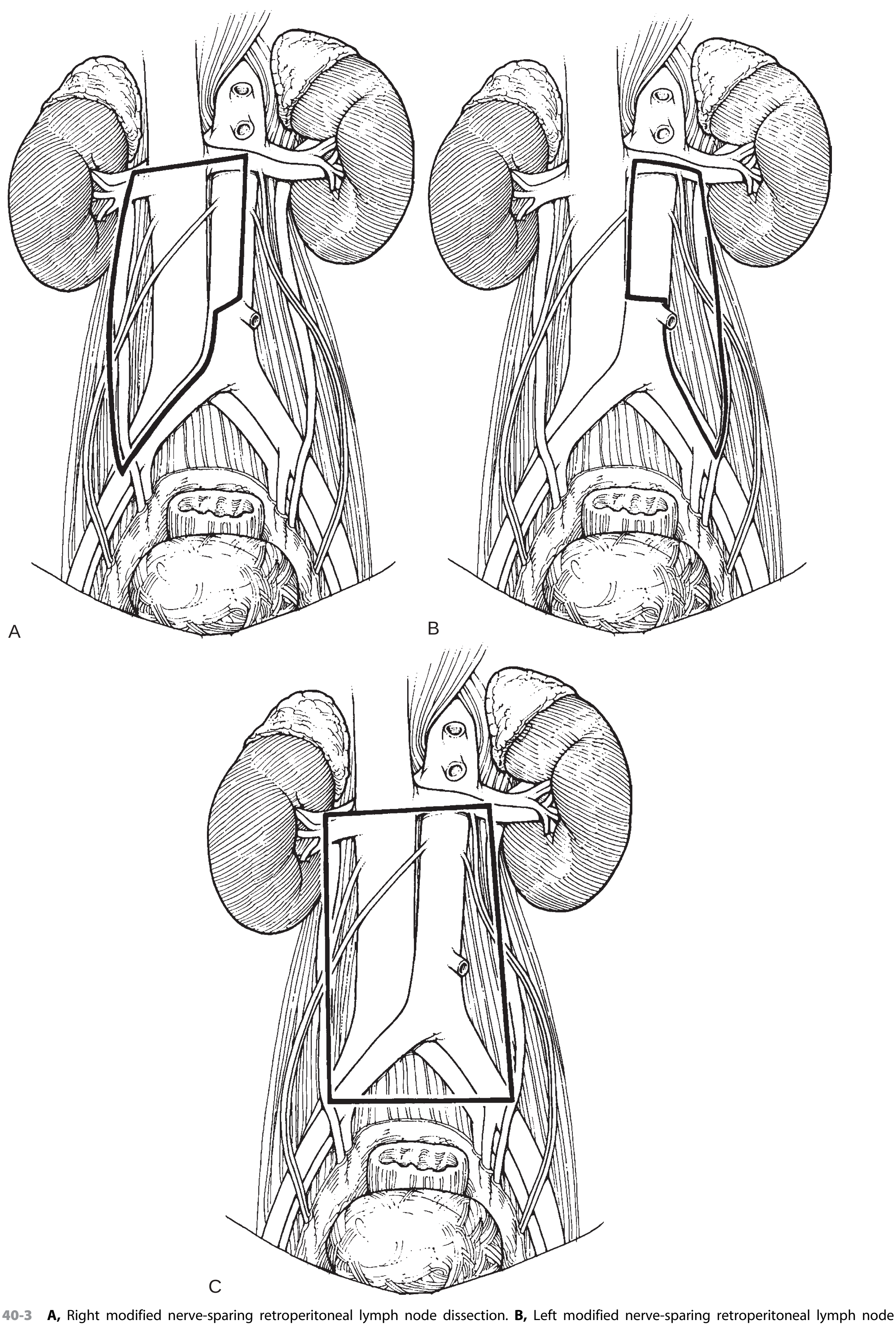

**FIGURE 40-3** **A,** Right modified nerve-sparing retroperitoneal lymph node dissection. **B,** Left modified nerve-sparing retroperitoneal lymph node dissection. **C,** A full retroperitoneal dissection involves left and right combined. (From Marshall FF [ed]: Operative Urology. Philadelphia, WB Saunders, 1996, p 368-369.)

in all patients undergoing RPLND in other centers.[46] In advanced-stage/high-volume disease bilateral RPLND is always used, as shown in Figure 40-3, *C*.[45] With either technique, the nodal packets are split at the 12 o'clock position over the vessels and rolled laterally away. The sympathetic fibers are carefully identified and preserved as they cross the iliac bifurcation.

## CHEMOTHERAPEUTIC STRATEGIES AND SURVIVAL IN CHILDREN WITH MALIGNANT GERM CELL TUMORS

Prior to effective chemotherapy, children with malignant germ cell tumors (MGCT) had 3-year survival rates of 15% to 20% with surgery and radiation.[7,49] The introduction of cisplatin-based regimens has dramatically improved outcomes (Table 40-3).[11] In patients with low- and intermediate-risk (<15 years of age) MGCT, the 6-year overall survival rates for advanced gonadal tumors (stages III and IV) are now greater than 94%.[7] Standard chemotherapy for children with MGCT of the testes includes standard-dose cisplatin, etoposide, and bleomycin (PEB) for 4 to 6 courses.[2] The current protocol under investigation examines stages II to IV with three courses of chemotherapy. Management of patients is based upon risk groups as proposed by the Children's Oncology Group (COG) as follows (see Table 40-3)[11]:

1. **Low risk:** Stage I immature teratoma and MGCT of the testis. Recommend surgery and close follow-up observation to document normalization of tumor markers following resection
2. **Intermediate risk:** Stages II-IV gonadal tumors (excluding patients >15 years with stage IV testicular tumors).

**TABLE 40-3**
**Standard Treatment for Children Younger Than 15 Years with Testicular Germ Cell Tumors by Histology and Stage**

| *Histology* | *Stage* | *Treatment* | *Overall Survival (6-Year)* |
|---|---|---|---|
| Mature teratoma | Localized | Surgery + observation | 100% |
| Immature teratoma | Localized | Surgery + observation | 100% |
| MGCT | Stage I | Surgery + observation | 100% |
| | Stage II-IV* | Surgery + PEB | 94% |

From Cushing B, Giller R, Cullen JW, et al: Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study—Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol 2004;22:2691-2700; Rogers PC, Olson TA, Cullen JW, et al: Treatment of children and adolescents with stage II testicular and stages I and II ovarian malignant germ cell tumors: A Pediatric Intergroup Study-Pediatric Oncology Group 9048 and Children's Cancer Group 8891. J Clin Oncol 2004;22:3563-3569.

*Patients greater than 15 years old with stage IV testicular tumors should be discussed in a multidisciplinary oncology group for more intensive therapy.

MGCT, malignant germ cell tumors; PEB, cisplatin, etoposide, and bleomycin.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 41

# Adrenal Tumors

Michael G. Caty and Mauricio A. Escobar, Jr.

## Anatomy

The adrenal glands are found anteromedially to the superior pole of the kidneys, are covered by perirenal fat, and enclosed by Gerota fascia. In adults, the glands weigh approximately 5 g each. The right gland abuts the inferior vena cava and liver and lies on the posterior extension of the diaphragm. The left gland lies next to the splenic vessels and the tail of the pancreas.

Although the blood supply to the adrenal glands is variable, it generally comes from three sources: the inferior phrenic artery superiorly, the aorta medially, and the renal arteries inferiorly. The venous drainage does not parallel the arterial supply; instead, a single large adrenal vein provides the majority of the venous drainage for each gland. The right adrenal vein empties into the inferior vena cava, and the left adrenal vein joins the left renal vein.

The adrenal lymphatics arise from one plexus beneath the capsule and from a second plexus in the medulla. The right adrenal lymph vessels drain into the periaortic lymph nodes near the diaphragmatic crus, and the left adrenal lymphatics empty into lymph nodes near the origin of the left renal artery.

The innervation of the adrenal glands arises from the celiac plexus and the greater thoracic splanchnic nerves. The preganglionic sympathetic fibers enter the hilum and end in ganglia within the medulla.

The cortex and medulla form two distinct regions of the adrenal gland. These regions are distinct on gross examination as well as embryologically, structurally, and functionally. The adrenal medulla is derived from ectodermal cells from the neural crest. These precursors form the chromocell system and the neuronal system, accounting for the potential development of two distinct medullary neoplasms: pheochromocytoma and neuroblastoma. Preganglionic sympathetic neural cells innervate the secretory chromaffin cells, which synthesize norepinephrine and epinephrine.

The cortex comprises the outer portion of the adrenal gland and secretes sex hormones, mineralocorticoids, and glucocorticoids. It is divided into three separate zones that have distinct synthetic functions. The zona glomerulosa is the outermost cortical zone and produces aldosterone and related mineralocorticoids. The zona fasciculata lies beneath the zona glomerulosa and secretes cortisol and the adrenal sex hormones. The inner zona reticularis maintains cholesterol stores as a precursor for steroidogenesis and secretes cortisol, androgens, and estrogens.

## Embryology

The primordium of the adrenal cortex becomes visible as early as the fourth week of gestation and is clearly seen by the sixth week. On prenatal ultrasonography (US), the adrenal glands may be visible as early as 20 weeks' gestation and are identifiable in the majority of fetuses by 30 weeks' gestation.[1] During the fourth to sixth weeks of gestation, the mesodermal cells of the posterior abdominal wall at the adrenogenital ridge become more columnar and invade the mesenchyma beneath the epithelial surface, ultimately forming the fetal adrenal cortex. Another proliferation of epithelial cells subsequently forms a cap over these primitive cortical cells, becoming the zona glomerulosa of the definitive cortex. The ectodermal chromaffin cells of the adrenal medulla arise from the neural crest as early as the fifth week, with primitive cells from the thoracic ganglia from the 6th to 12th segments invading the gland and forming the medulla. Differentiation of these primitive medullary cells into chromaffin cells begins at the third month of gestation, ultimately leading to the cells' production of epinephrine and norepinephrine.

The fetal zone of the adrenal cortex begins to appear around the sixth week of gestation. This zone continues to enlarge and occupy the majority of the gland. In fact, because of the large size of the fetal cortical zone, the fetal adrenal gland is 4 times the size of the kidney during the fourth month of gestation. This fetal cortex subsequently decreases in size, disappearing in the first year of life.

During fetal development, ectopic rests of medullary and cortical tissue may remain and persist after birth. Extraadrenal medullary rests are usually found along the aorta and its branches. The organ of Zuckerkandl is an example of a chromaffin mass at the origin of the inferior mesenteric artery. Most extraadrenal chromaffin rests involute after birth; the chromaffin cells in the medulla differentiate.

Extraadrenal cortical rests are common in children and are found in the kidney or liver or along the migratory path of the gonads, in hernia sacs, or in the gonads themselves. Approximately 50% of newborns have adrenocortical rests, but these rests typically atrophy and disappear within a few weeks after birth.[1]

# Physiology

## ADRENAL MEDULLARY FUNCTION

The adrenal medulla synthesizes and releases catecholamines: dopamine, epinephrine, and norepinephrine. Catecholamine synthesis begins with tyrosine, a nonessential amino acid. Tyrosine hydroxylase converts tyrosine into dihydroxyphenylalanine (DOPA) and is the rate-limiting step in the synthetic pathway. DOPA decarboxylase converts DOPA into dopamine. Phenylamine beta-hydroxylase converts dopamine into norepinephrine. Finally, phenylethylamine *N*-methyltransferase converts norepinephrine into epinephrine.

The chromaffin cells within the medulla contain cytoplasmic granules that store the catecholamines. Preganglionic sympathetic nerve endings release acetylcholine, which causes calcium-dependent exocytosis of these cytoplasmic storage granules and release of the catecholamines. Regulation of adrenal medullary catecholamine release is accomplished through inhibitory feedback mechanisms involving norepinephrine. Norepinephrine inhibits acetylcholine release from the presynaptic $alpha_2$ receptors and also inhibits tyrosine hydroxylase activity when present in high concentrations.

## ADRENAL CORTICAL FUNCTION

The adrenal cortex synthesizes three types of hormones: glucocorticoids, mineralocorticoids, and sex hormones. Regulation of these is accomplished by the hypothalamic-pituitary-adrenal axis. The hypothalamus produces corticotropin-releasing hormone (CRH); this is transported to the anterior pituitary gland where it stimulates the release of adrenocorticotropic hormone (ACTH). ACTH then stimulates the production of hormones (glucocorticoids, mineralocorticoids, and sex hormones) from the adrenal cortex.

The physiologic diurnal variation in CRH release leads to a cyclic variation in ACTH and the hormones regulated by it. Serum concentrations peak shortly before or at the time of awakening and decline throughout the remainder of the day. Both cortisol and ACTH inhibit CRH release, creating a negative feedback loop.

Adrenocortical production of glucocorticoids begins with a cholesterol substrate and is regulated by ACTH. The majority of serum cortisol is bound by cortisol-binding protein (90%) and albumin (6%), leaving only a small percentage (4%) free and physiologically active. As with most steroids, the unbound cortisol fraction is lipophilic and therefore readily crosses the plasma membrane of target cells. Specific receptors then bind with cortisol and act in the cell nucleus to regulate messenger RNA synthesis.

Cortisol affects metabolism primarily by opposing insulin. It causes hyperglycemia by increasing the proteolysis necessary for gluconeogenesis and inducing hepatic gluconeogenic enzymes. Cortisol also decreases the use of glucose by peripheral tissues; it inhibits glucose uptake into fat cells and decreases the amount of insulin bound by insulin-sensitive tissues.

Cortisol also decreases inflammation and immune function, affecting wound healing. Cortisol lowers both the lymphocytic and the granulocytic cellular immune response by decreasing the lymphocyte response to antigenic stimulation and impairing chemotaxis and phagocytosis of leukocytes. These two immune functions are an important part of early wound healing; thus wounds have decreased tensile strength and impaired healing in the setting of excess cortisol.

Aldosterone, a mineralocorticoid, is synthesized in the zona glomerulosa and metabolized primarily by the liver. The renin-angiotensin system controls the majority of aldosterone regulation, with ACTH playing only a small role. The macula densa of the renal juxtaglomerular apparatus releases renin in response to a drop in renal perfusion or hyponatremia. Renin converts angiotensinogen, which is produced by the liver, to angiotensin I. Angiotensin-converting enzyme, found in the lung, converts angiotensin I to angiotensin II. Angiotensin II stimulates the synthesis of aldosterone by directly acting on the cells of the adrenal zona glomerulosa; it also acts as a vasoconstrictor. By increasing the renal retention of sodium, aldosterone increases blood pressure and corrects hyponatremia, thus reducing the release of renin.

The serum potassium concentration also provides a small amount of aldosterone regulation. Hyperkalemia leads to increased aldosterone production by directly acting on the zona glomerulosa cells, as well as increasing renin release from the juxtaglomerular cells. Aldosterone promotes an increased renal excretion of potassium, thus lowering aldosterone production and providing another feedback mechanism.

Adrenal androgens are synthesized in the zona reticularis and are regulated primarily by ACTH. These hormones are released in a cyclic manner, correlating with the release of cortisol and ACTH. The adrenal androgens are only weakly active but are converted by peripheral tissues into more active forms such as testosterone and dihydrotestosterone. Metabolism of these hormones occurs in the liver.

# Lesions of the Adrenal Medulla

## PHEOCHROMOCYTOMA

In 1886, Frankel of Freiburg, Germany, published the first description of bilateral pheochromocytomas found during the postmortem examination of an 18-year-old woman who had presented with symptoms of anxiety, palpitations, and headache.[2] In 1912, Pick named the tumor for its predominant cell type, the pheochromocyte, but it was not until 1922 that Labbe and colleagues first described a clear relationship between pheochromocytoma and paroxysmal hypertension. In 1927, Mayo performed the first successful removal of a pheochromocytoma in a patient with paroxysmal hypertension who underwent surgical exploration without a preoperative diagnosis. In 1929, Pincoffs made the first correct preoperative diagnosis, and the successful operation was performed by Shipley.[3] Since that time, the behavior of pheochromocytomas has become better understood, particularly with respect to children.

Pheochromocytoma is an uncommon tumor of childhood, and there are several characteristics that distinguish its presentation between adults and children. The incidence of pheochromocytoma in childhood is 10% of the adult incidence, occurring in approximately 1 in 500,000 children compared with 1 in 50,000 adults.[4] Approximately 10% of childhood pheochromocytomas are familial, which is about 4 times the frequency in adults. Whereas only 7% of pheochromocytomas are bilateral in adults, the reported incidence of

**TABLE 41-1**
**Comparison of Pheochromocytoma in Children and Adults**

| | *Pediatric* | *Adult* |
|---|---|---|
| Incidence | 1:500,000 | 1:50,000 |
| Familial pattern (%) | 10 | 2-3 |
| Bilateral (%) | 24-70 | 10 |
| Extraadrenal site (%) | 30 | 10 |
| Malignant (%) | 3 | 10 |

bilateral pheochromocytomas in children ranges from 24% to as high as 70%. Extraadrenal pheochromocytomas are approximately twice as prevalent in children as in adults (Table 41-1).[5,6]

Pheochromocytomas originate from medullary chromaffin cells, which produce the catecholamines that cause the associated symptoms. These cells migrate along the aorta, usually remaining near the branches of the aorta.

## SYMPTOMS

In children with pheochromocytoma, the average age at presentation is 11 years, although the tumor can occur at any age. Over half the children present with headaches, fever, palpitations, thirst, polyuria, sweating, nausea, and weight loss, but the most common presentation is sustained hypertension.[4,6,7] In children, most causes of hypertension are secondary, with renal abnormalities being most common (78%), followed by renal artery disease (12%), and coarctation of the aorta (2%).[8] Pheochromocytoma accounts for 0.5% of children with hypertension and must be considered once other causes are eliminated. In children with pheochromocytoma, hypertension is sustained in up to 70% to 90% of cases, with only a small minority presenting with paroxysmal hypertension. In contrast, up to 50% of adults with pheochromocytoma have paroxysmal hypertension.[6]

## DIAGNOSIS

The diagnosis of pheochromocytoma relies on the demonstration of elevated levels of blood and urinary catecholamines and their metabolites. A 24-hour urine measurement of catecholamines, metanephrine, and vanillylmandelic acid is the best diagnostic test.[9,10] Urinary metanephrine levels are increased in about 95% of patients, and urinary vanillylmandelic acid and catecholamine levels are increased in approximately 90% of patients.[10] There is also a linear relationship between the amount of vanillylmandelic acid and the size of the pheochromocytoma.[11] The normal 24-hour urinary secretion is less than 100 mg for free catecholamines, less than 7 mg for vanillylmandelic acid, and less than 1.3 mg for metanephrine. Plasma catecholamines can also be measured by radioenzyme assay. However, patients must remain supine and calm during the blood draws, which can be difficult in children. Patients with normal plasma catecholamine levels during a hypertensive episode probably do not have pheochromocytoma, but levels greater than 2000 pg/mL are diagnostic of pheochromocytoma. Plasma catecholamine levels between 500 and 1000 pg/mL are suspicious for a pheochromocytoma, and further testing is indicated.[6] It must be remembered, however, that neuroblastoma can in some cases secrete significant levels of catecholamines.

After establishing the chemical diagnosis of pheochromocytoma, the tumor must be localized. Although large masses such as a neuroblastoma can be seen on plain abdominal films, most adrenal masses cannot be visualized without the use of other imaging methods. Almost all pheochromocytomas occur in the abdomen or pelvis, and although the adrenal gland is the most common site, up to 43% of children may have multifocal disease.[6] The initial study in infants and children is often US, which can be useful in distinguishing between solid and cystic masses while determining their vascularity and avoiding ionizing radiation, but it may not visualize small adrenal lesions. Additionally, it may be difficult to identify the adrenal gland as the organ of origin for large masses, because of compression from adjacent organs such as the kidney. Computed tomography (CT) and magnetic resonance imaging (MRI) offer the advantage of much better resolution and sensitivity (Fig. 41-1). Although CT is an accurate method of diagnosing adrenal lesions, it is less accurate in younger children because of the absence of retroperitoneal fat. Other disadvantages of CT are the need for intravenous contrast material and exposure to ionizing radiation. Simultaneous scanning of the chest to rule out pulmonary metastases in patients suspected of having adrenal carcinoma is a benefit of CT. Currently, both CT and MRI offer multiplanar imaging. Coronal imaging is a useful modality to distinguish

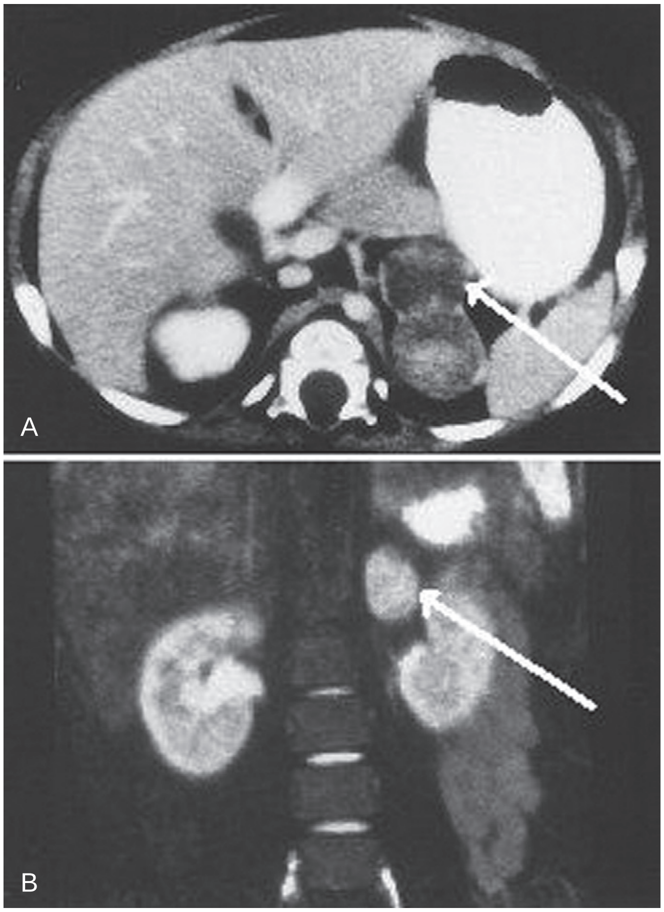


FIGURE 41-1 **A,** Computed tomography of the abdomen in a 10-year-old girl with a left adrenal mass associated with hypertension. **B,** Magnetic resonance image demonstrates a left adrenal pheochromocytoma. No other masses were noted. No contrast agent was required.

adrenal masses from the adjacent kidney and vice versa.[12–14] Pheochromocytomas demonstrate low or intermediate signal intensity on T1-weighted images and enhance with gadolinium-diethylenetriaminepentaacetic acid (DTPA).[15] One significant disadvantage to MRI is that children often require sedation or general anesthesia, given the length of time the study requires, which may be a risk if children have not been treated with blocking agents.

Another useful imaging technique is $^{131}$I-labeled metaiodobenzylguanidine (MIBG) scanning; this radioisotope accumulates where norepinephrine is taken up and allows detection of the tumor. MIBG, which is structurally similar to norepinephrine, is taken up by the norepinephrine transporter system into intracytoplasmic vesicles. Radionuclide imaging is achieved by labeling MIBG with one of two iodine isotopes at the meta position of the benzoic ring. The iodine isotope $^{131}$I has a half-life of 8.2 days and emits high-energy radiation. The iodine isotope $^{123}$I has a shorter half-life and emits lower-energy radiation.[16] Patients undergoing MIBG scanning should be given a saturated solution of potassium iodide to block thyroid uptake of the free iodine isotope. Scintigraphy is performed at 24 and 48 hours. This technique can be particularly useful in localizing extraadrenal tumors or sites of metastasis. It also confirms the adrenal location of a pheochromocytoma in patients with positive urine or serum catecholamine tests. The head and neck may be a more common site of these tumors in children compared with adults, followed by the retroperitoneum.[17]

Positron emission tomography (PET) may be a useful imaging study for pheochromocytoma in the near future. PET scanning uses short-lived positron-emitting agents to identify specific areas of uptake in the body. Because of the increased metabolism of tumors, labeled glucose can be used to identify malignant tissue. The most common form of labeled glucose in use for PET scanning is ($^{18}$F)-fluorodeoxyglucose (FDG). However, resolution of pheochromocytoma and distinction between benign and malignant pheochromocytoma are not optimal with FDG PET. A more useful agent may be 6-($^{18}$F)-fluorodopamine (DA). The similarity between norepinephrine and DA allows selective uptake by sympathoadrenal tissue.[18] One study found that FDG PET demonstrated metastases better than MIBG scanning did in adults (one patient was 16 years old in this cohort of 29 patients).[19] PET scanning results in lower radiation exposure than standard scintigraphy. When specific agents, such as DA, become generally available, PET scanning may prove to be the imaging method of choice.

## TREATMENT

The treatment of pheochromocytoma is surgical excision, although medical management of the hypertension is an essential part of the preoperative preparation. The high levels of catecholamines increase the risk of sudden and severe intraoperative hypertension, as well as profound hypotension once the tumor is removed and catecholamine release has ceased. In fact, these complications accounted for the high mortality rate associated with surgical resection in the past.[6] Improvements in preoperative and intraoperative management have reduced the operative mortality of 24% to 45% in the past to less than 10% today.[20] Preoperative use of alpha-adrenergic blockers, such as oral phenoxybenzamine and phentolamine, reduces the effects of epinephrine and norepinephrine by blocking the alpha-adrenergic receptors. These agents should be started at least 3 to 7 days before the procedure and the dose increased until the pressures are well controlled to minimize the intraoperative risks. Replacement of intravascular volume is often required as alpha blockade is achieved, because patients with pheochromocytomas tend to be hypovolemic at baseline, with an average 15% reduction in plasma volume. This volume re-expansion also helps minimize intraoperative blood pressure fluctuations and cardiac arrhythmias.

Beta-adrenergic blockade with agents such as propranolol and labetalol may be used once an alpha-adrenergic blockade is achieved, particularly if a resting tachycardia develops despite adequate volume replacement. If these agents are used, it is crucial that alpha blockade be established first. Administration of a beta blocker before an alpha blockade can worsen hypertension secondary to unopposed vasoconstriction.

Methyl-para-tyrosine (metyrosine) competitively inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis. Treatment with metyrosine reduces tumor stores of catecholamines, decreases the need for intraoperative antihypertensive drugs, lowers intraoperative fluid requirements, and attenuates blood loss. It has not been tested in children less than 12 years of age. Metyrosine may not be necessary for patients with minimal or no symptoms from a minimally functioning pheochromocytoma.[21]

Despite good preoperative normalization of blood pressure, the anesthesiologist must be prepared for sudden fluctuations. The times of significant intraoperative risk are during anesthetic induction and intubation, during surgical manipulation of the tumor, and immediately following ligation of the tumor's venous drainage.[22] An arterial catheter and a central venous line are crucial for monitoring intraoperative blood pressure and fluid status. The anesthesiologist must also be prepared to use fast-acting agents to raise or lower blood pressure as needed. Sodium nitroprusside and nitroglycerin are useful agents, as are vasopressors and intravenous fluids. Cardiac arrhythmias can be managed with the use of propranolol, esmolol, and lidocaine. Adrenalectomy is described later.

An adrenal pheochromocytoma is typically encapsulated, and although there may be small amounts of normal adrenal tissue, the entire adrenal gland should be removed. It is rarely necessary to perform a nephrectomy, because the tumor is rarely adherent to the kidney.

As previously mentioned, once the adrenal vein is ligated and the tumor is removed, the patient may become hypotensive because of the removal of the catecholamine excess. In fact, it may be several days before the blood pressure normalizes. If hypertension returns postoperatively, one should suspect a second pheochromocytoma. All patients should undergo follow-up to confirm normalization of catecholamine levels. Long-term follow-up is indicated because of the possibility of a metachronous occurrence of a multifocal pheochromocytoma or occult metastasis.[6,22]

## ASSOCIATED DISORDERS

Familial pheochromocytomas may occur in the setting of several syndromes. The most common syndromes are multiple endocrine neoplasia type 2 (MEN-2) and von Hippel-Lindau disease. There is a smaller incidence of familial

pheochromocytomas in patients with neurofibromatosis type 1 and in patients without any other abnormalities.

Traditionally, a 10% incidence of familial cases of pheochromocytoma was expected. However, a germline mutation has been identified in up to 59% of apparently sporadic pheochromocytomas presenting at 18 years of age or younger and in 70% of those presenting before 10 years of age in one series.[21] The inherited predisposition may be attributable to a germline mutation in the von Hippel-Lindau gene, the genes encoding the subunits B and D of succinate dehydrogenase, the *RET* proto-oncogene predisposing to multiple endocrine neoplasia type 2, or the neurofibromatosis type 1 gene. Of these, the von Hippel-Lindau gene is the most commonly mutated gene in children presenting with a pheochromocytoma. A mutation of the von Hippel-Lindau gene on chromosome 3 leads to von Hippel-Lindau disease. This condition is characterized by retinal angiomas, hemangioblastomas of the central nervous system, renal cysts, renal cell carcinoma, pancreatic cysts, and pheochromocytomas. These pheochromocytomas are often multifocal and are frequently extraadrenal.

Multiple endocrine neoplasia type 2 is an autosomal dominant disorder caused by a mutation of the *RET* proto-oncogene on chromosome 10. These patients are at risk for medullary thyroid carcinoma, and up to 50% will develop adrenal pheochromocytoma. These tumors are almost always bilateral and are almost never malignant. Patients with MEN-2A are also at risk for hyperparathyroidism, and patients with MEN-2B may have a marfanoid habitus or mucosal ganglioneuromas.

Malignancy has been reported to occur in up to 10% of children with pheochromocytoma.[7] The diagnosis of malignancy is generally based on the tumor's clinical behavior, because the histologic examination is not an accurate predictor. A malignant pheochromocytoma may have local infiltration or distant metastasis, which most commonly occurs in bone, liver, lymph nodes, lung, and the central nervous system. Synchronous or metachronous pheochromocytomas may present anywhere along the sympathetic chain. Although surgical resection remains the treatment of choice, long-term palliation may be obtained through a multimodal approach, including local excision, radiation, and chemotherapy.[23]

# Lesions of the Adrenal Cortex

Adrenocortical neoplasms are rare in the pediatric population, accounting for less than 0.2% of all pediatric tumors and 6% of all adrenal tumors in children.[24] The incidence of these neoplasms has been reported to be approximately 25 cases per year in the United States, of which about 75% are adrenocortical carcinomas.[25,26] Adrenocortical tumors occur more frequently in girls, with a male to female ratio of approximately 1:2 to 1:3.[27] Like pheochromocytomas, adrenocortical neoplasms behave differently in children than in adults. Approximately 85% to 95% of these tumors are hormonally active in children, compared with less than 50% in adults.[28,29] Further, whereas there are clear pathologic criteria for malignancy in the adult population, these guidelines are not reliable in the pediatric population. Because the clinical behavior of these tumors does not always correlate with the pathologic appearance, the diagnosis of malignancy should be based on clinical behavior. Age less than 3.5 years at the time of diagnosis and symptom duration of less than 6 months before diagnosis are favorable prognostic indicators in adrenocortical carcinoma. Early detection is essential in these children, because a delay in diagnosis adversely affects clinical outcome.[1]

Adrenocortical tumors are associated with several congenital anomalies, including hemihypertrophy; other tumors associated with hemihypertrophy include nephroblastoma and hepatoblastoma. Patients with Beckwith-Wiedemann syndrome (exomphalos, macroglossia, and gigantism) also have a higher than expected incidence of adrenocortical carcinoma.[30] Most adrenocortical tumors, however, occur sporadically.[1]

## CUSHING SYNDROME

In 1932, Cushing first described the syndrome that bears his name in a patient with a pituitary adenoma. Since that time, the understanding of the pathophysiology and cause has expanded considerably. Endogenous Cushing syndrome is a rare condition in the pediatric population. In general, the incidence of spontaneous Cushing syndrome is approximately 5 per million persons; it occurs primarily in young adult women, with a female to male ratio of 9:1. Ten percent of cases occur in children and adolescents.[31]

The typical manifestation of Cushing syndrome in children is generalized obesity and long bone growth retardation.[31] Other symptoms include hypertension, weakness, thin skin with striae and easy bruising, acne, menstrual irregularity, osteoporosis, and glucose intolerance. Unlike in adults with Cushing syndrome, muscle weakness, sleep disturbances, and mental changes, such as emotional lability, irritability, or depression, are rare in children.[31] Cushing syndrome can be divided into ACTH-dependent and ACTH-independent types. In the former condition, the inappropriately high ACTH levels stimulate the adrenal cortex to produce excessive cortisol. In the ACTH-independent type, abnormal adrenal tissue produces excessive cortisol irrespective of ACTH levels.

Cushing disease refers to Cushing syndrome caused by pituitary tumors that lead to excessive ACTH production. Typically, these tumors are microadenomas and are less than 1 cm in diameter; however, large, invasive pituitary adenomas may develop. These tumors lead to bilateral adrenocortical hyperplasia, with a corresponding glucocorticoid excess. As the age of the patient increases, there is a greater likelihood of a pituitary cause of the syndrome. In patients younger than 6 years, the most likely cause of endogenous Cushing syndrome is an adrenal tumor. Although adrenocortical carcinomas represent only 0.2% of all childhood malignancies and 6% of adrenal cancers, approximately 60% to 80% of pediatric Cushing syndrome cases are caused by adrenocortical carcinomas.[28]

The clinical diagnosis of hypercortisolism must be confirmed biochemically to diagnose Cushing syndrome. In addition, the specific source of the syndrome must be localized (Fig. 41-2). Cortisol production is normally suppressed at night, but in Cushing syndrome, this suppression does not occur. The normal circadian rhythm of cortisol secretion is lost in Cushing syndrome. Random serum cortisol levels are of limited value. The three most common tests used to diagnose Cushing syndrome are the 24-hour urinary free cortisol test,

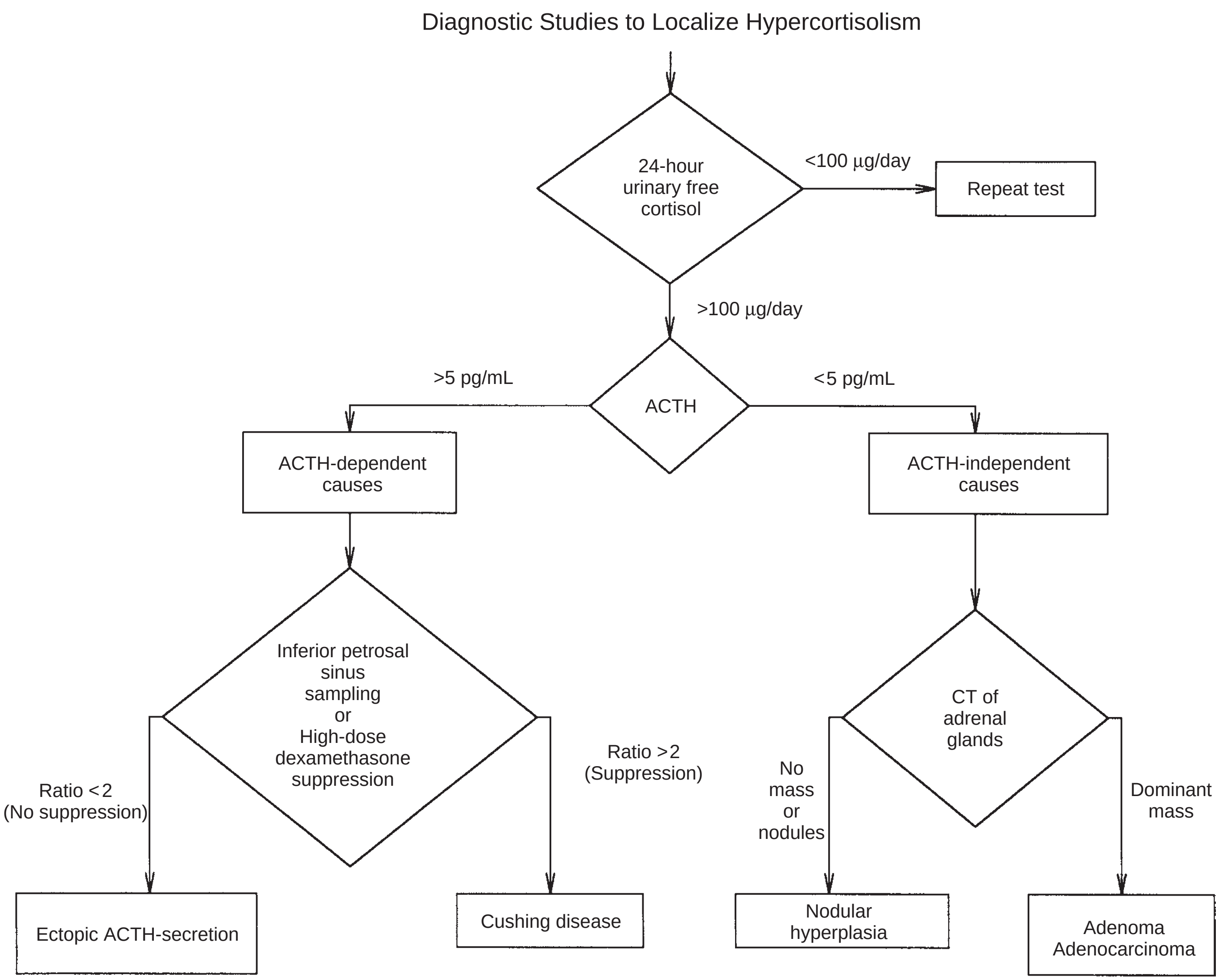


**FIGURE 41-2** Algorithm to localize the cause of hypercortisolism in children with suspected Cushing syndrome. ACTH, adrenocorticotropic hormone; CT, computed tomography.

measurement of midnight plasma cortisol or late-night salivary cortisol, and the low-dose dexamethasone suppression test. The dexamethasone-corticotropin-releasing hormone test may be needed to distinguish Cushing syndrome from other causes of excess cortisol. The 24-hour urinary free cortisol level has a sensitivity of approximately 98%.[32] In children, this value must be corrected for size. A normal value is less than 70 µg/m$^2$ per day; this is elevated with Cushing syndrome. Another useful test is the 24-hour urinary 17-hydroxysteroid excretion; this is an indirect measure of cortisol secretion and is elevated with hypercortisolism. Once it is corrected for creatinine excretion, the normal value is between 2 and 7 mg per gram of creatinine per day. The overnight dexamethasone suppression test is administered as follows: After the administration of 1 mg (or 0.3 mg/m$^2$ in children) of dexamethasone, a morning cortisol level greater than 5 µg/dL indicates unsuppressed cortisol secretion consistent with Cushing syndrome.

Once the diagnosis of Cushing syndrome has been established, the next step is to determine the underlying cause of the hypercortisolism. As shown in Figure 41-2, measurement of the ACTH level can distinguish between ACTH-dependent and ACTH-independent causes. If the ACTH level is greater than 5 pg/mL, the source is ACTH dependent; if the level is less than 5 pg/mL, it is ACTH independent.

ACTH-dependent causes of hypercortisolism include both pituitary and ectopic ACTH-secreting neoplasms. Although ectopic production of ACTH is rare in children, Wilms' tumors and tumors of the thymus, pancreas, or neural tissue can produce ACTH. Most patients with ACTH-secreting tumors have Cushing disease (Cushing syndrome caused by a pituitary tumor). Although a high-dose dexamethasone suppression test or an inferior petrosal sinus sampling can distinguish a pituitary source from an ectopic source, MRI can also show a pituitary tumor. An ectopic tumor producing CRH is another ACTH-dependent source of Cushing syndrome, but this condition has not been reported in a child.[32,33]

In both adults and children, the treatment of choice for Cushing disease is a transsphenoidal resection of the pituitary adenoma. In patients with no postoperative improvement or with recurrence, some response may be obtained with pituitary irradiation using cobalt 60.

If an ectopic ACTH-secreting tumor is indicated by the workup, the patient must undergo screening for medullary carcinoma of the thyroid (serum calcitonin levels) and screening for pheochromocytoma (24-hour urine measurement of catecholamines, metanephrine, and vanillylmandelic acid). Other ectopic locations, such as a bronchial, thymic, or intestinal carcinoid tumor, may be seen on CT of the chest and abdomen. Ectopic ACTH-producing tumors should be resected if possible. If resection is not possible, bilateral adrenalectomy can offer an effective treatment of Cushing syndrome.

ACTH-independent causes of Cushing syndrome include adrenal neoplasms and nodular adrenal hyperplasia. ACTH-independent Cushing syndrome is relatively more frequent in children than in adults.[32] In children, an adrenocortical tumor most frequently occurs in the setting of a virilizing syndrome, and the majority of children present with virilizing symptoms. Approximately 33% of these patients have Cushing syndrome; less than 10% present with isolated Cushing syndrome without any virilizing signs.[29,25]

Nodular adrenal hyperplasia is a rare condition that occurs in children and young adults. This disease usually presents in the first 2 decades of life, predominantly in girls. Although this entity can occur sporadically, many cases are familial and appear in an autosomal dominant fashion.[32] The adrenal glands contain multiple nodules approximately 3 to 5 mm in size. Histologic examination reveals lymphocytic infiltration of the cortex, suggesting an autoimmune cause of the disorder. The treatment of this cause of Cushing syndrome is bilateral adrenalectomy.[32] This procedure is associated with significant morbidity and requires permanent postoperative mineralocorticoid and glucocorticoid replacement.

### SEX HORMONE–PRODUCING TUMORS

An adrenocortical lesion may lead to either a virilizing or a feminizing tumor. As previously mentioned, most adrenocortical tumors in children are hormonally active. Virilization with or without hypercortisolism is the most common presentation.[26,29,34,35] These virilizing tumors may be more difficult to recognize in boys than in girls. Boys may present with precocious puberty, including penile enlargement, acne, and premature development of pubic, axillary, and facial hair. Girls may develop clitoral hypertrophy, hirsutism, and acne. The treatment of choice is adrenalectomy.

Although feminizing adrenocortical tumors are rare in children, they are usually malignant. In the normal adrenal gland, very small amounts of estrogens may be secreted. With adrenocortical tumors, however, overproduction of estrogens, particularly estradiol, may occur. In girls, these tumors present with precocious isosexual development, including early breast enlargement, accelerated growth, and advanced bone age. In boys, these tumors cause bilateral gynecomastia, accelerated growth rate, and delayed pubertal development; there is also an absence of spermatogenesis.

### TREATMENT OF ADRENOCORTICAL TUMORS

Surgical resection is the mainstay of treatment for adrenocortical tumors. The treatment of choice for a benign adrenal adenoma is adrenalectomy. Adrenocortical carcinomas, however, require a wide excision with adequate abdominal exploration for metastatic disease. In either case, postoperative steroid replacement is typically required until the contralateral gland can recover from its suppression.

Computed tomography or magnetic resonance imaging can help distinguish between adrenal hyperplasia and an adrenal tumor. A $^{131}$I-iodomethyl-1-19-norcholesterol (NP-59) scintiscan may aid in the evaluation of an adrenal lesion. This cholesterol analogue is taken up as cholesterol into the steroid pathways of the adrenal cortex. Adrenal adenomas usually have an increased uptake of NP-59, whereas adrenocortical carcinomas typically do not take up the isotope. Bilateral uptake of NP-59 indicates bilateral adrenal hyperplasia, which can be the result of ACTH oversecretion.

The most common sites of metastatic adrenocortical carcinomas are the lung, liver, lymph nodes, contralateral adrenal gland, bones, kidneys, and brain. If complete resection is not possible, tumor debulking may be of some benefit to control symptoms. Medical therapy with mitotane may also play a role in treating patients with unresectable disease. Mitotane acts as an adrenolytic agent by altering mitochondrial function, blocking adrenal steroid hydroxylation, and altering the extra-adrenal metabolism of cortisol and androgens. The success of chemotherapy has not been clearly shown, however, and complete surgical resection is the primary determinant of survival.[36]

## Hyperaldosteronism

Overproduction of aldosterone, or hyperaldosteronism, may be due to either adrenal dysfunction or overproduction of renin. Primary hyperaldosteronism refers to adrenal dysfunction, such as an aldosterone-secreting tumor or bilateral adrenal hyperplasia. Secondary hyperaldosteronism refers to an overproduction of renin, which can be caused by cirrhosis, congestive heart failure, a renin-producing juxtaglomerular cell tumor, or renovascular abnormalities, such as renal artery stenosis.

The symptoms of hyperaldosteronism include headaches, fatigue, weakness, lethargy, poor weight gain, polyuria, polydipsia, and nocturia. Hypertension develops as a result of increased sodium and water reabsorption. Weakness occurs because of hypokalemia, which is the most common laboratory finding, although metabolic alkalosis may be observed from the loss of hydrogen ions in the urine. The biochemical diagnosis of hyperaldosteronism is demonstrated by excessive aldosterone secretion in the setting of suppressed renin secretion. Once the diagnosis of primary hyperaldosteronism has been established, patients with aldosterone-secreting adrenal tumors must be distinguished from those with the more common condition of bilateral adrenocortical hyperplasia. In patients with bilateral adrenocortical hyperplasia, dexamethasone administration normalizes the abnormally high aldosterone level and low renin level.[10]

In the pediatric population, the incidence of aldosteronoma, or an adrenal adenoma causing primary hyperaldosteronism, is extremely low, with only a handful of reported cases in the literature. As previously mentioned, the more common cause of primary hyperaldosteronism is bilateral cortical hyperplasia.[37] An aldosteronoma is best treated by unilateral adrenalectomy. Patients with bilateral adrenocortical hyperplasia do not respond well to surgical treatment and are best

managed with medical therapy using spironolactone and amiloride.[10] Adrenal insufficiency resulting from bilateral adrenalectomy is more difficult to manage than hyperaldosteronism.

## Addison Disease

Insufficient production of steroid hormones (either glucocorticoids or mineralocorticoids) can lead to Addison disease. Children with Addison disease present with a variety of symptoms, including weakness, anorexia, weight loss, fatigue, nausea, vomiting, and diarrhea. If the child has an elevated ACTH level, hyperpigmentation will develop, because melanocytes are stimulated by ACTH. Seizures may also occur in the setting of the hypoglycemia, which occurs with adrenal crisis.

There are many causes of adrenal insufficiency in children. Congenital adrenal hypoplasia can result from either an autosomal recessive disorder or an X-linked disorder that occurs in boys. Errors in steroid metabolism can also lead to adrenal insufficiency. The most common group of inborn errors involves defects in glucocorticoid synthesis and is collectively known as congenital adrenal hyperplasia. Acquired lesions involving the hypothalamus or pituitary can also lead to adrenal insufficiency through a reduction in CRH or ACTH secretion.

Destruction of the adrenal glands can also lead to adrenal insufficiency. Conditions causing adrenal demise include hemorrhage, infection, adrenoleukodystrophy, and autoimmune diseases. In older patients, overwhelming infection can lead to adrenal hemorrhage. Tuberculosis used to be a common cause of infectious destruction of the adrenal; however, the incidence of this condition has fallen in modern times. One of the more common causes of acute adrenal insufficiency is cessation of chronic exogenous glucocorticoid administration.

In newborns, adrenal hemorrhage is not an uncommon event. In fact, the adrenal gland is the second most common source of hemoperitoneum in the newborn period.[38] The pathogenesis of adrenal hemorrhage in newborns is not fully understood. Associated factors include traumatic delivery, asphyxia, maternal hypotension, overwhelming infection, or hemorrhagic disorders.[35,39] The incidence of adrenal hemorrhage is almost 2 cases per 1000 live births,[1] but as the sensitivity of imaging technology improves, this number may increase. Adrenal hemorrhage occurs 3 to 4 times more frequently in the right adrenal gland than the left and is bilateral in 8% to 10% of patients.[39] This bias toward the right side may be due to the direct drainage of the right adrenal gland into the inferior vena cava, making the right gland more susceptible to changes in venous pressure. The left gland remains somewhat protected by its drainage into the left renal vein. The fetal cortex contributes to fetal and neonatal adrenal hemorrhage because of both its size and its later involution. The large size of the fetal cortex makes the adrenal glands relatively large, increasing their vulnerability to trauma. The normal adrenal gland is easily visualized by US during the first week of life. The adrenal soon involutes, and the distinction between the cortex and the medulla is lost. The physiologic involution of the fetal cortex may occur quite rapidly, tearing the unsupported central adrenal gland vessels.[38]

On prenatal US, adrenal hemorrhage appears as an echogenic mass. This mass becomes increasingly hypoechoic and usually involutes on subsequent sonograms.[40] The lesion may completely resolve, leaving only residual calcifications. Adrenal hemorrhage may be confused with neuroblastoma. Patients with normal urinary catecholamine levels and the appropriate risk factors for adrenal hemorrhage can be observed and undergo repeat US. Differentiation of adrenal adenoma and carcinoma by US is difficult; in addition, both resemble an adrenal pheochromocytoma. An ultrasonographic characteristic that suggests malignancy is central necrosis from rapid growth. Biochemical testing and the use of CT, MRI, and nuclear medicine studies narrow the diagnostic possibilities.

The treatment of Addison disease is replacement of the deficient steroid hormone. This may be accomplished with a mineralocorticoid, such as fludrocortisone, or a glucocorticoid, such as hydrocortisone or prednisone. During periods of acute stress, such as infection or operation, increased doses of glucocorticoids are needed.

## Incidental Adrenal Mass

The incidental discovery of adrenal lesions on imaging studies performed for other reasons has been increasing in both children and adults, perhaps because of the increased frequency of imaging studies being performed and the increased sensitivity of those imaging modalities. In adults, the current recommendation is to remove all hormonally active tumors regardless of size. In the case of nonfunctional adrenal masses, it is considered safe to observe a mass less than 4 cm in size.[41–43] In the pediatric population, however, there are no clear guidelines about incidental, nonfunctional adrenal masses. Because of the higher incidence of both functional tumors and malignant tumors in the pediatric adrenal gland, many surgeons recommend adrenalectomy in this setting.[43]

## Adrenalectomy

The objective of adrenal surgery is to attain complete tumor resection, resulting in normalization of endocrine function and cure of malignancy. Perioperative planning includes correction of potential electrolyte abnormalities, establishing alpha and beta blockade in the case of pheochromocytoma, and performing localizing studies to guide the surgical approach. The surgical approach is based on the probable histology of the adrenal mass, the presence of bilaterality, and the surgeon's preference. The introduction of laparoscopic adrenal resection has provided an attractive alternative for the resection of many adrenal masses in children.

Traditional approaches to adrenal resection have included anterior, posterior, and thoracoabdominal approaches. The anterior approach uses a transabdominal incision, usually subcostal, which permits resection of either the left or the right adrenal gland. It also allows bilateral resection through a single incision, as well as visualization of the periaortic sympathetic ganglia, the small bowel mesentery, and the pelvis. More than 95% of pediatric pheochromocytomas are located in the abdomen, and this approach reveals the majority of tumors. The surgeon must make a conscious effort to minimize direct manipulation of the tumor during dissection.

Early control and ligation of the adrenal vein limit the release of catecholamines as the tumor is removed.

During the anterior approach to right adrenalectomy, the duodenum is mobilized by the Kocher maneuver (Fig. 41-3) by reflecting the transverse colon inferiorly and mobilizing the duodenum medially. This exposes the upper portion of the right kidney as well as the right adrenal gland. The Gerota fascia is opened, and the right lobe of the liver is retracted in a cephalad direction. The most important element of the procedure is the dissection between the medial border of the adrenal mass and the lateral wall of the inferior vena cava. This plane is developed in a cephalad direction until the relatively short right adrenal vein is identified entering the vena cava. There is a greater risk of hemorrhage on the right side than on the left, because of the shorter length of the right adrenal vein and the greater risk of tearing this vessel. Multiple veins may be present and should be identified to prevent accidental avulsion. During the anterior approach to the left adrenal gland, the initial maneuver is to mobilize the splenic flexure of the colon. The pancreas and spleen are retracted superiorly, and the Gerota fascia is opened, exposing the left adrenal gland. Alternatively, the surgeon can divide the gastrocolic ligament, mobilizing the stomach superiorly and the transverse colon inferiorly. The posterior peritoneum along the inferior pancreatic border can then be incised, allowing mobilization of the pancreatic tail and exposure of the adrenal vein. The left adrenal vein enters the renal vein superiorly and can be ligated in this plane. Several arteries enter the medial surface of the adrenal gland from the lateral side of the aorta; these arteries need to be divided before adrenal

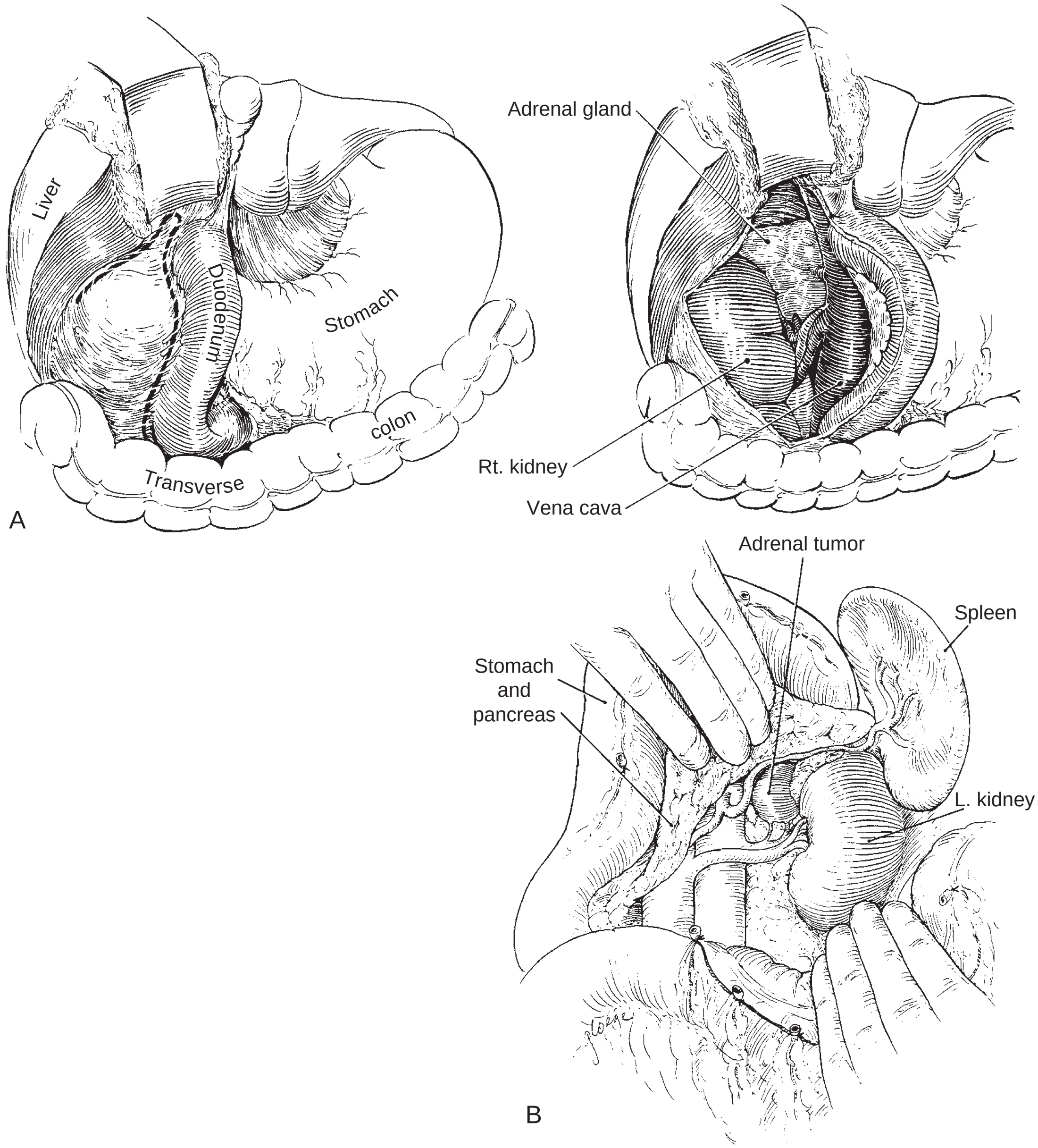


**FIGURE 41-3** Transabdominal approach to tumors of the adrenal glands. **A,** The right adrenal gland is exposed by reflecting the transverse mesocolon inferiorly, mobilizing the duodenum medially with a Kocher maneuver, and incising the posterior fascia to expose the diaphragm, adrenal gland, and superior pole of the right kidney. **B,** The left adrenal gland is exposed by dividing the gastrocolic ligament and elevating the stomach. The colon is retracted inferiorly, and the pancreas is elevated, exposing the adrenal gland and left adrenal vein that enters the renal vein.

removal. The posterior approach to the adrenal gland is accomplished most commonly through the bed of the 11th rib. This strategy avoids intraperitoneal dissection, eliminates postoperative adhesions, and decreases postoperative ileus. The posterior approach is not useful for bilateral adrenal lesions, malignancies, or large vascular tumors. The thoracoabdominal approach to adrenalectomy is best applied to very large unilateral lesions. Although this approach provides optimal exposure of large vascular tumors; postoperative pain and impairment of ventilation limit its application.

The first laparoscopic adrenalectomy was reported in an adult in 1991.[44] Since then, a number of studies involving laparoscopic adrenalectomy in children have been published,[45,46] demonstrating the feasibility and safety of this approach. Most commonly, laparoscopic adrenalectomy is performed with the patient in the lateral position. A kidney rest elevates the flank opposite the adrenal lesion. Four or five trocars are placed in a subcostal position on the side of the adrenal gland to be resected. Exposure is improved on the right side by dividing the right triangular ligament of the liver. Division of the lienocolic ligament on the left improves exposure of the left adrenal gland. When possible, the adrenal vein is ligated with clips at the initial point of dissection. The adrenal specimen should be removed in a specimen bag because of the potential for malignancy. Most adrenal lesions in children are small and benign, making laparoscopic resection an appropriate choice in the majority of cases. Although no absolute contraindications to laparoscopic resection exist, an open approach should be considered in patients with large tumors, malignancies with potential lymph node involvement, and highly vascular pheochromocytomas.

Partial adrenalectomies (termed *cortical-sparing* or *adrenal-sparing*) have been described for bilateral pheochromocytomas, wherein a portion of a single gland or portions of bilateral glands are retained. Preliminary reports indicate few recurrences and maintenance of corticosteroid independence. Children are included in these cohorts but not individually evaluated as a sub-group. Reports are surfacing of successful laparoscopic cortical-sparing adrenalectomies as well.[47] Long-term follow-up and continued surveillance are essential.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 42

# Tumors of the Lung and Chest Wall

Stephen J. Shochat and Christopher B. Weldon

The majority of pulmonary neoplasms in children are due to metastatic disease; however, primary pulmonary tumors of the lung do occur in the pediatric age group. The approximate ratio of primary pulmonary tumors to metastatic neoplasms and non-neoplastic lesions of the lung is 1:5:60.[1] Although primary pulmonary tumors are rare in children, the majority of these tumors are malignant. In a review of 383 primary pulmonary neoplasms in children by Hancock and colleagues,[2] 76% were malignant and 24% were benign. This incidence is similar to that previously reported by Hartman and Shochat.[3] Table 42-1 demonstrates the variety of primary pulmonary neoplasms seen in children. This chapter addresses the more common benign and malignant primary pulmonary tumors in children and discusses the treatment of pulmonary metastatic disease in the pediatric population.

## Benign Tumors of the Lung

### PLASMA CELL GRANULOMA (INFLAMMATORY PSEUDOTUMOR)

Plasma cell granuloma has also been called inflammatory myofibroblastic tumor, fibroxanthoma, histiocytoma, and fibrohistiocytoma.[4] This lesion, which is seen frequently in adults, occurs rarely in children younger than 10 years (approximately 8% of cases). However, plasma cell granuloma is the most common benign tumor in children and accounts for slightly more than 50% of all benign lesions and approximately 20% of all primary lung tumors.[3] These tumors usually present as peripheral pulmonary masses but occasionally present as polypoid endobronchial tumors.[5,6] The pathogenesis of plasma cell granuloma is not well understood, but an antecedent pulmonary infection has been reported in approximately 30% of cases. The mean age at presentation in children is 7 years of age, and 35% of the children are between 1 and 15 years of age.[5–7] Many children are asymptomatic at the time of presentation, but fever, cough, pain, hemoptysis, pneumonitis, and dysphagia may be present. The natural history is that of a slow-growing mass, starting as a focus of organized pneumonia with a tendency for local invasion. However, rare cases of rapid growth have been reported.[8] Extension of the tumor beyond the confines of the lung is common. At least four deaths have been reported resulting from tracheal obstruction or involvement of the mediastinum by massive lesions.

Treatment consists of a conservative pulmonary resection with removal of all gross disease if possible. Primary hilar adenopathy may be present, and local invasion with disregard for tissue planes mimics malignancy. A frequent problem is identifying the benign nature of these masses. However, the diagnosis can usually be confirmed by frozen section. Malignant fibrous histiocytoma of the lung, an extremely rare tumor in children, can mimic plasma cell granuloma and must be considered in the differential diagnosis.[9] Recurrences following resection are rare but have been reported. Nonsteroidal anti-inflammatory drugs have been used to treat large inoperable lesions, with encouraging results.[10]

### HAMARTOMA

Pulmonary hamartoma is the second most frequent benign lesion seen in children. These lesions usually present as parenchymal lesions and can be quite large. Approximately one quarter are calcified, and "popcorn-like" calcification is pathognomonic.[11] Two endobronchial lesions have been reported. Four tumors occurring in the neonatal period were quite large and were associated with significant respiratory distress; all were fatal. An interesting triad is the combination of pulmonary hamartoma, extraadrenal paraganglioma, and gastric smooth muscle tumors; the majority of these patients are young women. Carney triad, in addition to its female predilection, is seen in young patients, is associated with multifocal gastrointestinal stromal tumors (GISTs) and has an unpredictable biological behavior.[12] Conservative pulmonary resection is the treatment of choice; however, lobectomy, or even pneumonectomy, may be required, especially for large lesions and endobronchial lesions when sleeve resection is not possible.

## Malignant Tumors of the Lung

### BRONCHIAL ADENOMA

The most frequently encountered malignant primary pulmonary tumor is bronchial adenoma. These tumors are a heterogeneous group of primary endobronchial lesions. Although adenoma implies a benign process, all varieties of bronchial

adenomas occasionally display malignant behavior. There are three histologic types: carcinoid tumor (most common), mucoepidermoid carcinoma, and adenoid cystic carcinoma. Carcinoid tumors account for 80% to 85% of all bronchial adenomas in children.[13] The presenting symptoms are usually due to incomplete bronchial obstruction, with cough, recurrent pneumonitis, and hemoptysis. Because of diagnostic difficulties, symptoms are often present for months; occasionally, children with wheezing have been treated for asthma, delaying diagnosis for as long as 4 to 5 years. Metastatic lesions are reported in approximately 6% of cases, and recurrences occur in 2%. There is a single report of a child with a carcinoid tumor and metastatic disease who developed the classic carcinoid syndrome.[14] Bronchial adenomas of all histologic types are associated with an excellent prognosis in children, even in the presence of local invasion.[15]

The management of bronchial adenomas is somewhat controversial, because most are visible endoscopically. Biopsy in these lesions may be hazardous because of the risk of hemorrhage, and endoscopic resection is not recommended. Bronchography or computed tomography (CT) may be helpful to determine the degree of bronchiectasis distal to the obstruction, because the degree of pulmonary destruction may influence surgical therapy.[16] However, Tagge and colleagues[17] described a technique for pulmonary salvage despite significant distal atelectasis. Conservative pulmonary resection with removal of the involved lymphatics is the treatment of choice. Sleeve segmental bronchial resection is possible in children and is the treatment of choice when feasible.[18–20] Adenoid cystic carcinomas (cylindroma) have a tendency to spread submucosally, and late local recurrence or dissemination has been reported. In addition to en bloc resection with hilar lymphadenectomy, a frozen section examination of the bronchial margins should be carried out in children with this lesion.

**TABLE 42-1**
**Primary Pulmonary Neoplasms in Children**

| *Type of Tumor* | *No. of Patients (%)** |
|---|---|
| **Benign ($n$ = 92)** | |
| Plasma cell granuloma | 48 (52.2) |
| Hamartoma | 22 (23.9) |
| Neurogenic tumor | 9 (9.8) |
| Leiomyoma | 6 (6.5) |
| Mucous gland adenoma | 3 (3.3) |
| Myoblastoma | 3 (3.3) |
| Benign teratoma | 1 (1.1) |
| **Malignant ($n$ = 291)** | |
| Bronchial "adenoma" | 118 (40.5) |
| Bronchioalveolar carcinoma | 49 (16.8) |
| Pulmonary blastoma | 45 (15.5) |
| Fibrosarcoma | 28 (9.6) |
| Rhabdomyosarcoma | 17 (5.8) |
| Leiomyosarcoma | 11 (3.8) |
| Sarcoma | 6 (2.1) |
| Hemangiopericytoma | 4 (1.4) |
| Plasmacytoma | 4 (1.4) |
| Lymphoma | 3 (1.0) |
| Teratoma | 3 (1.0) |
| Mesenchymoma | 2 (1.7) |
| Myxosarcoma | 1 (0.3) |

Modified from Hancock BJ, DiLorenzo M, Youssef S, et al: Childhood primary pulmonary neoplasms. J Pediatr Surg 1993;28:1133-1136.
*Percent of benign or malignant tumors.

## BRONCHOGENIC CARCINOMA

Although bronchogenic carcinoma is rare in children, this tumor was the second most common malignant lesion reported by Hancock and colleagues.[2] Interestingly, squamous cell carcinoma was rare, with the majority of tumors being either undifferentiated carcinoma or adenocarcinomas. The term bronchioalveolar carcinoma has been used in most cases.[21] These tumors are associated with both cystic adenomatoid malformations and intrapulmonary bronchogenic cysts (Table 42-2).[4,11,21–38] Only rare survivors have been reported,

**TABLE 42-2**
**Bronchioalveolar Carcinoma Associated with Congenital Cystic Lung Malformations**

| | *Year of Publication* | *Type of Lung Cyst* | *Age at Diagnosis (Year)* | *Author Comments* |
|---|---|---|---|---|
| Prichard[22] | 1984 | CCAM type 1 | 30 | Died of metastatic disease |
| Hurley[23] | 1985 | CCAM type 1 | | |
| Benjamin[24] | 1991 | CCAM type 1 | 19 | BAC diagnosed in same lobe with segmental resection 19 years earlier; died at 23 years of age |
| Morresi[21] | 1995 | CCAM type 1 | 20 | |
| Ribet[26] | 1995 | CCAM type 1 | 42 | |
| Kaslovsky[27] | 1997 | CCAM type 1 | 11 | Incomplete resection of CCAM in neonatal period |
| Granata[28] | 1998 | CCAM type 1 | 11 | Lobectomy for recurrent infection; BAC was finding |
| Endo[29] | 1982 | Bronchogenic (intrapulmonary) | 37 | Abnormal CXR noted 10 years earlier; presented with dyspnea, BAC was incidental finding |
| De Perrot[30] | 2001 | Bronchogenic (intrapulmonary) | 79 | Long-standing history of cyst infections |
| MacSweeney[31] | 2003 | CCAM type 1, 0.5, 13, 18, 30, 36 | | 1 BAC in a recurrent cyst; one other patient with a typical adenomatous hyperplasia (both patients underwent segmental resection) |
| Sudou[32] | 2003 | CCAM type 1 | 17 | Abnormality seen on CXR from 10 years earlier |

Adapted from LaBerge JM, Puligandla P, Flageole H: Asymptomatic congenital lung malformations. Semin Pediatr Surg 2005;14:16-33.
BAC, bronchioalveolar carcinoma; CCAM, congenital cystic adenomatoid malformation; CXR, chest radiograph.

and mortality exceeds 90%. The majority of children present with disseminated disease, and the average survival is only 7 months. Localized lesions can be treated by complete resection, followed by adjuvant therapy. Mucoepidermoid carcinoma of the bronchus has also been described in children as young as 4 years (Fig. 42-1).[39]

## PULMONARY BLASTOMA

Pulmonary blastoma is a rare malignant tumor that occurs primarily in adults and arises from mesenchymal blastema. This tumor is an aggressive lesion, with metastatic disease at presentation in approximately 20% of cases.[40,2] They may arise from the lung, pleura, and mediastinum.[41] These tumors are classified into three types: type I (purely cystic), type II (cystic and solid), and type III (completely solid).[42] Type I tumors may be difficult to distinguish from cystic adenomatoid malformation.[43] Occasionally, these tumors may arise in an extralobar sequestration or in a previous lung cyst (Table 42-3).[22,25,29,36,41,44–73] The majority of cases occur in the right hemithorax (Fig. 42-2). Frequent sites of metastases

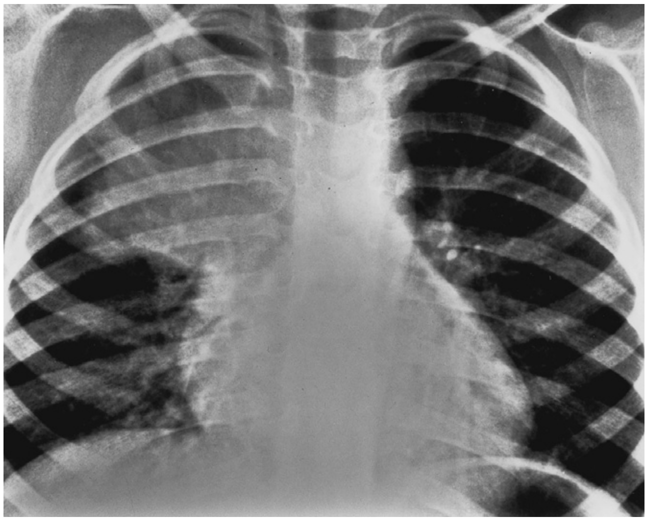

FIGURE 42-1 Anteroposterior view of a right upper lobe lesion in a 4-year-old girl. The tumor was resected by right upper lobectomy and was shown to be a mucoepidermoid carcinoma. (Courtesy Jay L. Grosfeld, MD.)

**TABLE 42-3**
**Mesenchymal Malignancy and Cystic Lung Malformations**

| *Author* | *Year* | *Type of Lung Cyst* | *Type of Malignancy* | *Age at Diagnosis (Months)* |
|---|---|---|---|---|
| Stephanopoulos[44] | 1963 | "Cystic hamartoma" | Myxosarcoma | |
| Ueda[45] | 1977 | CCAM | RMS | 18 |
| Martinez[46] | 1978 | "Polycystic disease" | Pulmonary blastoma | 24 |
| Valderrama[47] | 1978 | Extralobar sequestration | Pulmonary blastoma | |
| Sumner[48] | 1979 | Peripheral cyst | Pulmonary blastoma | 48 |
| Weinberg[49] | 1980 | Congenital lung cyst | Mixed mesenchymal sarcoma | 108 |
| Krous[50] | 1980 | Bronchogenic cyst (intrapulmonary) | Embryonal RMS | 30 |
| Weinblatt[51] | 1982 | "Cystic lung disease" | Pulmonary blastoma | 30 |
| Holland-Moritz[36] | 1984 | "Pneumatocele" | PPB | 48 |
| Morales[25] | 1986 | Congenital cyst | Pulmonary blastoma | |
| Williams[52] | 1986 | CCAM | Embryonal RMS | 21 |
| Allan[53] | 1987 | "Congenital origin of cysts not confirmed" | RMS | 21, 30 |
| Hedlund[54] | 1989 | "Cystic hamartoma" | RMS | 18, 22 |
| Cairoli[55] | 1990 | CCAM | RMS | 36 |
| Domizio[56] | 1990 | "Congenital cyst" | Malignant mesenchymoma | 48 |
| Senac[57] | 1991 | | PPB | |
| Murphy[58] | 1992 | Bronchogenic cyst, CCAM (2) | Embryonal RMS | 24, 36, 42 |
| Bogers[59] | 1993 | Lobar emphysema | RMS | 18 |
| Calabria[60] | 1993 | "Pneumatoceles" | Pulmonary blastoma | |
| McDermott[61] | 1993 | Congenital cyst | Embryonal RMS | 36 |
| Seballos[62] | 1994 | CCAM | Pulmonary blastoma | 22 |
| Tagge[63] | 1996 | Bilateral pneumatocele | PPB | 45 |
| Adirim[64] | 1997 | CCAM type 1 | Pulmonary blastoma | |
| D'Agostino[65] | 1997 | CCAM type 2 | Embryonal RMS | 22 |
| Federici[66] | 2001 | CCAM type 1 | PPB | 36 |
| Ozcan[67] | 2001 | CCAM | Embryonal RMS | 13 |
| Papagiannopoulos[68] | 2001 | CCAM type 4 | PPB | 30 |
| Stocker[69] | 2002 | CCAM type 4 | PPB | 48 |

Adapted from LaBerge JM, Puligandla P, Flageole H: Asymptomatic congenital lung malformations. Semin Pediatr Surg 2005;14:16-33.
CCAM, congenital cystic adenomatoid malformation; CPAM congenital pulmonary airway malformation; PPB, pleuropulmonary blastoma; RMS, rhabdomyosarcoma.

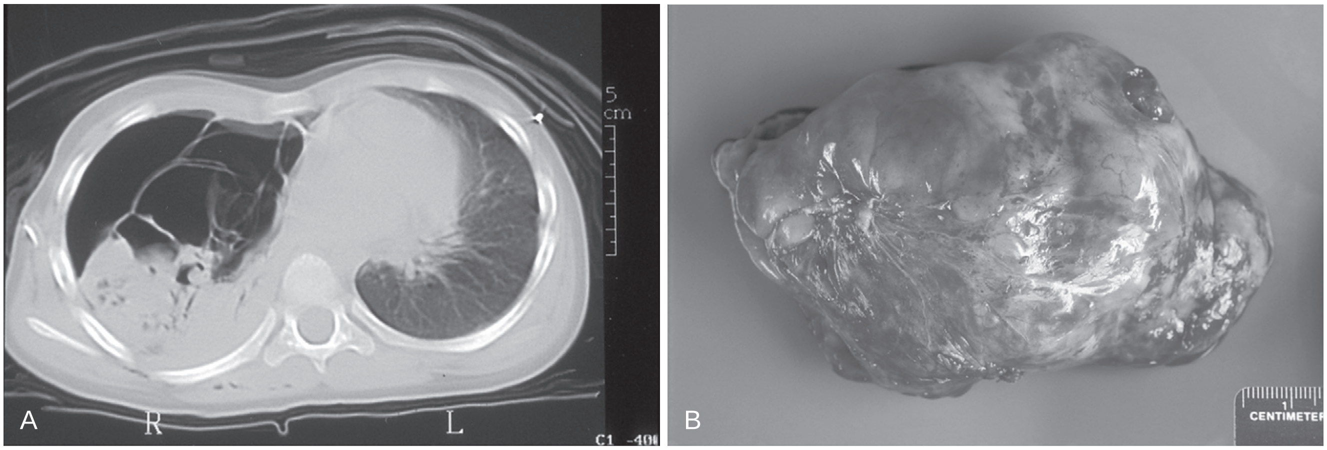


FIGURE 42-2 **A,** Computed tomography scan of the chest shows a cystic lesion in the right hemithorax. **B,** The tumor was resected (lobectomy), and the histology showed findings consistent with a pleuropulmonary blastoma. (Courtesy Jay L. Grosfeld, MD.)

are the liver, brain, and spinal cord. Local recurrences are frequent, and the mortality rate is approximately 40%.[2,74–76] The majority of children present before 4 years of age, and symptoms include persistent cough, chest pain, episodes of pneumonia that are refractory to antibiotics, and hemoptysis. Diagnosis is achieved by CT of the chest, bronchoscopy, and biopsy. Because most of these tumors are located peripherally, resection is usually possible by segmental or lobar resection. The use of multimodal neoadjuvant chemotherapy and radiation following surgical resection has shown promising results in a few patients with extensive disease and dissemination.[41,75] Chemotherapeutic agents that have been used include actinomycin D, vincristine, cyclophosphamide alternating with courses of doxorubicin, and cisplatin. Histologic evaluation of the tumor shows an exclusive mesenchymal composition, including primitive tubules, immature blastema, and spindle cell stroma. Some demonstrate elements of embryonal rhabdomyosarcoma (RMS) arising within a multicystic lesion.

## RHABDOMYOSARCOMA

RMSs of the lung are rare and account for only 0.5% of all childhood RMSs (see Chapter 35).[45,77] Many of the lesions are endobronchial in origin (Fig. 42-3); however, several cases apparently originated in congenital cystic anomalies. (see Table 42-3).* This is an important issue because 4% of benign tumors and 8.6% of malignant tumors enumerated in Table 42-1 were associated with previously documented cystic malformations.[2] Tumors that developed in these malformations included 11 sarcomas, 9 pulmonary blastomas, 3 bronchogenic carcinomas, and 2 mesenchymomas.

## COMMENTS

Although children with primary lung tumors represent a heterogeneous group of patients, analysis of the reported cases suggests that evaluation and treatment are similar in the majority of patients. Many children are asymptomatic, especially those with benign tumors; however, cough, recurrent pneumonitis, and symptoms of atypical bronchial asthma may be the initial presentation. Radiographic findings usually indicate a solitary mass lesion or evidence of airway obstruction with resultant atelectasis and pneumonitis. Because many of these tumors can be visualized by bronchoscopy, a bronchoscopic examination should be performed. Flexible bronchoscopic techniques may be helpful for diagnosis, but the use of rigid bronchoscopy with modern magnification, along with general anesthesia, is necessary if endoscopic biopsy is contemplated. Preparation for emergency thoracotomy should be made at the time of bronchoscopy in the event of life-threatening hemorrhage.

Bronchoscopic removal of some isolated lesions may be attempted, but because of the high incidence of recurrence and the possibility of severe hemorrhage, this technique should be used selectively. Conservative surgical resection is the procedure of choice for benign pulmonary tumors to achieve histologic diagnosis and preserve maximum functioning lung tissue. Thoracoscopic resection is an option in these children.[83] CT and magnetic resonance imaging should be performed in children with large space-occupying lesions to determine resectability. Fine-needle aspiration for cytology or core needle biopsy may be performed as the initial procedure for diagnosis in selected cases. Treatment of malignant lesions varies, depending on location and histology. Sleeve resections should be considered for bronchial adenomas. Resection of involved lymphatics should be considered with malignant lesions. Combined-modality therapy with adjuvant chemotherapy and possibly radiation therapy may be helpful in children with large primary malignancies or dissemination.

An important consideration is the association of primary lung tumors with congenital cystic pulmonary malformations. These lesions may be asymptomatic and are often discovered incidentally. In some instances, the natural history of the lung cyst is unknown, and a few may regress.[80] Although some authors recommend simple observation, most pediatric surgeons argue against prolonged observation of cystic lesions because of an increased risk of infection, pneumothorax, sudden cyst enlargement with potential respiratory compromise, and associated malignancy.* As mentioned previously,

* References 3, 23, 25, 26, 31, 36, 44–69, 77–82.

* References 46, 57, 60, 63, 64, 68, 80.

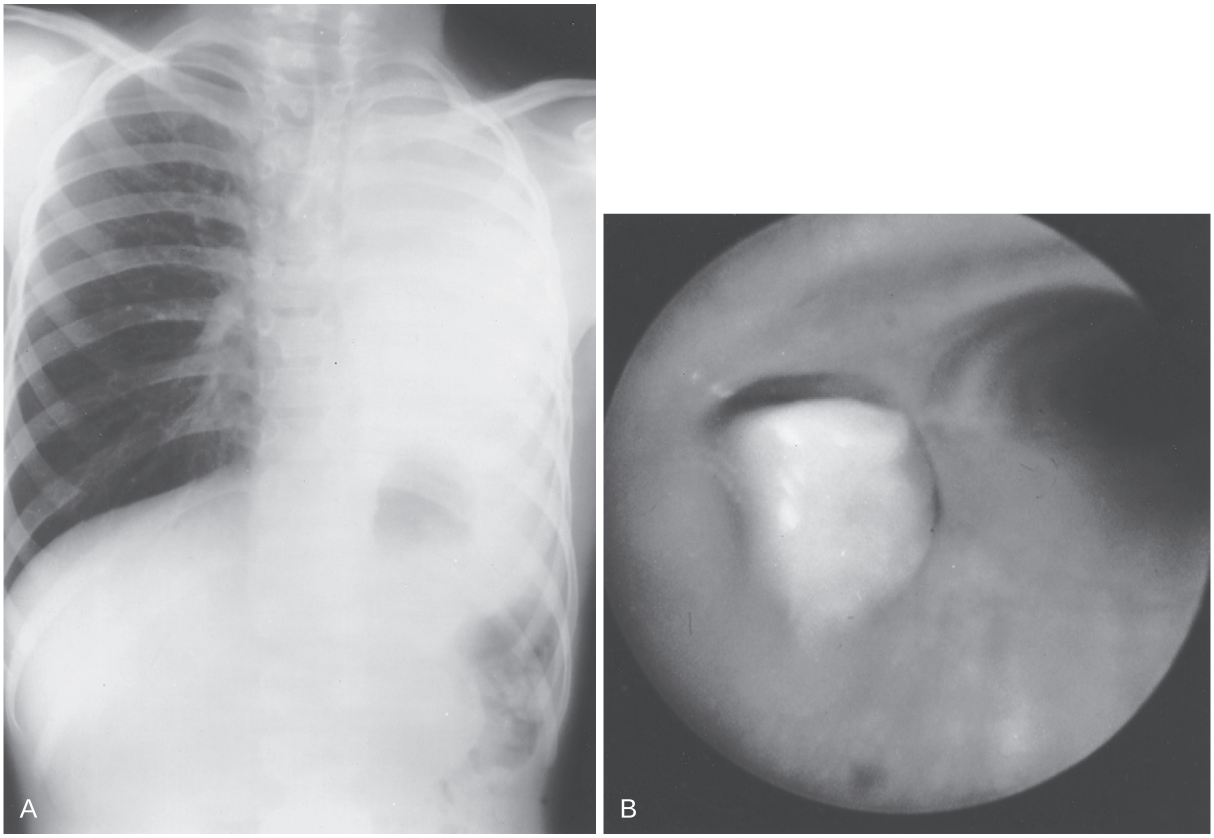


**FIGURE 42-3** Patient with complete atelectasis of the left lung **(A)** and obstruction of the left main bronchus secondary to rhabdomyosarcoma **(B)**.

there is evidence suggesting a relationship between type IV cystic adenomatoid malformation and type I pulmonary blastoma. Although complete lobectomy with negative margins is adequate treatment for these patients, close observation is recommended.[31,35,84] If patients with asymptomatic cystic malformations are observed without resection, they should be followed closely and evaluated frequently.

# Treatment of Metastatic Disease

Pulmonary metastases occur much more frequently than primary tumors in children, and the surgical approach depends on the histology of the primary tumor and the response of the primary site to combined-modality therapy.[72,85] Pulmonary metastases should not be considered for resection until the primary tumor is eradicated, without evidence of recurrence and other sites of metastatic disease ruled out. Tumors most frequently considered for pulmonary metastasectomy are osteosarcoma (OS), soft tissue sarcoma, and Wilms' tumor.[86]

## OSTEOSARCOMA

Children with OS should be considered for resection of pulmonary metastases once the primary lesion is controlled. The overall disease-free survival is approximately 40% in children who develop metachronous pulmonary metastases. Multiple factors, such as number of pulmonary nodules and time of recurrence, play an important role in children with OS and pulmonary metastases.[87,88] Roth and colleagues[73] showed that patients with fewer than four pulmonary nodules had an improved survival versus those with more than four lesions. According to Goorin and colleagues,[89] a complete resection of all pulmonary lesions is an important determinant of outcome, and penetration through the parietal pleura is associated with an adverse outcome. Although somewhat controversial, the outlook seems to be somewhat improved, even in patients presenting with pulmonary metastases, if complete resection of all metastatic lesions can be accomplished.[90] Harris and colleagues[91] reported a 68% survival rate in 17 patients with fewer than eight pulmonary nodules at presentation following chemotherapy, resection of the primary tumor, and pulmonary metastasectomy. The data in Table 42-4 suggest that an aggressive attempt at surgical resection of pulmonary metastases is indicated in OS, possibly irrespective of the number of lesions or the interval to the development of metastases.*
A number of recent studies have shown a survival advantage in patients with repeated metastasectomy, including patients with as many as five recurrences.[74,78,79]

## SOFT TISSUE SARCOMA

The usefulness of resecting pulmonary metastases in patients with soft tissue sarcoma depends on the histologic subtype. Rarely is pulmonary resection of metastatic lesions required in RMS, and resection of pulmonary metastasis in Ewing

* References 34, 38, 70, 82, 89, 92–95.

**TABLE 42-4**
**Pulmonary Metastasectomy for Osteogenic Sarcoma**

| | *Average Interval to Relapse* | *No. of Procedures (Months) (Range)* | *Disease-Free Survival, (No. of Lesions)* | *Median Follow-up for Survivors/ Author No. (%) (mo)* | *No. of Patients (Range)* |
|---|---|---|---|---|---|
| Martini[92] | 22 | 10 (2-25) | 59 (113) | 7 (32) | 33 (15-234) |
| Spanos[93] | 29 | 15.7 (4-30) | 52 (124) | 11 (37) | 36 (9-234) |
| Telander[82] | 28 | 9/6 (2-34) | 60 (173) | 13 (46) | 25 (6-48) |
| Giritsky[34] | 12 | 9 (1-21) | 19 | 6 (50) | 17 (9-39) |
| Rosenberg[94] | 18 | – | – | 7 (39) | – |
| Marion[70] | 12 | 13 (2-20) | 9 | 5 (42) | (36-72) |
| Schaller[38] | 17 | – | 34 | 7 (41) | (12-192) |
| Goorin[89] | 32 | 12.5 (4-59) | 26 (>63) | 9 (28) | 55 (19-101) |
| Carter[95] | 43 | 13 (1-83) | – | 4 (10) | 69 (59-80) |

From LaQuaglia MP: The surgical management of metastases in pediatric cancer. Semin Pediatr Surg 1993;2:75-82.

sarcoma has not been found to be efficacious.[71,72] Several European protocols are being developed to better define the role of pulmonary resection in Ewing sarcoma. The remaining sarcomas should be considered for resection if complete excision is possible and the patient's primary tumor is under control. The time to development of pulmonary metastases, number of lesions, and tumor doubling time are all significant prognostic factors in soft tissue sarcomas. Historically, approximately 10% to 20% of these patients can be salvaged by resection of pulmonary metastases.[37]

### WILMS' TUMOR

Rarely is pulmonary resection of metastatic disease required in children with Wilms' tumor. In a review of the National Wilms' Tumor Study by Green and colleagues,[96] no advantage of pulmonary resection was found compared with chemotherapy and radiation therapy alone. In an attempt to avoid pulmonary radiation, de Kraker and colleagues[33] suggested a protocol using primary pulmonary resection after chemotherapy for pulmonary metastases. Only 5 of 36 patients ultimately required resection of pulmonary metastases following chemotherapy, because most patients had a complete response with chemotherapy alone. One encouraging finding was that only 4 of 36 children required whole-lung irradiation. Because the results of chemotherapy and whole-lung irradiation are excellent for children with Wilms' tumor and pulmonary metastases, pulmonary resection of metastases should be reserved for selected cases (see Chapter 30).

### COMMENTS

Operation for pulmonary metastases in children depends on the histology of the primary tumor, the extent of the metastatic disease, and whether the metastatic disease is responsive to chemotherapy. The surgical approach varies, depending on the disease process and the age of the patient. No difference in survival has been demonstrated with sequential lateral thoracotomy versus sternotomy, but the latter is preferable in older patients with OS. Complete resection of all metastatic disease is an important consideration, and the use of automatic stapling devices can be helpful. Wedge resection is usually possible in children with OS. However, formal lobectomy or segmentectomy may be required to remove all of the tumor completely, especially when the primary tumor is not responsive to chemotherapy or radiation.[97] Muscle-sparing techniques are available in those children requiring posterolateral thoracotomies, and thoracoscopy may be appropriate in certain cases.[37] New localization techniques are being developed to aid in the thoracoscopic resection of lung lesions.[81] However, port site recurrences have been reported following thoracoscopic resection of pulmonary metastatic disease.[98,99]

## Tumors of the Chest Wall

### EPIDEMIOLOGY

Tumors of the chest wall are rare entities in the pediatric population with an incidence of no more than 2%,[100,101] and up to two thirds of these lesions are malignant.[102] The majority arise from the bony structures of the chest wall (55%), as opposed to soft tissue (45%).[103] Collectively, a 60% 5-year overall survival rate for all tumors has been reported, with a recurrence rate of 50% (local and distant) and subsequent 5-year survival rate of only 17%.[104]

### PRESENTATION

Masses of the chest wall typically present as lumps bulging underneath the skin, and the majority of malignant lesions have pain as a presenting symptom as well. In young children and infants, they are often found incidentally by caregivers, while older children and young adults may present with larger masses that have been present and growing for some time. Incidental discovery on routine chest imaging has been reported to be as high as 20%.[105] They can be found anywhere on the thorax, and the tissue of origin is generally mesenchymal in nature, regardless of whether the tumors are malignant or benign. Hence, sarcomatous variants are the most common malignant tumors, while carcinomas are almost nonexistent. The minority of patients present with nonspecific symptoms of respiratory compromise or dysfunction (tachypnea, hypoxia, cough, dyspnea on exertion), and these symptoms may have been present for quite a while before seeking medical advice. Symptoms stem from parenchymal compression from the mass intruding into the pleural space and onto the lung or from malignant effusions, both of which interfere with normal respiratory mechanics. Regardless of the presentation, a full history and physical exam, including a family

history, travel history, injury history, and extensive review of systems, is warranted to document other etiologies or associated conditions. Finally, depending on the degree of respiratory embarrassment, pulmonary function tests may be indicated prior to proceeding with any intervention.

## DIAGNOSTIC ADJUNCTS

Once the initial evaluation has been performed in the office, basic laboratory evaluations for complete blood count, coagulation profile, and baseline chemistries are needed. Imaging studies should consist first of erect, posterior-anterior, and lateral chest radiographs to evaluate the location, size, presence of calcifications, osseous involvement, and the presence of pulmonary parenchymal disease. Next, an ultrasound exam to determine the echo features (solid versus cystic, degree of homogeneity) and vascularity of the mass is recommended. Axial imaging (computed tomography or magnetic resonance imaging [MRI]) is performed afterward. The advantages of CT reside in its ability to clearly define the lung parenchyma and pleural space in relation to the osseous, vascular, and soft tissue components of the thorax (and hence mass), and the fact that it is a fast technique requiring minimal to no sedation even in the youngest of patients. The negative aspects of CT are the radiation exposure with subsequent risk of a secondary malignancy.[106] The benefits of MRI include better definition of the soft tissue components versus CT, as well as enhanced evaluation of the osseous and neural structures to determine the extent of central or peripheral nerve involvement and/or the presence of skip lesions or metastases. Unfortunately, this technique is time consuming and generally requires sedation or even general anesthesia to adequately acquire the data. Motion artifact from the heart and lungs can also interfere with this technique, limiting its utility, but this obstacle is being overcome with the use of cardiac-gated, respiratory-triggered protocols.[107,108] Determination of the precise entity from radiology studies alone is impossible, but the accurate construction of a differential diagnosis is readily possible, including the differentiation of malignant versus benign lesions.[107,108] Finally, other imaging studies may also be indicated to determine the presence of metastases (brain and abdominal CT, bone scan, positron emission tomogram [PET] scan) depending on the type of lesion, especially if malignant. Recent reports have suggested that the combination of PET and CT scans yields more accurate data in assessing the primary tumor, local and regional lymph node basins, evidence of recurrence, and for response to ongoing therapies.[109,110] Once initial studies have been performed, retrieval of tissue for histopathologic evaluation and diagnosis is warranted.

## DIAGNOSIS

Biopsy options include small or large specimen approaches. If a mass is small (less than 3 centimeters) or thought to be benign, then an upfront excisional biopsy may be warranted. However, the incision should be oriented so that a future reexcision, if needed, can be performed without compromising oncologic principles. Excising a normal rim of tissue circumferentially around the mass is also something for which the surgeon should opt. If the mass is large (greater than 4 to 5 centimeters), fixed to surrounding structures, involving many structures in the thorax, or if it is considered malignant by imaging, then either an incisional biopsy or core needle biopsy is warranted. Placing the incision in-line with any future resection is of paramount importance, regardless of the technique used, and either approach will yield enough tissue for histopathologic and cytogenetic analyses.[111] Once a diagnosis is confirmed, then disease-specific treatment algorithms may be initiated.

## THERAPEUTIC PRINCIPLES

Though treatment regimens are tumor specific, there are certain general principles that apply. For malignant lesions, multimodality therapy is the accepted paradigm for the majority of lesions, while simple extirpation is the rule with benign entities. With surgery, the most important concept to emphasize is that of the need for negative margins to decrease the risk of recurrence and subsequent therapy. Surgical extirpation also mandates wound reconstruction, which must be considered prior to the initiation of operative therapy. Large defects (greater than 5 centimeters, except for posterior and superior lesions where the defect will be buttressed by the scapula) will require the use of prosthetic materials—rigid (silicone, Teflon [DuPont, Wilmington, Del.], methyl methacrylate) or flexible (Prolene mesh [Ethicon, Cincinnati, Ohio], PTFE mesh, Marlex mesh [Chevron Phillips Chemical, Bartlesville, Okla.], Gore-Tex [WL Gore & Associates, Newark, Del.])—and/or autologous tissues (pedicle or free flaps [latissimus dorsi, rectus abdominis, or pectoralis major]) to reconstruct the chest wall and thus ensure normal chest wall mechanics and prevent respiratory embarrassment.

## TUMOR TYPES

Chest wall tumors are separated into benign and malignant cohorts (Table 42-5), as well as primary and secondary lesions. Specific tumors and their treatment will be outlined in the subsequent sections, but a discussion concerning secondary tumors is beyond the scope of this work.

### Benign Chest Wall Tumors

***Aneurysmal Bone Cyst*** Aneurysmal bone cysts (ABCs) can be found anywhere on the chest wall, and they generally arise in the ribs. They have characteristic patterns of appearance on both chest radiographs and MRI,[107] and they can grow to be quite large, producing local destruction to the adjacent tissues. Surgical extirpation with complete excision is the treatment of choice, and recurrence is rare. Histologically, the lesions are blood-filled cysts composed of fibrous tissue and giant cells.

***Chondroma*** Chondromas are slow growing, painless masses that usually arise in the costal cartilages. On imaging studies, they are lytic lesions with sclerotic margins, and unfortunately, they are difficult to distinguish radiographically from their malignant brethren, chondrosarcomas. Hence, complete resection with a wide margin of normal tissue is advocated.[112]

***Desmoid*** Desmoid tumors are fibrous neoplasms that can be found anywhere in the body. They are thought to be benign, but they have also been reported to undergo malignant degeneration.[112] Desmoid tumors infiltrate adjacent and surrounding tissues, and they are known to travel down fascial planes and to encase neurovascular structures in the mediastinum or

**TABLE 42-5**
**Pediatric Chest Wall Tumors**

| |
|---|
| **Benign** |
| Aneurysmal bone cyst |
| Chondroma |
| Desmoid |
| Fibroma |
| Fibrous dysplasia |
| Lipoblastoma |
| Lipoma |
| Mesenchymal hamartoma |
| Osteochondroma |
| Osteoma |
| Vascular malformations |
| **Malignant** |
| Chondrosarcoma |
| Ewing sarcoma family |
| Fibrosarcoma |
| Langerhans cell histiocytosis |
| Leiomyosarcoma |
| Leukemia |
| Liposarcoma |
| Lymphoma |
| Neuroblastoma |
| Rhabdomyosarcoma |
| Osteosarcoma |

the thoracic inlet. MRI is the radiologic procedure of choice to best define the extent of involvement and the structures involved. Treatment is wide local excision with negative margins, but recurrence rates from 10% (negative margins) to 75% (positive margins) have been described by some authors.[113–115] If a complete resection is not possible, or if vital structures are meant to be sacrificed during operative extirpation, then multimodality therapy consisting of radiation (50 to 60 Gy), and cytotoxic (vinblastine and methotrexate) and cytostatic (tamoxifen and diclofenac) chemotherapy is recommended, though the exact regimen is not well defined.[116–119]

***Fibrous Dysplasia*** Fibrous dysplasia is a benign condition where normal bone is replaced by fibrous tissue. These lesions are generally not large, and patients present with pain, generally from a pathologic fracture. On plain radiographs, these lesions are described as lytic in nature with a characteristic "soap bubble" appearance.[120] Treatment is based on symptoms and concerns for possible fracture secondary to the inherent structural weakness the lesion produces in the bone. Simple excision is the recommended procedure.

***Mesenchymal Hamartoma*** Mesenchymal hamartomas (MH) are masses found in infants or young children that can also be discovered antenatally. The lesions are generally well circumscribed, and though emanating from the chest wall (one or several ribs), they abut or compress, as opposed to invade, thoracic structures (Fig. 42-4). Hence, presenting symptoms are primarily from respiratory embarrassment. These lesions are well defined by radiographic features on cross-sectional imaging, including mineralization and hemorrhagic cystic structures.[121] Histopathologically, these lesions consist of chondroid tissue with blood-filled, endothelial-lined spaces

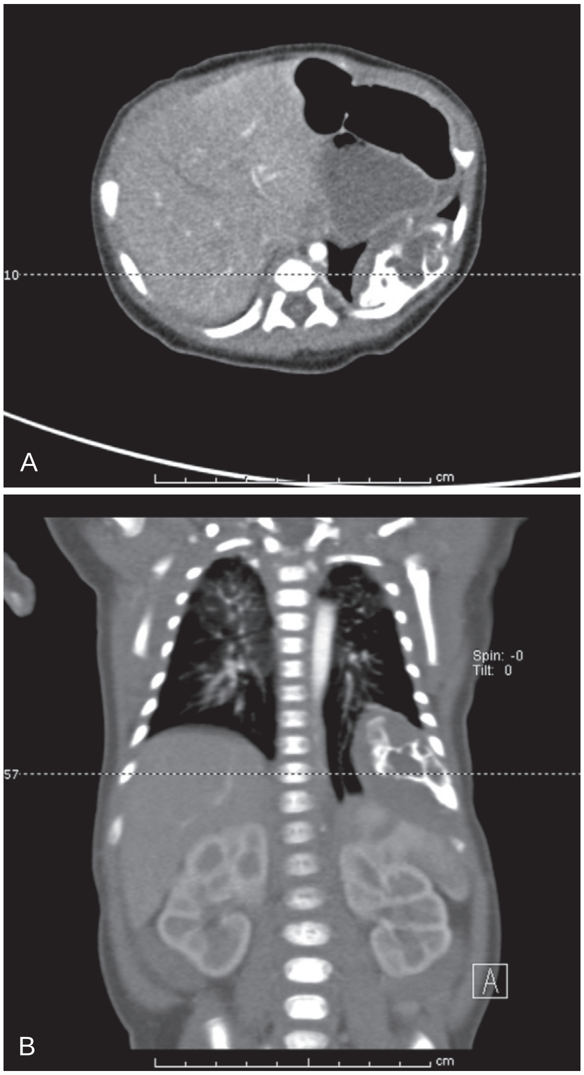


FIGURE 42-4 Axial **(A)** and coronal **(B)** images of a computed tomography scan of the chest in an infant with a mesenchymal hamartoma.

interspersed with osteoclastic giant cells. Treatment strategies have traditionally consisted of complete resection with subsequent chest wall reconstruction, but considering the large size of these lesions and the small volume of the chest cavity in the infants in which they are discovered, concern over the future complications of scoliosis and respiratory compromise from this approach has been considerable. In light of the fact that they are not known to undergo malignant degeneration,[122] observation[123,124] or other less morbid approaches (radiofrequency ablation[125]) have been described and recommended.

***Osteochondroma*** Osteochondromas are tumors composed of bony and cartilaginous elements more commonly found in males (3:1 ratio).[112] The lesion can present with pain from a pathologic fracture or compression of nearby nerves, or it can be asymptomatic if it grows inward into the thoracic cavity. The lesion is well characterized on plain radiographs, and it arises from the cortex of the rib at the metaphysis and has a "cartilage cap."[120] Malignant degeneration has been documented,[107] and resection is warranted in all postpubertal patients, with symptoms, or if the mass is growing.

## Malignant Chest Wall Tumors

The majority of clinically prevalent malignant tumors in the pediatric population are sarcomatous lesions, and a select sampling of these tumors will be addressed individually in the following sections.

***Chondrosarcoma*** Chondrosarcomas (CSs) are derived from cartilaginous elements (costal cartilages) that are the most common primary malignant bone tumor of the chest wall in adults,[126] and they are more common in males.[112] CSs have been associated with a prior history of trauma,[127] as well as being known to form from malignant degeneration of the benign counterpart discussed previously.[126] Some 10% of patients will present with metastatic disease,[103] especially in the lungs and brain. Primary therapeutic intervention is complete surgical extirpation with a margin of normal tissue of at least 4 centimeters[112] secondary to the high risk of local recurrence (up to 75% with positive margins), even with negative margins at the initial operation (10%).[128] These tumors are not chemotherapy responsive, and the role of radiation is only for those lesions that are unresectable or have known positive margins. Five-year survival has been reported to range from 60% to 90%,[128,129] and beneficial prognostic factors are the absence of metastases at presentation and a complete resection.[103,128]

***Ewing Sarcoma Family/Primitive Neuroectodermal Tumors*** Ewing sarcoma family/primitive neuroectodermal tumors (EWS/PNETs) are the most common malignant chest wall lesions in the pediatric population.[123] They are aggressive tumors requiring multimodality therapy, but survival is still poor despite these interventions. The tumors often present as painful masses with frequent metastases (25%) to the lung, bone, or bone marrow.[103] EWS/PNET lesions are characterized by a balanced gene translocation *(EWS/FLI1)* (t11:22 [q24:q12]),[130] and these tumors are defined histologically as sheets of small, round cells with scant cytoplasm. On imaging studies, they have characteristic bony destruction described as lytic or sclerotic lesions.[108] Treatment involves an initial biopsy followed by neoadjuvant chemotherapy (four cycles) with vincristine, actinomycin, cyclophosphamide, and Adriamycin (Adria-VAC) alternating with etoposide and ifosfamide. This regimen has demonstrated a great deal of success in shrinking the tumor to improve survival and facilitate complete resection (Fig. 42-5).[131,132] In fact, with the use of neoadjuvant chemotherapy, complete surgical extirpation with negative margins was possible in 71% of patients versus 37% who underwent primary surgical intervention.[132] The extent of surgery should include all involved structures and a soft tissue or osseous margin. Postoperative adjuvant therapy uses the same preoperative chemotherapy regimens, but not radiotherapy if complete resection is achieved. This should be the goal, despite the known radiosensitivity of this tumor,[133] because of the concern over the late effects (scoliosis, pneumonitis, cardiotoxicity, secondary malignancy, growth retardation, and breast hypoplasia or aplasia) radiotherapy poses.[132] The use of radiotherapy is for residual and unresectable disease and for patients who present with a malignant pleural effusion, where it is an accepted therapeutic intervention. A recent European consensus conference advocated for surgery rather than irradiation in all cases.[134] Five-year survival using the previously mentioned protocol was around 70% for nonmetastatic disease,[135] and the 8-year survival was roughly 30% with metastatic disease.[136] In patients presenting with metastatic disease, the European Intergroup Cooperative Ewing's Sarcoma Studies Group demonstrated improved survival with the use of myeloablative chemotherapy followed by stem cell rescue at the conclusion of conventional treatment protocols.[137]

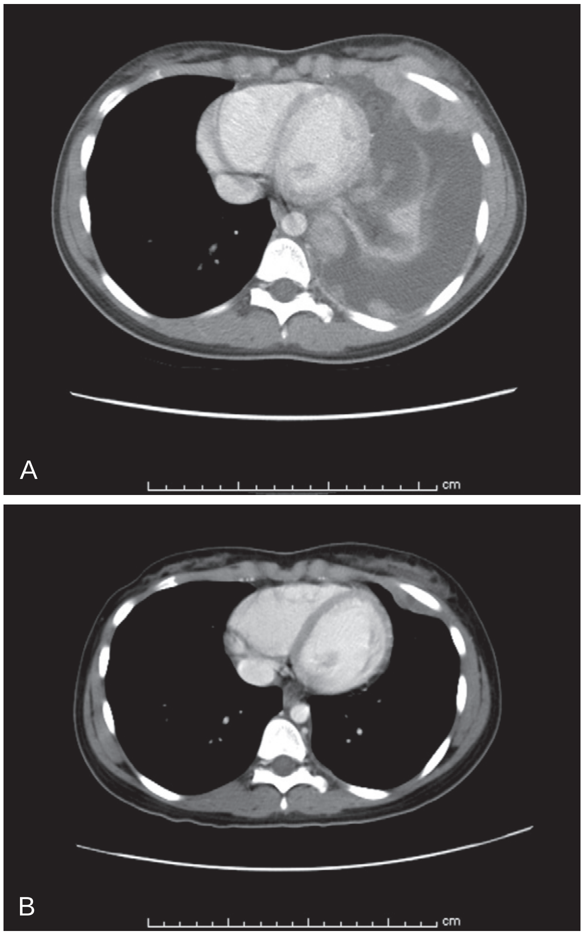


**FIGURE 42-5** Axial images of a computed tomography scan of the chest in a child with a Ewing sarcoma family/primitive neuroectodermal tumor (EWS/PNET) of the chest wall before **(A)** and after **(B)** neoadjuvant chemotherapy.

***Fibrosarcoma*** Fibrosarcoma (FS) (also known as infantile or congenital fibrosarcoma) are malignant tumors found throughout the body in infants who present with large masses that often involve, invade, and surround adjacent structures. FS have been found in the chest wall, and several reports have documented the success of multimodality therapy in combating these tumors.[138,139] FS can be distinguished from other myofibrous and sarcomatous lesions by the presence of a unique gene rearrangement between the *TEL* gene (12q13) and *TRKC* gene (15q25).[138] FSs are chemotherapy sensitive, and reports demonstrating the effectiveness of neoadjuvant chemotherapy with vincristine, actinomycin, cyclophosphamide, and Adriamycin, followed by surgical extirpation, are well accepted.[138,139] A recent report[139] from Europe

demonstrated that 5-year overall and event-free survival rates were 89% and 81%, respectively. The authors reported that in their series complete surgical extirpation was rarely feasible and that conservative surgical approaches should be adopted. Furthermore, 71% of patients responded to alkylating agent-free and anthracycline agent-free regimens, and hence, this regimen should be started first to limit toxicity.

***Osteosarcoma*** OS of the chest wall can be primary or secondary tumors (prior sites of irradiation or from preexisting osseous lesions [Paget disease]).[112] Primary lesions are primarily of the ribs, and on imaging, they can be confused with chondrosarcomas.[140] Chest radiographs will demonstrate a "sunburst pattern," and axial imaging concentrating on regional (bony skip lesions) and distant (lung, liver, brain) metastases must be sought.[112] Pretherapy biopsy is the rule, and neoadjuvant therapy precedes extirpative procedures. Overall survival rates are poor (15% to 20%),[103] but in the presence of nonmetastatic disease, 5-year survival rates can exceed 50%.[103] Prognosis is related to the presence of metastases, the degree of tumor burden, and the response to chemotherapy.[141]

***Rhabdomyosarcoma*** RMS of the chest wall is a rare tumor and encompasses no more than 7% of all RMS in Intergroup Rhabdomyosarcoma Studies (IRS).[142–144] The chest wall site is deemed an unfavorable site, and therefore this is an adverse prognostic factor.[142,143] Other adverse prognostic factors have been reported to be histopathologic findings (alveolar versus embryonal), tumor burden and size, incomplete resection, and presence of metastatic disease (including lymph node metastases).[143,145] Despite advances in the treatment of RMS over the last 40 years, unfavorable sites carry an overall survival of only 55% (versus 90% for favorable sites),[143] and those with truncal RMS have been reported to have a failure-free survival rate of no greater than 67%.[146] These tumors require multimodality therapy, and neoadjuvant chemotherapy followed by surgical extirpation is the norm. Radiation is reserved for lesions with positive margins following surgery, or in unresectable tumors. A report from Saenz and colleagues documented the utility of radiation (median dose of 44 Gy) to salvage some patients with residual disease.[146] However, the necessity for complete surgical resection has been called into question by a recent report from the Children's Oncology Group (COG),[147] where the outcome of patients enrolled in IRS I-IV with chest wall RMS were analyzed. The report documents that regardless of clinical group (I-III) and other tumor-specific factors (histologic subtype, tumor size), the only critical factor to influence failure-free and overall survival was the presence of metastatic disease. In the face of metastases, patients with chest wall RMS had an overall and failure-free survival of 7% and 7% versus 49% and 61%, respectively, in the cohort without metastases ($P < 0.001$). Therefore the authors suggest where gross total surgical resection will produce significant morbidity or physical debilitation, less aggressive operative approaches should be entertained.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 43

# Bone Tumors

Saminathan S. Nathan and John H. Healey

Bone tumors are rare. In the United States, there were 166,487 cases of breast cancer and 164,753 cases[1] of prostate cancer in 2000. By comparison, there were only 2,051 cases of all types of bone sarcomas that year. A large proportion of these tumors, 26.8% in one published database, occur in the pediatric population. There are no population-based benign bone tumor registries; so, it would be impossible to establish their true incidence. Most databases of this nature derive from tertiary referral institutions, and so, benign conditions, which are often asymptomatic, would be grossly underrepresented. Nevertheless, one study has shown that up to 43% of children have a bone lesion that mimics or is a true neoplasm during skeletal development.[2] This implies that the overwhelming majority of lesions are benign.

The pediatric surgeon will often be called into the management of the patient with bone tumors for a number of reasons. The very young child on follow-up for an unrelated condition may manifest with a bone lesion secondary to osteomyelitis or leukemia. The older child with a metastatic osteogenic sarcoma may require the expertise of the pediatric thoracic surgeon for the resection of pulmonary nodules. The teenager with a pathologic fracture through a unicameral bone cyst or nonossifying fibroma may present first to the pediatric surgeon on call in the pediatric emergency department.

The diagnosis of these rare conditions is readily attained through a careful clinical evaluation. In that regard, the utility of plain radiographs can never be overstated. They facilitate the initial workup and allow these patients to be referred to specialized centers with multidisciplinary expertise. Although the subsequent imaging modalities are important, the radiographs form a key part of surgical planning.

It is with the pediatric surgeon in mind that this chapter is written. Lengthy discourse on the pathology is avoided, and several excellent references exist.[3–6] Instead, the format adopted is a practical approach to the management of these conditions. Where prudent, insights and controversies are highlighted to spur interest in specific areas.

## General Considerations

### PATHOPHYSIOLOGY

The main aim of this section is to illustrate the specific issues of the pathophysiology of bone tumors that distinguish them from tumors of soft tissue. Bone tumors should be approached initially from the standpoint of whether they are benign or malignant. Whereas traditional approaches regarding the treatment of most nonskeletal benign lesions have been ones of benign neglect (if these lesions are not perceived to be causing problems), the management of benign bone lesions is complicated by the potential compromise of skeletal structural integrity. Cortical deficiency weakens bones and can mandate treatment to prevent fracture. The prudent, if rare, consideration is one of syndromic presentation and malignant transformation. Many of these principles are applicable to malignant lesions as well. However, malignant lesions have, as the cornerstone of consideration, their implications on survival, which will be elaborated. Metastatic lesions to bone are uncommon in the pediatric age group. Their pathophysiologic implications tend to be structural or diagnostic.

In the pediatric age group, benign lesions far outnumber primary malignant lesions, which in turn outnumber metastatic lesions. Because of the protean manner in which benign lesions behave, some are not evident in the physician's office. Conclusions about their natural history and malignant potential are therefore difficult to ascertain.[4] This is obviously not the situation with malignant and metastatic lesions. In this section, we discuss pathologic conditions of the bone that occur most commonly in the pediatric age group. In the pediatric population, the commonly occurring benign lesions are the unicameral bone cyst, aneurysmal bone cyst, enchondroma, osteochondroma, nonossifying fibroma, and osteoid osteoma. The common malignant bone tumors are osteogenic sarcomas and Ewing family tumors (Table 43-1). Here we highlight specific features of each tumor. For a more thorough understanding of the pathology, the reader is directed to any of a number of fine books on the subject.[3–6]

#### Benign Lesions

The typical benign lesion in the pediatric age group (Table 43-2) is identified incidentally, because they rarely cause symptoms. They are often diagnosed when a parent notices a lump or deformity (e.g., osteochondroma) or a radiograph is obtained for an unrelated condition (e.g., nonossifying fibroma). The two main surgical issues are diagnosis

**TABLE 43-1**
**Commonly Occurring Tumors by Age Group**

| *Age* | *Benign Tumors* | *Malignant Tumors* | *Tumor-like Conditions* |
|---|---|---|---|
| Birth to 5 years | Eosinophilic granuloma | Leukemia<br>Metastatic neuroblastoma | Osteomyelitis<br>Nonaccidental injury |
| 5 to 15 years | Unicameral bone cyst<br>Osteochondroma<br>Aneurysmal bone cyst<br>Osteoid osteoma<br>Enchondroma<br>Nonossifying fibroma<br>Chondromyxoid fibroma<br>Chondroblastoma | Ewing sarcoma<br>Osteogenic sarcoma | Fibrous dysplasia<br>Osteomyelitis<br>Osteofibrous dysplasia<br>Stress fracture |
| 15 to 20 years | Unicameral bone cyst | Osteogenic sarcoma | Fibrous dysplasia |
| | Osteochondroma | Ewing sarcoma | Stress fracture |
| | Osteoid osteoma | | |
| | Aneurysmal bone cyst | | |
| | Nonossifying fibroma | | |
| | Giant cell tumor | | |
| | Enchondroma | | |
| | Chondroblastoma | | |
| | Chondromyxoid fibroma | | |

By considering the factors of age, frequency, and location in the long bones (see Fig. 43-3), a diagnosis can be proposed in the majority of cases. The possibility of trauma should always be borne in mind, and in the noncommunicative child younger than 5 years old, nonaccidental injury may be the cause.

**TABLE 43-2**
**Incidence of the More Commonly Diagnosed Bone Tumors**

| *Bone Tumors* | *All Bone Tumors (%)* | *Bone Tumors in the First Two Decades (%)* |
|---|---|---|
| Benign | | |
| Osteochondroma | 7.86 | 4.69 |
| Aneurysmal bone cyst | 2.60 | 1.96 |
| Osteoid osteoma | 2.99 | 1.94 |
| Nonossifying fibroma | 1.13 | 0.99 |
| Enchondroma | 3.02 | 0.98 |
| Giant cell tumor | 5.10 | 0.80 |
| Chondroblastoma | 1.07 | 0.66 |
| Chondromyxoid fibroma | 0.41 | 0.14 |
| Unicameral bone cyst | Unknown | Unknown |
| Malignant | | |
| Osteogenic sarcoma | 14.9 | 7.53 |
| Ewing sarcoma | 4.6 | 3.50 |

In using this table, a number of caveats need to be remembered. Most benign lesions are often asymptomatic, and only symptomatic ones will present. Of these, most will be managed in the primary care setting. Malignant lesions will, however, usually present at a referral center. Hence, in terms of population incidence, these figures are unreliable. In relative terms, however, they have some utility in indicating their prevalence. Unicameral bone cysts are left in this list as a reminder of their frequency.

through a biopsy and stabilization of bones that have fractured or are at risk to fracture, especially through a precarious location. For example, a bone cyst in the neck of a femur should be seriously considered for surgical stabilization, because a fracture at this site may result in avascular necrosis of the femoral head. The biopsy itself cannot be undertaken lightly, because it can weaken the bone, mandating surgical or external splinting. The challenge is to use a high-yield biopsy with minimal morbidity.

***Size of the Tumor*** Size is an important consideration for surgical approach. For example, cartilaginous rib tumors larger than 4 cm were found to have increased likelihood of malignant behavior.[3] Hence they should be resected widely despite their relatively bland histologic appearance (Fig. 43-1). Large tumors can also grow into neighboring compartments and cause mechanical compromise to joints. Although this is less critical in joints of the upper limb, it is important in the spine and in the lower limbs, where they cause mechanical impingement and pain. The disruption of a tubular bone by growth of a neoplasm weakens the bone. Lesions that involve more than 50% of the cross section of a bone are at risk of fracture and should be treated from a mechanical standpoint.[7–9] Fracture of a malignant lesion may require amputation rather than a limb-sparing operation.

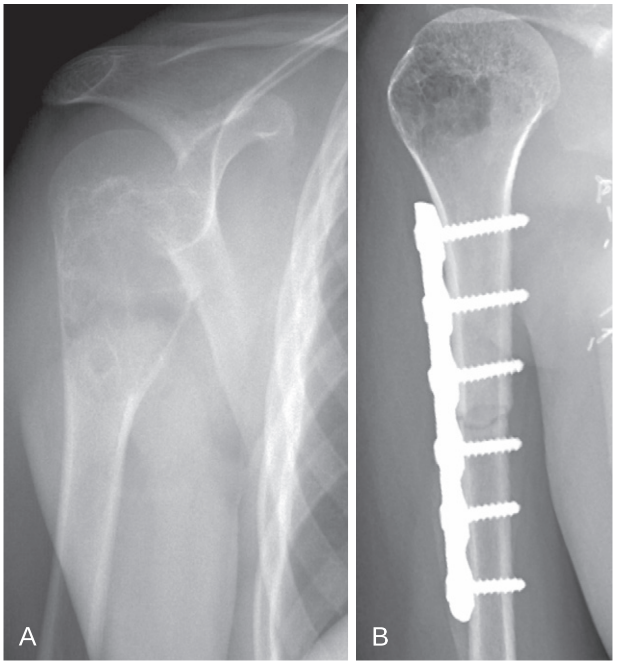


**FIGURE 43-1** **A,** Chondrosarcoma in the proximal humerus of a 13-year-old boy. This is an exceedingly rare diagnosis in this age group. **B,** A proximal humeral resection with allograft reconstruction was performed. In children, the available prostheses may be too large, and hence bulk allografts may be the only choice.

***Fracture Through a Benign Lesion*** The fractured benign lesion is typified by the unicameral bone cyst. These lesions may appear radiographically to be aggressive, but a careful history and physical examination with appropriate imaging modalities will usually establish their benign nature

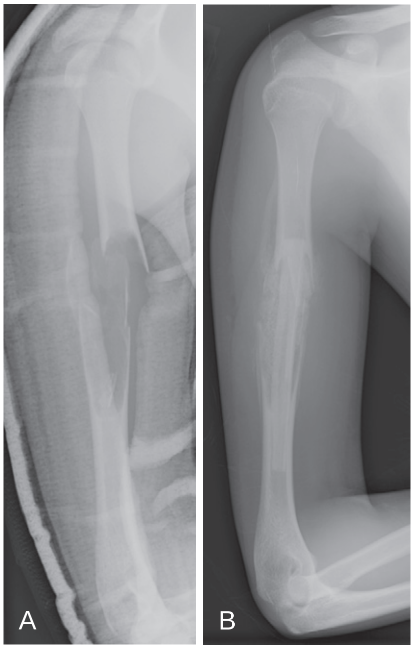


**FIGURE 43-2** **A,** Large unicameral bone cyst of the proximal humerus that had fractured. The aggressive appearance may lead one to suspect a malignant process, but a careful evaluation of the margins of this lesion and absence of periosteal reaction reaffirms the management decision of observation before surgery. **B,** This cyst was curetted and packed with an allograft 1 month after the fracture. Treatment with an intramedullary fibular graft provided stabilization, and supplemental bone graft healed the lesion.

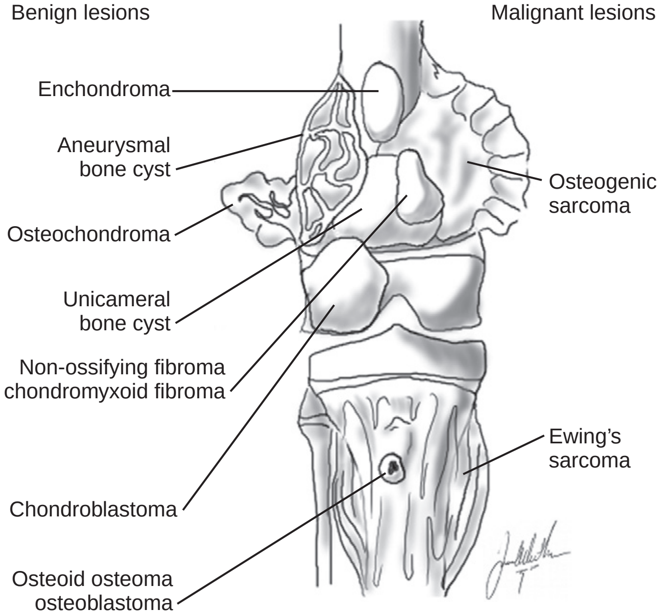


**FIGURE 43-3** The location of lesions in relation to the physis gives a clue to the diagnosis. In most cases, the diagnosis can be made on radiographs, leaving further imaging to plan for surgery.

(Fig. 43-2). Unicameral bone cysts that fracture may resolve spontaneously. However, the vast majority continue to fracture throughout a child's lifetime and prove to be disabling.[10] In general, they should be treated surgically, especially if they are symptomatic.

The timing of surgery is critical. An early biopsy after fracture would show callus formation difficult to distinguish from a malignant process. Therefore these lesions should be observed during healing of the fracture for about a month, after which a biopsy and definitive procedure are performed.

***Location in Relation to the Physis*** Location in relation to the physes is an important consideration distinguishing tumor assessment and management of children versus adults (Fig. 43-3). The term diaphyseal aclasis was coined to highlight a condition in which multiple osteochondromas, a condition primarily of the growth plate, caused disordered linear growth of the long bone.[6] These cases are often familial, and children are rarely compromised by their condition. Joints of the upper limb generally have a high tolerance for the resultant deformity. However, occasionally, degenerative arthritis develops, especially in the lower limb, then requiring early surgery.

***Multiplicity of Bone Tumors*** Multiple bone lesions in an individual are often syndromic and may confer a higher incidence of malignant degeneration than when they occur singly.[4–6] Multiple osteochondromas occur in multiple hereditary exostoses—an autosomal dominant condition caused by abnormalities of the *EXT1, EXT2,* and *EXT3* genes on chromosomes 8, 11, and 19.[11–13] Although each osteochondroma has a low probability of malignant transformation, the cumulative risk is high. Children with this condition have an increased incidence of 10% to 27.6% for malignant degeneration of an osteochondroma into a chondrosarcoma. By comparison, isolated osteochondromas have a malignant degeneration rate of about 1%.[3–5] Because only symptomatic lesions will present to the physician, the true incidence of malignant degeneration in isolated lesions is impossible to ascertain with certainty. Multiple enchondromatoses is a sporadic condition that confers an increased incidence of malignant transformation of up to 50% in the involved bones.[4] Limb-length inequality and malalignment are also common. Ollier disease, as this condition is termed, has another counterpart classically affecting one limb anlage. A variant, Maffucci syndrome, involves widespread enchondromas associated with hemangiomas of the hand. The occurrence of multiple nonossifying fibromas, associated with mental retardation, café-au-lait spots, endocrine disorders, cardiovascular malformations, and ocular abnormalities has been termed Jaffe-Campanacci syndrome, but this entity has no malignant implications.[4,14]

***Site of Involvement*** The site of benign cartilaginous lesions has important implications for malignant potential. Peripheral lesions in the hand rarely turn malignant, while those closer to the axial skeleton have important malignant potential even if they appear benign histologically.[3–6,14,15] Lesions in bones adjacent to weight-bearing joints should be regarded with special concern. In the pediatric group, these lesions are usually chondroblastomas. They grow epiphyseally and in so doing can cause weakening of the subchondral bone and, ultimately, an intraarticular extension or fracture that may even mimic

osteochondral defects. In the case of sarcomas, a relatively conservative resection in this context would have to be deferred to an extraarticular resection.

***Metastatic Potential*** A unique feature of benign bone tumors is that there is a small incidence of metastasis in these lesions. Accordingly, 1.7% of chondroblastomas and 3% of giant cell tumors[5,16–18] do metastasize. There is a controversy about whether some of these lesions were, in fact, malignant from the outset.[19] However, the truly benign lesions that do metastasize are atypical lesions that have had surgical manipulation, which may have embolized tumor cells. When followed, some of these metastatic lesions, primarily in the lung, may remain dormant and not progress. The possibility, therefore, is that they represent a transport phenomenon more akin to a mechanical embolism and not a true metastasis.[3,19]

## MALIGNANT LESIONS

### Epidemiology

The main histologic types of bone tumors are osteogenic sarcoma, Ewing family tumor, chondrosarcoma, and other sarcomas. They affect children at a rate of 6:3:2:1, respectively.[1,5]

Osteogenic sarcomas (also known as osteosarcomas) are malignant bone-forming tumors of the bone. They occur at any age but most frequently present in an extremity in the middle teenage years. There are various subtypes with varying implications for survival. In general, the subtypes behave similarly, except perhaps for telangiectatic osteogenic sarcoma, which bears special mention. In the prechemotherapy era this was regarded as the tumor with the worst prognosis.[20] Presently, however, it has the best prognosis.[21] The lytic nature of these sarcomas weakens bone, resulting in the highest rate of pathologic fracture. Increasingly, rarer forms of osteogenic sarcoma are described. Two variants of note are the small cell sarcoma and giant cell-rich osteogenic sarcoma. The former can be confused with a Ewing family tumor and thus is often treated by similar chemotherapy protocols.[22,23] The latter can be confused, in the appropriate setting, with a giant cell tumor of the bone, which is a benign condition.[24–26]

The Ewing sarcoma occurs at a younger age (see Table 43-1) and may affect any bone, particularly, the femur, pelvis, and humerus. It is the most common cancer in the pelvis, ribs, foot, and fibula. It was once considered to be distinct from peripheral neuroectodermal tumors but has been shown to be genetically identical to this entity. It is presently considered to be in the same family of neoplasms also known as Ewing family tumors.[3,6]

Chondrosarcoma is less prevalent in the pediatric age group. It is more widely distributed in the body compared with its occurrence in adults.

***Genetics*** There have been few consistent genetic or syndromic associations with osteogenic sarcoma. Patients with the Li-Fraumeni syndrome[27] have a *TP53* germline mutation[28,29] on 9p21 and are predisposed to osteogenic sarcoma, breast cancer, and leukemia (Fig. 43-4). Two to 3 percent of patients with osteogenic sarcoma will be the proband for Li-Fraumeni families.[30] Another germline mutation of 13q14, hereditary retinoblastoma (RB), predisposes to osteogenic sarcoma.[31] Children who received radiation therapy for retinoblastoma, Hodgkin and non-Hodgkin lymphoma, Ewing family tumor, and other cancers are at a 5% to 10% risk of developing osteogenic sarcoma. Patients with an *RB* gene deletion and a history of alkylating agent exposure from a prior malignancy are predisposed to this complication as well. About 5% of all osteogenic sarcomas occur as postradiation sarcomas.

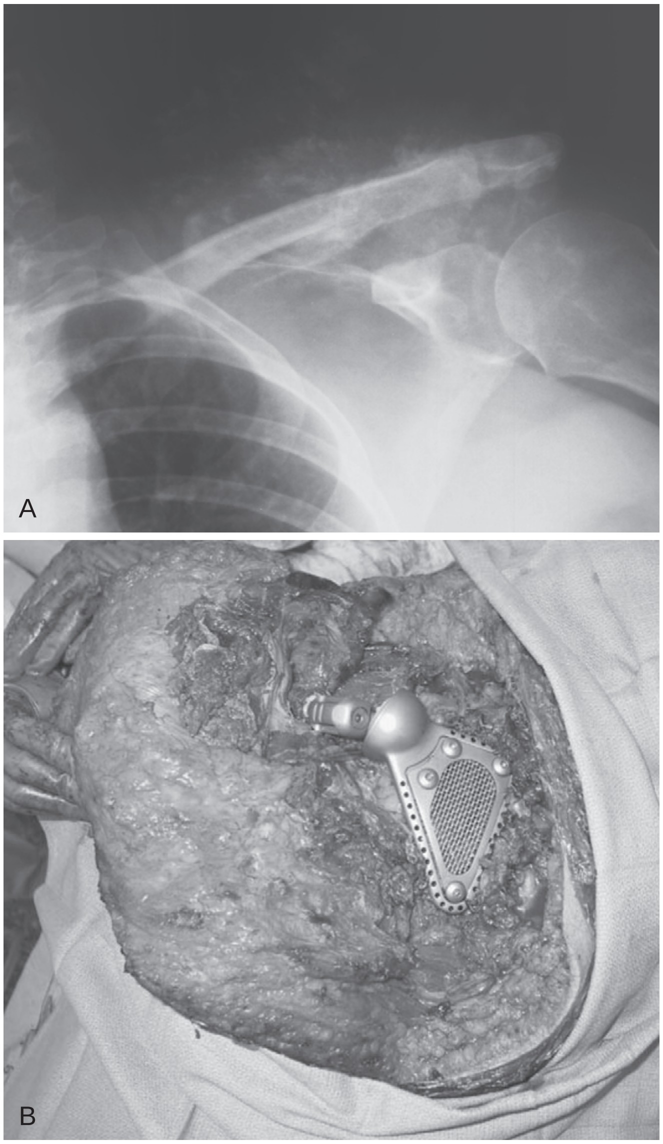


**FIGURE 43-4** **A,** Osteogenic sarcoma in the left scapula of a female patient with Li-Fraumeni syndrome. This patient had a family history of osteogenic sarcoma in a first-degree relative. At the time of staging for the osteogenic sarcoma in the scapula, a lesion in the breast was discovered on computed tomography (CT) of the chest. This was subsequently found to be an adenocarcinoma. **B,** The patient underwent a scapular replacement. A latissimus dorsi flap was used for skin cover.

The Ewing family tumor is a malignancy associated with a number of translocations. The 11 to 22 translocation, resulting in an EWS-FLI1 fusion transcript, is the most common variant, and type 1 is associated with the best prognosis.[32] Other translocations include type 2 EWS-FLI1, EWS-ERG from a 21,22 translocation, and EWS-ETV1 from a 7,22

translocation. These rarer variants have not been as well studied but appear to confer a poorer prognosis.[32] Further additive mutations involving cell-cycle genes reduce the prognosis of these tumors still more. The Ewing family tumor is the most common solid tumor to metastasize to the brain.[33]

## DIAGNOSIS AND STAGING

Bone tumors are diagnosed based on the well-recognized triad of history, physical examination, and investigation. After a clinical diagnosis, it is imperative that imaging and staging procedures are done before biopsy. Preoperative imaging allows for planning of the definitive procedure and hence placement of the biopsy incision. In addition, changes that would occur in the lesion after biopsy would be difficult to distinguish from changes resulting from tumor growth on imaging. Furthermore, changes in the lung after general anesthesia (e.g., atelectasis) are difficult to distinguish from metastatic deposits.

### Clinical Evaluation

Although it is not possible to be comprehensive in this section, the history and physical examination are important parts of the assessment of a patient with a bone tumor. Patient demographics and tumor location narrow the differential diagnosis and focus the workup efficiently.

The patient's age is important (see Table 43-2). Most malignancies occur in the second decade of life.[3–6] Among children, subtle variation occurs in the prevalence of disease with respect to age (see Table 43-1). Demographically, it is exceedingly rare for patients of African descent to have a Ewing family tumor.[6]

Pain at rest is an important sign that occurs in tumors and in other organic conditions, such as infection and bone infarction. It distinguishes these conditions from mechanical pain, which occurs with activity. Most malignant tumors will present with pain. Pain relieved by nonsteroidal antiinflammatory drugs (NSAIDs) is pathognomonic of osteoid osteoma.[34] This lesion can occur at any age and is characterized by painful scoliosis when it occurs in the spine.

A family history of malignancy should be discerned, especially in possible sentinel cases of the Li-Fraumeni syndrome.[27–29] Such patients should have systemic evaluation in the form of radioisotope bone scans or positron emission tomographic scans, to rule out other sites of involvement.

As described earlier, the surgeon should be alert to any dysmorphism that the patient may have. Cutaneous stigmata are evident in patients with neurofibromatosis, fibrous dysplasia, and Jaffe-Campanacci syndrome.[14] Limb length discrepancies are seen in patients with multiple enchondromatoses and multiple hereditary exostoses.[35]

Infection should be considered in the differential diagnosis in almost every case seen. Tumor epidemiology is very telling. For example, childhood leukemia is nearly 10 times as common as Ewing family tumor, and so, rare manifestations of leukemia are more common than routine presentations of Ewing family tumor.

The nature of bony reconstruction also requires that the method chosen be matched with the demands of the patient. As such, an idea of the patient's expectation should be sought at this time.

### Radiology

The minimal radiologic assessment at the first visit should be two orthogonal radiographic views of the area in question. A radiograph remains the most specific diagnostic imaging test and is the only one that gives the "gestalt" of overall assessment of skeletal biology and mechanics. By analyzing the location of the tumor (see Fig. 43-3), as well as whether it is benign or malignant, the diagnosis can be made in the majority of cases.[3–6]

Benign lesions are well circumscribed, with a good sclerotic border, and produce no soft tissue edema. Malignant lesions have lucent or variegated matrices and permeative borders. Edema is often apparent with the presence of fat lines.

The often-quoted eponymous phrases are not specific to distinct malignancies. The Codman triangle refers to the lifting and ossification of periosteum at the periphery of an osteogenic sarcoma. The sunburst appearance is due to the ossification of fibers and vessels subperiosteally, as the tumor expands out of the cortex. Onion skinning refers to the periodic ossification and expansion of periosteum from the cortex. Any of these conditions can be seen in tumors or infections that are sufficiently fast growing.

In Figure 43-3, epiphyseal lesions are typical of chondroblastoma or giant cell tumors; physeal lesions are typical of osteochondromas; metaphyseal lesions are typical of osteogenic sarcomas, unicameral bone cysts, aneurysmal bone cysts, and nonossifying fibromas; and diaphyseal lesions are typical of Ewing family tumor, fibrous dysplasia, or enchondromas.

### Laboratory Evaluation

The main blood parameters of importance are lactate dehydrogenase and alkaline phosphatase.[36–38] Lactate dehydrogenase levels have been used as a surrogate for tumor load and have been correlated with survival in the case of Ewing family tumor.[36] Serum alkaline phosphatase elevation is characteristic of osteogenic sarcoma and is correlated with poor survival in this condition.[37,38] Glucose intolerance is associated with chondrosarcoma of the bone.[39,40] Erythrocyte sedimentation rates, C-reactive protein, and white blood cell and differential counts should be sought to rule out infection.

### Preoperative Planning

Magnetic resonance imaging (MRI) of the lesion offers an assessment of compartmentalization of the tumor. A compartment is an abstract concept and refers to any plane that offers a fascial or cortical bone barrier to contiguous spread. It has implications for the extent of surgery, which by definition must be outside the compartment to be radical (see later).[41] Also, by forming a baseline assessment, one is able to make an assessment of response to chemotherapy in the case of neoadjuvant treatment.[42] It has secondary importance in providing the actual diagnosis. In specific examples it is useful in histologic diagnosis. The aneurysmal bone cyst shows fluid-fluid levels on an MR image. Pigmented villonodular synovitis is hypointense (dark) on T1- and T2-weighted imaging because of hemosiderin deposition. Cartilaginous lesions are hyperintense (light) on T2-weighted imaging. Mineralized and dense fibrous tissues are dark on T1- and T2-weighted imaging.[43,44]

### Staging

Staging studies are meant to assess the degree of spread of the disease. In the case of bone tumors two systems are used: the Enneking system or surgical staging system (SSS),[45] as adopted by the Musculoskeletal Tumor Society and the American Joint Committee on Cancer (AJCC) system, which at the time of writing is in its sixth revision.[46] In the case of Ewing family tumor, a different classification than Enneking is used.[47]

In the SSS, tumors are designated G0, G1, and G2 for benign, low-grade, and high-grade lesions, respectively. Benign lesions (G0) are classified as latent, active, or aggressive—designated by Arabic numerals 1, 2, and 3, respectively. Malignant lesions are designated with the Roman numeral I if low grade and II if high grade. The further designation A or B denotes intracompartmental or extracompartmental disease. Stage III disease is metastatic disease. Therefore in this classification, grade, compartmentalization, and metastases are the fundamental prognostic factors.

In the AJCC system, I and II similarly designate low- and high-grade lesions. The letters A and B designate tumors smaller or larger than 8 cm, respectively. The Roman numeral III denotes multicentric disease, and IV denotes metastatic disease. The designation IVA denotes pulmonary metastases, and IVB denotes extrapulmonary metastases. Therefore this classification considers grade, size, multicentricity, and metastases as prognostic factors.

In the Enneking staging system of Ewing family tumor, stage I tumors are solitary intraosseous lesions, stage II are solitary lesions with extraosseous extension, stage III are multicentric lesions, and stage IV are metastatic. It is unclear how to stage patients who have independent sites of bone marrow involvement versus those who have circulating tumor cells identified by light microscopy (i.e., Enneking stage III or IV). Modern pathology analysis extends these concepts to include immunohistochemistry or reverse transcriptase polymerase chain reaction (RT-PCR) of recombinant gene products.

The modalities used for staging are bone scans and computed tomography (CT) of the chest.[45] Positron emission tomography scans are presently being evaluated, but have fundamental utility in the management of recurrent or metastatic disease.[48] In the case of Ewing family tumor, bone marrow biopsies are obtained to try capturing cases that are multicentric at presentation. The utility of this approach is being evaluated.[49]

## BIOPSY

The biopsy is a critical procedure that can complicate management severely if not performed appropriately. Misplaced incisions continue to be an important cause of resectable tumors being rendered nonamenable to limb salvage surgery.[41,50] A good pathologist who is comfortable handling bony tissue is critical to this process. In the appropriate case, extra tissue may be needed for cytogenetic studies. Ewing family tumors are particularly fragile, and biopsy specimens should be handled carefully to allow for processing.

### Presurgical Considerations

As a general rule, all imaging and staging should be completed before biopsy. The lesion that warrants biopsy should be given consideration for a primary wide excision. This approach is typically applicable to small lesions that are less than 3 cm, lesions in expendable bones (e.g., distal phalanx), distal lesions of the ulna, and proximal lesions of the fibula, where there is a risk of common peroneal nerve contamination (Fig. 43-5).

The lesion should preferably be sampled in the institution where the definitive procedure will be performed and by the same surgeon. It has been shown repeatedly, that when this approach is not used, the results are compromised.[50,51]

Consideration should be given to needle biopsies in the case of lesions in the pelvis or the spine, where the exposure necessary for an open biopsy may be extensive and obliges commitment to a definitive procedure.

A pathologist familiar with processing bone tissue should be on hand to evaluate the biopsy. If tumor tissue can be cut with a knife, then it can be cut with a microtome. Frozen-section analysis is required primarily to ascertain the adequacy and representativeness of the specimen and secondarily for the definitive diagnosis.

Antibiotics should be withheld before the biopsy to improve the yield of cultures. The biopsy may be done with use of a tourniquet, to prevent bleeding and dissemination of the tumor locally. When the tourniquet is applied, simple elevation should be used for exsanguination. Compressive exsanguination should be avoided, because this could rupture the tumor. At all times, the limb should be protected from fracturing, because this would cause extensive local dissemination of disease.

### Surgical Considerations

The planned incision for the definitive surgery should be marked. This should generally follow extensile exposures and be longitudinal along the line of the definitive incision. The incision should be placed directly over the lesion. Flaps and dissection should be avoided.

The incision is developed directly into the tumor. If there is a soft tissue component of the tumor, then this alone needs be sampled. If a bone biopsy is necessary, then the edges of the biopsy specimen should be rounded to minimize a stress riser. Frozen-section analysis will confirm the adequacy of the biopsy. In the meantime, a culture is taken, the tourniquet is released, and antibiotics are given. Absolute hemostasis is needed at the conclusion of the procedure to minimize spread of tumor cells in the hematoma.

The wound is closed in layers. If a drain is necessary, this should be brought out in the line of the incision so that it can be excised at the time of definitive surgery.

### Postsurgical Considerations

The patient should be limited to protected weight bearing, at least until some healing of the biopsy or ossification of the tumor as a response to neoadjuvant chemotherapy occurs. This typically takes up to 6 weeks.

Fractures through osteogenic sarcomas have traditionally precluded limb salvage surgery. Recent studies have shown that limb salvage may still be possible in selected cases.[52–55] Special surgical consideration is needed in these cases.


**FIGURE 43-5** **A** and **B,** An aneurysmal bone cyst of the right proximal fibula in a 17-year-old boy. **C,** In this instance, a primary wide resection was done, because the bone was expendable and it prevented contamination of the common peroneal nerve (*arrow*).

## ADJUVANT THERAPY

This section concentrates on the use of radiation and chemotherapy. In general, these modalities are not used in the treatment of benign conditions. Up to 10% risk of malignant transformation occurs when benign lesions are irradiated.[3–6]

Both chemotherapy and radiation therapy can be used in the neoadjuvant (preoperative) or adjuvant (postoperative) setting in the treatment of malignant conditions. The neoadjuvant approach has the advantage of "shrinking" the tumor and provides a more discernible margin, theoretically improving local control of the disease. In the case of chemotherapy, before the era of modular prostheses, the neoadjuvant route was necessary while the custom prostheses were manufactured. This technique has been shown to be as efficacious as primary surgery. Even so, the one randomized trial of preoperative and postoperative chemotherapy versus only postoperative chemotherapy failed to show any difference in survival. Therefore in selected cases, it is reasonable and may be prudent to perform surgery first.[56]

## SURGERY

In bone tumors, resection and reconstruction are two aspects of management that have largely complementary but occasionally conflicting goals (e.g., cryotherapy is good for extending the margins of resection of a tumor but results in weakening of the bone). Therefore, while the goals of resection are generally quite clear (i.e., cure), the goals of reconstruction are often compromised, especially in malignant conditions. In benign conditions, reconstruction usually restores more function. In this section, we present a general list of considerations that will be elaborated further in the section on specific considerations.

### Minimally Invasive Options

The minimally invasive option is reserved for benign conditions. It is born of two management philosophies—the desire to effect local control and the hesitation to cause more morbidity than the primary lesion. Whichever modality is chosen, it is imperative that a histologic diagnosis be obtained a priori.

***Radiofrequency Ablation*** Radiofrequency ablation uses high-intensity heat in proximity to a lesion, to effect thermal necrosis. It has wide utility in the ablation of various solid tumors. In bone tumors, it has been used principally in the ablation of osteoid osteomas. This condition is a painful one, marked by increased night pain and is promptly relieved by the use of NSAIDs. Otherwise, it is relatively benign. It can be found most commonly in the proximal femur. In these locations, surgical ablation in the form of a resection can incur high morbidity. Hence, an option such as radiofrequency ablation is ideal, although it incurs a 10% to 15% recurrence rate[57,58] compared with surgery, which has a near 0% recurrence rate.[59] It has limited utility in the spine because of the indiscriminate high heat generated.

***Injection*** This technique is principally used in the treatment of unicameral bone cysts. Clinically apparent bone cysts have a tendency to recurrent fracture and need to be treated.[10] However, they have no malignant potential and have been known to regress.[4,10] There is controversy about whether corticosteroid injection is a necessary element of treatment; it has been shown that simple decompression of a cyst is sufficient to induce a regression.[60] Rates of cure up to 50% are reported, with a median injection rate of three and a range of one to nine injections.[61,62] Each of these sessions requires the child to be under anesthesia. Therefore it has not been widely embraced.

As alluded to earlier, various forms of decompression have been advocated in the literature with varying success. One approach involves the injection of bone marrow.[63–67] Rates of cure of up to 50% to 70% may be achieved. However, with this technique, repeated injections may be necessary, incurring multiple episodes of anesthesia and donor-site morbidity.

Curettage, widely regarded to be the gold standard treatment, has a recurrence rate of 5% to 50%.[10] Thus there is no clearly superior modality in the treatment of this condition.

### Resection

Surgical decisions are based on the concept of compartments in relation to a tumor (Fig. 43-6). The compartment is bound by a barrier, which naturally limits the expansion of a tumor. When first described, it was useful in teaching the principles of wide resection or a resection with a margin of healthy tissue: If a resection was performed outside a compartment, it resulted in a margin that was free of malignant involvement.[45] This idea was useful in drawing parallels to conventional cancer surgery of that time. We realize now that this theory is flawed at many levels. For example, most osteogenic sarcomas present with tumors that have breached the cortex, and so, their distinction from a "contained" osteogenic sarcoma is moot. In the lower limb, a tumor that has involved the rectus femoris has involved a compartment extending from the anterior inferior iliac spine of the pelvis to the tibial tubercle. Clearly, it would not be practical, in this setting, to perform a hindquarter amputation. Finally, especially in the region of the linea aspera, there are numerous perforating vessels, which penetrate the lateral intermuscular septum; clearly these do not form a continuous barrier to tumor spread.

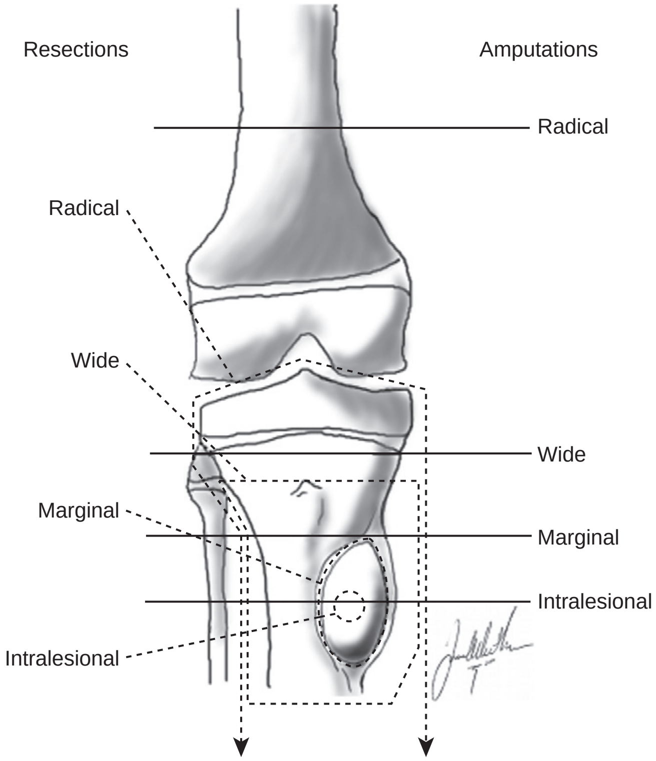


**FIGURE 43-6** Surgical margins in relation to the compartments involved. At left are the resections, and at right are the amputations. These classifications are largely academic, because in the strictest terms, most of the resections, except radical resections and only wide or radical amputations, are performed. Radical resections involve the compartment bearing the tumor, and hence, in this case, would amount to removing the tibia (*arrows*). Marginal amputations may be used in the spine and pelvis, whereupon local adjuvants assume significant roles in disease control (see Fig. 43-7). Intralesional amputations are obviously not therapeutic applications in tumor surgery but are included here for completeness. Of interest, intercalary amputations in the pediatric population can be problematic, when the remnant stump elongates through appositional growth. To avoid this complication, it may be necessary to use a through-joint (e.g., through-knee) amputation.

Still, the concept of compartmentalization is useful when one describes the surgical procedures as intralesional, marginal, wide, and radical.[41] Although not often used in the context of amputations, the concept of compartmentalization applies here as well. Intralesional procedures, as the name implies, are procedures that leave macroscopic residual tissue. A biopsy or injection of a lesion is an intralesional procedure. A marginal procedure stops at the level of the extent of maximal expansion of a tumor. Curettage is a marginal procedure. A wide procedure goes beyond the reactive zone of the tumor. When first described, the "reactive zone" referred to the zone of reaction around the tumor, marked by inflammatory change (i.e., hyperemia and edema).[41,47] This assessment was made predominantly at the time of surgery. With the advent of more sophisticated imaging modalities, it can now be demonstrated that this "zone" may extend further than previously appreciated. Therefore it appears that the description of a reactive zone is rather more abstract than real. As a general rule, resecting a tumor beyond its capsule, where vessel tortuosity and

edema is seen, is a wide resection, and hence this appreciation, while strongly influenced by newer imaging, remains largely surgical. Most malignant tumors are resected widely. A radical resection is an excision of the compartment in which a tumor resides. An above-knee amputation for a tibial lesion is a radical resection.

There are a number of surgical adjuvants that may be used. This can be in the form of heat (e.g., argon beam coagulator) or cold (e.g., liquid nitrogen cryotherapy).[68,69] In addition, chemical measures may be used (e.g., phenol, polymethylmethacrylate cement).[70,71] In the occasional case, specialized forms of radiation (e.g., brachytherapy, intraoperative radiation therapy) may be used, especially in the pelvis (Fig. 43-7). The purpose of these surgical adjuvants is to extend the margins of resection beyond what can be mechanically removed by the surgeon. These improve local control of the tumor.

***Benign Lesions*** It is useful at this juncture to recall the staging system for benign lesions. These are classified as benign, active, and aggressive. It is evident in these entities that, even within this group, specific nuances of the condition warrant special considerations. In benign bony conditions, the procedures available are curettage, high-speed burring of lesion walls, adjuvant procedures, and wide resection.[68,70] It is helpful to describe these procedures from most to least aggressive.

In benign conditions, wide resection may occasionally be used, when the involved bone is expendable (e.g., rib or terminal phalanx of the little toe) or at the end of a bone (e.g., distal ulna or proximal fibula). In these situations, reconstruction provides little value and can, in fact, be the source of considerable morbidity. Additionally, it may be used in the context of a recalcitrant recurrent benign or aggressive lesion. Typical lesions that are resected in this manner are giant cell tumors, aneurysmal bone cysts, or fibrous dysplasia.

Marginal excision is typified conceptually by the technique used to excise a soft tissue lipoma. Such a procedure is not technically feasible in most bony lesions. Osteochondromas and periosteal chondromas may be removed in such a fashion.

Intralesional procedures are more commonly performed in benign tumors. This typically involves curettage of a lesion with high-speed burring of the wall. In general, this is the typical procedure for most latent or active benign bony conditions (e.g., unicameral bone cyst). The use of heat, cold (Fig. 43-8), or chemical modalities serves to extend this margin of clearance further and is typically used in active or aggressive tumors (e.g., giant cell tumor, chondroblastoma).

### Malignant Lesions

The sine qua non of the resection of a malignant bone lesion is that, at minimum, a wide resection must be performed. In certain situations, however, this may not be possible (e.g., a tumor that has expanded into the spinal canal or a tumor that has invaded the pelvic cavity). In these instances, the outcome tends to be suboptimal.

With newer imaging modalities, it is now often possible to perform a physeal-sparing procedure in growing children (Fig. 43-9). Although the physis was thought to be an effective barrier to tumor spread, it has been shown that up to 80% of tumors abutting the physis have, in fact, breached it.[72–75] Physeal-sparing procedures must therefore be carefully balanced with the response to chemotherapy, to determine if this is feasible.

Occasionally, a variation on this theme is to save the epiphysis, and hence the neighboring joint, by performing a distraction procedure through the growth plate. This effectively increases the margin of normal tissue proximal to a tumor. A resection may then be performed through this now-lengthened segment.[76]

Another approach to retaining a joint would be to perform a Van Nes rotationplasty (Fig. 43-10).[77] This procedure, generally undertaken for high-grade tumors near or involving the knee, involves wide extraarticular resections, whereupon the distal leg and foot are joined to the remaining proximal femur. In the process, the sciatic nerve is retained, and a segmental resection of the femoral artery with a true femoral-popliteal arterial anastomosis is performed. The foot is rotated with

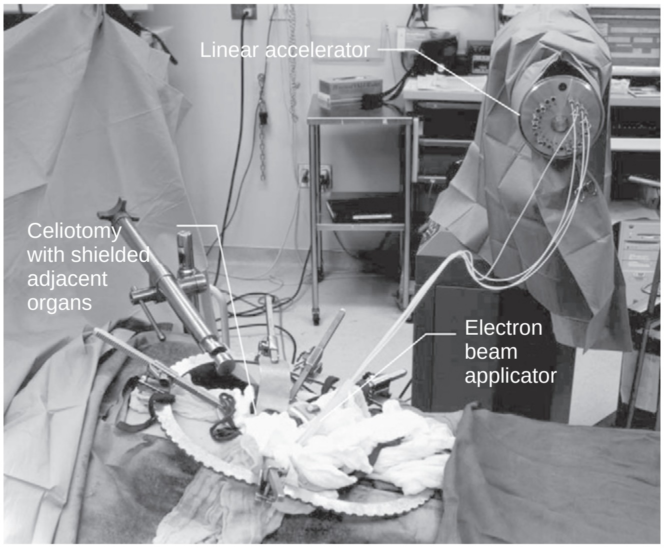


**FIGURE 43-7** Intraoperative radiation therapy in a 19-month-old girl who underwent a wide resection with nodal clearance for a rhabdomyosarcoma of the pelvis.

**FIGURE 43-8** Cryosurgery in a patient with chondrosarcoma. Liquid nitrogen is poured into a funnel that directs the agent into the lesion, while avoiding contact with the surrounding skin. The effect of freezing extends the margins of necrosis beyond that which can be felt by the surgeon, effectively extending the surgical margins from an intralesional or marginal excision to a wide resection.

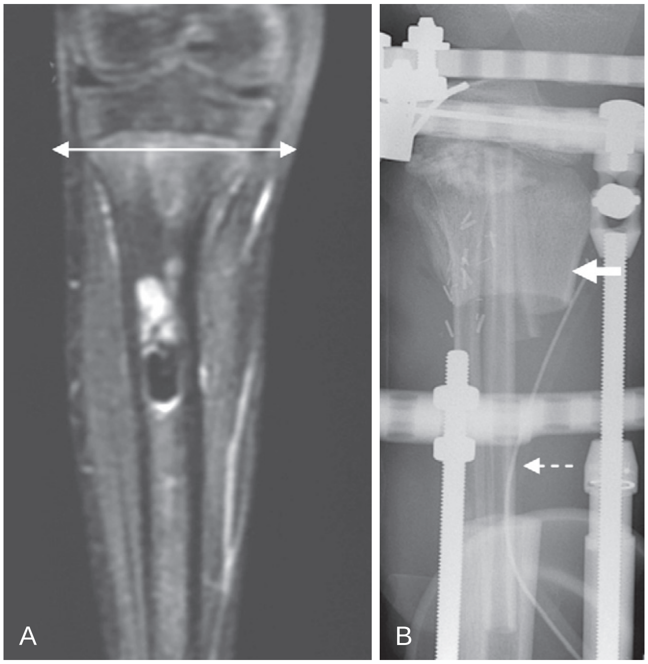


**FIGURE 43-9** **A,** Ewing sarcoma of the tibia in an 11-year-old boy. The lesion extended to 1 cm from the growth plate. It responded well to chemotherapy, with virtually no remaining soft tissue involvement. A physeal-sparing resection was done along a resection plane (*double-headed arrow*), carefully performed under image intensifier guidance. **B,** The use of a pin fixator, in this regard, is extremely advantageous, because it allows stabilization of the small proximal tibial segment that precludes routine pin fixation. The remaining gap was reconstructed with a proximal tibial allograft (*thick arrow*) and vascularized fibular graft (*broken arrow*) harvested with a paddle of skin, which provided skin cover of the construct.

the heel pointing anteriorly. Of practical interest, the distal segment is rotated externally, bringing the sciatic nerve and vessels anteromedial. This should be documented in the surgical note to facilitate further surgical procedures that may be necessary. The ankle, therefore, functions as a knee joint. This procedure has poor acceptance among patients because of their cosmetic abhorrence, but it is highly functional and durable.[78] A similar Winkelmann procedure may be performed, where the proximal tibia is brought to the hip. In children, it is remarkable to note the plasticity and remodeling of these disparate bones, which in time will accommodate each other in a stable fashion.[79,80]

Radical procedures and amputations have received poor support, because they are regarded as being disfiguring. Studies have shown that patients with limb salvage procedures do better in terms of function and cost savings.[81,82] Although this appears true at face value, in-depth analysis shows that these studies are too heterogeneous to allow any firm conclusions. With the aid of modern prostheses, patients with amputations are able to achieve very high levels of activity. Furthermore, complications are 3 to 4 times higher in limb salvage compared with limb ablative surgery. Although most series have not shown a significant survival benefit comparing amputation and limb-sparing surgery, these studies are underpowered or include cases of amputation being used as salvage procedures.[56,83,84] The primary remaining question is whether there is any survival and functional benefit in two-site and stage-controlled groups with respect to amputation or wide resection. This would require a case-controlled study with amputation and wide resection arms, and it is a safe assumption that this will never be performed.

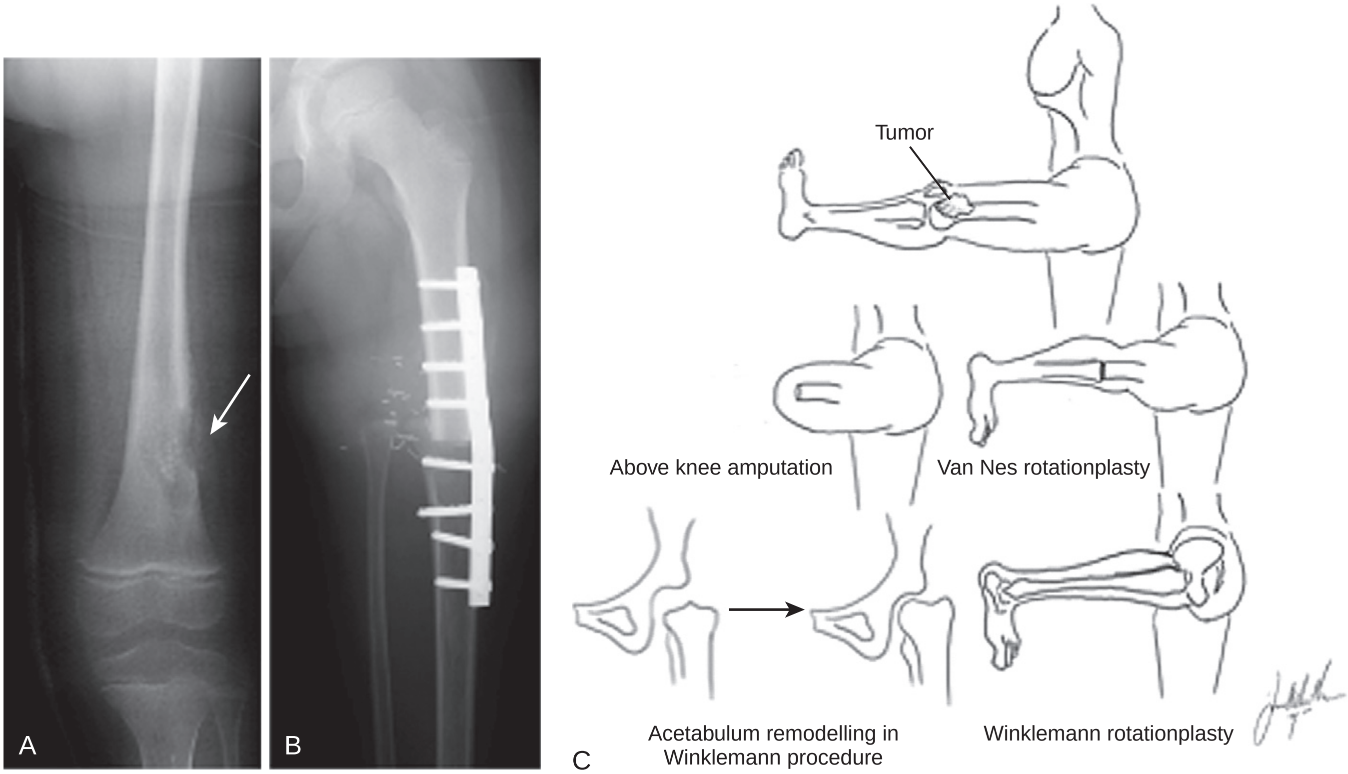


**FIGURE 43-10** **A,** Osteogenic sarcoma (*arrow*) with large soft tissue extension in an 8-year-old child. The small size of the child and high level of activity precluded endoprosthetic reconstruction. **B,** A Van Nes rotationplasty was performed. **C,** Variants of the rotationplasty are compared with the above-knee amputation. The bottom panel illustrates how the proximal tibia remodels and accommodates the acetabulum in the Winkelmann procedure.

There is still a role for amputations, especially when the tumor is in the distal extremity, adjuvant therapies are ineffective, or reconstruction is too problematic because of nerve, vessel, or soft tissue problems.

Local recurrence in malignant lesions is a poor prognostic factor and is associated with a 90% mortality rate. It is generally a reflection of compromised local control, although in one study good chemotherapy response was associated with a low local recurrence rate.[83] Specifically, in this series, when intralesional procedures had been performed for osteogenic sarcoma, standard responders were 3 times as likely to get a local recurrence as good responders. However, even among good responders, local recurrence was 14 times more likely if an intralesional procedure had been done rather than a wide resection. This underscores the need both for good surgical margins and effective chemotherapy.

## Reconstruction

In most instances, after the resection of benign lesions, small defects result. These are easily dealt with through the use of various gap fillers. With malignant lesions, large creative solutions are needed. It becomes difficult to determine which lesions are best treated by which technique because of the relative paucity of cases and the high-risk nature of these procedures. In this section, we will highlight the various modalities available and the pertinent qualifiers for each modality.

***Benign Lesions*** Following resection of benign lesions, a small defect usually remains. Thus the aim becomes reconstitution of bone. The modalities that have been used are bone graft and bone graft substitutes. In general, autografts tend to have better rates of incorporation but incur the risk of donor-site morbidity—or worse, donor-site tumor implantation. Allografts have a low risk of disease transmission and immunologic response.[85,86] Synthetic grafts tend not to incorporate as well as allografts or autografts.[87,88]

In the more aggressive lesions, the risk of recurrence increases. In these situations, bone substitutes could be resorbed by the disease process and would increase the delay before subsequent radiologic imaging is able to distinguish between postoperative change and recurrence. In this setting, bone cement becomes a good alternative.[69,71] Furthermore, radiopaque cement acts as a contrast agent. Recurrence at the margin of the cemented defect can be identified readily and treated.

***Malignant Lesions*** The solutions that have been used to solve the complex bone, joint, and soft tissue defects left after tumor resections form a veritable cornucopia of techniques, spanning all of orthopedic and plastic surgery. It is impossible to reiterate all these solutions here. Instead, we present a list of principal solutions pertinent to the specific reconstructive option.

The paramount requirement of all solutions is to provide a space filler and skin closure. Without meeting these two requirements, chemotherapy cannot resume, and the patient will not survive. Most solutions will provide space-filling ability if there is adequate skin for closure. If skin closure is not possible, a local flap or vascularized pedicular graft may be necessary. In some instances, especially with intercalary resections, the ability to provide intercalary stability with overlying skin closure can be provided by a vascularized fibular graft with a skin paddle. The skin paddle affords the additional advantage of monitoring the viability of the flap. Rotationplasties and their variants are remarkably functional solutions to the problem but have poor acceptance among patients because of their appearance. Similarly, amputations are often an instant solution to the problem, although, even here, the occasional exception exists.[82]

Joint reconstruction is a challenging endeavor. Biologic solutions include the use of bulk allograft (Fig. 43-11). They have the advantage of becoming incorporated by the body. The disadvantages[89] are a high fracture rate of 19%, a nonunion rate of 17%, and an infection rate of 11%. Osteoarticular allografts also become arthritic (16%) with time. Theoretically, however, with good incorporation of the allograft, a conventional, less-constrained joint replacement can be performed (Fig. 43-12). The endoprosthetic solution tends to be easier

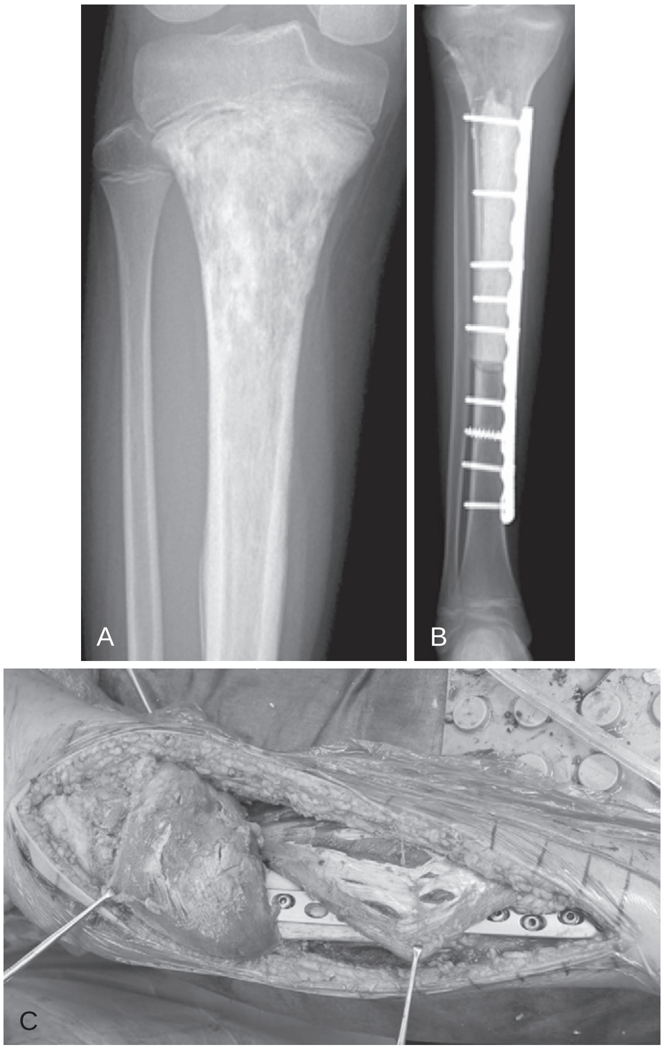


**FIGURE 43-11** **A,** Ewing sarcoma of the proximal tibia in an 11-year-old child. **B** and **C,** This was widely resected and reconstructed with an osteoarticular tibial allograft. A gastrocnemius flap was raised to provide soft tissue cover to the construct.

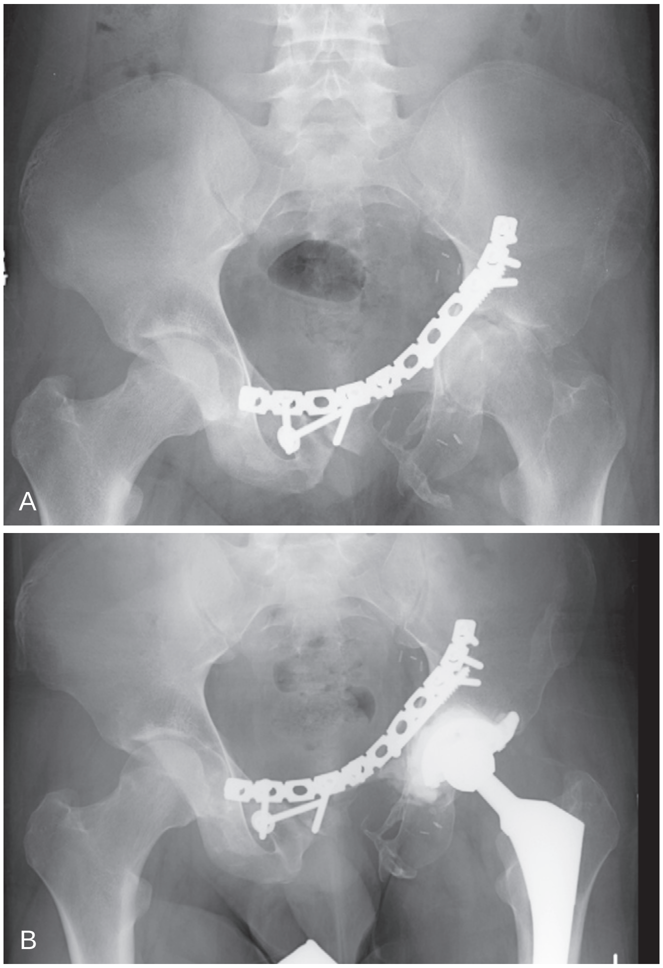

FIGURE 43-12 **A,** Resection and reconstruction of a Ewing sarcoma of the pelvis in a boy. **B,** Two years later, degenerative changes developed in the boy's hip, and he required hip replacement surgery.

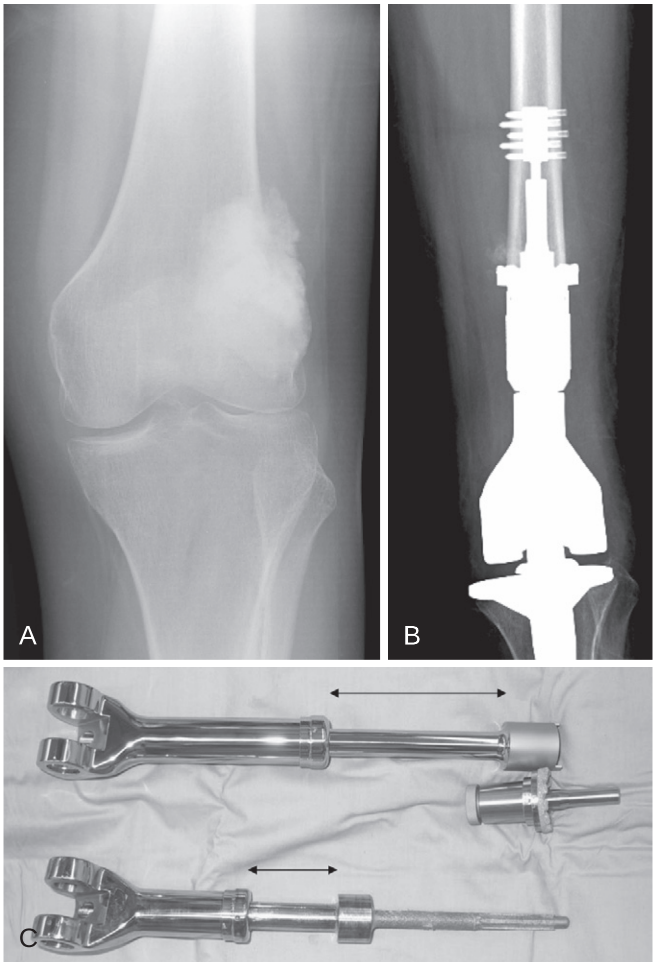

FIGURE 43-13 **A,** Osteogenic sarcoma in a 16-year-old girl. **B,** An endoprosthetic device was placed in the patient after resection of the lesion. **C,** As a child grows, it occasionally becomes necessary to swap implants with devices that can provide further extensibility.

but is less resilient, suffering from wear and loosening with time.[90–92] With advances in technology, better designs will lead to longer-lasting implants (Fig. 43-13). The allograft prosthetic composite is another approach that appears to capitalize on the lasting nature of allografts and their soft tissue capsular attachments and the simplicity of prosthetics (Fig. 43-14). In very young children, the available endoprostheses may be too large, and this may be a relative indication for the use of bulk allografts instead (see Fig. 43-1). Downsized pediatric implants are incapable of holding up in adults and are destined for failure and revision (Fig. 43-15). Prosthetic reconstruction has the distinct advantage of allowing immediate weight bearing, which is very important in patients who may have a reduced life expectancy. In truth, the various modalities are complementary rather than independent.

Growth is a complex issue in the management of patients with bone resection. In the year that patients receive chemotherapy, growth is often stunted. After this, however, the child resumes normal growth. There are various means to predict this growth.[93,94] As a rule of thumb, the distal femur grows 1 cm/year and the proximal tibia grows 7 mm/year. Girls generally stop growing at 14 years of age and boys at 16 years. Therefore a 10-year-old boy who has an extraarticular resection potentially would have 10 cm of growth to accommodate. In general, a 2-cm length discrepancy is considered compensable and does not require treatment. Thus, in this example, an additional 8-cm correction is needed.

The modalities available include contralateral epiphysiodeses. This method ablates the growth plate of the contralateral knee. The procedure needs to be timed accurately and tends to be practical only in the older child approaching the last few centimeters of growth.

Bone transport is another option. This yields good results, but the child must remain in the apparatus for long periods of time. At an elongation rate of 1 mm/day, the child with an 8-cm defect must remain in the apparatus, at minimum, for 3 months for the elongation and a further 3 months for consolidation of the regenerate (Fig. 43-16). This duration is commonly doubled when distraction osteogenesis is done during chemotherapy. Even in healthy individuals, the risk of pin-tract infection during the procedure is greater than

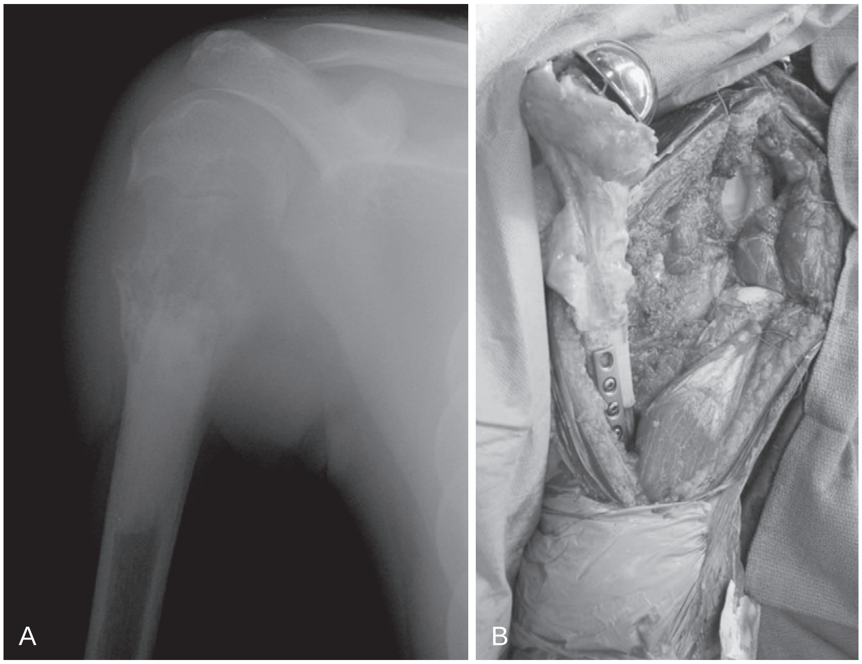


**FIGURE 43-14** **A,** Osteogenic sarcoma in proximal humerus of a 16-year-old boy. **B,** A proximal humeral resection with allograft and prosthetic composite was used to reconstruct the defect.

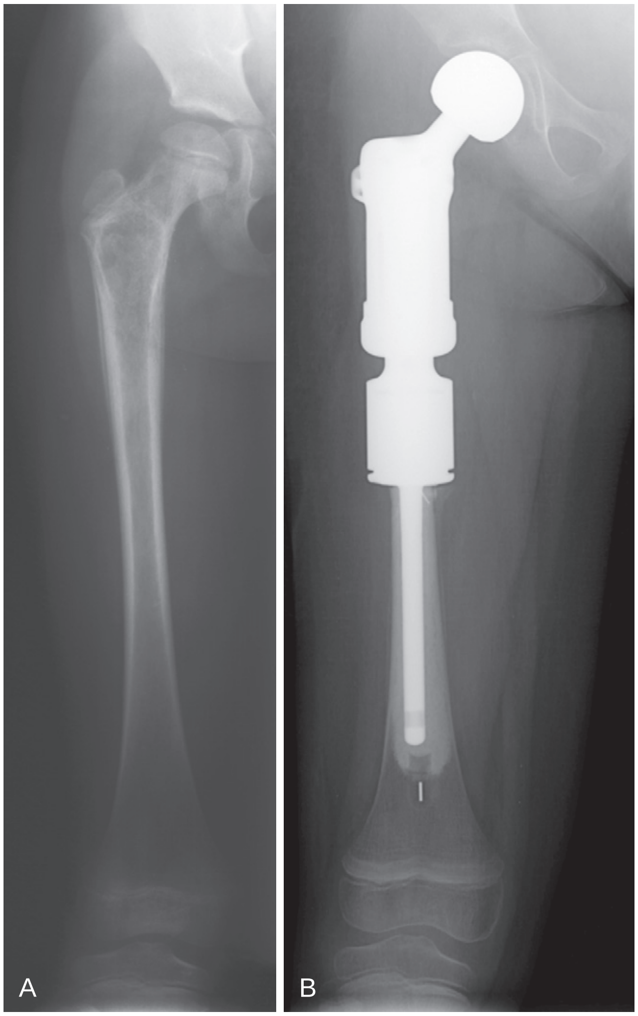


**FIGURE 43-15** **A,** Osteogenic sarcoma of the proximal femur in a 14-year-old girl. **B,** A wide resection and bipolar hemiarthroplasty with proximal femoral replacement was performed. Of note, the femoral head matched the acetabulum; so, an additional bipolar component was not added.

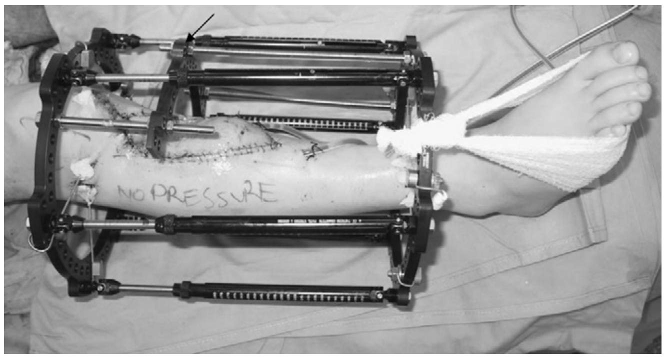


**FIGURE 43-16** Ewing sarcoma of the tibia. The patient underwent wide resection and a planned bone transport procedure. The middle ring (*arrow*) is secured to a segment of bone that has been osteotomized. This segment of bone is allowed 5 days for a provisional callus to form. By progressively advancing the ring distally at a rate of 1 mm/day, the segment of bone is transported to fill the defect, while at the same time remaining connected to the proximal tibia. This regenerate is weak and requires an equivalent amount of time to consolidate. For example, an 80-mm defect would require 5 days to form a provisional callus, 80 days to lengthen, and 80 days to consolidate before removal of the frame. This ungainly device needs to be tolerated by the patient for the duration of the limb-lengthening procedure.

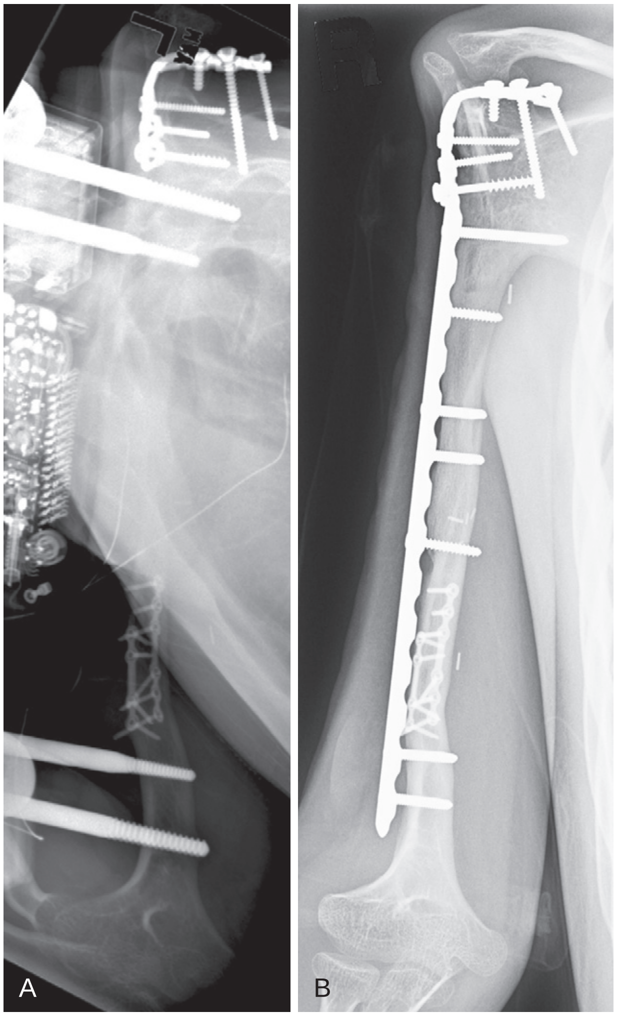


**FIGURE 43-17** **A,** A patient presented with osteogenic sarcoma of the proximal humerus that was resected and reconstructed with a vascularized fibular graft shoulder arthrodesis at 6 years of age. He developed a shortened humerus at maturity, which was lengthened. **B,** After lengthening, the regenerate was protected with a plate and hypertrophied with time.

90%.[95] In the patient with malignant disease who is to receive chemotherapy, this would be an important consideration.[96] In addition, the regenerate tends to be weak and is prone to fracture (Fig. 43-17). Patients on chemotherapy are prone to osteoporosis and are already at risk for fracture.

The extensible prosthesis is a marvel of modern science that is presently undergoing "teething" issues.[97–99] The manual expansion designs require repeated surgical procedures to periodically lengthen the limb to keep pace with normal growth (see Fig. 43-13, *C*). The Stanmore implants (Stanmore Implants Worldwide, Elstree, United Kingdom) have been used for nearly 20 years and have a 23% revision rate.[91] Survivorship analysis, however, shows a near-zero survivorship at 10 years.[100] Self-extending designs work through electromagnetic couplers or heating coils that allow motors or heat-release springs to extend the implant. The Phenix device (Phenix Medical, Paris, France) is presently undergoing evaluation in the United States.[101] Preliminary results show a complication rate of up to 44%, necessitating revision. The Repiphysis system (Wright Medical Technology, Inc., Arlington, TN) uses an external electromagnetic field to provide controlled released of a spring held in place by a locking mechanism. This device is associated with an implant revision rate of 44%.[102] In general, the stems in these devices are too narrow and mechanically insufficient, and fixation techniques remain inadequate. Thus all these designs have poor longevity but reduce immediate surgical complications (e.g., infection). They are well tolerated by patients and families.

There are many solutions to the problem of limb reconstruction in the skeletally immature child, but none is perfect. Therefore it is apparent that the surgeon dealing with potential limb length inequality after tumor resection and subsequent growth must be able to perform, or at least facilitate, the reconstructive procedures previously discussed. Any one of these procedures is applicable to an individual case, and they remain complementary to each other.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 44

# Brain Tumors

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With the exception of trauma, neoplasms are the most common cause of death in children less than 19 years of age. Tumors of the central nervous system are the most common solid neoplasms found in the pediatric population, accounting for 20% of cancer deaths, and are second only to leukemia in overall cancer frequency.[1,2] Approximately 4030 brain tumors are diagnosed each year in the United States, for an overall incidence of 4.71 cases per 100,000 person-years. Of these cases, it is estimated that 2880 will occur in children less than the age 15 years.[1,3]

The important factors in diagnosing brain tumors are location, age, and cell type. Location is probably the most important factor radiographically, followed by the age of the patient. The brain is divided into two compartments by the tentorium. Above the tentorium (supratentorial) are the cerebral hemispheres, basal ganglia, and the thalamus. Below the tentorium (infratentorial) are the pineal gland, the tectum, the pons, the medulla, and the cerebellum. Adult brain tumors tend to be supratentorial; however, pediatric tumors are evenly split between supratentorial and infratentorial. This division of location in the pediatric population is dependent on the age of the patient. In children younger than 2 years of age, the tumors are predominantly supratentorial, whereas children between the ages of 3 and 15 years more often have infratentorial tumors (Table 44-1).[1] The prognosis is usually poor in children with brain tumors younger than the age of 1 year, with choroid plexus papilloma being the main exception.[1,4]

The development of immunohistochemical staining techniques allows pediatric tumors to be classified by histology. Tumors can arise from any of the cell types of the central nervous system. The brain is composed of neurons and glial cells. Glial cells far outnumber the neurons, and provide a nourishing and supportive role. The three main types of glial cells are astrocytes, oligodendrocytes, and ependymal cells, and the neoplasms they give rise to are gliomas. More specifically, they form astrocytomas, oligodendrogliomas, and ependymomas, respectively. Tumors involving both neuronal and glial cells are called ganglion cell tumors and consist of gangliogliomas, desmoplastic infantile gangliogliomas, and gangliocytomas. Another mixed neuronal and glial tumor is a dysembryoplastic neuroepithelial tumor (DNET). Finally, there are embryonal tumors, which include medulloblastoma, primitive neuroectodermal tumors (PNETs), medulloepithelioma, neuroblastomas, melanotic neuroectodermal tumors in infancy, and atypical teratoid/ rhabdoid tumors (ATRTs).[4] Other primary brain tumors include germ cell tumors, choroid plexus tumors, craniopharyngiomas, and meningiomas.

## Clinical Features

The signs and symptoms of brain tumors in children vary considerably based on tumor type, location, and age of the patient. In the absence of a seizure or a focal neurologic deficit (e.g., diplopia caused by sixth nerve paresis), the vast majority of the symptoms are nonspecific and easily attributable to many more common and less serious causes. Common symptoms may include headache, nausea, vomiting, lethargy, subtle changes in personality, and worsening school performance. This constellation of symptoms can often be attributed to gastrointestinal problems, depression, school anxiety, migraines, sinusitis, or the need for prescription eyeglasses. Even a long-standing seizure disorder may ultimately be diagnosed as a supratentorial brain tumor. Infants typically present with failure to thrive, decreased intake, macrocephaly, or lethargy. Because of the nonspecific nature of these symptoms, it is common for a patient to present for neurologic evaluation after having visited numerous other specialists without establishing a diagnosis.

Most pediatric patients with brain tumors are between the ages of 2 and 14 years and typically present with a few days to weeks of headache, nausea/vomiting, gait ataxia, and/or diplopia. This constellation of symptoms is caused by hydrocephalus resulting from obstruction of the ventricles by tumor, commonly located in the midline posterior fossa. Headaches are common in children with viral infections, whereas frequent, daily morning headaches should raise the clinical suspicion of an intracranial mass lesion. This is especially true in the absence of a fever or other viral sequelae. Patients with elevated intracranial pressure often have an exacerbation of their symptoms in the morning. Both lying in the recumbent position overnight and sleep-induced hypoventilation (which leads to an increase in $Pco_2$) cause an increase in intracranial pressure. Elevated intracranial pressure can also cause the cerebellar tonsils to herniate into the foramen magnum and result in occipital headaches and neck pain.

There are two instances in which tumors cause nausea and vomiting. One is the elevation of intracranial pressure, and the other is direct irritation/infiltration of the vomiting center. The

**TABLE 44-1**
**Brain Tumors in Children**

| *Age* | *Tumor Histology* |
|---|---|
| 0 to 2 years | Teratoma |
| | Primitive neuroectodermal tumor |
| | Astrocytoma (high grade) |
| | Choroid plexus papilloma |
| 2 to 15 years | Supratentorial tumors (50%) |
| | Astrocytoma (low grade) |
| | Craniopharyngioma |
| | Hypothalamic glioma |
| | Primitive neuroectodermal tumor |
| | Ependymoma |
| | Choroid plexus papilloma |
| | Infratentorial (50%) |
| | Primitive neuroectodermal tumor: medulloblastoma |
| | Cerebellar astrocytoma |
| | Ependymoma |
| | Brainstem glioma |

vomiting center (area postrema) is located on the floor of the fourth ventricle and is vulnerable to compression from large posterior fossa tumors or from direct invasion of intrinsic brainstem tumors. Given that an intrinsic tumor in the medulla can cause vomiting in the absence of other neurologic symptoms, persistent vomiting should raise the possibility of a posterior fossa tumor, which could be confirmed through a detailed history and neurologic examination. Ataxia is commonly associated with tumors in the cerebellum and is often described by the parents as clumsiness, "walking like he is drunk," walking with the head tilted to one side, or falling to one side.

The visual complaints associated with posterior fossa tumors are frequently diplopia, difficulty looking up (sunsetting eye or Parinaud syndrome), and occasionally decreased visual acuity. As mentioned before, these symptoms are a result of the hydrocephalus. A decrease in visual acuity can result from papilledema. Loss of vision is a more common symptom of supratentorial tumors, because of optic nerve atrophy from direct compression. Patients with posterior fossa tumors are usually diagnosed with magnetic resonance imaging (MRI), because their other symptoms occur long before any visual defects. Therefore lack of visual signs and symptoms does not exclude a brain tumor. However, patients with poor access to health care can present with posterior fossa tumors and accompanying visual deficits.

Supratentorial tumors are especially common in patients younger than 2 years of age. These children often present with a failure to thrive, hemiparesis, seizures, or a full bulging anterior fontanelle and a rapid increase in head circumference.[5,6] At more than 2 years of age, supratentorial tumors present similarly in both children and adults, most commonly with headaches and/or seizures. When a patient presents with sudden onset of severe headaches or a rapid decline in mental status, it usually indicates a hemorrhage into their lesion. Rarely, obstructive hydrocephalus can cause such a rapid decline in mental status, but this is unlikely because of the slow growth rate of most tumors.

Less commonly, brain tumors can present with endocrine abnormalities. These can include weight gain or loss, diabetes insipidus, short stature, truncal obesity, galactorrhea, and precocious or delayed puberty. These symptoms result from tumors affecting the hypothalamic-pituitary axis. Because of the proximity of these tumors to the optic nerves and chiasm, they often cause decreased vision and visual field deficits.

# Radiographic Evaluation

Patients suspected of having a brain tumor should be evaluated with an MRI with and without gadolinium. Although MRI is the gold standard for evaluating tumors, many patients presenting in the emergency department with progressive clinical signs and symptoms of a brain tumor are evaluated with a head computed tomography (CT) without instillation of a contrast medium. CT is the ideal imaging modality to use during emergent situations for a number of reasons. CT is excellent in evaluating hydrocephalus and hemorrhage, the two main causes of rapid neurological decline. Furthermore, CT can be performed in minutes, frequently does not require sedation, gives excellent detail and information, and is considerably less expensive. If the patient's condition is rapidly deteriorating, a contrast agent–enhanced head CT is occasionally performed to better characterize the lesion for the radiologist and neurosurgeon when the patient requires emergent surgical intervention. If the patient's condition is stable, the contrast agent may be omitted, and MRI with and without gadolinium should be performed, the timing of which is dictated by the clinical signs and symptoms.

Magnetic resonance imaging provides much better resolution of the brain and provides images in the sagittal, axial, and coronal planes. Standard MR imaging combined with newer imaging sequences and spectroscopy can even point to a specific histologic diagnosis.[7] Furthermore, it is difficult to evaluate the lower brainstem with CT, because of the bony artifact from the skull base. One limitation of MRI is that it does not show intratumoral calcifications very well, and occasionally, patients require both studies to aid in establishing the proper diagnosis.

Magnetic resonance imaging with and without gadolinium can provide significantly more information about the patient's tumor. The blood–brain barrier is made up of tight junctions in the endothelial cells lining the capillaries in the brain, which prevent most blood contents from entering the brain, including gadolinium. However, certain brain tumors cause breakdown of the blood–brain barrier and permit the gadolinium to enter the tumor and then enhance the tissues (appear bright on T1-weighted images). In general, in the adult population, enhancement in an intra-axial lesion means a more aggressive brain tumor and a poorer prognosis. This is not as consistent in pediatric tumors. There are many enhancing pediatric brain tumors that are not aggressive and are curable with total resection.

When viewing an MRI, the important factors to consider are (1) the location of the tumor (e.g., supratentorial, infratentorial, pineal region, suprasellar), (2) whether the tumor is intra-axial (within the brain tissue) or extra-axial (outside the brain tissue), (3) the age of the patient, (4) whether the tumor enhances, and (5) if there are single or multiple lesions. By systematically assessing the scans and considering these factors, the differential diagnosis can be narrowed considerably, which can be extremely helpful in preoperative planning.

If there are multiple lesions in the brain, or the location and enhancement suggest a tumor type associated with leptomeningeal metastases or "drop mets" to the spine, then a spinal MRI with and without gadolinium is performed. It is preferable to obtain the spinal MRI preoperatively, but this is often dictated by the patient's clinical examination. Postoperatively, brain tumor patients should have an MRI within 36 to 48 hours to evaluate the extent of the resection and rule out hydrocephalus, bleeding, or ischemia. The timing is important, because after 36 to 48 hours, expected postoperative changes can enhance and make it difficult to distinguish scarring from residual tumor. If the patient did not get a preoperative MRI evaluation of the spine and the histologic diagnosis is consistent with tumors that can metastasize to the spine, then the study should be done 2 weeks after surgery, because postoperative debris and blood can be mistaken for metastatic disease

## Surgical Intervention

The goal of a surgical intervention for brain tumors is to safely debulk as much tumor as possible, to obtain a histologic diagnosis, to reestablish normal cerebrospinal fluid (CSF) pathways, or to divert CSF. The location of the tumor is often the determining factor as to how aggressively the tumor is debulked. In fact, some tumors, because of their location and their ability to be diagnosed with MRI, are not biopsied. For example, an intrinsic pontine glioma, which is an astrocytoma of the brainstem, cannot be debulked safely and has a characteristic appearance on MRI. Therefore these patients are referred to a neuro-oncologist for management without a tissue diagnosis. Pineal region tumors are another example of a lesion that may be diagnosed without surgical intervention. Patients with pineal region masses should have serum β-human chorionic gonadotropin (β-HCG) and alpha fetoprotein (AFP) levels obtained. If these are negative, then CSF markers are needed. If the serum or CSF markers are positive, then a diagnosis of a germ cell tumor can be made without the need for a biopsy.

However, most tumors require surgical intervention, consisting of either a stereotactic biopsy or an open craniotomy to obtain tissue for a definitive diagnosis. The most important tool for preoperative planning is MRI. Diffuse intrinsic tumors of the thalamus or basal ganglia typically undergo stereotactic biopsy. This procedure involves rigidly fixing an MRI-compatible frame to the patient's skull. The patient then has an MRI, and the *x, y,* and *z* coordinates are determined. These coordinates are then used to position the frame and the arc so that the tip of the needle is exactly where these three points intersect in the brain. Given the improvements in frameless stereotaxy, all but the smallest lesions can be biopsied without a rigid frame.[8] The advantages of a stereotactic biopsy include a short procedure time, the possibility of diagnosis in areas of the brain that carry an unacceptable morbidity and mortality with an open craniotomy, and the patient is discharged on postoperative day 1. The disadvantages are that only a small amount of tissue is obtained, which may be nondiagnostic or result in the wrong diagnosis, and if bleeding occurs it is difficult to treat, or it may not be recognized until the patient deteriorates neurologically after the procedure. Lastly, if the diagnosis cannot be made with a stereotactic biopsy or the diagnosis requires aggressive debulking, the patient will require a second operative procedure.

Because of the fact that the prognosis of many pediatric tumors is strongly influenced by the amount of postsurgical residual tumor,[9] the majority are approached with a craniotomy/craniectomy for open biopsy, with an attempt at maximal microsurgical tumor resection. Cerebral hemispheric tumors are approached through a craniotomy. Preoperative planning consists of an MRI coupled with a frameless stereotactic navigation study. The navigation study allows the neurosurgeon to view the tumor in the operating room in the sagittal, axial, and coronal planes and can be used to find the tumor and plan the incision and approach. However, the main limitation of this technology is that it is not a real-time study, and actions such as retracting the brain or draining cysts or CSF spaces may cause the brain to shift position, thus compromising the accuracy of the intraoperative navigation system. When this occurs, intraoperative ultrasonography is extremely helpful in localizing lesions.

Intraoperative MRI aims to correct the limitations of the navigation system by providing a real-time image. Previous intraoperative MRIs were limited because of poor resolution; however, newer intraoperative suites have 3-tesla magnets and provide excellent resolution. The drawbacks of the intraoperative MRI suites are that they are prohibitively expensive for many institutions, are helpful in only a small number of procedures, and significantly extend the time of the procedure. Nevertheless, this is exciting technology, and as the expense decreases and the efficiency improves, it will be an invaluable tool to surgeons operating upon brain tumors. Functional MRI (fMRI) techniques can localize speech and motor cortex. When tumors involve these areas of eloquent cortex, fMRI can aid in selecting the safest site to incise the cortex.[10] In the pediatric population, fMRI can prove challenging, because it requires a cooperative non-sedated patient. Electrophysiologic recording and stimulation are sometimes helpful in locating the motor strip. Recently, magnetoencephalography (MEG) is being used to help localize motor, sensory, and language cortex for both tumor surgery and epilepsy surgery.[11]

Such advances undoubtedly aid the neurosurgeon throughout the surgical procedure; however, there is still no substitute for an outstanding understanding of the three-dimensional anatomy of the brain. When choosing an approach, anatomic planes, such as the interhemispheric fissure, the sylvian fissure, and the cranial base are used, if possible, to avoid resecting normal brain. If there is no plane available, the approach is usually through the least amount of tissue, while avoiding areas of eloquent language, motor, and visual cortex.

Tumors of the midline (hypothalamus, thalamus, basal ganglia, and brainstem) were once considered inoperable. However, advances in microsurgical techniques and innovative instrumentation now make these tumors approachable. At the same time, advances in chemotherapy and single-dose and fractionated radiosurgery offer alternatives, and it is currently unclear which strategy or combination of strategies is best for a particular tumor. Advances in surgical techniques now allow for multiple options for the approach to tumors. For example, pineal region tumors may be approached through a posterior fossa route (retracting the cerebellum from the underside of the tentorium), by a supratentorial route between the hemispheres and through the posterior corpus

callosum, or through the tentorium itself. The relationship of the pineal tumor to the tentorium dictates the approach.

Tumors of the cerebellum and the lower brainstem are approached through a posterior fossa craniotomy or craniectomy.[12] Midline tumors of the fourth ventricle usually present with obstructive hydrocephalus. Some neurosurgeons prefer to place a shunt before tumor resection; however, most now favor giving the child corticosteroids and placing a ventriculostomy at the time of the craniectomy. The ventriculostomy is either removed or converted to a shunt if needed in the postoperative period. Between 20% and 40% of children will ultimately require a shunt.[13] Many neurosurgeons are performing an endoscopic third ventriculostomy (ETV) at the time of the resection. This procedure involves inserting an endoscope into the lateral ventricle, passing it through the foramen of Monro and making a small hole in the floor of the third ventricle. This allows the CSF to bypass the distal obstruction and enter directly into the cisternal system.[14] One series of patients with posterior fossa tumors showed a reduction in the postoperative shunt rate of 26.8% to 6% in patients treated with EVT and tumor removal versus tumor removal alone.[15]

To access the fourth ventricle, the patient is placed in the prone position, and the bone overlying the cerebellum is removed, occasionally including the posterior ring of the C1 vertebrae. After opening the dura, the cerebellar vermis is vertically incised, providing access to the tumor and the fourth ventricle. The tumor is removed with bipolar cautery, suction, or an ultrasonic aspirator. Laterally placed tumors of the cerebellopontine angle are reached by retracting the cerebellum medially. Electrophysiologic monitoring of cranial nerves V, VII, VIII, IX, X, XI, and XII is often required throughout this approach. Tumors of the brainstem may be debulked, if they are dorsally exophytic. The dura is closed and covered with DuraGen (Integra LifeSciences, Plainsboro, NJ), a collagen product that augments dura integrity. Replacement of the bone is not required, but we prefer to whenever possible. Postoperative problems include acute hydrocephalus, pseudomeningoceles, aseptic meningitis, mutism, pseudobulbar palsy,[16] cranial nerve or brainstem dysfunction, and gastrointestinal hemorrhage.[17] Patients with swallowing dysfunction and aspiration may require tracheostomy and feeding gastrostomy.

# Tumor Types

## CEREBELLAR ASTROCYTOMAS

These tumors are usually low-grade and curable with total surgical resection. The average age at presentation is 9 years, and the patient normally presents with pernicious vomiting, intermittent morning headaches, and disturbances of balance, usually spanning a period of months. The classical CT appearance of these tumors is a hypodense, cystic cerebellar mass (usually around the vermis) with a brilliantly enhancing "mural nodule."[18] However, about one fourth will be entirely solid tumors. MRI is helpful in defining the surgical anatomy, such as the relationship of the tumor to the brainstem, and the nature of the cyst wall. Cerebellar astrocytomas are typically of low signal intensity on T1-weighted MRI sequences, demonstrate increased intensity on T2-weighted sequences, and show enhancement of the solid component with gadolinium (Fig. 44-1). Because of their location and size, they cause effacement of the fourth ventricle, resulting in obstructive hydrocephalus.

Histologically, they consist of benign-appearing astrocytes.[19] Subtypes are the juvenile pilocytic form (80% to 85%) and the fibrillary form.[4] Detailed examination may reveal cellular pleomorphism and tumor extension to the subarachnoid space, but these tumors rarely disseminate. High-grade astrocytomas in this location are rare and usually follow radiation therapy given for a previous low-grade tumor.[20]

Treatment for cerebellar astrocytomas is complete surgical resection. In tumors with no brainstem involvement, this can be accomplished in a high percentage of cases. If complete surgical excision can be demonstrated radiographically, these tumors rarely recur, and no adjuvant therapy is indicated.[21] Therefore if there is residual tumor on the postoperative scan, reoperation for total excision is recommended. Radiation therapy can be considered for multiple recurrent lesions or in cases in which brainstem involvement precludes complete removal. However, even in these cases, residual tumor may remain indolent for years without additional therapy. Regular postoperative surveillance scanning is appropriate, especially when there is suspicion for residual tumor. Recurrence is treated with reoperation if this is feasible.

## PRIMITIVE NEUROECTODERMAL TUMOR AND MEDULLOBLASTOMA

Primitive neuroectodermal tumor and medulloblastoma are related tumors; and, in fact, the term medulloblastoma and posterior fossa PNET are often used interchangeably. Medulloblastoma is the most common malignant brain tumor of childhood. Histologically, the classical medulloblastoma is composed of densely packed cells with hyperchromatic nuclei and little cytoplasm, giving the histologic slides a blue color when stained with hematoxylin and eosin. Tumors with identical histology can occur in the cerebral hemispheres and are termed supratentorial PNETs. Children with medulloblastoma typically present with headache, vomiting, and lethargy of relatively short duration, and the mean age (3 to 4 years) is typically younger than that seen with cerebellar astrocytomas. Infants typically present with failure to thrive. Supratentorial PNETs present with increased intracranial pressure and focal neurologic deficits, depending on the location of the tumor.

On a CT scan, medulloblastomas typically appear as well-marginated homogeneously dense masses filling the fourth ventricle, causing obstructive hydrocephalus. They usually enhance brilliantly with contrast. However, unlike ependymomas, they lack calcifications. On MRI, they can show variable signal characteristics. The images are often slightly hypointense on T1 weighting, becoming brighter on fluid-attenuated inversion recovery (FLAIR) sequences, and may be bright or dark on T2-weighted studies. They usually enhance on MRI (Fig. 44-2) and show restricted diffusion on diffusion-weighted imaging (DWI). MRI of the spine is indicated 2 weeks postoperatively to evaluate for spinal metastases ("drop mets"; Fig. 44-3).[22]

Treatment begins with biopsy and surgical excision. Medulloblastoma and PNET tumors are not curable with surgery alone; and in cases with metastases at diagnosis or extensive brainstem involvement, the major mass should be debulked,

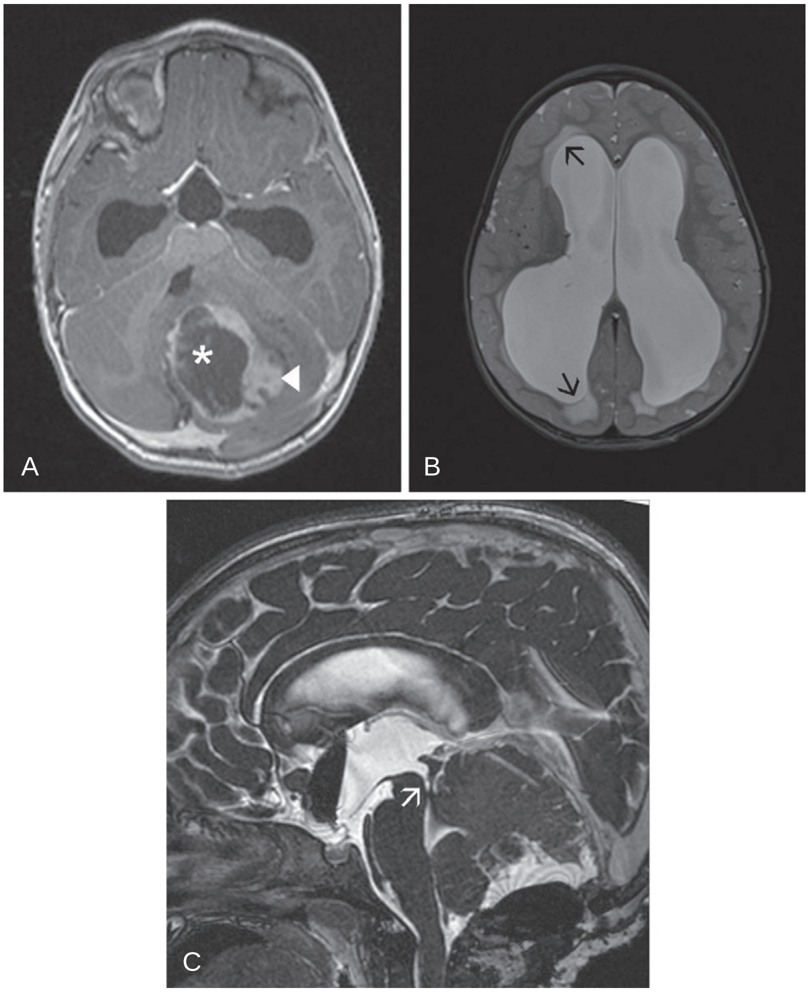


**FIGURE 44-1** **A,** Axial T1WI postgadolinium image of a cerebellar pilocytic astrocytoma, in a 3-year-old boy, showing a large cyst *(white asterisk)* and enhancing mural nodule *(white arrowhead)*. **B,** Axial T2WI image showing markedly dilated lateral ventricles and transependymal flow of cerebral spinal fluid (CSF) out of the ventricles into the surrounding brain parenchyma *(black arrows)*. The obstructive hydrocephalus is a result of the cerebellar astrocytoma. **C,** Sagittal T2WI postoperative image showing resection of tumor and flow through the floor of the third ventricle *(white arrow)* after the endoscopic third ventriculostomy done at the time of tumor resection.

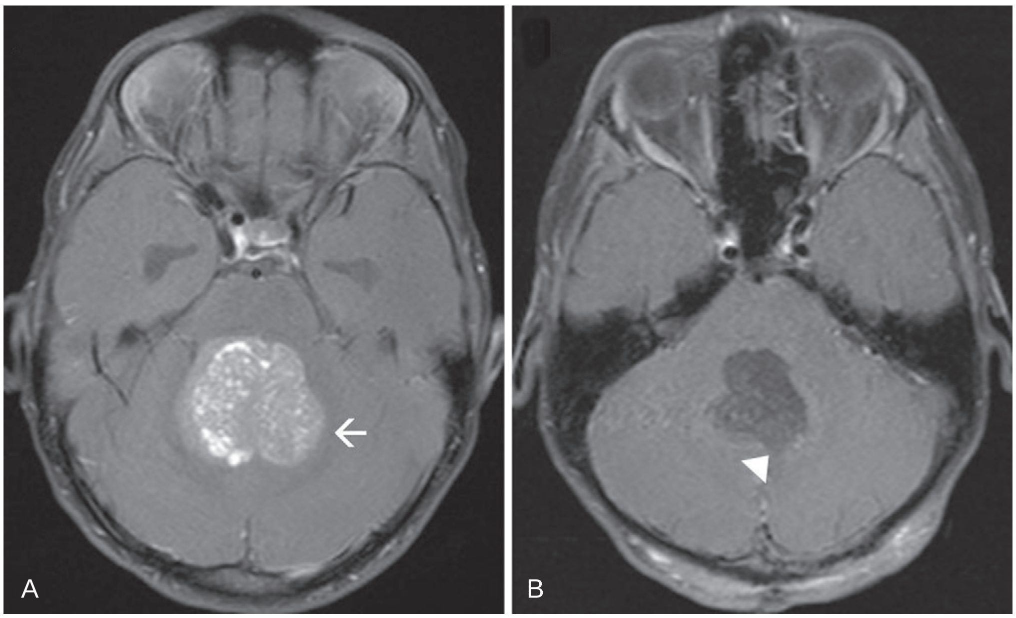


**FIGURE 44-2** **A,** Axial T1WI postgadolinium image, in an 8-year-old boy, showing an enhancing primitive neuroectodermal tumor (PNET) arising from the roof of the fourth ventricle and involving the cerebellar vermis *(white arrow)*. **B,** Axial T1WI postoperative image showing resection of tumor and partial splitting of the vermis *(white arrowhead)*. The patient suffered severe postoperative mutism.

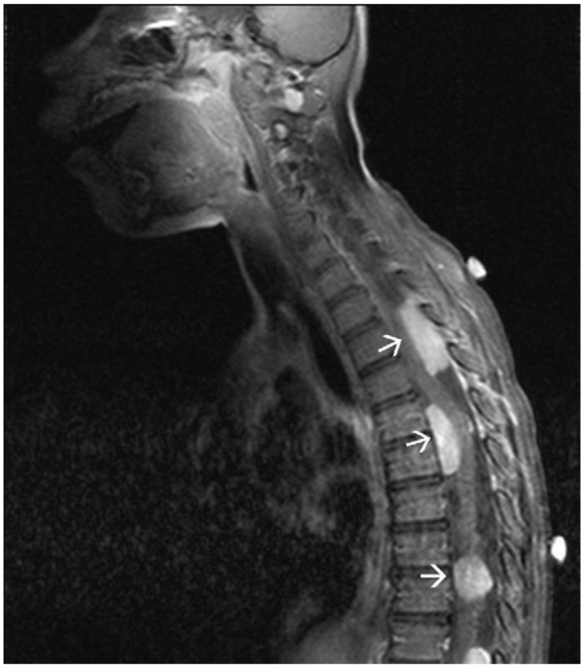

FIGURE 44-3 Sagittal T1WI postgadolinium image of a 4-year-old with metastatic primitive neuroectodermal tumor (PNET) to the spine *(white arrows)* from her fourth ventricular tumor. The "drop mets" were present at the time of her diagnosis.

but no attempt should be made to resect tumor in vital areas.[23] After the operation, radiation therapy is usually administered to the entire brain and spinal canal, with a boost to the tumor bed. Younger children (less than 9 years old) suffer significant, global cognitive problems as a result of whole-brain radiation in an age- and dose-dependent fashion.[24] They are chemotherapy sensitive, and various chemotherapy combinations have been used to improve outcomes and allow for a reduction in craniospinal radiation dose.[25–28] Chemotherapy alone has been shown to have some success in treating these tumors and can be used in the treatment of infants (for whom craniospinal radiation is contraindicated); however, the long-term survival of a chemotherapy-only approach is not as good as combined modality treatment.[29–32] In determining the best treatment, staging criteria are important to define risk groups. In the past, the Chang system was used, which incorporated the surgeon's estimate of the tumor size at operation and the extent of metastatic disease based on postoperative imaging.[33] In most centers today, patients are assigned to a high-risk group based on younger age (<3 years old), supratentorial tumor location, postoperative residual disease greater than a volume of 1.5 cubic centimeters, or presence of disseminated disease.[28,34] Molecular markers have been identified that have prognostic significance, but are not yet being used to dictate therapy.[35–39] The rate of progression-free survival at 5 years ranges from more than 80% in groups with standard-risk factors[40,41] to less than 70% in high-risk groups.[28,42–44] Infants treated with chemotherapy alone historically have progression-free survival rates in the range of 20% to 40%,[29–31] although recent studies suggest that intensification of therapy may improve survival rates.[32,45]

Patients require long-term supportive care, preferably in the setting of a multidisciplinary pediatric neuro-oncology clinic. Surveillance scanning is standard practice, and although rates of cure for recurrent tumors are low, high-dose chemotherapy and stem cell rescue can salvage some patients at relapse.[46,47] Late sequelae of therapy include pituitary dysfunction, hearing loss, growth delay, cardiomyopathy,[48] cognitive delay,[49] psychosocial adjustment and family problems, and radiation-induced meningiomas, astrocytomas, and sarcomas.[50]

## EPENDYMOMAS

Ependymomas occur in the region of the fourth ventricle or cerebellopontine angle, spinal cord, or supratentorial compartment. Most are histologically benign, but despite this, they have a tendency to recur in the local tumor bed and disseminate throughout the neuraxis. The median age at diagnosis is between 3 and 5 years, although tumors in infants and adults are not uncommon.[51] Tumors typically arise in the posterior fossa (60% of cases), and symptoms are similar to those of other tumors in this region. Cranial nerve and brainstem involvement can occur. Vomiting may arise without hydrocephalus, which suggests infiltration of the region of obex, which is characteristic of ependymomas. When the tumors do arise in the supratentorial compartment in children, they are often extremely large, and despite their presumed ependymal origin, may demonstrate no connection with the ventricle.

Computed tomography typically shows an isodense mass with flecks of calcification and an inhomogeneous pattern of enhancement. Posterior fossa lesions may extend through the foramina of Luschka into the cerebellopontine angle (Fig. 44-4). On MRI, ependymomas are usually isointense to hypointense on T1-weighted images, hyperintense on T2/FLAIR images, do NOT show restricted diffusion on DWI, and often enhance inhomogeneously with gadolinium.[52]

FIGURE 44-4 Axial T2WI image of a fourth ventricular ependymoma, in a 5-year-old boy, growing out of the foramen of Luschka into the cerebellopontine angle *(white arrows)*.

Treatment for ependymomas primarily consists of surgery and radiation. Prognosis is highly dependent on the extent of surgical resection as determined by postoperative imaging. The 5-year progression-free survival after complete resection is 60% to 80%, compared with less than 30% after incomplete resection.[53] However, radical surgical resection may result in permanent neurologic damage and may not be possible in some cases. Unless the tumor has disseminated at diagnosis, postoperative radiation is confined to the operative bed. Trials of radiosurgery for unresectable tumors are ongoing at several centers. Ependymomas are now being treated with proton beam therapy because of the decreased radiation exposure to the adjacent, normal uninvolved structures. Adjuvant chemotherapy has minimal impact on survival[54]; however, several chemotherapy agents have activity in this tumor,[30,55] and chemotherapy is being evaluated in a neoadjuvant setting to see whether giving chemotherapy after a subtotal resection may shrink the tumor in such a way that a complete resection can be achieved at a second surgery.

## BRAINSTEM GLIOMAS

It is now recognized that there are several types of brainstem gliomas, each associated with very different outcomes.[56] The most common variety is the diffuse intrinsic brainstem glioma, which is not amenable to surgical resection. These tumors are often centered in the pons and typically present with cranial neuropathies rather than hydrocephalus. Patients tend to be less than the age of 4 years, with sixth nerve palsies, facial weakness, and ataxia. The diagnosis is established by MRI, which shows a swollen pons with diffuse signal abnormalities (Fig. 44-5). Surgery is not indicated. Radiation therapy can provide symptomatic relief and prolong survival, but most children die within a year.[57] Chemotherapy has not been shown to be effective.

Cervicomedullary astrocytomas are considered to be rostral extensions of intrinsic spinal cord tumors and carry a better prognosis. Signs and symptoms may include vomiting, torticollis, and slowly evolving motor weakness. MRI shows an enlarged upper cervical spinal cord, with a rostral extension presenting in the cisterna magna. They are often amenable to aggressive surgical resection, and if the histology is benign, adjuvant radiation therapy is usually deferred.

Dorsally exophytic brainstem tumors arise from the floor of the fourth ventricle and present with symptoms of hydrocephalus. These tend to be pilocytic astrocytomas.[58] Treatment is primarily surgical. Gross total resection is difficult to achieve without unacceptable neurologic risk; however, most patients remain progression-free after resection because of the indolent nature of the tumor. Radiotherapy is reserved for recurrence or progression.[59]

Tectal gliomas are now recognized to be a not infrequent cause of hydrocephalus.[60] They typically present with symptoms referable to ventricular obstruction and are usually treated with either a ventriculoperitoneal shunt or endoscopic third ventriculostomy. Biopsy is not required. They are usually extremely indolent, and treatment of the tumor itself is required only if it progressively enlarges.

## HYPOTHALAMIC/CHIASMATIC ASTROCYTOMAS

Suprasellar astrocytomas are usually low-grade neoplasms, which may occur in association with neurofibromatosis type 1 or as isolated tumors. The etiology of these tumors is not well described, but the association with neurofibromatosis type 1, which is localized to chromosome 17q, suggests a molecular genetic basis. They may present primarily with vision abnormalities (visual field cuts, asymmetric loss of visual acuity in association with optic atrophy, or nystagmus) or as hypothalamic dysfunction (precocious puberty, diabetes insipidus, other endocrine dysfunction, growth failure, obesity, or diencephalic syndrome, which consists of failure to thrive and vomiting). Often both visual and hypothalamic complaints coexist.[61]

Imaging studies usually cannot distinguish hypothalamic tumors from those arising from the visual apparatus. The tumors typically do not calcify, which helps distinguish them from craniopharyngiomas, and appear as solid hypodense lesions on CT or T1-weighted MRI sequences and enhance

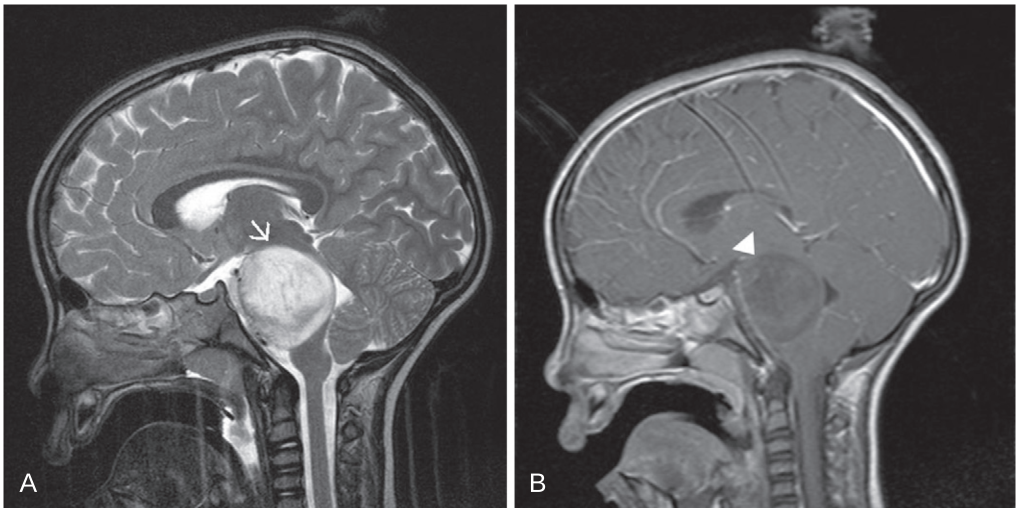


**FIGURE 44-5** **A,** Sagittal T2WI image in a 4-year-old girl showing an infiltrative, hyperintense tumor in the pons *(white arrow)*. **B,** Sagittal T1WI postgadolinium image showing that the tumor does not enhance *(white arrowhead)*. This tumor is an intrinsic pontine glioma, and the diagnosis is made by MRI alone, a biopsy is not required.

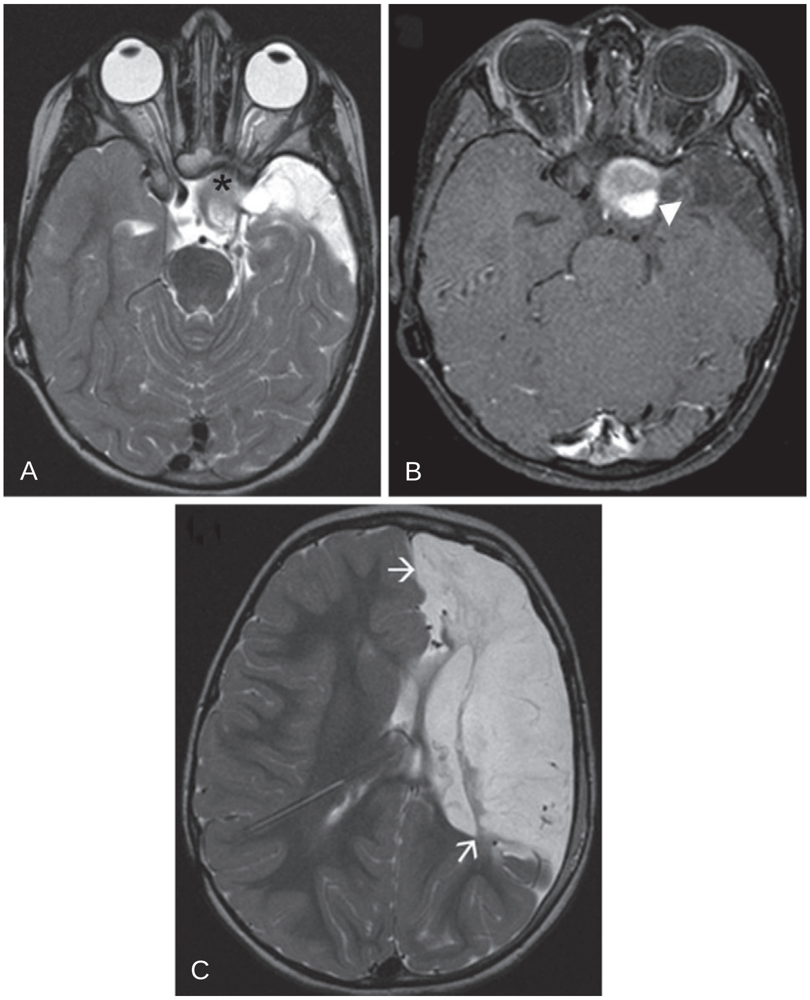


**FIGURE 44-6** **A,** Axial T2WI image in a 3-month-old girl who has a hyperintense lesion *(black asterisk)* in the left optic nerve and into the optic chiasm. **B,** Axial T1WI postgadolinium image showing an enhancing tumor *(white arrowhead)*. The tumor causes stretch on the internal carotid artery and middle cerebral artery, putting the patient at risk of a postoperative stroke when this chiasmatic/hypothalamic glioma is resected. **C,** Axial T2WI postoperative image showing a large left internal carotid stroke *(white arrows)* that occurred on postoperative day 4 and was a result of vasospasm in the stretched arteries.

after administering contrast. Extension to the intraorbital optic nerves or along the optic radiations is diagnostic and rules out craniopharyngiomas, germinomas, or other tumors in this location (Fig. 44-6).

Because most of these tumors will not progress significantly (especially in the setting of neurofibromatosis type 1), initial management is usually observation with serial imaging and ophthalmologic screening. Tumors that progress significantly and/or cause worsening vision are treated with chemotherapy. The most common regimen used is vincristine and carboplatin[62,63]; however, thioguanine, procarbazine, lomustine (CCNU), and vincristine (TPCV) are also effective.[64] Radiotherapy is avoided if possible because of the high risk of secondary effects, such as endocrine dysfunction, stroke, secondary malignant neoplasms, and neurocognitive deficits. Although radical surgical resection results in prolonged disease stability in the majority of patients, it carries a higher risk of stroke and injury to the optic pathways and the hypothalamic/pituitary axis.[65,66] Surgery is reserved for cases when the diagnosis is unclear, there is a unilateral optic nerve tumor with severe visual impairment or painful proptosis, and tumors are causing obstruction of the third ventricle or exerting mass effect on surrounding areas of the brain.

## CRANIOPHARYNGIOMA

Craniopharyngiomas are histologically benign masses believed to arise from embryonic rests derived from the hypophyseal-pharyngeal duct. Symptoms result from optic chiasm or nerve compression, hypopituitarism, hypothalamic dysfunction, or increased intracranial pressure in association with hydrocephalus.[67] They also occur in adults, but the childhood form represents a distinct entity characterized by large size and extensive calcification. There are two varieties of craniopharyngiomas, the papillary and adamantinomatous types, the latter being the most common in the pediatric population. Histologically, they typically are composed of a squamous epithelial cyst wall, with cystic fluid composed of cholesterol crystals, and calcifications. They tend to be inseparable from the pituitary stalk and may have an interdigitating gliotic interface with the hypothalamus above. This makes complete surgical removal challenging, because small rests of tumor may reside in the brain. This is also the reason for hypothalamic dysfunction that may be seen after surgical excision.[68]

Computed tomography can reveal either a cystic mass with basal calcifications or an entirely solid tumor. MRI shows

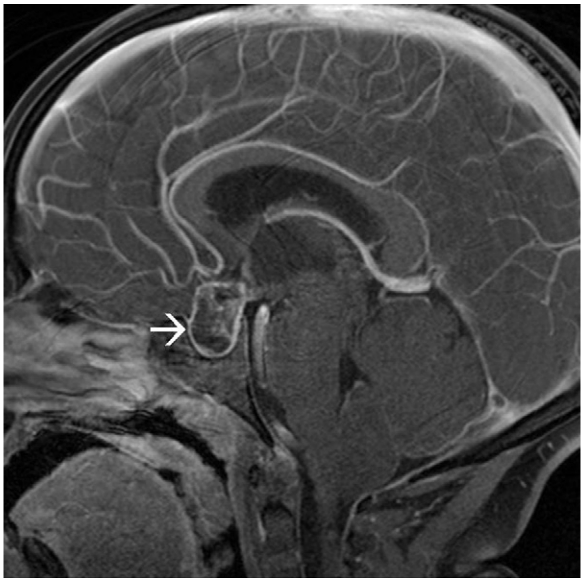

**FIGURE 44-7** Sagittal T1WI postgadolinium image, in a 6-year-old boy, showing a sellar/suprasellar craniopharyngioma growing down into the sella turcica and up into the third ventricle *(white arrow)*.

the sagittal anatomy well, but may miss the calcifications[69] (Fig. 44-7). In some instances, imaging cannot distinguish a craniopharyngioma from a hypothalamic glioma.

Controversy persists regarding the best treatment approach for patients with this tumor. Gross total resection and subtotal resection with adjuvant radiation have similar local control rates.[70–72] Both are associated with potential post-treatment problems, including panhypopituitarism, diabetes insipidus, obesity, visual problems, stroke, behavioral difficulties, poor school performance, and pseudoaneurysms of the carotid artery.[73–75] Although aggressive resection of very large craniopharyngiomas is often associated with more significant post-treatment complications, gross total resection of smaller tumors in high-volume centers are more likely to be achieved safely. Long-term survival is in the range of 90% at 10 years, but local recurrences are not uncommon.[76] Recurrences are treated by reoperation,[77] instillation of colloidal $^{32}$P into cysts, or radiosurgery.

## LOW-GRADE SUPRATENTORIAL ASTROCYTOMAS

Low-grade astrocytomas and gangliogliomas involving the cortical regions and temporal lobes can often present with intractable seizures. CT may show masses of low density. MRI usually shows a mass of decreased signal on T1-weighted images and increased signal on T2-weighted images that may or may not enhance with gadolinium.

Complete resection is the goal of surgery, but this may prove difficult because of problems in defining the tumor margins and its proximity to eloquent areas. Adjuncts to aid in this include language and motor mapping using implantable grids or intraoperative electrophysiologic monitoring techniques,[78] functional MRI techniques, and image-directed tumor resection.[79] Tumors of the temporal lobe are often treated by formal temporal lobectomy to decrease the incidence of seizures. Seizure mapping techniques have also been employed with cortical tumors, but simple removal of the tumor usually provides good seizure control, and the value of these strategies is uncertain.[9,80]

The outcome of low-grade astrocytomas,[9] gangliogliomas,[81](Fig. 44-8), and DNETs (Fig. 44-9) that are completely resected is favorable, although surveillance scanning is

**FIGURE 44-8** Axial T2WI image, in a 15-year-old girl, showing a small hyperintense right temporal tumor *(white arrow)*. The patient presented with seizures and the tumor was a ganglioglioma.

**FIGURE 44-9** Axial T2WI image showing a hyperintense lesion involving the white matter and overlying grey matter *(white arrow)*. This 5-year-old boy presented with a seizure, and the tumor was a dysembryoplastic neuroepithelial tumor (DNET).

warranted. About 70% of children will remain recurrence free. Recurrent tumors can be treated by reoperation alone or reoperation followed by radiation therapy.[82]

## PINEAL REGION TUMORS

Tumors of the pineal region encompass a wide range of histologic types. They can be divided into germ cell tumors (teratoma, germinoma, choriocarcinoma, embryonal carcinoma, yolk sac tumor), pineal parenchymal tumors (pineocytoma, pineoblastoma), tumors of surrounding structures (astrocytomas, meningiomas), and other benign conditions (cysts, vascular malformations). The older term pinealoma is no longer used.

Patients typically present with signs and symptoms of hydrocephalus and Parinaud syndrome (upgaze paresis, convergence nystagmus, and light-near dissociation). MRI confirms the presence of a tumor, but is nonspecific regarding histologic type. Specific germ cell tumors may secrete "tumor markers," which may be measured in CSF (obtained from a lumbar puncture or ventriculostomy) or blood. Elevated β-HCG is seen in choriocarcinomas, and elevated AFP is seen in yolk sac tumors and embryonal cell carcinomas.

In the past, surgery in the pineal region was considered prohibitively dangerous, and tumors were often treated without histologic confirmation. Today, this region is now readily approachable using supracerebellar/infratentorial or interhemispheric-transcallosal routes with minimal morbidity, and in most centers, biopsy is performed if germ cell markers are negative. As in the suprasellar region, pure germinomas of the pineal gland carry an excellent prognosis after radiation therapy. For focal disease, the radiation field usually includes the whole ventricular volume with a boost to the tumor bed. For disseminated disease, craniospinal radiation is required.[83] Initial treatment with chemotherapy, followed by response-based radiation field and dose, is advocated in some centers. The nongerminomatous germ cell tumors have a worse prognosis and require more intensive chemotherapy along with radiotherapy.[84] Pineoblastomas are treated like PNETs in other regions of the brain. Pineocytomas may be simply observed if totally resected or given focal radiation for residual tumor.

## ATYPICAL TERATOID/RHABDOID TUMORS

Atypical teratoid/rhabdoid tumors (AT/RTs) were previously misclassified as PNET tumors, but have been shown to be a distinct entity. They are highly malignant tumors with histologic resemblance to rhabdoid tumors of the kidney. Histologically, they can be distinguished from PNETs by larger cells with pink cytoplasm that show immunohistochemical staining for smooth muscle actin, vimentin, and epithelial membrane antigen. AT/RTs typically occur in young children and most commonly occur in the posterior fossa, but they may be located in the spine or supratentorial space. Fluorescence in situ hybridization (FISH) shows a deletion of the tumor suppressor gene *INI-1* in most cases.[85] The prognosis of these tumors is historically poor; however, treatment consisting of surgical excision, intensive chemotherapy, and radiation in older children has resulted in long-term survival in some patients with localized disease.

## MALIGNANT SUPRATENTORIAL ASTROCYTOMAS

Anaplastic astrocytomas and glioblastoma multiforme account for roughly 9% of pediatric tumors, which is a smaller incidence than in the adult population. Clinical signs and symptoms are reflective of their location. Imaging features are similar to those seen in adults, and the masses are often large, with enhancing rings and necrotic centers (Fig. 44-10). Dissemination occurs in about 10% of cases.[86]

Treatment includes maximal resection followed by radiation therapy. Unfortunately, the prognosis is still poor. Although more extensive resection confers better outcome, this may be due to the fact that more favorable tumors are more amenable to aggressive surgery. Chemotherapy has a modest impact on survival.[87,88]

## CHOROID PLEXUS TUMORS

Tumors of the choroids plexus are divided into the benign choroid plexus papilloma (CPP) and the malignant choroid plexus carcinoma (CPC). In children, they tend to arise in the trigone of the left lateral ventricle, and the patients often present with hydrocephalus during infancy. On imaging, the appearance is an intraventricular, homogenously enhancing, lobulated mass (Fig. 44-11). Carcinomas are typically larger and may disseminate. The vascular supply is from the choroidal arteries, which may be seen on high-resolution MRI.

Treatment is surgical excision, which is curative for papillomas. The procedure is hazardous, because of the highly vascular tumors and the small size of the patients. Carcinomas are particularly difficult to remove, because of extreme vascularity. This has led some surgeons to biopsy CPCs, followed by chemotherapy and then second-look surgery.[89] Otherwise,

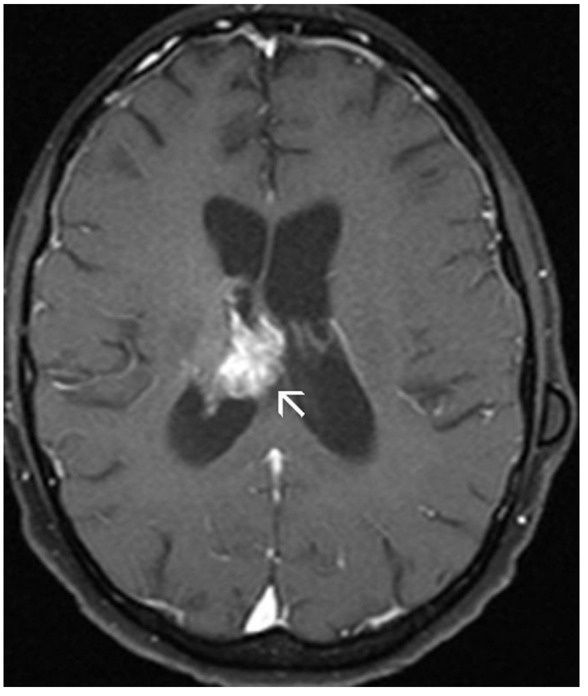

FIGURE 44-10 Axial T1WI postgadolinium image showing a thalamic enhancing tumor in a 14-year-old girl with headaches *(white arrow)*. The tumor was a glioblastoma multiforme (GBM).

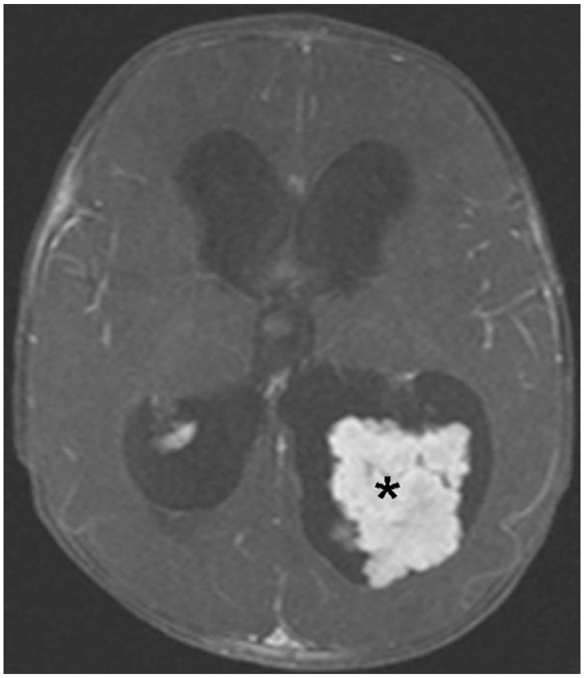


**FIGURE 44-11** Axial T1WI postgadolinium image showing an avidly enhancing tumor in the atrium of the left ventricle in a 6-month-old girl with a rapidly growing head circumference *(black asterisk)*. The tumor was a choroid plexus papilloma.

the benefit of chemotherapy and radiotherapy is unproven. With complete tumor removal, prolonged survival and even cure are possible even in the case of CPCs.

### MENINGIOMAS

Meningeal tumors are uncommon in childhood, accounting for about 2% of intracranial tumors. Meningiomas can occur in the orbit, sphenoid wing, or virtually any portion of the intracranial compartment, and do not necessarily need a dural attachment. Radiographically, they typically enhance and may be extremely large. Treatment is surgical resection. In adults, a gross total resection is curative; however, in the pediatric population, it is less common to have a meningioma with the typical benign histology seen in adults. Meningiomas in pediatric patients are usually much more aggressive and carry a worse prognosis than in adults.[90]

### METASTASES AND DURAL-BASED MASSES

Sarcomas, particularly rhabdomyosarcoma and Ewing sarcoma, are the most common, primary, dural-based non-CNS tumors in children. Metastatic brain tumors are extremely uncommon in the pediatric population and have been reported with most tumor types, including neuroblastoma, Wilms' tumor, osteogenic sarcoma, and hepatoblastoma. Presentation is often abrupt, with potential catastrophic neurologic symptoms resulting from hemorrhage.

## Tumor Genetics

In the past 2 decades, there has been a rapid development in imaging, navigational systems, and surgical instruments and techniques. However, despite this rapid increase in surgical technologies, many tumors, especially high-grade lesions, are still incurable with either surgery alone or in conjunction with chemotherapy and radiation therapy. Like much of medicine, the future in treating brain tumors lies in better biological, molecular, and genetic understanding. For example, such techniques have given physicians a better understanding of neurofibromatosis type 2, which is associated with the development of meningiomas and acoustic neuromas in the pediatric population. The gene locus was identified on chromosome 22,[91] the same chromosome that has been identified in pediatric meningiomas in patients without neurofibromatosis type 2.[92] These tumors have been shown to arise from a loss of a tumor suppressor gene.

In contrast, neurofibromatosis type 1 is associated with childhood gliomas, particularly of the optic pathway, hypothalamus, and brainstem. The affected gene locus, located at 17q11.2, encodes for the protein neurofibromin. This protein acts as a negative regulator of the RAS signaling pathway; therefore, a mutation in neurofibromin results in dysregulated RAS signaling, leading to cell growth and differentiation.[93]

Although molecular markers with prognostic significance have previously been identified for medulloblastoma, only recently have pathways been identified that may be implicated in the pathogenesis of certain medulloblastoma subtypes.[35–37,94] Approximately one third of medulloblastoma samples show increased signaling of the Sonic Hedgehog (SHH) pathway, and constitutive activation of SHH pathway promotes medulloblastoma formation in mice. Based on the work implicating this pathway and the preclinical efficacy of inhibition of this pathway on medulloblastoma formation in mice, clinical trials of SHH pathway inhibitors are underway.[84,85]

It has also recently been demonstrated that DNA from sporadic (non–NF1-associated) pediatric low-grade astrocytomas contain a novel duplication at chromosome band 7q34.[95] This duplication was identified in both juvenile pilocytic astrocytomas and fibrillary astrocytomas. This area of duplication contained approximately 20 genes, one of which was shown to be *BRAF*, which plays a regulatory role in the mitogen-activated protein kinase (MAPK) pathway. Reverse transcription polymerase chain reaction–based sequencing reveals that this duplication results in a fusion product between *KIAA1549* and *BRAF*. It is predicted that this fusion gene would lack the N-terminal regulatory domains and could result in constitutive BRAF kinase activity and subsequent unregulated activation of the MAPK pathway. Western blot analysis revealed phosphorylated MAPK protein in tumor cells with this duplication.[95] Further studies are required to determine the actual expression and function of this KIAA1549-BRAF fusion protein. However, neuroscientists are already exploring *BRAF* as a potential tumor marker or even a potential therapeutic target.

This discovery of a novel tumor pathway represents the ongoing trend in how the medical community is approaching the treatment of brain tumors. The future will require continued collaboration between neurosurgeons, oncologists, radiologists, and molecular neuroscientists to continue improving outcomes and diagnosis of patients with pediatric brain tumors.

*The complete reference list is available online at www.expertconsult.com.*

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# Part IV

# TRANSPLANTATION

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CHAPTER 45

# Principles of Transplantation

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The replacement of failing body parts with the transplantation of organs, cells, and tissues has been a centuries-old dream, fulfilled in the last 50 years. This success with both solid organ and bone marrow cell transplantation has been established on the following principles: histocompatibility matching, immunosuppression, tissue preservation, and techniques of implantation. However, neither kind of transplantation could have emerged as a clinical service if not for the induction by the graft itself of various degrees of donor-specific nonreactivity (tolerance). Without this fifth factor, no transplant recipient could survive for long, if the amount of immunosuppression given to obtain initial engraftment had to be continued.

## Enigma of Acquired Tolerance

The variable acquired tolerance on which transplantation depends has been one of the most enigmatic and controversial issues in all of biology. This was caused, in part, by the unexpected achievement of organ engraftment (the kidney) at an early time (a decade before successful bone marrow transplantation) and in ostensible violation of the very principles that would shape the impending revolution in general immunology. As a consequence, clinical organ transplantation was developed empirically rather than as a branch of classic immunology. This occurred in four distinct phases, each lasting more than a decade. Only at the end was it possible to explain organ engraftment and thereby eliminate the mystique of transplantation.

### PHASE 1: 1953 TO 1968

The modern era of transplantation began between 1953 and 1956 with the demonstration that neonatal mice[1,2] (with an immature immune system) and irradiated adult mice[3] (with an immune system weakened by total-body irradiation) develop donor-specific tolerance after successful engraftment of donor hematolymphopoietic cells. The key observation was that the mice bearing donor cells (donor leukocyte chimerism) could now accept skin grafts from the original donor strain but from no other strain (Fig. 45-1). The chimeric neonatal mice and the irradiated adult mice were analogues of today's bone marrow transplantation into immune-deficient and cytoablated humans, respectively. But because a good histocompatibility match was required for avoidance of graft-versus-host disease (GVHD) and of rejection,[4] clinical application of bone marrow transplantation had to await discovery of the human leukocyte antigens (HLAs). When this was accomplished,[5–7] the successfully treated human bone marrow recipients of 1968 were oversized versions of the tolerant chimeric mice.

By the time of the clinical bone marrow transplant breakthrough of 1968, kidney transplantation[8–14] already was an established clinical service, albeit a flawed one.[15] In addition, the first long-term survivals had been recorded after liver[16] and heart transplantation[17]; these were followed between 1968 to 1969 by the first prolonged survival of a lung[18] and a pancreas recipient[19] (Table 45-1). All of the organ transplant successes had been accomplished in the ostensible absence of leukocyte chimerism, without HLA matching, and with no evidence of GVHD. By going beyond the leukocyte chimerism boundaries established by the mouse tolerance models, organ transplantation had entered unmapped territory.

#### "Pseudotolerant" Organ Recipients

Two unexplained features of the alloimmune response had made it feasible to forge ahead precociously with organ transplantation.[14] The first was that organ rejection is highly reversible. The second was that an organ allograft, if protected by nonspecific immunosuppression, could induce its own acceptance. "Self-induced engraftment" was observed for the first time in 1959 in two fraternal twin kidney recipients, first in Boston by Joseph Murray[12] and then in Paris by Jean Hamburger.[8] These were the first successful transplantations in the world of an organ allograft, in any species. Both patients had been conditioned with 450-rad sublethal total-body irradiation before transplantation. The renal allografts functioned for more than 2 decades without a need for maintenance drug therapy, which was, in fact, not yet available.

A similar drug-free state was next occasionally observed after kidney transplantation (and more frequently after liver replacement) in mongrel dogs who were treated with a single immunosuppressive agent: 6-mercaptopurine (6-MP),[20,21] azathioprine,[22,23] prednisone,[24] or antilymphocyte globulin (ALG).[25] After treatment was stopped, rejection in some

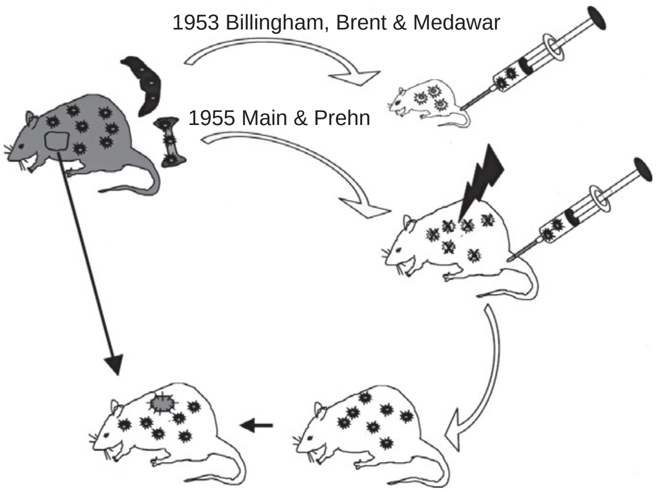



FIGURE 45-1 The mouse models of acquired tolerance described between 1953 and 1956. White cells (leukocytes) were isolated from the spleen or bone marrow of adult donor mice *(upper left)* and injected into the bloodstream of newborn mice *(upper right)* or of irradiated adult mice *(middle right)*. Under both circumstances, the recipient immune system was too weak to reject the foreign cells *(dark shaded)*. With engraftment of the injected cells (i.e., donor leukocyte chimerism), the recipient mice now could freely accept tissues and organs from the leukocyte donor but from no other donor *(bottom left)*.

**TABLE 45-1**
**First Successful Transplantation of Human Allografts (Survival >1 Year)**

| *Physician/ Organ* | *City* | *Date* | *Surgeon* | *Reference* |
|---|---|---|---|---|
| Kidney | Boston | Jan. 24, 1959 | Merrill/ Murray | 42, 48 |
| Liver | Denver | July 23, 1967 | Starzl | 72 |
| Heart | Cape Town | Jan. 2, 1968 | Barnard | 5 |
| Lung | Ghent | Nov. 14, 1968 | Derom | 18 |
| Pancreas | Minneapolis | June 3, 1969 | Lillehei | 34 |

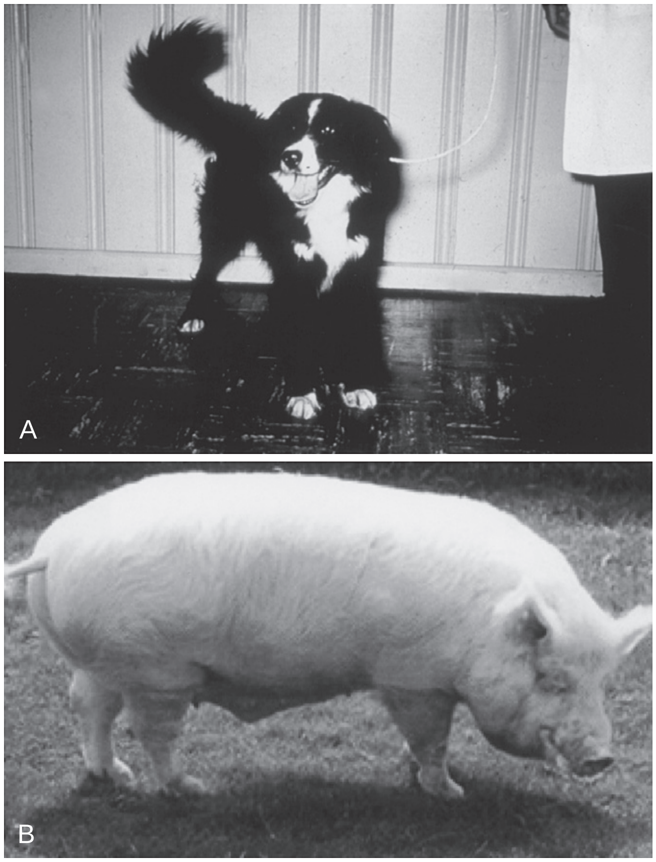



FIGURE 45-2 **A,** Canine recipient of an orthotopic liver homograft, 5 years later. The operation was on March 23, 1964. The dog was treated for only 120 days with azathioprine and died of old age after 13 years. **B,** A spontaneously tolerant pig recipient described by Calne.[29]

animals never developed (Fig. 45-2, *A*). Such results were exceedingly rare, less than 1% of the canine kidney experiments done under 6-MP and azathioprine up to the summer of 1962. However, the possibility that an organ could be inherently tolerogenic was crystallized by the human experience summarized in the title of a report in 1963 of a series of live-donor kidney recipients treated in Denver, "The Reversal of Rejection in Human Renal Homografts with Subsequent Development of Homograft Tolerance."[14] The recipients had been given azathioprine before as well as after renal transplantation, adding large doses of prednisone to treat rejections that were monitored by serial testing of serum creatinine (Fig. 45-3, *A*). Rejection occurred in almost every case, and 25% of the grafts were lost to uncontrolled acute rejection. However, the 1-year survival of 46 allografts, obtained from familial donors during a 16-month period from 1962 to 1963, was an unprecedented 75%.

The development of partial tolerance in many of the survivors was inferred from the rapidly declining need for treatment after rejection reversal (see Fig. 45-3, *A*). Nine (19%) of the 46 allografts functioned for the next 4 decades, each depicted in Figure 45-4 as a horizontal bar. Moreover, all immunosuppression eventually was stopped in seven of the nine patients without rejection for periods ranging from 6 to 40 years (the solid portion of the bars). Eight of the nine patients are still alive and bear the longest surviving organ allografts in the world.[26]

What was the connection between the tolerant mouse models, the irradiated fraternal twin kidney recipients in Boston and Paris, the ultimate drug-free canine organ recipients (see Fig. 45-2, *A*), and the unique cluster of "pseudotolerant" human kidney recipients in Denver (Fig. 45-4)? What were the mechanisms of engraftment and what was the relationship of engraftment to tolerance? The mystery deepened with the demonstration in 1966 in France,[27] England,[28–31] and the United States[32] that the liver can be transplanted in about 20% of outbred pigs without any treatment at all (see Fig. 45-2, *B*). Because graft-versus-host disease had yet to be seen (despite the use of organs from HLA-mismatched donors) none of the animal or human organ recipients, whether off or on maintenance immunosuppression, was thought to have donor leukocyte chimerism to explain organ engraftment.

## False Premises of Phase 1

Organ transplantation became disconnected at a very early time from the scientific anchor of leukocyte chimerism that had been established by the mouse models and was soon to

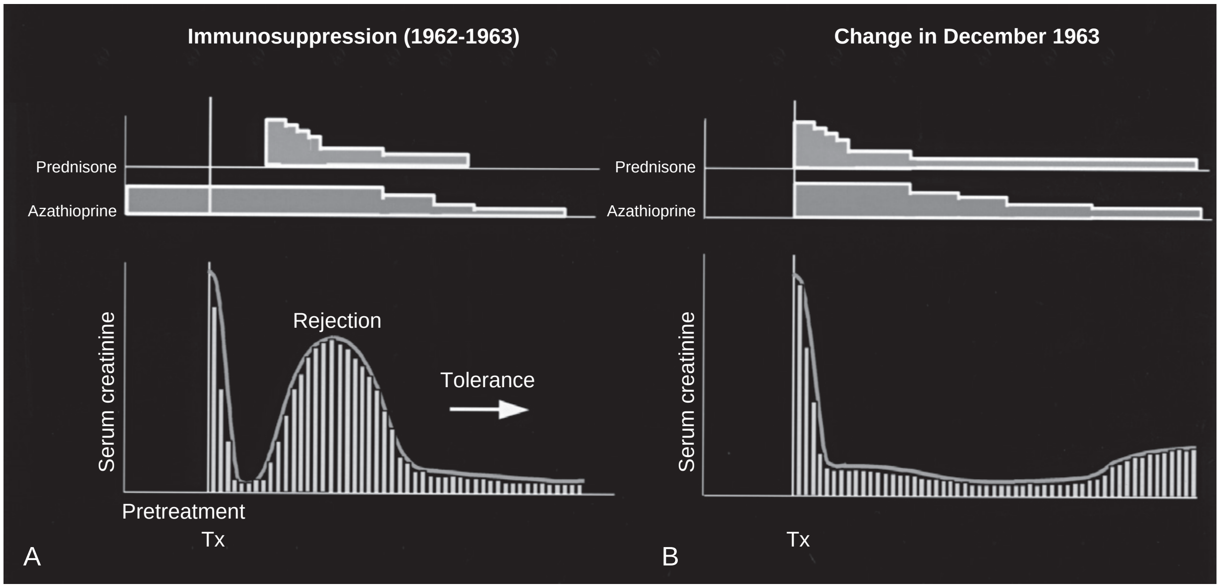



**FIGURE 45-3** **A,** Empirically developed immunosuppression used for kidney transplant recipients from 1962 to 1963. Note the reversal of rejection with the addition of prednisone to azathioprine. More than a third of a century later, it was realized that the timing of drug administration had been in accord with the tolerogenic principles of immunosuppression (see text). **B,** Treatment revisions in immunosuppression made at the University of Colorado in December 1963, which unwittingly violated principles of tolerogenic immunosuppression. Pretreatment was de-emphasized or eliminated, and high doses of prednisone were given prophylactically instead of as needed. Although the frequency of acute rejection was reduced, the drug-free tolerance shown in Figure 45-4 was no longer seen. Tx, treatment.

be exemplified by human bone marrow transplantation. The resulting intellectual separation of the two kinds of transplantation (Fig. 45-5) was an unchallenged legacy of phase 1, passed from generation to generation.

There was another dark legacy of phase 1 that began in 1964. This was a modified version of the treatment strategy that had been developed with azathioprine and prednisone (see Fig. 45-3, *B*). The principal change was the use of large prophylactic doses of prednisone from the time of operation, instead of the administration of corticosteroids only when needed. In a second modification, the pretreatment was de-emphasized (see Fig. 45-3, *B*). The incidence of acute rejection was greatly reduced after these changes. However, no cluster of drug-free kidney recipients, such as shown in Figure 45-4, was ever seen again, anywhere in the world. More than 35 years passed before the long-term immunologic consequences of the modifications were realized.

## PHASE 2: 1969 TO 1979

Throughout the succeeding phase 2 that began in 1969, immunosuppression for organ transplantation was based on azathioprine and prophylactic high-dose prednisone to which ALG was added after 1966[25,33] in about 15% of centers. Phase 2 was a bleak period. In the view of critics, the heavy mortality, and particularly the devastating morbidity caused by corticosteroid dependence, made organ transplantation (even of kidneys) as much a disease as a treatment. Most of the liver and heart transplant programs that had been established in an initial burst of optimism after the first successful cases closed down.

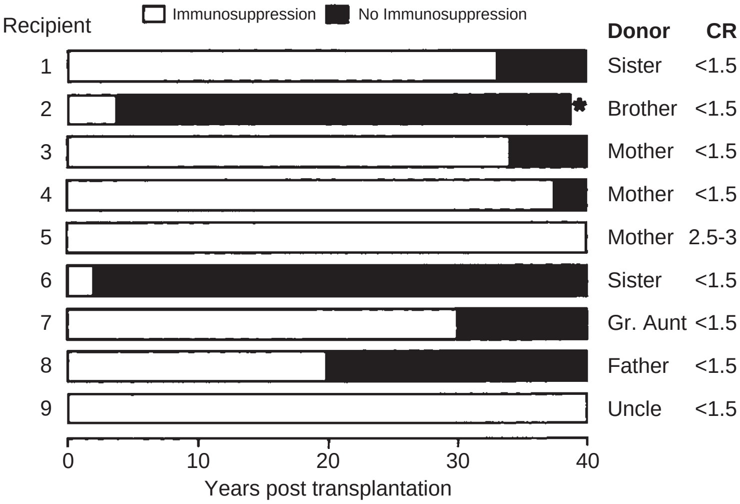



**FIGURE 45-4** Nine (19%) of the 46 live-donor kidney recipients treated at the University of Colorado during an 18-month period beginning in the autumn of 1962. The solid portion of the horizontal bars depicts the time off immunosuppression. Note that the current serum creatinine concentration (CR) is normal in all but one patient. *Murdered: kidney allograft normal at autopsy.

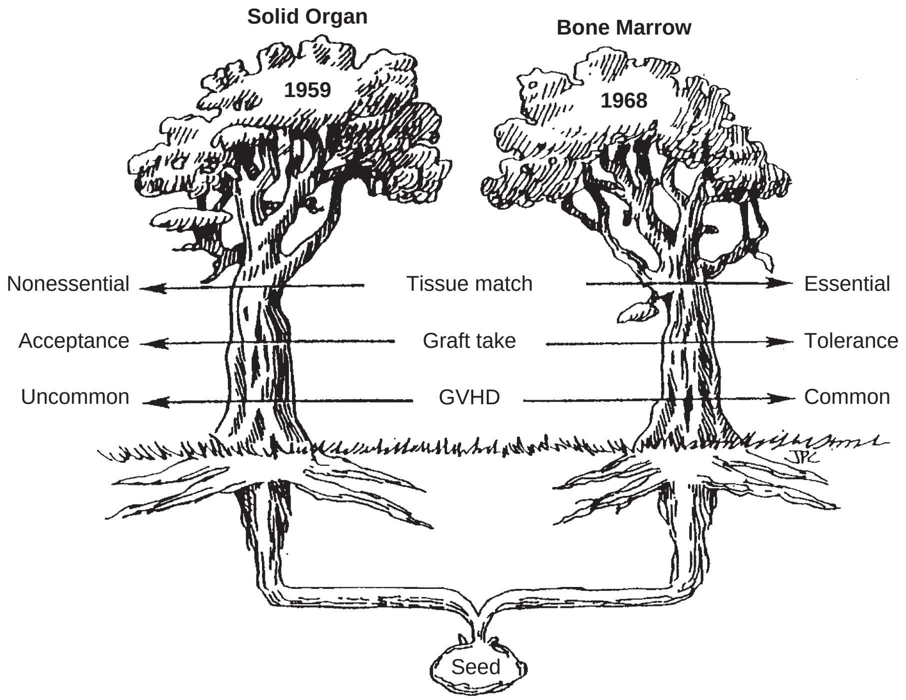



**FIGURE 45-5** The developmental tree of bone marrow *(right)* and organ transplantation *(left)* after it was demonstrated that rejection is an immunologic response. GVHD, graft-versus-host disease.

But in the few remaining centers, patients, such as the one shown in Figure 45-6, bore witness to what some day would be accomplished on a grand scale. Four years old at the time of her liver replacement for biliary atresia and a hepatoma in 1969, the patient depicted is the longest surviving recipient of an extrarenal organ.

## PHASE 3: 1980 TO 1991

In fact, what had appeared to be the sunset of extrarenal organ transplantation was only the dawn of phase 3, which began with the clinical introduction of cyclosporine,[34–37] followed a decade later by that of tacrolimus.[38–41] The use of these drugs was associated with stepwise improvements with all organs, but their impact was most conclusively demonstrated with liver and heart transplantation. The results with liver transplantation shown in Figure 45-7 using azathioprine-, cyclosporine-, and tacrolimus-based immunosuppression were presented at the meeting of the American Surgical Association in April 1994.[42] By then, intestinal transplantation under tacrolimus-based immunosuppression had become a service.[43,44]

As the new agents became available, they were simply incorporated into the modified formula of heavy prophylactic immunosuppression that had been inherited from phases 1 and 2. Used in a variety of multiple-agent combinations from

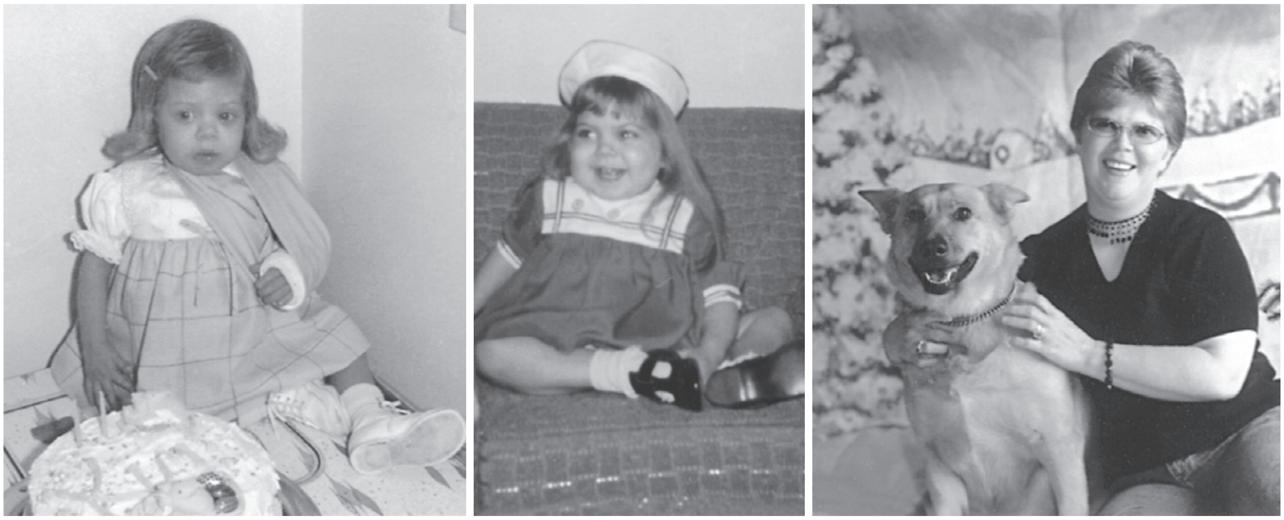


**FIGURE 45-6** Four years old at the time of liver replacement for biliary atresia and a hepatoma, but now in her 40th post-transplant year (shown here at 35 years post-transplant), the (former) patient is the longest-surviving recipient of an extrarenal organ.

the time of surgery, the better drugs fueled the golden age of transplantation of the 1980s and early 1990s. Acute rejection had become almost a "nonproblem." However, the unresolved issues now were chronic rejection, risks of long-term immunosuppression (e.g., infections and de novo malignancies), and drug toxicity (e.g., the nephrotoxicity of cyclosporine and tacrolimus).

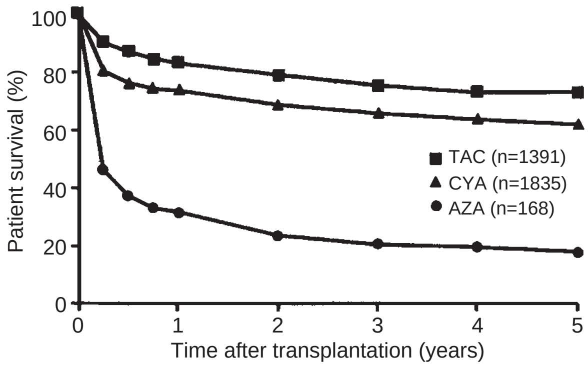



**FIGURE 45-7** Patient survival: results with orthotopic liver transplantation at the Universities of Colorado (1963 to 1980) and Pittsburgh (1981 to 1993), in periods defined by azathioprine (AZA)-, cyclosporine (CYA)-, and tacrolimus (TAC)-based immune suppression. Stepwise improvements associated with the advent of these drugs also were made with other organs.

## PHASE 4: 1992 TO PRESENT

It was clear that relief from the burden of lifetime immunosuppression would require elucidation of the mechanisms of alloengraftment and of acquired tolerance. An intensified search for the engraftment mechanisms has dominated the current phase 4, which began in the early 1990s. There was a growing realization (particularly with recipients of liver allografts), that immunosuppression could be withdrawn successfully in selected cases, which sparked various prospective trials of immunosuppression withdrawal.[45]

### Historical Dogma

Until this time, organ engraftment had been attributed to mechanisms that did not involve either the presence or a role of leukocyte chimerism. Although it was known that organs contain large numbers of passenger leukocytes, these donor cells were largely replaced in the successfully transplanted allograft by recipient leukocytes as shown in Figure 45-8, *A*. The missing donor cells were thought to have undergone

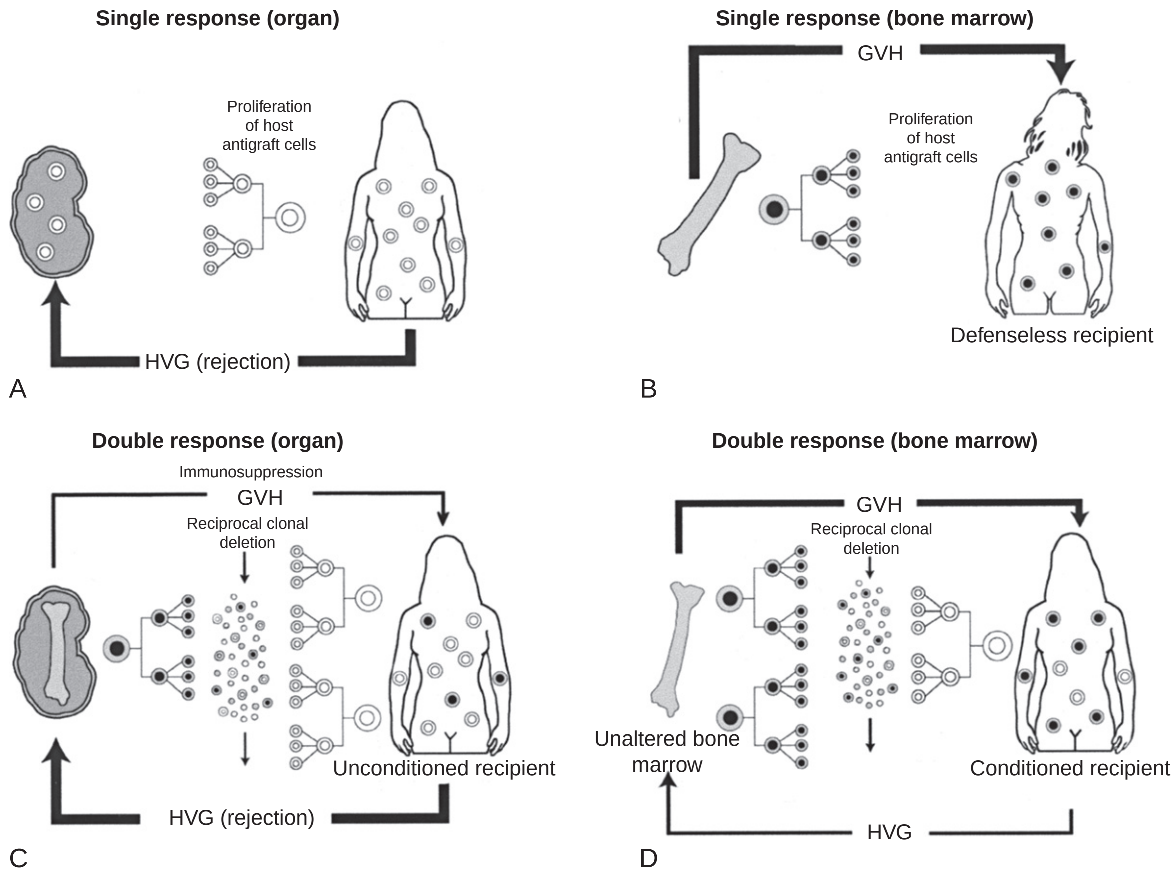



**FIGURE 45-8** Old (**A** and **B**) and new views (**C** and **D**) of transplantation recipients. **A,** The early conceptualization of immune mechanisms in organ transplantation in terms of a unidirectional host-versus-graft (HVG) response. Although this readily explained organ rejection, it limited possible explanations of organ engraftment. **B,** Mirror image of **A** depicting the early understanding of successful bone marrow transplantation as a complete replacement of the recipient immune system by that of the donor, with the potential complication of an unopposed lethal unidirectional graft-versus-host (GVH) response, that is, rejection of the recipient by the graft. **C,** Our current view of bidirectional and reciprocally modulating immune responses of coexisting immune-competent cell populations. Because of variable reciprocal induction of deletional tolerance, organ engraftment was feasible despite a usually dominant HVG reaction. The bone silhouette in the graft represents passenger leukocytes of bone marrow origin. **D,** Our currently conceived mirror image of **C** after successful bone marrow transplantation. Recipient's cytoablation has caused a reversal of the size proportions of the donor and recipient populations of immune cells.

immune destruction with selective sparing of the specialized parenchymal cells. As for bone marrow transplantation (see Fig. 45-8, *B*), the ideal result had been perceived as complete replacement of recipient immune cells (i.e., total hematolymphopoietic chimerism).

### Discovery of Microchimerism

A flaw in this historical dogma began to be exposed in the early 1990s. The first puzzling observation in Seattle[46] and Helsinki[47] was the invariable presence of a small residual population of recipient hematolymphopoietic cells in patients previously thought to have complete bone marrow replacement (see Fig. 45-8, *D*). This was followed in 1992 by the discovery of donor leukocyte microchimerism in long-surviving human organ recipients. Now it was evident that organ engraftment (see Figure 45-8, *C*) and bone marrow cell engraftment (see Fig. 45-8, *D*) were mirror-image versions of leukocyte chimerism, differing in the reversed proportion of donor and recipient cells.

The discovery of microchimerism in organ recipients was made with a very simple clinical study.[48–52] With the use of sensitive detection techniques, donor hematolymphopoietic cells of different lineages (including dendritic cells) were found in the blood, lymph nodes, skin, or other tissues of 30 of 30 liver or kidney recipients who had borne functioning allografts for up to 30 years. The donor leukocytes obviously were progeny of donor precursor or pluripotent hematolymphopoietic stem cells that had migrated from the graft into the recipient after surviving a double immune reaction that presumably had occurred just after transplantation, years or decades earlier.[53–56]

It was concluded that organ engraftment had been the result of "responses of coexisting donor and recipient cells, each to the other, causing reciprocal clonal exhaustion, followed by peripheral clonal deletion."[48,50] The host response (the upright curve in Fig. 45-9) was the dominant one in most cases of organ transplantation but with the occasional exception of GVHD. In the conventionally treated bone marrow recipient, host cytoablation simply transferred immune dominance from the host to the graft (the inverted curve in Fig. 45-9), explaining the high risk of GVHD. All of the major differences between the two kinds of transplantation were caused by the recipient cytoablation. After an estrangement of more than a third of a century, the intellectual separation of bone marrow and organ transplantation was ended (Fig. 45-10).

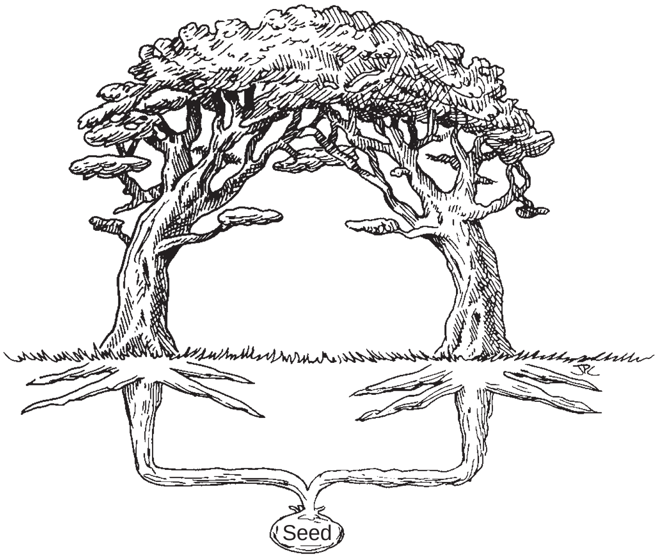


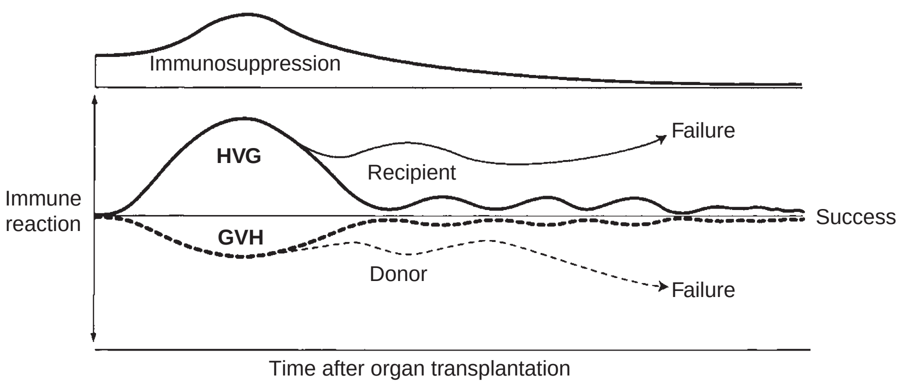

FIGURE 45-10 Unification of organ and bone marrow transplantation (see text).

### Immune Regulation by Antigen Migration and Localization

But how was the exhaustion-deletion of the double immune reaction shown in Figure 45-9 maintained after its acute induction by the first wave of migratory leukocytes? Rolf Zinkernagel, in Zurich (Fig. 45-11), had addressed this question during the 1990s in experimental studies of the nonresponsiveness that may develop to intracellular microorganisms, such as tubercle bacillus and noncytopathic viruses.[57–60] The analogies between the syndromes caused by such infectious agents and the events following transplantation were described in 1998 in a joint review with Zinkernagel in the *New England Journal of Medicine*.[61]

The analogies between transplantation and infection had been obscured by the characteristic double immune reaction of transplantation and by the complicating factor of immunosuppression. Now, these analogies were obvious. The antidonor response induced by the initially selective migration of the graft's leukocytes to host lymphoid organs (Fig. 45-12, *left*)[62–65] is comparable to the response induced by a spreading intracellular pathogen. The migration patterns of the donor leukocytes were the same whether these cells emigrated from an organ or were delivered as a bone marrow

FIGURE 45-9 Contemporaneous HVG *(upright curves)* and GVH *(inverted curves)* responses after transplantation. In contrast to the usually dominant HVG reaction of organ transplantation, the GVH reaction usually is dominant after bone marrow cell transplantation to the irradiated or otherwise immunodepressed recipient. Therapeutic failure with either type of transplantation implies the inability to control one, the other, or both of the contemporaneous responses with a protective umbrella of immunosuppression.[61]



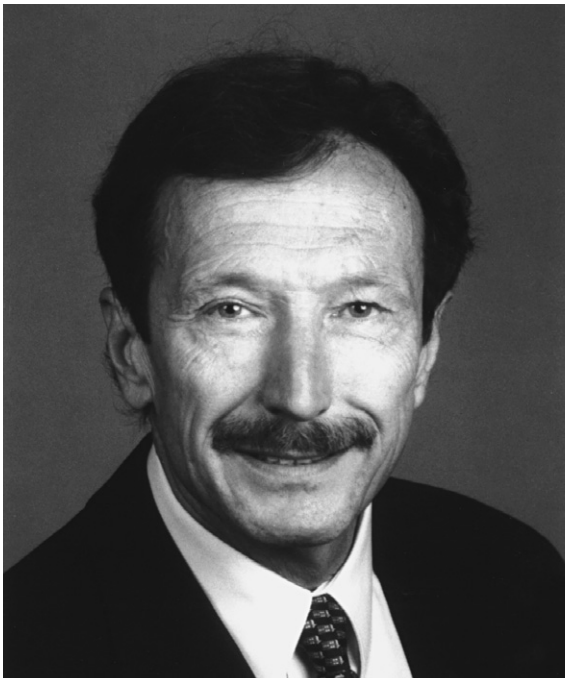


**FIGURE 45-11** Rolf Zinkernagel. Swiss physician-immunologist whose discovery, with Peter Doherty, of the mechanisms of the adaptive immune response to noncytopathic microorganisms earned them the Nobel prize in 1996.

cell infusion. Cells that survived the antidonor response that they had induced begin within a few days to move on (see Fig. 45-12, *right*) to protected nonlymphoid niches, where their presence no longer may be detected by the immune system (immune ignorance[61,66–69]). This was a survival tactic of noncytopathic microorganisms.

The migration of donor leukocytes is shown schematically in Figure 45-13, *left* by centrifugal arrows: first by hematogenous routes to lymphoid organs and, after a few weeks, on to nonlymphoid sites *(outer circle)*. A subsequent reverse migration of donor cells from protected nonlymphoid niches back to host lymphoid organs is depicted by the inwardly directed *dashed arrows* in Figure 45-13, *right*. The retrograde migration is a two-edged sword. On the one hand, these cells may sustain the clonal exhaustion-deletion induced at the outset, usually requiring an umbrella of maintenance immunosuppression. But on the other hand, these cells can perpetuate alloimmunity in the same way as surviving residual microorganisms perpetuate protective immunity. Not surprisingly, therefore, an alternative consequence of microchimerism may be the high-panel reactive antibody (connoting sensitization to HLA antigens) that commonly develops after unsuccessful transplantation.[70,71]

## Therapeutic Implications

How could the new insight be exploited clinically? The window of opportunity for the donor leukocyte-induced clonal deletion that corresponds with collapse of the antigraft response (Fig. 45-14, *left*) is open only for the first few

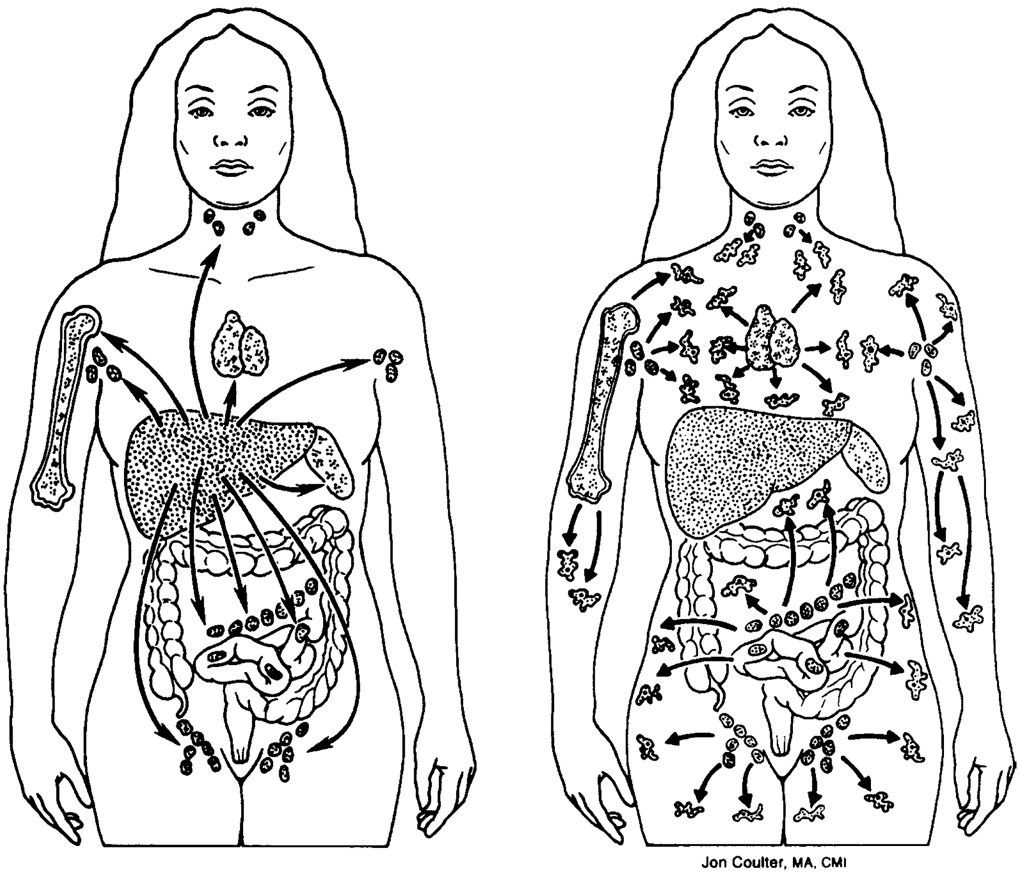



**FIGURE 45-12** Initial preferential migration of passenger leukocytes from organ allografts (here a liver) to host lymphoid organs *(left)*, where they induce a donor-specific immune response. After about 30 days, many of the surviving cells move on to nonlymphoid sites *(right)*.

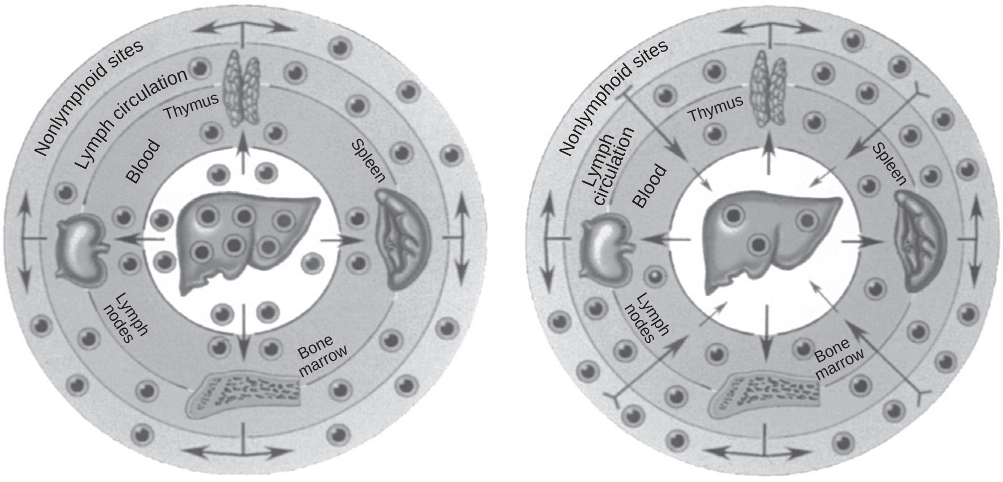



**FIGURE 45-13** The migration routes of passenger leukocytes of transplanted organs are similar to those of infused bone marrow cells. *Left,* Selective migration at first to host lymphoid organs. After 15 to 30 days, surviving leukocytes begin to secondarily move to nonlymphoid sites. *Right,* Establishment of reverse traffic by which the exhaustion-deletion induced at the outset can be maintained.

post-transplant weeks.[55,72–74] It was apparent that the window could be closed by excessive postoperative immunosuppression (Fig. 45-14, *middle*). With later reduction of the initial overimmunosuppression, recovery of the inefficiently deleted clone would be expected, leading to the delayed acute rejection, or the chronic rejection, that was being seen in the transplant clinics. Even in the best-case scenario, the patients would be predestined to lifetime dependence on immunosuppression. However, too little immunosuppression would result in uncontrolled rejection (Fig. 45-14, *right*).

The problem faced by clinicians was how to find just the right amount of post-transplant immunosuppression. In 2001, it was suggested that this dilemma could be addressed by successively applying two historically rooted therapeutic principles: recipient pretreatment, followed by minimalistic post-transplant immunosuppression.[75] With pretreatment, the recipient's immune responsiveness would be reduced before exposure to donor antigen, thereby lowering the anticipated donor-specific response to a more readily deletable range (Fig. 45-15). Clonal deletion by the kidneys' passenger leukocytes undoubtedly is what had been accomplished after sublethal irradiation alone in the ground-breaking fraternal twin (i.e., sublethal total-body irradiation or myelotoxic drugs) cases of 1959.[8,12] In fact, radical pretreatment by recipient cytoablation ultimately became the essential therapeutic step for conventional bone marrow transplantation. Because of the high risk of GVHD, this approach was too dangerous and too restrictive to be practical for organ transplantation.

However, less drastic lymphoid depletion by ALG or other measures (so-called nonmyeloablative conditioning) had been repeatedly shown since the 1960s to be effective without causing GVHD[33] (see Fig. 45-15).

After pretreatment with one of today's potent antilymphoid antibody preparations, the preemptively weakened clonal activation could proceed efficiently to clonal deletion under minimalistic short- and long-term maintenance therapy (Fig. 45-16). In July 2001, we instituted the double-principle strategy in adult organ recipients. The pretreatment was with a single infusion of 5 mg/kg of Thymoglobulin. Beginning in 2002, a single Campath dose of 30 mg was substituted for Thymoglobulin in most adult cases. After either kind of lymphoid depletion, treatment after transplantation was given with a conservative daily dose of a single drug (usually tacrolimus), adding other agents only in the event of breakthrough rejection and for as brief a period as

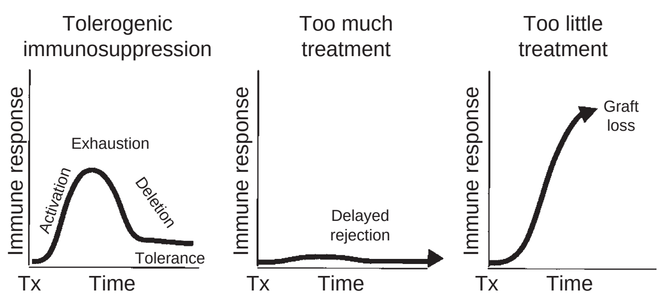



**FIGURE 45-14** The effect of post-transplant immunosuppression on the seminal mechanism of clonal exhaustion-deletion. *Left,* Just the right amount. *Middle,* Too much. *Right,* Too little (see text). Tx, treatment.

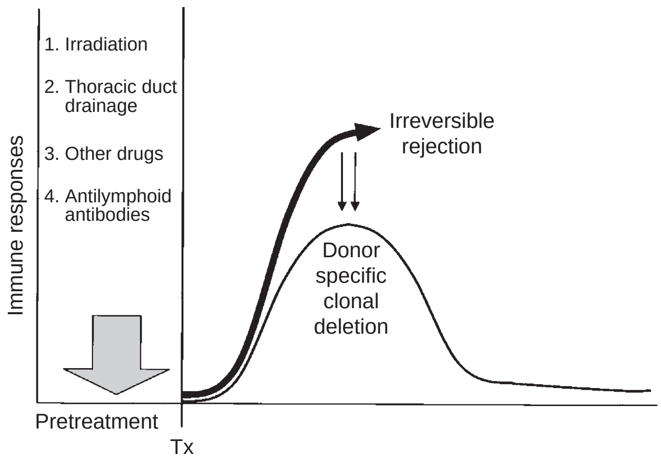



**FIGURE 45-15** Rather than producing rejection *(thick dark arrow),* the donor-specific immune response to allografts may be exhausted and deleted, as depicted by the fall of the initially ascending continuous thin line, when recipient immune responsiveness is weakened in advance of transplantation (the pretreatment principle). Tx, treatment.

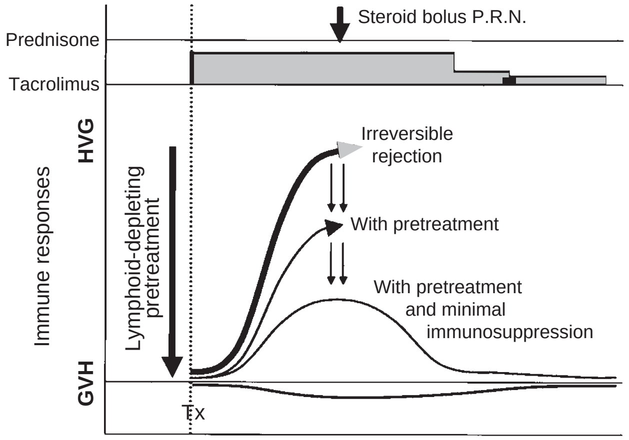



**FIGURE 45-16** Conversion of rejection *(thick dark arrow)* to an immune response that can be exhausted and deleted by combination of pretreatment and minimalistic post-transplant immunosuppression. Tx, treatment.

possible. The strategy was extended to infants and children for intestinal transplantation in 2002 and for all kidney transplantations after April 2003.[76]

After 4 to 8 months, weaning from monotherapy to less-than-daily doses was begun in adults whose graft function was stable: every other day, then three times per week, twice a week, and in many cases to once a week by 1 year (Fig. 45-17). The strategy has been used for the treatment of more than 1000 adult kidney, liver, intestine, pancreas, and lung recipients.[77–79] This experience has demonstrated that the quality of life of transplant recipients can be improved. For the first time, children are being considered for spaced weaning.

These and other clinical trials have spawned definitions of clinical or operational tolerance (normal graft function without features of graft rejection and without the need for immunosuppressive drugs), and "prope," or "near" tolerance (the state of normal graft function in the presence of minimal or undetectable levels of immunosuppression).[80,81] However, achieving this on a consistent basis may hinge on the development of standardized clinically applicable markers of immune tolerance that can assess the appropriateness of this clinical strategy on the individual patient. Prospective weaning trials sponsored by the Immune Tolerance Network are currently underway in stable adult and pediatric recipients of liver allografts, incorporating the aforementioned strategies and mechanistic studies.[82]

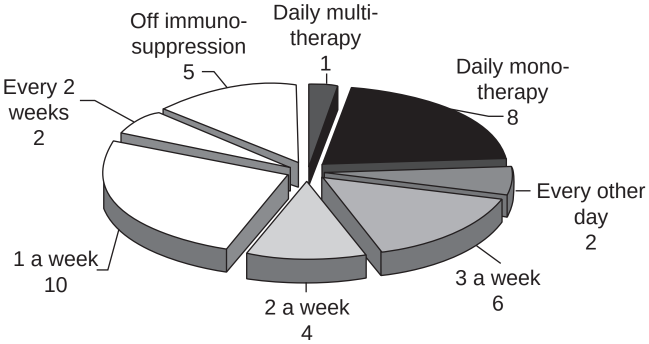



**FIGURE 45-17** Diagram of 2.5-year follow-up.

# Organ Preservation

## PROCUREMENT

The breakthroughs of the early 1960s that made transplantation clinically practical were so unexpected that almost no formal preparation had been made to preserve the transplanted organs. Cardiac surgeons had used hypothermia for open-heart operations from 1950 onward and knew that ischemic damage below the level of aortic cross-clamping could be reduced by cooling the subdiaphragmatic organs.[83] In an early report, Lillehei and colleagues[84] immersed intestines in iced saline before autotransplantation. In Boston, Sicular and Moore[85] reported greatly slowed enzyme degradation in cold slices of liver.

Despite this awareness, kidneys were routinely transplanted until 1963 with no protection from warm ischemia during organ transfer. The only attempt to cool kidney allografts until then was by the potentially dangerous practice (used by thoracic surgeons for open-heart surgery) of immersing the live donor in a bathtub of ice water (total-body hypothermia).[86] This cumbersome method of cooling was quickly replaced by infusion of chilled solutions into the renal artery after donor nephrectomy,[87] exploiting a principle of core (transvascular) cooling that had been standardized several years earlier for experimental liver transplantation.[88]

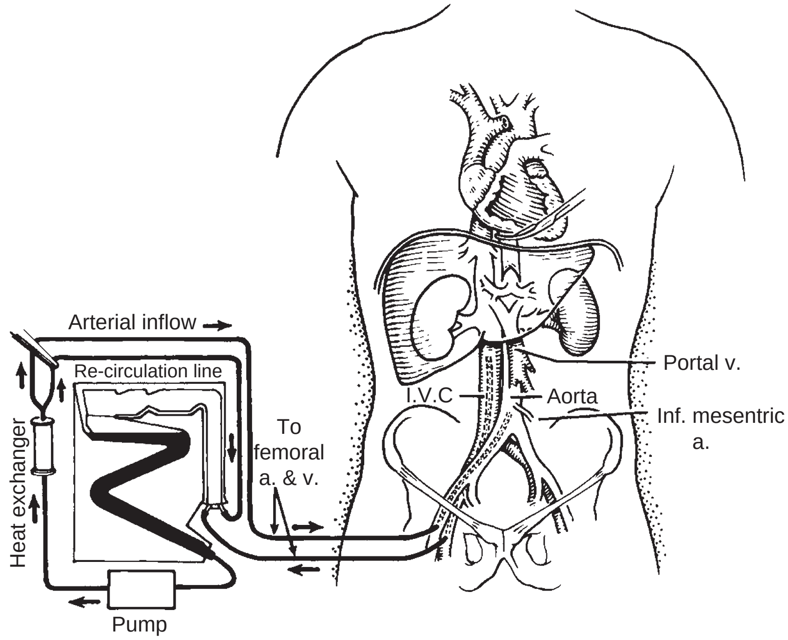
Core cooling in situ, the first critical step in the preservation of all cadaveric whole organs, is done today with variations of the technique described in 1963 by Marchioro and coworkers,[89] which permits in situ cooling to be undertaken[90] (Fig. 45-18). Ackermann and Snell[91] and Merkel and associates[92] popularized in situ cooling of cadaveric kidneys with simple infusion of cold electrolyte solutions into the donor femoral artery or distal aorta. Procurement techniques were eventually perfected that allowed removal of all thoracic and abdominal organs, including the liver, without jeopardizing any of the individual organs (Fig. 45-19).[93] Modifications of this flexible procedure have been made for unstable donors and even for donors whose hearts have stopped beating.[94] During the 5 years between 1980 and 1985, such techniques had become interchangeable in all parts of the world, setting the stage for reliable organ sharing. After the chilled organs are removed, subsequent preservation is possible with prototype strategies: simple refrigeration or continuous perfusion (see later).

## EXTENDED PRESERVATION

### Continuous Vascular Perfusion

Efforts to continuously perfuse isolated organs have proved to be difficult. For renal allografts, Ackermann and Barnard[95] used a normothermic perfusate primed with blood that was oxygenated within a hyperbaric chamber. Brettschneider and colleagues[96] modified the apparatus and were able to preserve canine livers for 2 days, an unprecedented feat at the time. When Belzer and associates[97] eliminated the hemoglobin and hyperbaric chamber components, their asanguineous hypothermic perfusion technique was immediately accepted for clinical renal transplantation but then slowly abandoned

FIGURE 45-18 First technique of in situ cooling by extracorporeal hypothermic perfusion. The catheters were inserted into the aorta and vena cava through the femoral vessels as soon as possible after death. Temperature control was provided with a heat exchanger. Cross-clamping of the thoracic aorta limited perfusion to the lower part of the body. This method of cadaveric organ procurement was used from 1962 to 1969, before the acceptance of brain death criteria. The preliminary stages of this approach provided the basis for subsequent in situ infusion techniques.



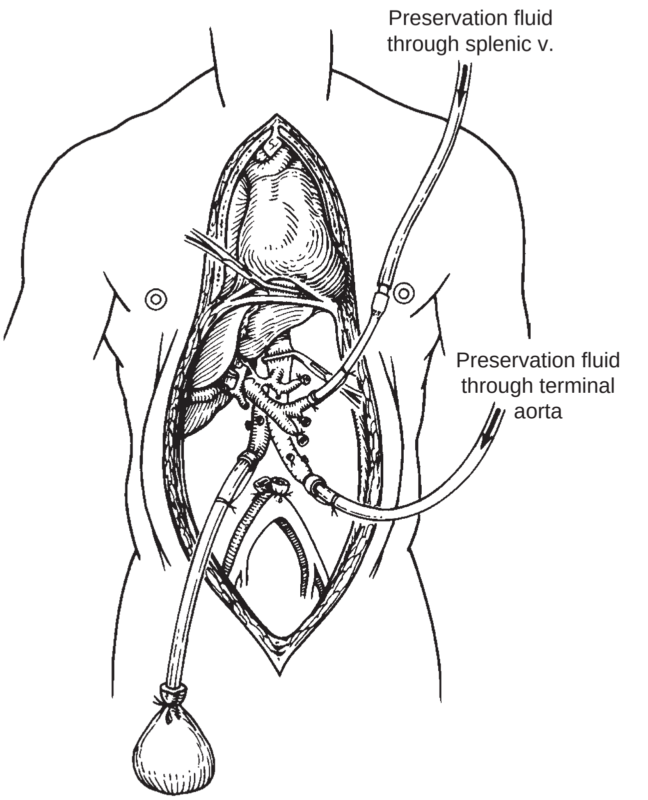




FIGURE 45-19 Principle of in situ cooling used for multiple organ procurement. With limited preliminary dissection of the aorta and of the great splanchnic veins (in this case, the splenic vein), cold infusates can be used to chill organs in situ. In this case, the kidneys and liver were being removed. Note the aortic cross-clamp above the celiac axis.

in most centers when it was learned that the quality of 2-day preservation was not markedly better than that of simpler and less expensive infusion and slush methods (see later). However, refinement of perfusion techniques may someday permit true organ banking.

### Static Preservation

With these "slush techniques," special solutions, such as those described by Collins and coworkers,[98] were instilled into the renal vascular system of kidneys or the vascular system of other organs after their preliminary chilling and separation. The original Collins solution or modifications of it were used for nearly 2 decades before they were replaced with the University of Wisconsin (UW) solution that was developed by the team of Folkert Belzer. Although it was first used for the liver,[99–101] the UW solution provides superior preservation of kidneys and other organs.[102,103] The UW preservation permitted longer and safer preservation of kidneys (2 days) and livers (18 hours), a higher rate of graft survival, and a lower rate of primary nonfunction. With the UW solution, national organ sharing was made economical and practical. This success has refocused efforts on understanding the mechanisms involved in the ischemia/reperfusion injury (deprivation and then restoration of tissue oxygen) that impacts organ function, and has resulted in the development of other preservation solutions (Celsior, HTK: histidine-tryptophan-ketoglutarate) and the inclusion of drugs that act on the mediators of injury.[104]

# Tissue Typing

## ANTIGEN MATCHING

The human leukocyte antigen (HLA) system has an important role in immune regulation and is thus a barrier that must be avoided (with better matching) or modified (with immunosuppressive strategies). HLA class I A, B, and C, and HLA class II DR, DQ, and DP molecules are expressed on various cell types that, when bound to a specific repertoire of peptides, present to CD8+ or CD4+ T cells. Patient and donor matching is of significant importance in bone marrow transplantation in order to prevent lethal GVHD but of variable importance in solid organ transplantation.[105]

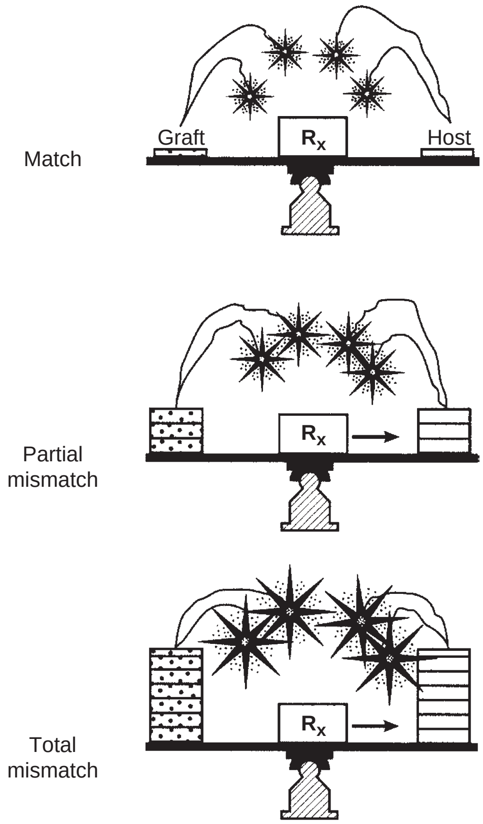



**FIGURE 45-20** The nullification effect of simultaneous host-versus-graft (HVG) and graft-versus-host (GVH) reactions when organs are transplanted to recipients whose immune system has not been cytoablated. The reciprocal induction of tolerance, each to the other, of the coexisting cell populations is the explanation for the poor correlation of human leukocyte antigen (HLA) matching with outcome after organ transplantation.

The first prospective antigen matching trials were begun in 1964 by Terasaki and associates[106] in collaboration with the University of Colorado kidney transplantation team. Although the value of this serologic technology was demonstrable when the kidney donor was a highly compatible family member (the "perfect match"),[107] lesser degrees of matching correlated poorly with renal transplantation outcome.[108] The reasons for this paradox were inexplicable until the discovery of recipient chimerism (Fig. 45-20). However, the belief that matching should be a prime determinant of success resulted in its use as an overriding factor for the allocation of cadaver kidneys in the United States.

The propriety of this kidney allocation policy has been repeatedly challenged on ethical as well as scientific grounds for nearly a third of a century. Those in favor of perpetuating the role of graded HLA matches cite multicenter case compilations in the United States and Europe showing a small gain in allograft survival with histocompatible kidneys, whereas many of the individual contributing centers see no such trend in their own experience.[83,109–111] In a compelling study, Terasaki and associates[112] reported that early survival and the subsequent half-life of kidneys from randomly matched, living unrelated donors was identical to that of parent–offspring (one haplotype–matched) grafts. The inescapable conclusion is that more effective timing and dosage of immunosuppressive therapy, rather than refinements in tissue matching and organ sharing, will be the primary method of improving the results of whole organ transplantation.

### CROSSMATCHING

None of the immunosuppressive measures available today can prevent immediate destruction of kidneys and other kinds of organ grafts in what has been called hyperacute rejection. This complication was first seen with the transplantation of kidneys from ABO-incompatible donors when they were placed in recipients with antidonor isoagglutinins.[113] After the description by Terasaki and associates[114] of hyperacute kidney rejection by a recipient with antidonor lymphocytotoxic antibodies, Kissmeyer-Nielsen and colleagues[115] and others[116–119] confirmed the association of hyperacute rejection with these antigraft antibodies. Although hyperacute rejection can usually be avoided with the lymphocytotoxic crossmatch originally recommended by Terasaki and associates, the precise pathogenesis of such rejection remains poorly understood more than 30 years after its recognition as a complement activation syndrome.[116,117]

## Future Prospects

The revisions in timing and dose control that encourage the seminal mechanisms of clonal exhaustion-deletion and immune ignorance should make it possible to systematically reduce exposure to the risks of chronic immunosuppression. Our prediction is that completely drug-free tolerance will be largely, but not exclusively, limited to recipients of HLA-matched organs. But variable partial tolerance will be more regularly attainable in most of the others, not so much by developing better drugs but by the mechanism-based use of drugs we already have in hand. Xenotransplantation will have to be developed within the same immunologic framework. Here, the problem, in principle, is to create a better interspecies tissue match by transgenic modification. Although the *α-1,3GT* gene responsible for hyperacute rejection of pig organs by higher primates has been knocked out in pigs,[120] it is not yet known what further changes have to be made before porcine organs can be used clinically. Where stem cell biology will fit remains unknown, but it also will have to conform to the same immunologic rules.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 46

# Renal Transplantation

John C. Magee

Transplantation is the preferred treatment for children with end-stage renal disease (ESRD), because it provides the best opportunity for health, growth, and development. Progress continues in pediatric transplantation, and current patient and graft survival is excellent.

Although single-center reports provide insight into many issues, larger registry data provide a more substantive overview of the state of transplantation. The leading registry is the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS).[1,2] In addition, data for all transplantations performed in the United States are collected through the Organ Procurement Transplant Network (OPTN), and they are regularly analyzed by the Scientific Registry of Transplant Recipients (SRTR).[3,4]

## End-Stage Renal Disease in Children

According to the United States Renal Data System (USRDS), 1343 individuals aged 19 years or younger began treatment for ESRD in 2008.[5] The incidence of ESRD in this age group is 15.5 per million per year. Because ESRD is much more uncommon in children, this rate is well below the overall national incidence of ESRD of 362 per million per year.

The etiology of renal disease in the pediatric transplantation population is summarized in Table 46-1. According to these NAPRTCS data, the five most common diagnoses are renal aplasia/hypoplasia/dysplasia, obstructive uropathy, focal segmental glomerulosclerosis (FSGS), reflux nephropathy, and chronic glomerulonephritis.[1] These diagnoses account for just over half the transplantations performed. The causes of renal failure are distinctly different from those in adults; specifically, congenital abnormalities and obstructive uropathy are the leading causes for transplantation. In addition, FSGS is the most common acquired renal disease and is much more common in children compared with adults.

Within the pediatric population, the prevalence of causes varies by age, sex, and race.[1] Congenital causes are more prevalent in younger children, whereas acquired diseases tend to become manifest in older children. Overall, 59.4% of the recipients are male, and males represent the majority of the recipients with obstructive uropathy (85.2%), aplasia/hypoplasia/dysplasia (61.8%), and FSGS (57.8%). Reflux nephropathy, chronic glomerulonephritis, and lupus nephritis are more prevalent in females, with females accounting for 56.7%, 57.0%, and 83.3%, respectively. Regarding race, for black children, FSGS was the most prevalent diagnosis (23.1%), followed by obstructive uropathy (15%) and aplasia/hypoplasia/dysplasia (13.5%). In white recipients, obstructive uropathy was the most prevalent etiology (17.0%), followed by aplasia/hypoplasia/dysplasia (16.9%) and FSGS (9.0%).

## Recipient Evaluation

Any child with ESRD should be considered for transplantation. Absolute contraindications are rare and include untreated malignancy or systemic sepsis. Relative contraindications include severe systemic disease that profoundly limits the patient's life span or a social situation that makes follow-up with post-transplantation care and immunosuppression regimen absolutely impossible. At times, the decision whether to transplant a child with a poor quality of life or significant impairment can be extremely difficult. In such situations, a thorough discussion focused on the expectations and goals for that child is helpful.

All children with progressive chronic renal insufficiency should be evaluated by a multidisciplinary pediatric transplantation team, including a pediatric nephrologist, a transplantation surgeon, social worker, and nutritionist. In addition, many teams include pediatric urologists and clinical psychologists, with other experts included as indicated. Ideally, the child would be fully evaluated before initiating dialysis. This can facilitate evaluation of potential living donors and permit preemptive transplantation, obviating the need for dialysis. Regarding infant size, although it is often stated that approaching 10.0 kg is ideal, it is clear that transplantation can be performed successfully in smaller infants at experienced centers.[6–8] The guiding principle should be to optimize the situation as much as possible but not let an arbitrary weight target compromise the health of the child.

Our standard evaluation process is summarized in Table 46-2. Every effort should be made to optimize the

**TABLE 46-1**

**Primary Diagnosis for Renal Transplantation Recipients ($N$ = 9854) Age 20 Years and Younger**

| *Disease* | % |
|---|---|
| Aplasia/hypoplasia/dysplasia | 15.9 |
| Obstructive uropathy | 15.6 |
| Focal segmental glomerulosclerosis | 11.7 |
| Reflux nephropathy | 5.2 |
| Chronic glomerulonephritis | 3.3 |
| Polycystic disease | 2.9 |
| Medullary cystic disease | 2.8 |
| Hemolytic-uremic syndrome | 2.6 |
| Prune-belly syndrome | 2.6 |
| Congenital nephrotic syndrome | 2.6 |
| Familial nephritis | 2.3 |
| Cystinosis | 2.0 |
| Pyelointerstitial nephritis | 1.8 |
| Membranoproliferative glomerulonephritis type I | 1.7 |
| Idiopathic crescentic glomerulonephritis | 1.7 |
| Systemic lupus erythematosus nephritis | 1.5 |
| Renal infarct | 1.4 |
| Berger (IgA) nephritis | 1.3 |
| Henoch-Schönlein nephritis | 1.1 |
| Membranoproliferative glomerulonephritis type II | 0.8 |
| Wegener granulomatosis | 0.6 |
| Wilms' tumor | 0.5 |
| Drash syndrome | 0.5 |
| Oxalosis | 0.5 |
| Membranous nephropathy | 0.4 |
| Other systemic immunologic disease | 0.3 |
| Sickle cell nephropathy | 0.2 |
| Diabetic glomerulonephritis | 0.1 |
| Other | 9.8 |
| Unknown | 6.2 |

From North American Pediatric Renal Trials and Collaborative Study (NAPRTCS) 2008 Annual Report. Available at www.naprtcs.org. Accessed March 20, 2010.

**TABLE 46-2**

**Evaluation of Pediatric Kidney Transplantation Candidate**

- History and physical examination
- Laboratory tests:
  - Hematologic (complete blood cell count with platelets; prothrombin time/partial thromboplastin time)
  - Biochemistry (renal function, electrolytes, liver function)
  - Serologic studies (hepatitis herpesvirus B and C, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, human immunodeficiency virus)
  - ABO blood typing
  - Tissue typing (human leukocyte antigen typing; alloantibody screening)
- Urinalysis
- Chest radiograph
- Electrocardiogram
- Psychosocial assessment
- As indicated evaluations:
  - Voiding cystourethrogram/urodynamic studies
  - Vascular imaging
  - Hypercoagulable workup

medical management of the child with ESRD, including management of bone disease, optimization of nutrition, and completing childhood immunizations. Several aspects of the evaluation of the pediatric recipient are unique and deserve special attention. One is the evaluation and management of bladder function. Urologic anomalies are common, and many will have also undergone previous urologic procedures. Rarely, the bladder may be inadequate for transplantation. Expertise in such issues, or a close working collaboration with pediatric urology, is essential. Nutrition is also of paramount importance to optimize growth and development. Finally, it is important to evaluate and optimize issues related to the psychological state of the child and caregivers.[9] Adequate social support is vital for all involved. The stress of a chronically ill child undergoing a complex procedure places a great strain on all, and the need for ongoing education and reassurance is significant. In older children, it is important to ensure they are actively involved. Adolescents can be particularly challenging, because the risk of noncompliance appears to be greatest in this group.

In addition to these factors, several other issues require special attention. One is the potential need to evaluate the patient's vasculature. As renal replacement therapy has improved, it is now possible to successfully hemodialyze smaller children, including neonates. These therapies require indwelling catheters, leading to increased rates of iliac and vena cava thrombosis. The lack of adequate venous outflow can make transplantation difficult and limit the standard options.[10] Thomas and coworkers proposed a screening algorithm for patients at risk, focusing on young children with a history of femoral vein catheterization or history of any intra-abdominal process associated with inflammation.[11] In addition, patients with a history of venous thrombosis, early graft loss, or recurrent vascular access thrombosis should be under evaluation for a hypercoagulable state. Good results can be obtained in such patients with anticoagulation prophylaxis.[12]

The potential need for native nephrectomy should be addressed. Native nephrectomy is much more common in children compared with adults. Nationally, 22% of children have had all native renal tissue removed before transplantation.[1] Potential indications for native nephrectomy include recurrent severe infections because of reflux nephropathy, uncontrolled hypertension, and congenital nephrotic syndrome. In the case of nephrotic syndrome, the concern centers on these children being hypercoagulable because of the significant proteinuria. Children with polycystic kidney disease may require native nephrectomies if there is recurrent bleeding, infections, or pain. In select cases, nephrectomy may be warranted if the kidneys are so enlarged that the transplanted kidney would be compromised. Some contend that massive polyuria in small infants is an indication for nephrectomy, arguing that postoperative fluid management is made easier, thus decreasing the risk of graft hypoperfusion. Although this may have appeal, careful attention to postoperative management can often avoid this as the sole indication for nephrectomy. In addition, some believe that children with FSGS should undergo native nephrectomy, suggesting it simplifies the diagnosis of recurrent disease, because any proteinuria reflects disease in the graft rather than persistent proteinuria from the native kidneys. In such situations, an attempt at "medical nephrectomy" with nonsteroidal therapy is worth consideration.

In addition to a rational consideration of the risks and benefits of native nephrectomy, the timing of the nephrectomy is important. In children on renal replacement therapy, bilateral native nephrectomies may be safer and easier to accomplish in the weeks before transplantation. In children not on renal replacement therapy, the issue is more complex. We prefer not to perform bilateral nephrectomies at transplantation because this combines two major procedures. We also perform the transplant through a retroperitoneal approach even in small infants, which does not provide access to the contralateral native kidney. For children requiring bilateral native nephrectomy, and who are not yet on dialysis, some will have sufficient renal reserve to tolerate a unilateral left nephrectomy before transplantation and still not require dialysis. In this situation, at transplantation we extend the standard right retroperitoneal incision slightly cephalad and perform a right native nephrectomy. In cases where unilateral native nephrectomy prior to transplantation would require initiation of renal replacement therapy, we typically remove the ipsilateral native kidney during the transplantation procedure. The remaining contralateral native kidney can be removed several months after transplantation if still indicated.

In considering when to perform the transplantation, any child currently on renal replacement therapy should undergo transplantation as soon as a suitable living donor is identified or a deceased donor organ becomes available. In children not yet on dialysis, transplantation should be performed before the onset of symptoms of uremia. It is important to be aware of the impact of ESRD on growth and development. In patients with FSGS or lupus nephritis, transplantation is typically delayed until the disease is quiescent, which may preclude preemptive transplantation. In most other situations, preemptive transplantation provides significant benefit by obviating the need for dialysis. Unfortunately, only 33% of children who receive a living donor transplant and only 13% of deceased donor recipients are transplanted before initiation of dialysis.[13]

## Urologic Issues

The high incidence of urologic issues in children requires careful evaluation of bladder function before transplantation.[14] In addition to dysplasia and bladder outlet obstruction, bladder function may be abnormal because of neuropathy, acquired voiding dysfunction, or acquired bladder pathology. Any previous surgical bladder augmentation will impair normal bladder function. A history of urinary incontinence, frequent urinary tract infections, previous urologic procedures, and the need for bladder catheterization should prompt further investigation. In patients with suspected bladder dysfunction, a voiding cystourethrogram (VCUG) should be obtained with urodynamic measurements. A pressure of less than 30 cm $H_2O$ during the filling portion of the VCUG generally indicates the bladder will be suitable.

The timing of any surgical intervention warrants careful consideration. In some patients with anuria/oliguria, the bladder may not be functional, although it is often too early to tell if it will eventually become suitable. Once bladder augmentation is performed, the patient will need to continue catheterizing long term, because the bladder will not have normal function. Urologic procedures that preserve native renal function for many years are clearly prudent, but interventions before transplantation should be planned by carefully considering the risks and benefits of the procedure and being mindful of the impact on subsequent transplantation and long-term management.

## Dialysis Access

For children who do not undergo preemptive transplantation or who initially present with ESRD, establishment of adequate dialysis access is of paramount importance. Proper dialysis access is necessary for adequate dialysis, which is directly linked to the quality of life and health of the patient. According to USRDS data, at the end of 2008, 60% of patients aged 19 years and younger were on hemodialysis, whereas 40% were on peritoneal dialysis.[5] Both are suitable options, and the choice is best made on an individual basis, considering the patient's and family's preferences and skill levels, as well as the treatment options available at the local site.

Regarding hemodialysis, all attempts should be made to create a primary arterial venous fistula. For patients without adequate veins, a polytetrafluoroethylene graft is required. A native fistula is preferred because of superior patency rates, but they require several weeks to mature before being accessed. For patients in need of urgent hemodialysis, the only option is a temporary catheter. Approximately three fourths of pediatric patients have a temporary catheter at the time of initiation of dialysis.[15] The use of these catheters is associated with increased risks of infection and poor clearance with dialysis. In addition, catheters can lead to central venous stenosis and thrombosis, making future vascular access efforts more difficult. Accordingly, the jugular vein is preferred rather than the subclavian vein for catheter placement.

Peritoneal dialysis requires placement of a Tenckhoff catheter. A double-cuffed peritoneal dialysis catheter is inserted with the loop of the catheter placed in the pelvis. During the procedure, it is important to ascertain that fluid can instill and drain easily. The use of double-cuffed catheters and orienting the catheter so that it exits the skin pointing downward are associated with a lower incidence of infection.[15]

## Donor Selection

Living donor transplantation is the preferred option for all patients with ESRD. Living donor transplantation offers the best outcomes, compared with deceased donor transplantation.[4,16] In addition, living donor transplantation can be performed as soon as a suitable donor is identified, minimizing exposure to ESRD. Living donors may be either genetically related or unrelated to the potential recipient. The results from both types of living donors are equivalent, and both are superior to outcomes from deceased donors. Potential living donors should undergo a full evaluation by a transplant center experienced in this process. The donor must be willing, be in good health, and have two normal kidneys. In addition, the donor and recipient must be ABO compatible. Although there is a growing interest in strategies to cross this barrier, efforts are relatively limited in the pediatric population.[17]

The recipient should also have a negative lymphocytotoxic crossmatch with the potential donor. Crossmatching is done to determine that the recipient does not have preformed antibodies directed against the donor's human leukocyte antigens (HLA), which would likely cause hyperacute rejection and rapid graft loss. The most common causes of anti-HLA antibodies are blood transfusions, previous transplantation, and pregnancy. Strategies to manipulate antidonor antibodies are being investigated and include intravenous immunoglobulin, plasmapheresis, and other agents designed to alter B-cell responses and/or complement.[18–21] Transplanting recipients who are either ABO or anti-HLA antibody incompatible with their donors requires additional immunologic manipulation, with its attendant risks, and the long-term results appear inferior compared with compatible transplantations. Accordingly, there is growing interest in paired kidney exchange programs, which offer a larger living donor pool and the possibility of finding a more compatible donor.[22]

## EVALUATION OF THE POTENTIAL LIVING DONOR

Evaluation of potential living donors should occur independent of the recipient's evaluation, giving donor safety the highest priority. Our standard evaluation process is summarized in Table 46-3. Although HLA matching has traditionally played an important role in choosing which living donor to evaluate, current immunosuppression has minimized the impact of matching, and we believe the best potential living donor is the individual who is most motivated. Lacking that distinction, and all other factors being equal, we would choose the donor with the best HLA match. It is also important to consider other issues unique to each donor, including psychosocial concerns (such as the need to care for other children), the need to care for the recipient, and what options would be least disruptive to the family unit. When discussing the situation with the family, it is important to consider other siblings who may also need renal transplantation in the future, because this can play a role in deciding which donor donates to which recipient.

Living-kidney donation appears to be safe and has been practiced for more than 50 years. The risk of operative mortality appears to be 3 in 10,000.[23,24] After the procedure, living kidney donors appear to do well over the long term as well. The introduction of laparoscopic donor nephrectomy has been a significant step forward for the individuals who consider kidney donation. For the donor, the laparoscopic procedure is associated with quicker recovery and appears as safe as open-donor nephrectomy. Although there was some concern that laparoscopic donation might result in inferior outcomes compared with open-donor nephrectomy, particularly in small infants, this concern has not been substantiated.[25–27]

**TABLE 46-3**

| Evaluation of Living Kidney Donor |
|---|
| History and physical examination |
| Laboratory tests: |
| Hematologic (complete blood cell count with platelets; prothrombin time/partial thromboplastin time) |
| Biochemistry (renal function, electrolytes, liver function) |
| Serologic studies (hepatitis herpesvirus B and C, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus) |
| ABO blood typing |
| Tissue typing (human leukocyte antigen typing) |
| Urinalysis |
| Chest radiograph |
| Electrocardiogram |
| Psychosocial assessment |
| Helical computed tomography scan |

## EVALUATION OF THE DECEASED DONOR

For children who do not have a living donor, deceased donor transplantation is the only option. Deceased donors are individuals who have either suffered brain death or whose heart has irreversibly stopped beating. The latter group has often been referred to as "DCD" for donation after cardiac death. In the United States, deceased donor organ allocation is governed by policies established by the OPTN. These policies undergo constant refinement as data support more rational and fair allocation strategies. After a potential deceased donor is identified, the blood type, HLA type, and other relevant donor factors are entered into the national database maintained by the United Network for Organ Sharing (UNOS). Kidney allocation is driven by a point system based on HLA matching, the level of anti-HLA antibodies in the candidate, and waiting time. Waiting times in many areas of the country for adults are 5 or more years.

The OPTN has recognized the special needs of children with end-stage organ disease and continuously reviews policy in an effort to provide them optimal access to deceased donors. In 2005, the kidney allocation system was changed from a system that provided pediatric priority points based on age and waiting time to a system that provides relative priority to donors less than 35 years of age. At present, candidates who are listed at less than 18 years of age are offered kidneys from donors less than age 35 after any zero mismatch candidates, candidates with a panel reactive antibody greater than 80%, or candidates receiving a kidney with a nonrenal organ. The rationale for this modification was based on the observation that pediatric waiting times remained substantial despite the efforts to provide priority. In addition, in an effort to optimize outcomes, centers were waiting for the best donors. The donor age threshold was based on an analysis demonstrating donor age between 5 and 35 years had the lowest relative risk of graft failure.[28,29]

The new policy has decreased pediatric waiting time while maintaining access to the best deceased donors. As was expected, the shorter waiting time has been associated with lower HLA matching, reflecting the greater priority for transplantation compared with HLA matching. The decrease in HLA matching is small, and there appears to be no adverse impact on outcomes.[28] Waiting for a better-matched kidney is not prudent, because there is no advantage, and it only delays the benefit of transplantation. In addition, because of the relatively good access to the best deceased donors, the need to use expanded criteria kidneys,[30] DCD kidneys,[31] and en-bloc kidneys from small pediatric donors[32] is less than in the adult population. An important exception might be the highly sensitized recipient who has waited for a long period of time. In such situations, the decision needs to consider the risks and benefits of the options available.

The improved access to deceased donors has been associated with a decrease in the number of living donor transplantations performed in children. Prior to 2005, living donors accounted for more than half of the pediatric transplantations. This proportion has fallen to less than 40% in recent years and is a source of concern. Although greater access to the best deceased donors is appealing, it is important to note that outcomes are significantly better with living donors compared with deceased donors. Specifically, living donors up to 55 years of age provide greater long-term survival compared with even the ideal deceased donor.[16]

# Transplantation

## PREOPERATIVE PREPARATION

Deceased donor recipients are admitted once a kidney is accepted. We typically also admit our living donor recipients, although they can be admitted on the day of surgery if their dialysis regimen is stable or if they are not on dialysis. On admission, the need for dialysis is assessed. It is important to ask about intervening health issues since the last visit, as well as examining for any evidence of ongoing infection.

## ANESTHESIA

Close coordination with the anesthesia team is vital to the conduct of any operation, and it is particularly important in kidney transplantation in small infants. Maintaining adequate volume status is critical. Because a kidney from an adult donor is typically used, blood flow to the graft often equals the entire cardiac output of the recipient. Hypotension can be particularly problematic. Many children have an obligate polyuria that can cause hypovolemia if not carefully monitored. After reperfusion, the new kidney can also sequester several hundred milliliters of blood, further aggravating hypovolemia.

## OPERATIVE PROCEDURE

After induction of general anesthesia, adequate intravenous access is established. In children larger than 20 kg, we do not place a central venous line if adequate peripheral access can be established. For smaller children, we find central venous access useful, both for fluid administration as well as for monitoring central venous pressure. In these smaller children, we also place an arterial line to permit constant blood pressure monitoring. The child is positioned supine. A Foley catheter is inserted and connected to a three-way irrigation system, using dilute providone-iodine (Betadine) in saline. In other centers, an antibiotic solution may be preferred. This arrangement allows the bladder to be filled and drained outside of the operative field as necessary. The child's temperature should be monitored closely, especially with small children who may become hypothermic with either fluid resuscitation or the perfusion of the cold kidney. In addition to routine monitoring, ongoing attention must be directed to volume status. It is vital that the arterial blood pressure and central venous pressure are adequate when the kidney is reperfused. For infants and small children, the central venous pressure is usually maintained in the range of 12 to 18 cm $H_2O$ by administration of crystalloid and/or colloid as necessary. Near completion of the vascular anastomoses, we typically give 0.5 mg/kg of mannitol intravenously. We do not routinely employ a loop diuretic.

## OPERATIVE TECHNIQUES

### Small Children (<20.0 kg)

Historically, many have performed kidney transplantations intra-abdominally in infants and small children using a midline incision. Since 1998, we have used a retroperitoneal approach similar to that used in adults, even in infants. Placing the kidney on the right side is preferable, because this gives the easiest access to the vena cava. A curvilinear skin incision is made in the lower quadrant. The abdominal wall musculature is divided, and the preperitoneal space is entered. Attempts are made to stay extraperitoneal. The spermatic cord is mobilized and preserved in males, whereas the round ligament is routinely divided in females. The dissection is carried medially until the common iliac vessels, the distal aorta, and vena cava are visualized. If a right native nephrectomy is necessary, this is performed at this point.

The site of the vascular anastomosis depends on kidney size as well as the size of the child. In general, in small children, the renal vein is anastomosed to the vena cava, and the renal artery is anastomosed to either the distal aorta or the common iliac artery. The lymphatics overlying these vessels are divided between ties in an effort to minimize the risk of a lymphocele. When an aortic anastomosis is planned, the aorta is mobilized from below the inferior mesenteric artery to the bifurcation. Lumbar branches are controlled with Pott ties rather than ligated. The common iliac arteries are controlled just distal to the aortic bifurcation. The vena cava is mobilized to allow placement of a side-biting vascular clamp, which can require ligation of several lumbar veins. Once the recipient's vessels have been exposed, the donor kidney is brought into the operative field. The kidney should be inspected for any evidence of unsuspected pathology. The renal vessels are examined. After preparing the kidney, thoughtful consideration needs to be given for the fit of the kidney in the recipient's body cavity. Particular attention must be focused on the length of the renal vessels as well as their orientation. It is important to consider the final resting position of the kidney after it is perfused, the retractor is removed, and the fascia closed.

The venous anastomosis is performed first. The vena cava or iliac vein is controlled with a side-biting clamp. A longitudinal venotomy is made along the anterolateral or lateral aspect of the vein. The renal vein is cut to length, again after considering the ultimate lie of the kidney, and mindful that a redundant renal vein may predispose to thrombosis. We place two corner sutures of 5-0 Prolene. The anastomosis is performed in a running manner. An end-to-side arterial anastomosis is then performed to the recipient's distal aorta or common iliac artery. The recipient vessels are controlled using vessel loops or gentle spring clips. A longitudinal arteriotomy is made, mindful of the final orientation of the renal artery. We enlarge the arteriotomy using a 4.0-mm aortic punch. The renal artery is then sewn end-to-side using a running 6-0 Prolene suture. We typically perform the procedure with loupe magnification.

If multiple renal arteries are present, they can either be implanted separately or syndactylized before reimplantation. When the vessels are syndactylized, it is important to consider if this will allow the vessels to lie in good position, because syndactylization will fix the vessels relatively firmly in two dimensions. This can limit the options of where the anastomosis can be suitably performed or lead to kinking of one or both of the donor arteries if the final position of the kidney is not anticipated.

Before completion of the arterial anastomosis, the hemodynamic state of the patient should be considered. Intraoperative assessment of the vascular volume by direct assessment of the vena cava is possible. Mannitol is also given at this time. Because of the size of the adult kidney, it can be both slow to perfuse as well as sequester a significant volume of blood. The anesthesiologist must be ready to give volume replacement promptly as indicated. At this point, the clamp is removed from the vein and bleeding assessed. Next, while the renal artery is gently compressed with vascular pickups, the arterial clamps are removed, restoring distal blood flow. After a few seconds, flow is established to the kidney. In small children, we occasionally will briefly reclamp the recipient's vessels distal to the arterial anastomosis to provide preferential flow to the kidney. The field is carefully examined for bleeding. The color and turgor of the graft are assessed. The renal artery should have a good pulse, and a thrill can usually be appreciated as well. Both the lower and upper poles should be assessed for perfusion. The renal vein should be full but not tense, with a turgor similar to the vena cava. The lie of the kidney is again examined.

Attention is then directed to the ureteroneocystostomy. We generally perform the ureteral anastomosis as an extravesical ureteroneocystostomy,[33–35] although others routinely prefer the transvesical Politano-Leadbetter approach.[7,36] The Foley catheter is clamped and the bladder is filled. A site on the dome of the bladder is selected where the ureter will sit without any angulation. The muscle wall of the bladder is divided, exposing the bladder mucosa. An opening is then made in the mucosa. The donor ureter is trimmed to length. Care should be taken to make sure it is sufficient to allow a tension-free anastomosis, but excessive length should be avoided because of the risk of ureteral obstruction or stricture resulting from inadequate perfusion of the distal ureter. The end of the ureter is spatulated, and a mucosa to mucosa anastomosis is performed using running 5-0 polydioxanone (PDS) suture. The caveat with running suture is that care must be taken to avoid cinching on the suture line, because this results in a purse-string effect causing stenosis. To prevent vesicoureteral reflux, the bladder muscle wall is approximated over the anastomosis using interrupted 4-0 PDS suture. This allows the ureter to take a tangential course under the bladder wall so that during micturition, the transvesical portion of the ureter is compressed by the overlying bladder wall. An adequate length for this tunnel is essential to prevent vesicoureteral reflux. In patients with a normal bladder and a good blood supply to the distal ureter, we do not routinely place a stent. If there is any concern regarding the ureteral anastomosis, either because of the donor ureter or the quality of the recipient's bladder, we place a double-J ureteral stent, which is removed after a few weeks as an outpatient procedure.

After completing the ureteral anastomosis, the kidney is again inspected with attention to the renal vessels and the lie of the kidney once the retractor is removed. Careful planning and attention to detail before performing the anastomosis is usually rewarded at this point. The fascia is closed in one layer with a running suture. The skin is closed using a running absorbable suture. The urinary catheter is flushed with saline to remove any clots that might obstruct the catheter. For small infants, the volume resuscitation required to ensure excellent renal perfusion, combined with the size of the kidney decreasing respiratory excursion, may make ventilatory support in the immediate postoperative period necessary. If the patient's oxygen saturation and pulmonary mechanics are satisfactory, the patient can be extubated in the operating room.

### Larger Children (≥20.0 kg)

The technique for transplantation in larger children is similar to that in adults. We prefer to put the kidney on the right side when possible. An incision is made in the right lower quadrant, extending from one to two fingerbreadths above the pubis to just lateral of the rectus sheath. As in smaller children, the placement of the arterial and venous anastomoses depends on the size of the child and the renal vessels. The venous anastomosis can be done to the vena cava, the common iliac, or the external iliac vein. The arterial anastomosis is performed to the distal aorta, the common iliac, or the external iliac artery. After revascularizing the kidney, the ureteroneocystostomy is performed using an extravesicular technique. At the completion of the operation, these larger children are extubated.

### Ureteral Reconstruction in Patients with Previous Urologic Procedures

The ideal urinary reservoir stores a reasonable volume at a low pressure, does not leak, and empties nearly completely with voiding.[14] In the majority of cases, the ideal reservoir is the patient's bladder. If the bladder functioned normally before development of oliguria, it is likely to function adequately after transplantation. Nonetheless, up to 30% of pediatric recipients will not have normal bladder function, and frequently a surgical augmentation or other urologic procedure has been performed before referral for transplantation.

Drainage into an augmented bladder or urinary conduit is an appropriate management strategy when the native bladder is unsuitable or absent.[37,38] When indicated, we prefer to have the intended urinary reservoir created and suitable for use before the transplant procedure. Intraoperatively, when planning the ureteroneocystostomy to an augmented bladder, it is important to consider the blood supply to the augmented section so as not to compromise it during the transplant. It is preferable to perform the ureteroneocystostomy to the native bladder, and this can be accomplished in most situations. An antireflux ureteroneocystostomy is essential, and it is most readily performed with the bladder wall.

Patients with an augmented bladder or urinary conduit are at increased risk for urine infection, but compared with historical controls, graft survival is not adversely affected.[39] The rate of surgical complications related to the ureteral anastomosis is higher in these patients, approximately 20%.[39–41] Regardless of the etiology of the bladder dysfunction, these patients require regular clean intermittent straight catheterization after transplantation.

Children with obstructive uropathy from posterior urethral valves will not have normal bladder function, and this can contribute to renal dysfunction after transplantation.[37]

Awareness of these issues is vital, and evaluation with follow-up urodynamic studies is frequently indicated in children with voiding disorders. Bladder dysfunction, such as hypocompliance and/or hyper-reflexia, requires medical or surgical treatment.

## Postoperative Care

Attention to detail in the postoperative period is essential. Special care must be directed to the fluid and electrolyte status. Many children are polyuric before transplant, and this obligate urine loss will continue in the immediate postoperative period. Intravenous fluids are administered, taking into account urine output as well as insensible losses. The composition of these solutions is adjusted as needed, depending on regular measurement of serum electrolytes. Serum sodium, potassium, and calcium levels are followed closely and replaced as necessary. Heart rate, blood pressure, and central venous pressure are carefully monitored. No single factor alone is entirely reliable in assessing intravascular volume.

For patients who were oliguric or who had native nephrectomies before transplantation, monitoring urine output is an excellent monitor of graft function. For patients who made significant urine before transplantation, evaluation of graft function is more difficult. The volume of urine production may be suggestive. In addition, the serum creatinine concentration should fall with time. Recipients with oliguria should be rapidly evaluated. The urinary catheter should be flushed with small volumes of sterile saline. The volume status of the patient should be carefully assessed. A fluid bolus is usually warranted, both as a diagnostic test and as therapeutic intervention. Doppler ultrasonography will confirm adequate arterial flow and venous outflow. Ultrasonography will also show evidence of fluid or blood around the kidney, as well as assess for possible ureteral obstruction. In patients who appear to be adequately volume loaded and hemodynamically stable, a dose of diuretic can be given. It is important to do this carefully, because sudden massive urine output can cause significant intravascular volume depletion, which can then lead to problems with renal perfusion. In patients who are massively volume overloaded or have significant electrolyte abnormalities, dialysis may be indicated.

If ventilated postoperatively, the smaller children are weaned from the ventilator generally within the first 24 hours. Enteral feedings can be started at a slow rate almost immediately after the extraperitoneal approach. Infants who were on tube feedings before transplantation should resume these tube feedings, because they usually will not feed orally in the immediate post-transplantation period. Hypertension can be problematic. The volume loading associated with the procedure as well as the use of calcineurin inhibitors (CNIs) for immunosuppression can result in significant hypertension, which can be severe and require aggressive therapy to prevent seizures and other sequelae.

To monitor and replace urine output on an hourly basis, we admit our children to the intensive care unit (ICU). If this can be accomplished on a surgical floor unit, larger children could be admitted to an area specializing in the care of renal transplant patients. Children who are admitted into the ICU are typically transferred to the floor unit within 1 to 2 days. Most children leave the hospital 5 to 7 days after transplantation, assuming the family is comfortable with the immunosuppression regimen.

## Evaluation of Early Allograft Dysfunction

Ideally, the donor kidney should begin to make urine shortly after revascularization. The likelihood of this occurring depends on multiple factors, beginning with the quality of the donor organ. Living donor kidneys will generally function immediately because of the healthy state of the donor as well as the shorter cold ischemic time for the kidney. For deceased donor kidneys, the cold ischemic time is generally longer. In addition and more important, there are multiple factors associated with the donor death, including hypotension, the potential need for high doses of vasopressors, and other issues related to the overall health of the donor.

Regardless of the donor source, the assessment of the graft begins in the operating room, evaluating the graft for color and turgor as well as vascular anastomoses. Particular attention should be directed to considering how the kidney is positioned once the abdomen is closed and how this could impact the vasculature. The renal artery will often have a thrill suggestive of excellent flow and low intrarenal resistance. Assuming the technical aspects of the procedure appear satisfactory, additional volume for the kidney not making urine is the best option. Once the patient is adequately volume loaded, loop diuretics may be used to gently encourage a diuresis. In patients who were anuric before the procedure, continued failure to make urine in the postoperative period should prompt a bedside Doppler ultrasound examination. For patients who made urine before the transplantation, determining whether the transplanted kidney is making urine is more difficult, although sometimes the amount of volume being produced will give a sign that the kidney is working. During the first 24 hours, the serum creatinine level should fall as well. If there is still concern about function, a Doppler ultrasound study should be obtained, and any suggestion of problems with the arteriovenous signal should initiate a prompt return to the operating room. In general, the ultrasound evaluation will be fine, or, occasionally, there will be a modest reduction in flow suggestive of increased intrarenal resistance, most commonly because of acute tubular necrosis. This condition resolves without any specific intervention. Other diagnostic studies are less frequently required. Renal arteriography is rarely indicated. Radionucleotide scans are used by some centers, but we find them less helpful than ultrasonography. A radionucleotide scan may be helpful in documenting a suspected urinary leak.

Complications related to the ureteral anastomosis include leaks and obstruction. The risk of ureteral complications is approximately 7% to 9%.[7,42,43] A leak at the ureteral anastomosis generally manifests in the first few days after the transplant. Leaks detected in the first 2 to 3 days may be repaired operatively. Leaks detected later can generally be managed nonoperatively with a percutaneous nephrostomy. This stent is subsequently advanced across the anastomosis into the bladder. The stent is usually left to external drainage for

several days and is then capped. If a large urinoma is present, separate drainage of this collection may be required.

Obstruction of the urinary system can occur at any time. An early obstruction is usually related to technical problems with the anastomosis or other mechanical issues, such as torsion of the ureter, while later obstruction often reflects ischemic stricture. Because the ureter relies on small arterial vessels from the lower pole of the kidney, it should be no longer than necessary. Late ureteral stenoses generally require operative intervention, with resection of the stenotic segment and reconstruction. Vesicoureteral reflux may cause recurrent urinary tract infections or graft dysfunction, and require operative intervention in up to 5% of patients.[44]

Another complication after retroperitoneal kidney transplantation is lymphocele. Lymphoceles may produce discomfort or allograft dysfunction. The diagnosis is established by ultrasound-guided percutaneous aspiration of clear fluid with a creatinine concentration equivalent to serum. Percutaneous drainage is associated with a very high incidence of recurrence, and the preferred treatment is creation of a peritoneal window. This can be accomplished laparoscopically or through a small open incision, with drainage of the lymphocele into the peritoneal cavity.

In instances of renal vein thrombosis, the graft is usually not salvageable. The causes of renal vein thrombosis are several, and the exact mechanism may be difficult to ascertain but include immunologic factors, a hypercoagulable state, and technical issues.

# Immunosuppression

Significant advances have been made in understanding the immune response and several new immunosuppressive agents have been developed. The introduction of new agents has permitted consideration of avoidance, conversion, and minimization strategies in an effort to minimize toxicities associated with specific agents. There are several potential regimens, but all require a balance between prevention of rejection and unwanted side effects of immunosuppression. Most centers use standardized protocols for recipients based on immunologic risk. Immunosuppressive agents are used for induction, maintenance, and treatment of rejection episodes.

## ANTIBODY PREPARATIONS

### Antilymphocyte Antibodies

Antilymphocyte antibodies include polyclonal preparations, such as equine antithymocyte globulin (ATGAM) and rabbit antithymocyte globulin (Thymoglobulin), and the monoclonal antibody preparations muromonab-CD3 (OKT3) and anti-CD52 (Alemtuzumab). Of these antilymphocyte agents, Thymoglobulin is currently predominant, and the use of the others is either rare or of historic interest. Antilymphocyte antibodies act by lymphodepletion, as well as by interactions with cellular receptors. The use of antilymphocyte induction regimens has declined precipitously with time.[1,2] We currently restrict the use of Thymoglobulin to recipients at higher risk for immunologic graft loss, such as patients requiring retransplantation, highly sensitized patients, or black recipients. These agents are also effective in the treatment of acute cellular rejection.

### Anti–interleukin-2 Receptor Monoclonal Antibodies

Two monoclonal antibodies have been developed that bind to the alpha subunit of interleukin (IL)-2 receptor (CD25) and inhibit IL-2–mediated lymphocyte proliferation. Basiliximab (Simulect) and daclizumab (Zenapax), received approval by the U.S. Food and Drug Administration (FDA) in 1998, though only basiliximab is currently marketed. Basiliximab is a chimeric human/mouse monoclonal antibody that is effective in reducing the incidence of acute cellular rejection, with good long-term results and no evidence of increased risk of infection or malignancy.[45–47] The IL-2 receptor antibody is used in induction regimens but is not effective in treating rejection.

## CALCINEURIN INHIBITORS

The introduction of cyclosporine after its FDA approval in 1983 was one of the most significant advances in transplantation. Tacrolimus received FDA approval in 1994. Both agents act through inhibition of calcineurin activity. They first bind to specific cytoplasmic proteins; cyclosporine binds to cyclophilin, and tacrolimus binds to tacrolimus binding protein (also known as FK-binding protein). Both drug-protein complexes then bind to calcineurin, a phosphatase that controls the transport of transcriptional regulator factors across the nuclear membrane. By inhibiting the translocation of these factors into the nucleus, both drugs inhibit transcription of several early T-cell activation genes, most significantly IL-2.

Both cyclosporine and tacrolimus are effective at preventing rejection. A randomized prospective open-label trial performed in Europe in pediatric renal recipients compared tacrolimus with cyclosporine, along with azathioprine and steroids. There was a significantly lower incidence of acute rejection in the tacrolimus group (36.9%) compared with cyclosporine therapy (59.1%).[48] In contrast with this observation, a retrospective analysis of NAPRTCS data comparing cyclosporine with tacrolimus, along with mycophenolate mofetil and corticosteroids, showed equal rates of rejection and graft survival. Although rejection rates were similar, tacrolimus therapy was associated with improved graft function at 1 and 2 years after transplant.[49] Currently, approximately 70% of pediatric recipients are reported as being discharged on tacrolimus compared with 10% on cyclosporine.[1,2]

Cyclosporine side effects include hirsutism and gingival hyperplasia, whereas tacrolimus is associated with increased incidence of post-transplantation diabetes and neurotoxicity. In children who develop a problematic side effect from one agent, conversion to the other agent is appropriate. Both calcineurin inhibitors have significant nephrotoxicity that impact graft function with time.

## MYCOPHENOLATE

Mycophenolate mofetil (MMF) (CellCept) and mycophenolic acid (MPA) (Myfortic) inhibit purine synthesis. MMF is converted in vivo to mycophenolic acid, a noncompetitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is a key enzyme in de novo purine biosynthesis. Although most cells can synthesize purines by either the de novo or the salvage pathway, B and T lymphocytes lack the

salvage pathway. Mycophenolate is thus a selective inhibitor of lymphocyte proliferation, and it has replaced azathioprine (Imuran) as the primary antiproliferative agent.[50] MMF has been demonstrated to be safe and effective in pediatric patients.[51] Experience with MPA in children is more limited, though it appears equivalent.[52,53] The primary side effects are related to leukopenia and gastrointestinal intolerance.

### PREDNISONE

Glucocorticoids have played an integral role in immunosuppression regimens since the earliest days of transplantation. They act primarily through transcriptional regulation, diffusing across the plasma membrane and binding to cytoplasmic steroid receptors. This complex is translocated to the nucleus, where it binds to specific gene promoters and other regulatory regions, inhibiting cytokine synthesis. Corticosteroids are also lymphocytotoxic and possess significant anti-inflammatory activity, inhibiting macrophage function and other nonspecific aspects of the inflammatory response.

Long-term corticosteroid therapy is associated with increased risk of hypertension, hyperlipidemia, diabetes, bone loss, cosmetic disfigurement, and cataracts. Attempts at minimizing corticosteroids have not had a significant effect on these side effects, and efforts are being directed to corticosteroid avoidance. Although it is appealing to consider withdrawal of corticosteroids with time, late corticosteroid withdrawal appears associated with increased risk of acute and chronic rejection. Early corticosteroid withdrawal and corticosteroid-free regimens, with and without antibody induction, have shown promise. Sarwal and associates, at Stanford University, have reported excellent results in a corticosteroid-free protocol using an extended induction with daclizumab, tacrolimus, and MMF.[54] In their recent report, 129 recipients have been treated with a mean follow-up of 5 years. One-year graft and patient survival were 93% and 96%, respectively. The rate of acute rejection was 12% during the first year. Significant improvements in post-transplantation growth and avoidance of steroid side effects were noted. This experience led to a prospective, multicenter randomized study that has been completed, though the results have not yet been published. Similar results have also been reported by the Stanford group in 13 recipients using Thymoglobulin induction in place of daclizumab.[55]

Another large randomized multicenter international trial with 196 pediatric kidney recipients compared rapid steroid withdrawal in children treated with daclizumab, tacrolimus, and MMF with recipients maintained on steroids along with tacrolimus and mycophenolate.[56] Early steroid withdrawal was associated with improved growth and metabolic profiles, with similar acute rejection rates (10.2% vs. 7.1%, respectively) and equivalent graft and patient survival during the first 6 months.

Although encouraging, efforts to withdraw steroids while maintaining acceptable rejection rates have also resulted in regimens with a greater rate of complications of immunosuppression. One multicenter randomized trial of steroid withdrawal after 6 months in recipients treated with basiliximab induction, cyclosporine or tacrolimus, sirolimus, and steroids was halted early because of a high rate of post-transplantation lymphoproliferative disorder (PTLD).[57]

It appears steroid avoidance or early withdrawal is possible in selected patients with good short-term results. Longer-term data are needed, and striking the correct balance of immunosuppression and other side effects remains critical.

### PROLIFERATION SIGNAL INHIBITORS

Proliferation signal inhibitors are a relatively new class of immunosuppressants. Sirolimus (rapamycin) and everolimus are macrolide agents that inhibit a protein, mammalian target of rapamycin (mTOR), which is a critical regulatory kinase controlling cytokine-mediated proliferation. A potential role for sirolimus in renal transplantation has been established.[58] Everolimus also appears effective.[59] There is interest in using mTOR inhibitors to avoid or minimize calcineurin inhibitors and/or corticosteroids, though the optimal strategy remains elusive. Experience to date suggests that complete CNI avoidance is often associated with higher rejection rates, while late CNI replacement or minimization may not offer any benefit with respect to reversing CNI nephrotoxicity.

Sirolimus interacts with calcineurin inhibitors, particularly cyclosporine, and careful monitoring is essential. Like many other immunosuppressive agents, there is evidence to suggest more rapid metabolism of sirolimus in children compared with adults.[60]

### TREATMENT OF REJECTION

Suspected rejection should be confirmed by biopsy. The first-line therapy for acute cellular rejection is pulse corticosteroids. Typically, intravenous methylprednisolone is administered for 3 days, with doses ranging from 5.0 to 25.0 mg/kg/day (maximum dose, 1.0 g). We use 10.0 mg/kg for children younger than aged 6 years and 5.0 mg/kg for children aged 6 years and older, with a maximum dose of 500 mg/day. Severe rejection or rejection refractory to corticosteroids is treated with Thymoglobulin. Treatment of acute rejection is nearly always successful, although late episodes of rejection are less likely to respond. After successful treatment, many consider altering maintenance immunosuppression, including changing to the other calcineurin inhibitor, or substituting sirolimus for MMF; however, there is little evidence to support this approach. An assessment of adherence to the immunosuppression regimen should also be initiated. If the patient's creatinine level does not return to baseline, a follow-up biopsy should be strongly considered. Although most acute rejection episodes reflect primarily T-cell–mediated processes, there is growing recognition of the role of B cells and alloantibodies in immunologically mediated graft injury.

## Outcomes

### GRAFT AND PATIENT SURVIVAL

There are approximately 800 pediatric kidney transplantations performed annually in the United States. In 2009, there were 866 transplantations, with 38.8% living donor and 61.2% deceased donor kidneys. Short-term graft and patient survival after transplantation is excellent. Current graft survival for living donor and deceased donor kidney transplantations in children, stratified by recipient age, is summarized in

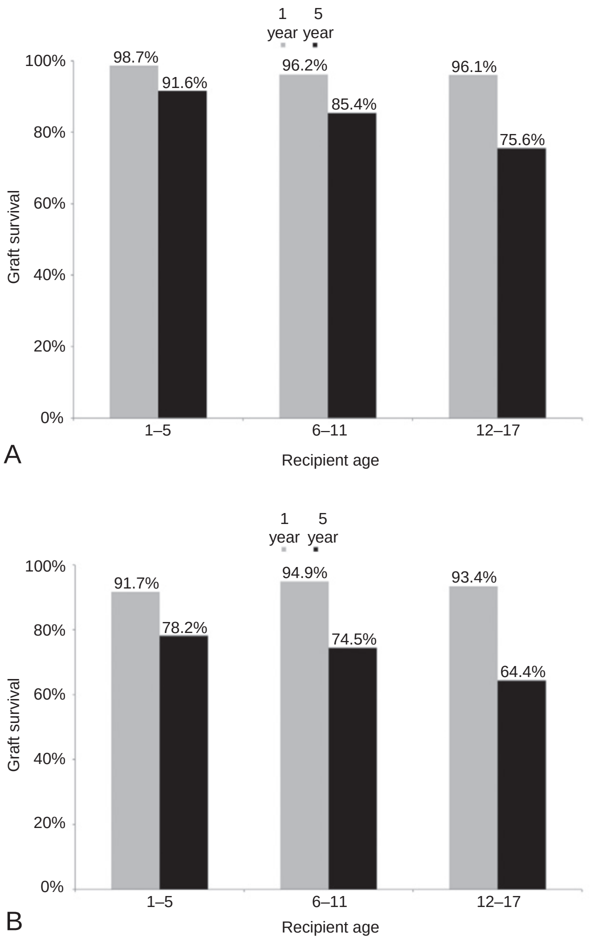


**FIGURE 46-1** **A,** One- and 5-year graft survival of living donor kidney transplantations by recipient age. **B,** One- and 5-year graft survival of deceased donor kidney transplantations by recipient age. (From Organ Procurement Transplant Network/Scientific Registry of Transplant Recipients: 2009 Organ Procurement Transplant Network/Scientific Registry of Transplant Recipients Annual Report: Transplant data 1999-2008. Health and Human Services/Health Resources and Service Administration/Special Pathogens Branch/Department of Transportation. Available at www.ustransplant.org. Accessed September 29, 2010.)

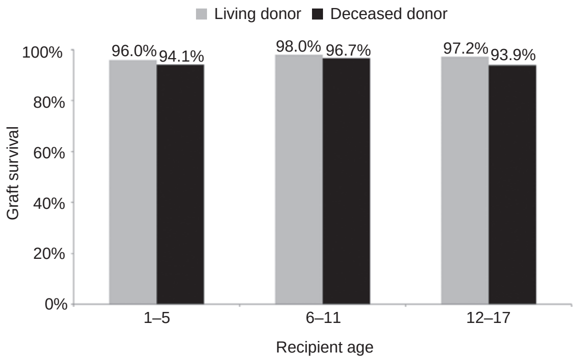


**FIGURE 46-2** Five-year patient survival of living donor and deceased donor kidney transplantations by recipient age. (From Organ Procurement Transplant Network/Scientific Registry of Transplant Recipients: 2009 Organ Procurement Transplant Network/Scientific Registry of Transplant Recipients Annual Report: Transplant data 1999-2008. Health and Human Services/Health Resources and Service Administration/Special Pathogens Branch/Department of Transportation. Available at www.ustransplant.org. Accessed September 29, 2010.)

Figure 46-1. Recipient survival stratified by age range is summarized in Figure 46-2. The leading causes of death are infection (28.9%), cardiopulmonary (15.7%), and malignancy (11.0%).[2] Although patient survival is good, it is important to realize that even with transplantation, these children face a significantly increased risk of mortality compared with the general population.[61]

With time there has been improvement in outcomes for all pediatric age ranges. This improvement is particularly noteworthy in children younger than 2 years of age who previously had the worst graft survival but now have outcomes that equal the outcomes of any age group.[13,50] In fact, the longest transplant half-lives of all recipients are now the youngest recipients, especially if the pediatric recipient receives an adult kidney that functions immediately.[62] These improvements likely reflect better donor selection, improvement in surgical techniques, better immunosuppression agents, and a better understanding of immunosuppression management in children.

Although short-term graft survival in children is excellent, it is important to appreciate that long-term graft survival in the adolescent group (ages 11 to 17 years) is poor (see Fig. 46-2). Adolescent graft survival is less than in all recipient age groups except adults older than 65 years.[4] The reasons behind this significant rate of graft loss are speculative, but noncompliance likely plays a significant role.[63] The higher incidence of recurrent FSGS in this age group may also contribute to graft loss. Regardless of the cause, improving the long-term outcomes in this patient population represents an important focus.

## POST-TRANSPLANTATION OUTCOMES AND RISK FACTORS ASSOCIATED WITH GRAFT LOSS

Smith and coworkers reported that the most common causes of allograft failure reported to NAPRTCS for transplantations performed between 2000 and 2005 are chronic rejection (41.3%), vascular thrombosis (8.1%), recurrence of the primary disease (7.9%), acute rejection (6.3%), and discontinuation of immunosuppression (6.3%).[2] Analysis of large single-center experiences and registry data has revealed risk factors associated with specific post-transplantation outcomes.[2,13,64] For a given child, some of these risk factors, such as their race, age, or primary disease, are not modifiable. Other factors are potentially modifiable, and efforts should be made to mitigate risk.

The type and timing of the transplant affect outcomes. Living donor transplantation is associated with better graft survival compared with deceased donor transplantation.[2,4] Preemptive transplantation is associated with better graft survival compared with patients on dialysis at the time of transplantation. For children on dialysis, the choice of dialysis therapy does not impact graft survival, although graft loss from vascular thrombosis is more common in children on peritoneal dialysis compared with hemodialysis.[65]

## DELAYED GRAFT FUNCTION

Delayed graft function (DGF) is defined as the need for dialysis during the first week after transplantation and is a manifestation of acute tubular necrosis (ATN). DGF is more common in recipients of deceased donor kidneys compared with living donors, because of the impact of cold ischemic time and donor

quality. Nationally, the incidence of DGF after deceased donor renal transplantation is 12.5% in pediatric recipients compared with 23.4% in adult recipients,[50] reflecting the differential donor selection made possible by the allocation system. An analysis of more than 5000 pediatric transplantations has demonstrated that DGF is an independent risk factor for subsequent graft loss.[66] DGF is also associated with increased risk for acute and chronic rejection, likely reflecting the impact of renal injury on the subsequent immune response. DGF limits the ability to use renal dysfunction as a sign of acute rejection, potentially delaying the diagnosis of rejection. We believe that all recipients with DGF longer than 5 to 7 days should be biopsied, and even earlier in patients with increased risk of rejection.

## VASCULAR THROMBOSIS

Vascular thrombosis is currently the second most common reported cause of graft loss.[2] Risk factors include donor age younger than 6 years, cold ischemic time greater than 24 hours, prior transplantation, and peritoneal dialysis before transplantation.[65] Careful consideration of donor quality, along with efforts to ensure adequate perfusion to the graft, may minimize the risk of thrombosis. Patients with ESRD have a higher incidence of hypercoagulable conditions, and any history of thrombosis, including recurrent or unexplained thrombosis of hemodialysis access, should prompt further evaluation.

## ACUTE REJECTION

Acute rejection typically occurs between 1 week and 3 months after transplantation, although it can happen at any time. A rise in the serum creatinine level is frequently the first sign of rejection. Findings such as low-grade fever, graft tenderness, hypertension, or decreased urine output are infrequent. Any renal dysfunction should be promptly investigated. A percutaneous biopsy should be obtained to confirm the diagnosis, because many other processes can lead to allograft dysfunction, including calcineurin inhibitor toxicity, ureteral obstruction, infection, renal artery stenosis, and recurrence of original disease. Acute rejection episodes are treated by either pulse corticosteroids or antilymphocyte antibodies as detailed previously.

Risk factors associated with acute rejection include African-American race, delayed graft function, and a history of allosensitization. Acute rejection, and, in particular, late acute rejection episodes occurring more than 1 year after transplant, are independent risk factors for graft loss because of chronic rejection.[67] One episode of acute rejection increases the risk of graft loss from chronic rejection graft failure threefold, and two episodes of acute rejection increase the risk 12-fold. The incidence of acute rejection is decreasing with time. In the 2003 to 2005 NAPRTCS cohort, 12.2% of living donor recipients and 15.8% of deceased donor recipients had a rejection episode in the first year after transplant.[2]

Acute rejection, even if successfully treated, impacts graft survival and all efforts to minimize this risk are important. Unfortunately, intensifying the immunosuppression regimen is limited by the consequences of nonspecific systemic immunosuppression. Ensuring the patient remains on therapeutic immunosuppression is vital, because noncompliance can be disastrous. Prompt recognition and treatment of rejection is important. Because serum creatinine is a relatively insensitive indicator, particularly in small children with an adult kidney, many advocate protocol biopsies to detect subclinical rejection that may benefit from treatment.

## CHRONIC ALLOGRAFT NEPHROPATHY

Whereas short-term results are excellent, progressive renal dysfunction frequently occurs and is the leading cause of graft failure. This process of chronic allograft nephropathy, often called “chronic rejection,” involves both immunologic and nonimmunologic factors. Although acute rejection episodes are a major risk factor for chronic allograft nephropathy, it is clear other processes can contribute as well. Evidence of antibody-mediated injury is also present in 57% of patients with late allograft dysfunction.[68] Efforts to reduce chronic allograft nephropathy are limited by our understanding of the process. Aside from graft loss, the gradual renal dysfunction associated with chronic allograft nephropathy also adversely impacts the recipient’s general health.

## NONADHERENCE

Adherence with the medical regimen is essential for the success of transplantation. Nonadherence is believed to be largely responsible for the poorer long-term graft survival seen in adolescent recipients. Shaw and coworkers reviewed 112 pediatric renal transplant recipients and found one third had clinically significant periods of medication nonadherence.[69] Nonadherence was significantly more common in adolescents compared with younger recipients. Nonadherence was associated with both acute and chronic rejection, as well as graft loss. The relative lack of reliable measures of adherence and effective interventions has focused research in the field.[70,71] Improved parental involvement and discussion of the child–parent relationship may improve adherence.

## RECURRENT DISEASE

The recurrence of the patient’s primary disease is variable, and recurrence may or may not lead to graft loss. Recurrent disease is a more significant issue in the pediatric population, because of the diagnoses leading to ESRD and their association with higher rates of graft loss after recurrence. FSGS is the most prevalent and clinically significant disease to recur after renal transplantation. In children, the recurrence rate can be as high as 40% to 50%.[72] It can recur almost immediately after transplant, and most recurrences are within the first month. Patients with FSGS should be followed closely after transplantation with urine protein measurements. Graft survival is often worse in adolescents with recurrent FSGS, with up to a 38% risk of graft loss.[73] A circulating permeability factor is believed to play a critical role in the pathogenesis of FSGS. Plasmapheresis is the most frequently used therapy for recurrence, although controlled trials supporting its efficacy are lacking. Some have proposed a role for preoperative plasmapheresis to decrease the risk of recurrence.[74] Others have suggested a role for intensifying the immunosuppression and potentially rituximab. In addition to FSGS, other primary renal causes associated with recurrent disease include membranoproliferative glomerulonephritis types 1 and 2 and IgA nephropathy.[75]

Again, the risk of graft loss is variable, and none constitute an absolute contraindication to transplantation.

In addition to these primary glomerulopathies, other recurrent diseases disproportionately affect the pediatric population. Hemolytic-uremic syndrome can recur after transplantation. Nearly all the risk of recurrence and subsequent graft loss is in those with atypical nondiarrhea-associated hemolytic-uremic syndrome.[76] The risk of recurrence appears related to specific defects of complement activation, and screening for these defects is recommended pre-transplant.[77] Henoch-Schönlein purpura can also recur. The overall risk of renal recurrence after transplantation is 29%, and the risk for graft loss appears equivalent to that observed in IgA nephropathy.[78]

Oxalosis (primary hyperoxaluria type 1) is a metabolic disease caused by a defect in hepatic peroxisomal alanine:glyoxylate aminotransferase, which leads to increased synthesis and excretion of oxalate. The excessive oxalate load leads to urolithiasis, medullary calcinosis, and eventual ESRD. The primary metabolic defect is not corrected by kidney transplantation, and the persistent oxalate load causes subsequent renal graft loss. Simultaneous liver-kidney transplantation is generally advocated as the primary treatment.[79,80] Kidney transplantation alone is uncommon, but has been advocated in selected patients, most notably those who are pyridoxine sensitive or those with lower oxalate burdens.[81]

## MEDICAL COMPLICATIONS

### Infection

Infection is a constant risk of immunosuppression and is one clinical representation of the precarious balance between overimmunosuppression and underimmunosuppression. Great vigilance should be maintained during periods of heaviest immunosuppression, as occurs immediately after transplantation or during treatment of rejection. Additional prophylaxis is warranted during these periods of greatest risk.[82]

Post-transplantation infection accounts for more hospitalizations than acute rejection, even in the first 6 months after transplantation.[83] Post-transplantation infections are predominantly bacterial and viral. Fungal infections, although accounting for 0.2% to 2.7% of infection-related hospitalizations, can be particularly dangerous. Pediatric recipients are often at higher risk, reflecting the fact that they are more likely to be naïve to a particular pathogen than the general population. Younger age and the use of antibody induction immunosuppression are significant independent risk factors for infectious complications.[84]

### Cytomegalovirus

Cytomegalovirus (CMV) represents the most common viral infection after transplantation. CMV infection can occur in any recipient, although the risk is highest when a seronegative recipient receives a kidney from a seropositive donor. Infection occurs in seropositive recipients as well because of activation of latent virus. The incidence and the severity of CMV have declined with more effective prophylaxis. The severity of CMV infection may range from asymptomatic to organ involvement and death. The typical presentation occurs 1 to 6 months after transplantation, with the patient feeling relatively well but having fevers or sometimes flulike symptoms. Leukopenia is common. Patients with tissue-invasive CMV disease will appear toxic, and there will be evidence of end-organ dysfunction. The diagnosis is confirmed using either a CMV pp65 antigenemia assay or the CMV polymerase chain reaction (PCR) assay. Both methods allow monitoring of the response to therapy. Valganciclovir is effective for both the prophylaxis and treatment of CMV disease.[85] In more severe cases, treatment with intravenous ganciclovir and CMV hyperimmune globulin may be helpful.

### Varicella-Zoster Virus

In pediatric recipients, there is high risk of a primary chickenpox infection. Treatment is with intravenous acyclovir until the lesions crust over, then conversion to oral acyclovir. Primary infections can be severe. We immunize our candidates who are seronegative for varicella-zoster virus (VZV) before transplantation. For seronegative recipients who have a defined exposure, we administer VZV immune globulin.

### BK Virus

BK virus is a ubiquitous polyomavirus that is a significant concern in renal transplantation.[86] There is a high incidence of seroconversion by late childhood, and the virus is dormant in the renal epithelium until reactivated. BK virus appears to be an under-recognized cause of allograft dysfunction, with BK interstitial nephritis resulting in a graft loss in 45% to 70% of affected recipients.

The incidence of BK virus-associated transplant nephropathy is estimated to be 4% to 7%.[86] Smith and coworkers evaluated a single-center cohort of 173 pediatric renal recipients and identified BK nephropathy in 6 children (3.5%).[87] The diagnosis was made on biopsy at a median of 15 months after transplantation. There was a strong association between BK nephropathy and recipient seronegativity. In a subsequent analysis of the NAPRTCS database from 2000 to 2004, the incidence of BK nephropathy was 4.6% with a median onset of 10.1 months post-transplantation. Graft failure occurred in 24% of patients at a mean of 24 months after diagnosis. There was an association with polyclonal antibody induction therapy.[88]

BK nephropathy should be considered in the evaluation of renal allograft dysfunction. BK nephropathy can be definitively diagnosed on biopsy using immunohistochemistry, but the histology can be confused with acute rejection. Treatment with additional immunosuppression does not improve renal function and often will cause further deterioration. The initial treatment for BK nephropathy consists of decreasing immunosuppression. The addition of antiviral therapy and intravenous immunoglobulin has been reported, but there are no controlled trials and compelling data are lacking.[89] Measurement of BK virus by PCR helps with diagnosis and subsequent monitoring of the response to treatment. It is hoped that improved awareness, prompt diagnosis, and treatment may reduce the risk of graft loss initially associated with this disease process.

### Malignancy

Transplant recipients face an increased risk of de novo malignancy related to their immunosuppression. Lymphomas, specifically post-transplantation lymphoproliferative disorder (PTLD), are the most common, with an incidence of 1% to 4% in renal transplantation.[90–92] PTLD actually represents a spectrum of pathology, and the treatment and prognosis

depends on the histology.[90,93] Epstein-Barr virus (EBV) is believed to be the causative agent in the progression to PTLD, especially in B-cell lymphomas. A wide variety of factors have been proposed to be associated with an increased risk, including the use of antilymphocyte induction therapy, EBV-seronegative recipient, EBV infection, and era of transplant. Young white males appear to be at greatest risk.[92] The incidence of PTLD is associated with the overall intensity of immunosuppression.[91,92,94,95]

The second most common cancer in pediatric recipients is skin cancer. Squamous cell carcinoma accounts for the majority, followed by malignant melanoma and basal cell carcinoma. The best strategy combines sunblock and sun avoidance. All recipients should undergo regular dermatologic follow-up, specifically focusing on this risk. Long-term immunosuppression is also associated with increased risks of cervical, vulvar, and anal carcinoma.

### Other Medical Issues

In addition to the risks of infection and malignancy, transplant recipients face many other risks secondary to their history of ESRD, their underlying renal disease, and the individual risks associated with all their medications.

Renal transplant recipients are at high risk for cardiovascular disease.[96] Preexisting renal insufficiency, time on dialysis, and immunosuppressive medications after transplantation all contribute to this risk. In addition, the prevalence of hypertension in pediatric kidney recipients is 50% to 80%.[97,98] The incidence of left ventricular hypertrophy at initiation of renal replacement therapy ranges from 54% to 82%, though it generally improves after transplantation.[99–101] Many children and adolescents will have additional cardiovascular risk factors, including hyperlipidemia, hyperhomocysteinemia, anemia, malnutrition, and chronic inflammation.

Although there are few data examining the magnitude of the risk in pediatric patients, young adult patients with ESRD have a 1000-fold higher risk of cardiovascular death compared with the general population. Although the risk of cardiovascular death decreases after successful transplantation compared with dialysis, it does not become normal.[102] In addition to contributing to cardiovascular risk, hypertension is associated with a higher risk of graft dysfunction and graft loss.[98,103]

Transplantation recipients also face significant problems with bone metabolism and growth because of a history of chronic renal insufficiency, malnutrition, graft dysfunction after transplantation, and immunosuppressive medications. Renal osteodystrophy is a substantial problem, but proper calcium and vitamin D supplementation, along with other agents, has improved overall bone health. The risk of osseous complications has decreased with time, and the risk decreases after transplantation compared with dialysis therapy.[104] The impairment in linear growth impacts final adult height, but significant progress has been made.[105,106] Height at transplantation is one of the best predictors of final adult height, and better management prior to transplantation, including nutrition and the use of recombinant human growth hormone, have improved height z-scores at transplantation. Catch-up growth post-transplantation occurs, but appears limited to recipients less than 6 years of age at transplantation. Steroid avoidance protocols are also associated with catch-up growth, adding a potential benefit to consider with respect to immunosuppression regimens.

### Cognitive and Psychosocial Development

The negative impact of ESRD on cognitive development has diminished because of significant improvements in medical management and renal replacement therapy. Children with ESRD who undergo transplantation appear to have improvement in their level of cognitive function.[107] Psychosocial development tends to be below the healthy population, though transplantation offers benefit compared with dialysis. Overall quality of life for the child and family appears to be better after transplantation compared with dialysis, although again, when compared with the normative population, there are disparities.[108–111]

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 47

# Pancreas and Islet Cell Transplantation

David E. R. Sutherland, Angelika C. Gruessner, Bernhard J. Hering, and Rainer W. G. Gruessner

Type 1 diabetes is an autoimmune disease in which the pancreatic islet insulin-producing beta cells are selectively destroyed.[1] It most commonly presents in childhood and continues to represent a therapeutic challenge. Secondary diabetes complications, observed in 30% to 50% of patients who live more than 20 years after onset of the disease, result in poor quality of life, premature death, and considerable health care costs.[2] The principal determinant of the risk of devastating diabetes complications is the total lifetime exposure to elevated blood glucose levels.[3] Therefore establishing safe and effective methods of achieving and maintaining normoglycemia will have substantial implications for the health and the quality of life of individuals with diabetes.

The Diabetes Control and Complications Trial (DCCT) demonstrated that, given a qualified diabetes care team and intensive insulin treatment control, near-normalization of glycemia could be achieved and sustained for several years.[4] However, such a near-perfect level of treatment would increase a patient's burden of day-to-day diabetes management, be difficult to implement for many patients, require more attention and medical services than are routinely available in clinical practice,[5] and be accompanied by an increased frequency of severe hypoglycemia.[4] Currently, the only way to restore sustained normoglycemia without the associated risk of hypoglycemia is to replace the patient's glucose-sensing and insulin-secreting pancreatic islet beta cells[6,7] either by the transplantation of a vascularized pancreas[8,9] or by the infusion of isolated pancreatic islets.[10–12] The trade-off is the need for immunosuppression to prevent rejection of allogenic tissue, and for this reason, most pancreas or islet transplant recipients have been adults. However, the potential for application earlier in the course of the disease exists, particularly in diabetic children already on immunosuppression for other indications.[13] Of the nearly 24 million people estimated to have diabetes mellitus in the United States, 5% to 10% have type 1 diabetes mellitus,[14] and the prevalence in children is increasing.[15]

## Pancreas Transplantation

### HISTORY

The first clinical pancreas transplantation was performed in 1966 by Drs. William Kelly and Richard Lillehei, simultaneous with a kidney transplantation, in a uremic diabetic patient at the University of Minnesota.[16] Shortly thereafter, a few institutions around the world began to perform pancreas transplantations, as detailed in a comprehensive history in another book.[17]

The success rate (long-term insulin independence) with pancreas transplantation was initially low but increased considerably in the 1980s, leading to increased application (Fig. 47-1). Innovations in both surgical techniques and immunosuppression were responsible for the improvements.

The first pancreas transplantation was a duct-ligated segmental (body and tail) graft,[16] but this approach was associated with multiple complications. In a series of 13 more pancreas transplantations between 1966 and 1973 at the University of Minnesota,[18,19] Lillehei devised the whole pancreas–duodenal transplantation technique to the iliac vessels with enteric drainage through a duodenoenterostomy to native small bowel, which is now routine at most centers. The initial results, however, were not as good as today, and several surgeons devised alternative techniques during the 1970s and early 1980s.[17] Dubernard, in Lyon, France, introduced duct injection of a synthetic polymer as a method to block secretions and cause fibrosis in the exocrine pancreas of a segmental graft, with sparing of the endocrine component,[20] and many pioneering centers adopted this technique, although it is little used today. Gliedman introduced urinary drainage through a ureteroductostomy for segmental grafts,[21] and Sollinger later modified this approach with direct anastomosis of a duodenal patch of a whole pancreas graft to the recipient bladder.[22] Drs. Dai Nghiem and Robert Corry did further modification of urinary drainage,[23] retaining a bubble of duodenum for duodenocystostomy, as Lillehei had done for duodenoenterostomy.[18] From the early 1980s until the mid-1990s, the bladder-drainage technique with duodenocystostomy was the predominant technique for pancreas transplantations. The bladder-drainage technique had a low acute complication rate and was helpful in monitoring for rejection by detection of a decline in urine amylase activity, but chronic complications, such as recurrent urinary tract

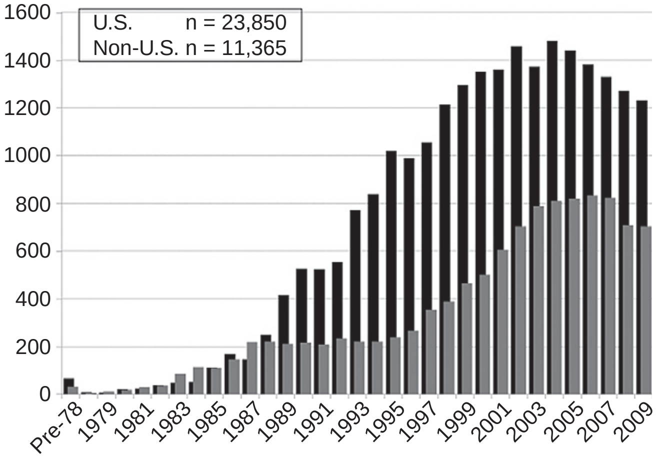


FIGURE 47-1 Annual number of U.S. and non-U.S. pancreas transplantations reported to the International Pancreas Transplant Registry (IPTR), 1978-2009.

infections or dehydration from fluid loss through the exocrine secretions, were common. Thus in the mid-1990s, described by Lillehei and colleagues,[18] a change occurred and enteric drainage, which was never totally out of fashion,[24,25] overtook bladder drainage as the predominant drainage procedure. In addition, portal rather than systemic venous drainage was used by some groups for enteric-drained whole pancreas–duodenal transplantations.[26] Portal venous drainage was originally introduced by Calne in 1984 for segmental pancreas grafts as a more physiologic technique[26] and was applied by several groups sporadically over the years.[17]

With advances in immunosuppression, including the introduction of cyclosporine by Calne and coworkers in 1979,[27] tacrolimus by Starzl and associates in 1989,[28] and mycophenolate mofetil by Sollinger and coworkers in 1995,[29] bladder drainage had become less important for monitoring rejection. Furthermore, in recipients of simultaneous pancreas and kidney transplants from the same donor, the kidney could be monitored for rejection episodes (elevation of serum creatinine) as a surrogate marker for pancreas rejection before there was sufficient pancreatic damage to cause hyperglycemia. However, in solitary pancreas transplants, serum creatinine could not be used as a marker for rejection, and in such cases, bladder drainage is useful and continues to be used.[17]

## DETAILS OF SURGICAL TECHNIQUES

As mentioned in the history section, a variety of techniques have been used for management of the exocrine secretions and venous drainage of pancreas transplants.[30,31] The majority of pancreas grafts are procured from multiorgan deceased donors, and because the liver and pancreas share the origins of their arterial blood supply, a whole organ pancreas graft usually requires reconstruction.[32,33] The blood supply to the tail of the pancreas is supplied by the splenic artery, originating from the celiac axis, and the head of the pancreas is supplied by the pancreaticoduodenal arcades, originating from the superior mesenteric artery and the hepatic artery. Because the latter goes with the liver, along with the celiac axis, the usual approach is to attach an arterial Y-graft of the donor iliac vessels, with anastomosis of the hypogastric artery to the graft splenic artery and the external iliac artery to the graft superior mesenteric artery, leaving the common iliac artery segment of the Y-graft for anastomosis to the recipient arterial system, usually the right common iliac artery. The portal vein of the donor is usually divided midway between the upper border of the pancreas and the liver, leaving adequate length for transplantations of both organs, but if necessary, an extension graft of donor iliac vein can be anastamosed to the pancreatic graft portal vein portion. In the recipient, the pancreas graft portal vein, with or without an extension graft, can be anastomosed to the systemic venous system (usually the iliac vein or vena cava) or to the portal system (usually the superior mesenteric vein).

When venous drainage is to the recipient's iliac vein, the whole pancreas graft can be oriented with the head directed into either the pelvis or the upper abdomen. When directed cephalad, enteric drainage is the only option. When directed caudad, the duodenum can be anastomosed to either the bladder (Fig. 47-2) or bowel (Fig. 47-3). Figure 47-2

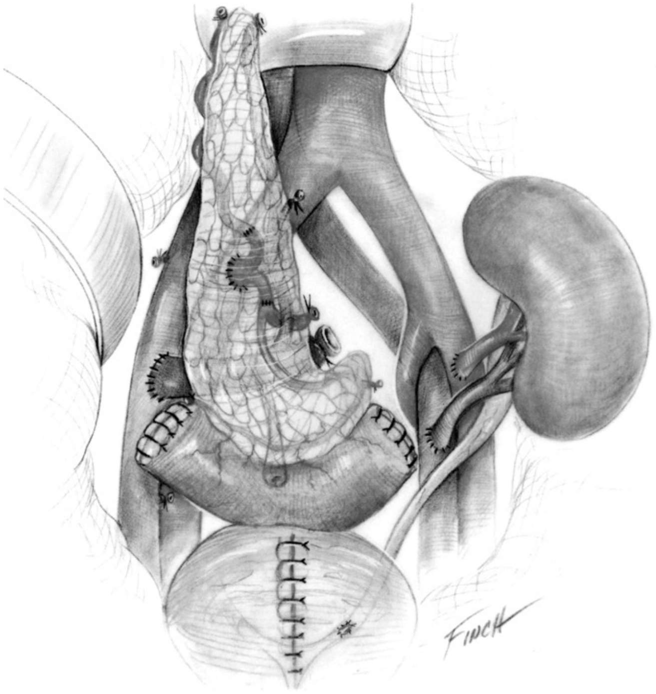

FIGURE 47-2 Simultaneous pancreas and kidney (SPK) transplantation using a whole pancreas/duodenal graft from a deceased donor with systemic venous drainage to the right iliac vein and bladder drainage of the pancreas exocrine secretions through a duodenocystostomy. Both the pancreas and kidney are placed in the peritoneum through a midline incision. The donor splenic artery, supplying the pancreatic tail, and the donor superior mesenteric artery, supplying the pancreatic head, have been joined by a Y-graft constructed from the donor common external/internal iliac artery complex during a bench procedure, and the base of the Y-graft is anastomosed to the recipient common iliac artery. The mid-duodenum is anastomosed to the posterior dome of the bladder, and the duodenal stumps are oversewn. The kidney graft could be from a living donor or the same deceased donor as the pancreas graft, but, in either case, is preferentially placed to the left iliac vessels so that the right side, with its more superficial vessels, can be used for the pancreas transplant. In this particular illustration, the donor ureter was implanted into the bladder using the Politano-Leadbetter technique through an anterior cystotomy, a technique that also allows the duodenocystostomy to be performed with an end-to-end anastomosis (EEA) stapler, with internal oversewing of the anastomotic line using an absorbable suture to cover the staples, followed by closure of the cystotomy. However, when enteric drainage is used for an SPK transplantation, an external ureteroneocystostomy is usually performed. (Reproduced from Gruessner RWG, Sutherland DER [eds]: Transplantation of the Pancreas. New York, Springer-Verlag, 2004.)

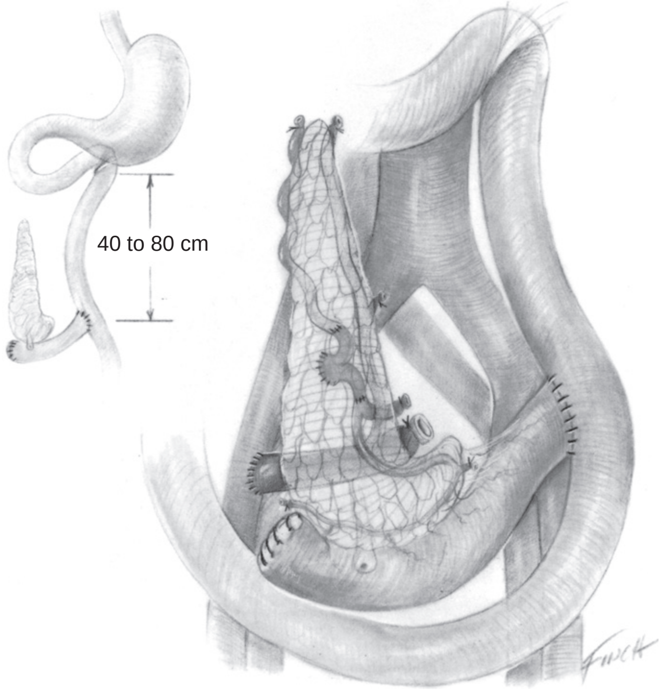


**FIGURE 47-3** Pancreas-duodenal transplantation using a deceased donor with systemic venous drainage and enteric drainage of graft exocrine secretions to a proximal loop of recipient jejunum. In this particular case, an end-to-side two-layer duodenojejunostomy, using the distal end of the graft duodenum, is illustrated, and the anastomosis is located 40 to 80 cm distal to the ligament of Treitz *(inset)*. Alternatively, a side-to-side stapled or handsewn duodenojejunostomy, with or without a Roux-en-Y loop, can be done. (Reproduced from Gruessner RWG, Sutherland DER [eds]: Transplantation of the Pancreas. New York, Springer-Verlag, 2004.)

shows the bladder-drainage technique and also depicts a kidney transplantation to the left iliac vessels, but, as mentioned, with a kidney transplantation, enteric drainage is more common than bladder drainage.

With the bladder-drainage technique, the anastomosis may be handsewn or performed with an end-to-end anastomosis (EEA) stapler brought through the distal duodenum (which is subsequently stapled closed) for connection to the post of the anvil projected through the posterior bladder by an anterior cystotomy (see Fig. 47-2). The inner layer is then reinforced with a running absorbable suture for hemostasis and for burying the staples under the mucosa.

With enteric drainage/systemic venous drainage, the anastomosis may be handsewn in an end-to-side fashion (see Fig. 47-3), or it can be done in a side-to-side fashion by handsewing or by using an EEA stapler.[34] The barrel of the EEA stapler is inserted into the end of the graft duodenum, and the post is projected through the side wall. The anvil is inserted into the recipient bowel through an enterotomy secured around the connecting post by a purse-string suture. The two posts are connected and the stapler is fired, creating the anastomosis. The end of the duodenum is then closed with a simple stapler. The enteric anastomosis can be done directly to the most convenient proximal small bowel loop of the recipient or to a Roux-en-Y segment of recipient bowel that is created at the time. Outcome analyses do not show any statistical advantage of a Roux-en-Y loop.

For portal drainage of the pancreas graft venous effluent (Fig. 47-4), the head and duodenum of the graft is oriented

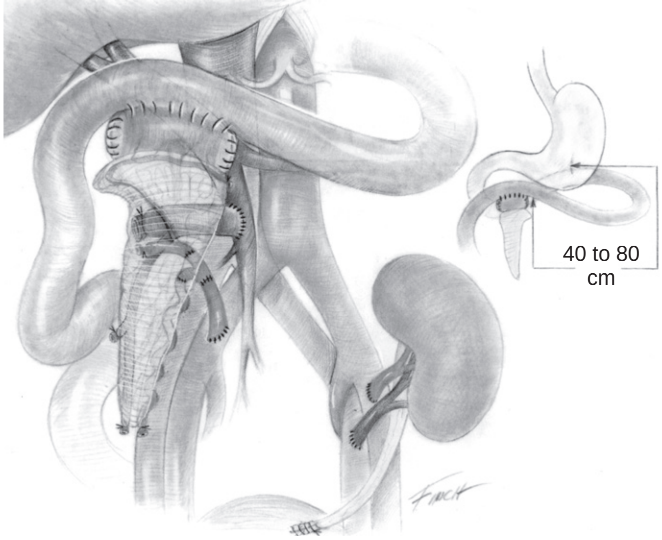


**FIGURE 47-4** Whole pancreas/duodenum transplantation using a deceased donor with portal venous drainage with an end-to-side anastomosis to the recipient superior mesenteric vein, accessed below its confluence with the splenic vein. Drainage of exocrine secretions is through a side-to-side duodenojejunostomy, 40 to 80 cm distal to the ligament of Treitz. Note that the cephalad position of the pancreatic head, when portal venous drainage is used, as opposed to the caudal orientation possible with systemic venous drainage, is no different than that needed when bladder drainage is done. In this particular illustration, the pancreas graft overlies the root of the small bowel mesentery, with the duodenal segment below the transverse colon, and the arterial Y-graft is anastomosed to the recipient common iliac artery through a mesenteric tunnel. However, a retroperitoneal approach under the right colon is also possible, in which case the arterial Y-graft can be anastomosed directly to the recipient iliac artery, but the enteric anastomosis must be through a Roux-en-Y limb of recipient bowel brought through the mesentery. If a kidney is simultaneously transplanted to the left iliac vessels, the ureter can be implanted into the bladder using the extravesical ureteroneocystostomy (Lich) technique, as illustrated. (Reproduced from Gruessner RWG, Sutherland DER [eds]: Transplantation of the Pancreas. New York, Springer-Verlag, 2004.)

cephalad, and the graft portal vein is anastomosed directly to the recipient superior mesenteric vein. In the illustration, the pancreas graft is ventral to the recipient small bowel mesentery so that the venous anastomosis is to the ventral side of the vein, and the arterial Y-graft must be brought through a window of mesentery for anastomosis to the recipient's aorta or common iliac artery. The graft duodenum is anastomosed to recipient's small bowel by the same techniques described for systemic venous drainage, with or without (as depicted) a Roux-en-Y loop of recipient bowel.

An alternative approach for portal venous drainage of the pancreas graft effluent is to place the pancreas retroperitoneally by reflecting the right colon to the left and exposing the dorsal surface of the superior mesenteric vein, as described by Boggi and associates.[35,36] The arterial Y-graft can then be anastomosed directly to the right common iliac artery, but this approach does mandate creation of a Roux-en-Y limb of recipient bowel to bring through the small bowel or transverse colon mesentery for a graft duodenoenterostomy.

Other techniques can be used, including duct injection for a segmental graft. Segmental grafts are rarely used, except in the few cases of living donor pancreas transplantations,[37–42] and most of these have the exocrine secretions managed by either a ductoenterostomy to a Roux-en-Y limb of recipient bowel or a ductocystostomy to the recipient's bladder

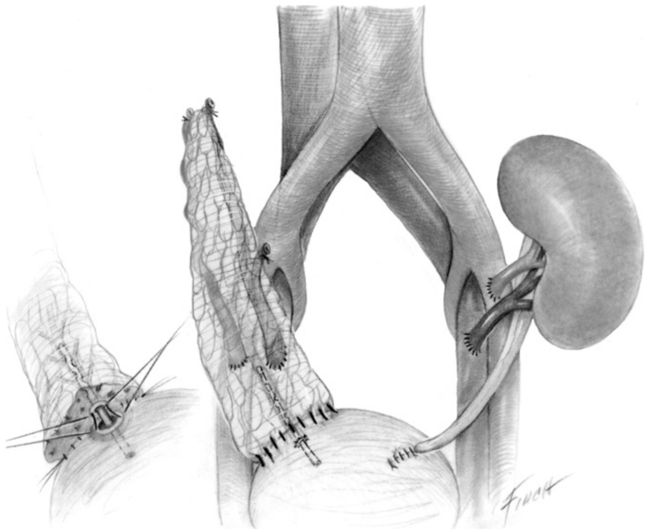

FIGURE 47-5 Living donor segmental (body and tail) pancreas transplantation to right iliac vessels (systemic venous drainage) and bladder drainage of exocrine secretions through a ductocystostomy by means of an intraperitoneal approach. The donor splenic artery and splenic vein are anastomosed end to side to the recipient external iliac artery and vein after ligation and division of all hypogastric veins to bring the main vein as superficial as possible. The splenic artery anastomosis is lateral and proximal to the splenic vein anastomosis. A two-layer ductocystostomy is constructed: The pancreatic duct is approximated to the urothelial layer (inner layer) using interrupted 7-0 absorbable sutures over a stent *(inset)*. If the kidney is transplanted simultaneously, the donor ureter is implanted into the bladder using the extravesical ureteroneocystostomy (Lich) technique. (Reproduced from Gruessner RWG, Sutherland DER [eds]: Transplantation of the Pancreas. New York, Springer-Verlag, 2004.)

(Fig. 47-5). Segmental pancreas transplantations from living donors, with or without a kidney transplantation, are particularly useful in candidates who would otherwise have a long wait for a deceased donor organ, such as those with a high level of human leukocyte antigen (HLA) antibodies but with a negative crossmatch to a living volunteer.[40] However, there are circumstances where a segmental graft from a deceased donor is still appropriate for technical reasons, particularly for retransplantations where conventional sites have been used previously in such a way they cannot be reused and one has to use unconventional sites, even orthotopically.[43] For more details concerning the variety of surgical techniques in pancreas donors (deceased and living) and recipients, the reader is referred to work by Benedetti and colleagues.[44]

## GENERAL INFORMATION, PANCREAS TRANSPLANTATION CATEGORIES, AND IMMUNOSUPPRESSION

By the late-1990s, more than 2500 pancreas transplantations were being done annually worldwide (see Fig. 47-1), as reported to the International Pancreas Transplant Registry (IPTR).[45] By 2010, more than 35,000 vascularized pancreas transplantations had been performed, more than half in the United States, with very large series at some centers,[25,46–48] more than 2000 total at the University of Minnesota,[49] and more than 1000 simultaneous pancreas and kidney (SPK) transplantations at the University of Wisconsin.[47] The vast majority were done to establish insulin independence in patients with de novo type 1 diabetes mellitus, but enteric-drained pancreas transplantations have been used to correct both endocrine and exocrine deficiency after total pancreatectomy in some patients[51–53] and to treat diseases such as cystic fibrosis in others.[54]

Specialists in more than 150 institutions in the United States, and nearly the same number elsewhere, have performed pancreas transplantations.[55] The IPTR was founded in 1980 to analyze the results.[56] In 1987, reporting of U.S. cases became obligatory through the United Network for Organ Sharing (UNOS), and near-annual reports have been made thereafter.[57–60]

There are three categories of pancreas transplantation recipients: (1) uremic diabetic patients who undergo a simultaneous pancreas and kidney transplantation from either a deceased or living donor[61]; (2) nephropathic patients who already have had renal insufficiency corrected, usually by a living donor kidney transplantation, and then undergo a pancreas after kidney (PAK) transplantation[62–64]; and (3) nonuremic diabetic patients who undergo a pancreas transplantation alone (PTA).[65] The Pancreas Transplant Registry has compared outcomes in the three categories spanning several eras of data collection.[57–60,66,67]

The majority of pancreas transplantations have been in the SPK category, but in recent years, there has been an increased emphasis in performing living donor kidney transplantations to preempt the need for dialysis in diabetics with nephropathy.[68] Thus until 2004, the number of PAK transplantations increased, but the number of SPK transplantations did not change (Fig. 47-6). Concomitantly, there has also been an increase in the number of PTA cases to treat diabetics without advanced nephropathy who have diabetic management problems justifying immunosuppression, and to treat patients who would also be candidates for islet transplantation, given the conditions discussed later. Although most pancreas transplantation recipients have type 1 diabetes, insulin-treated type 2 diabetics also become insulin-independent after a pancreas transplantation.[69–71]

Immunosuppression management of pancreas transplantation recipients is similar to that of recipients of other solid organs, including kidneys, which the majority of pancreas recipients also receive.[72] Thus induction immunosuppression

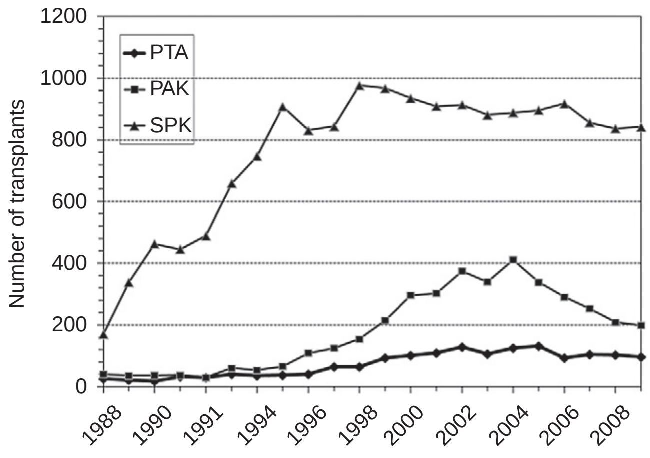


FIGURE 47-6 Number of pancreas transplantations performed annually in the United States from 1988 through 2009 by recipient category. PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation.

with anti–T-cell monoclonal or polyclonal depleting or nondepleting agents may be used or reserved for rejection episodes.[73] Maintenance immunosuppression usually consists of a combination of a calcineurin inhibitor (cyclosporine or tacrolimus), with the dose and blood levels adjusted to minimize nephrotoxicity, and an antiproliferative agent (mycophenolate mofetil or sirolimus), with or without prednisone. Corticosteroid-free regimens are now quite common for all organ transplantations, including the pancreas.[74–83] Suspected pancreas allograft rejection episodes, based on transient rise of serum amylase or lipase in enteric-drained grafts or on a decline in urine amylase in bladder-drained grafts, or by a rise in serum creatinine in SPK transplantations, can be confirmed by biopsy of the graft.[84,85]

## PANCREAS TRANSPLANTATION OUTCOMES

Current outcomes with deceased donor pancreas transplantations, according to recipient categories, surgical technique, and immunosuppression protocol, for U.S. cases as reported to UNOS from January 2005 to December 2009, are summarized here.[55] During this period, 5567 primary deceased donor pancreas transplantations were reported to UNOS, including 4155 SPK, 947 PAK, and 465 PTA transplantations.

The primary transplantation patient survival rates in the three recipient categories are shown in Figure 47-7. At 1 year, 96% of the SPK, 97% of the PAK, and 97% of the PTA recipients were alive; at 3 years, 92%, 91%, and 92%, respectively, were alive. The highest patient survival rate could be found in PTA subgroups, presumably because this group had less advanced complications before transplantation.

The primary pancreas graft survival rates in the three recipient categories are shown in Figure 47-8. At 1 year, 85% of the SPK, 79% of the PAK, and 78% of the PTA recipients were totally insulin-independent; at 3 years, 79%, 68%, and 62%, respectively, were insulin-independent ($P < 0.001$). The highest pancreas graft survival rates are in the SPK category, presumably because the kidney graft (usually from the same donor as the pancreas) can be used to detect rejection episodes earlier than in the other categories, where only the pancreas can be monitored. Support for this hypothesis comes

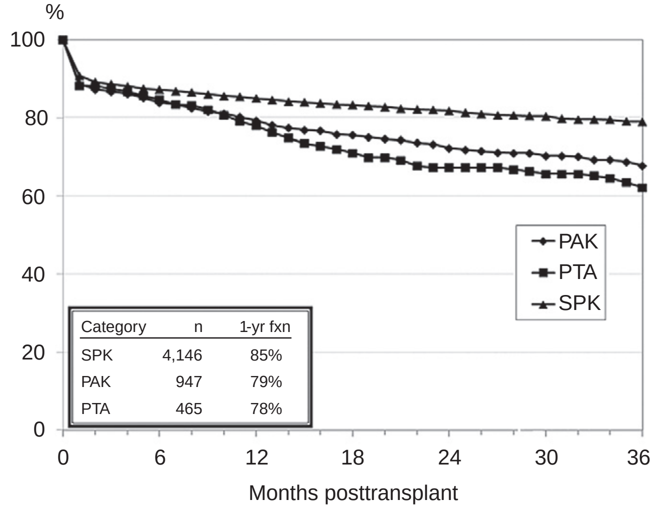


**FIGURE 47-8** Pancreas graft functional survival rates (insulin independence) for 2005 to 2009 U.S. deceased donor primary transplantations by recipient category. Fxn, function; PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation.

from Registry data showing significantly higher early technical failure rates and also large differences in rejection loss rates for solitary transplants.

Of the 2005 to 2009 primary pancreas grafts, 6% of SPK and 9% of solitary transplants failed for technical reasons, with thrombosis being the highest risk for technical loss (5%); infection, pancreatitis, and anastomotic leak made up the rest. Technical graft loss was significantly higher in solitary transplants than in SPK ($P = 0.0009$).

The primary pancreas graft failure rates from rejection are shown in Figure 47-9. At 1 year, 2% of the SPK, 4% of the PAK, and 6% of the PTA recipients of technically successful grafts had to resume exogenous insulin (significantly lower in the SPK category; $P = 0.0001$).

Regarding management of pancreatic duct exocrine secretions for the 2005 to 2009 cases, enteric drainage predominated

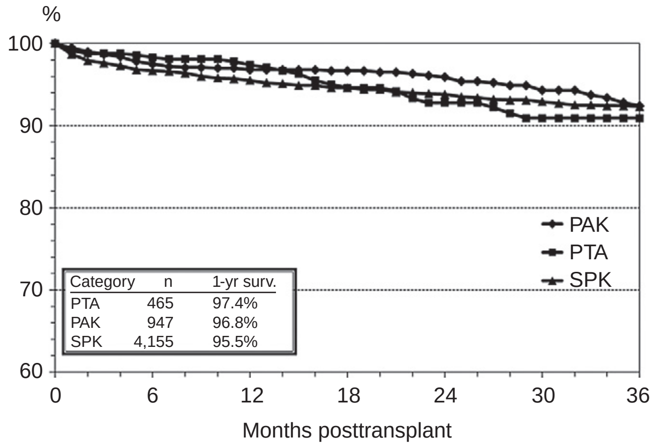


**FIGURE 47-7** Patient survival rates for 2005 to 2009 U.S. deceased donor primary transplantations by recipient category. PAK, pancreas after kidney transplant; PTA, pancreas transplant alone; SPK, simultaneous pancreas and kidney transplantation; surv., survival.

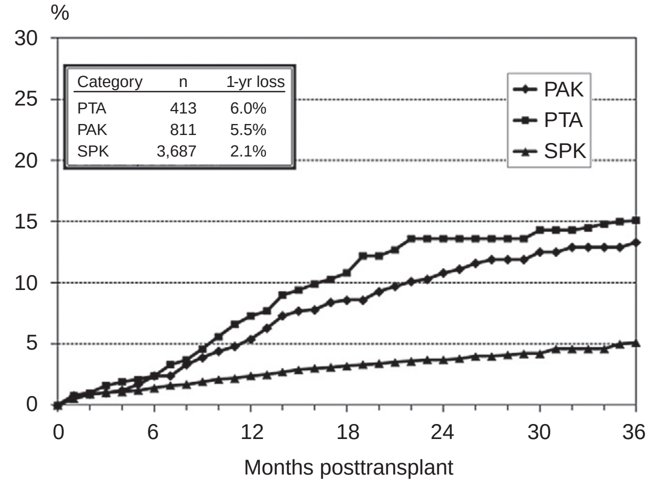


**FIGURE 47-9** Technically successful pancreas graft immunologic failure rates (return to exogenous insulin) for 2005 to 2009 U.S. deceased donor primary transplants by recipient category. PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation.

for SPK transplants (91%); for PAK and PTA, the proportion that were enteric drained was slightly lower (86% and 79%, respectively). Overall, the technical failure rate was significantly higher with enteric-drained SPK than with bladder-drained SPK (7% vs. 4%) transplants. No difference was found for solitary transplants. Pancreas graft survival rates, however, were not significantly different for enteric-drained versus bladder-drained transplantations in any of the categories: At 1 year, the rates were 85% ($n$ = 3665) versus 86% ($n$ = 366) for SPK, 79% ($n$ = 790) versus 82% ($n$ = 130) for PAK, and 80% ($n$ = 366) versus 75% ($n$ = 99) for PTA cases. No difference in the failure rate from rejection for technically successful grafts for enteric-drained versus bladder-drained transplantations could be found anymore.

In the SPK category, bladder drainage and enteric drainage would be expected to give similar results: In most cases, both grafts come from the same donor, and monitoring of serum creatinine serves as a surrogate marker for rejection in the pancreas transplant, allowing easy detection and reversal by treatment. In contrast, for solitary pancreas transplants (PAK and PTA), serum creatinine cannot be used as a marker of pancreas rejection, hyperglycemia is a late manifestation of rejection, and exocrine markers must be used. Although serum amylase and lipase may elevate during a rejection episode, this does not occur in all cases, but for bladder-drained grafts, a decrease in urine amylase eventually always accompanies rejection (100% sensitive, even though it is not specific) and nearly always precedes hyperglycemia so that a rejection episode is more likely to be diagnosed in a bladder-drained graft and lead to treatment and reversal.

Approximately one quarter of enteric-drained pancreas grafts reported to UNOS were done with a Roux-en-Y loop; in the past, the outcomes were not improved by this procedural addition,[45] and that is still the case.[55]

Another variation in surgical technique is portal drainage of the venous effluent for enteric-drained grafts.[30,86] It establishes normal physiology and a theoretic metabolic advantage versus systemic venous drainage, and some groups have reported that portal venous enteric-drainage grafts are less prone to rejection than systemic venous enteric-drainage grafts,[87,88] although others have not.[89] The latest Registry analysis shows that portal venous drainage was used for one fifth of enteric-drainage transplantations, but there were no significant differences in pancreas graft survival versus systemic venous enteric-drainage transplantations in any of the categories: at 1 year, 84% ($n$ = 718) versus 86% ($n$ = 2896) for SPK, 79% ($n$ = 130) versus 79% ($n$ = 651) for PAK, and 78% ($n$ = 51) versus 80% ($n$ = 305) for PTA cases.

Regarding immunosuppression, according to the latest Registry analysis, anti–T-cell agents were used for induction therapy for more than 80% of the 2005 to 2009 U.S. pancreas recipients in each category.[55] The most frequently used regimen for maintenance immunosuppression (more than two thirds of the recipients in each category) was tacrolimus and mycophenolate mofetil in combination, with or without prednisone. In recipients of primary deceased donor pancreas grafts given anti–T-cell agents for induction and tacrolimus and mycophenolate mofetil for maintenance immunosuppression (Fig. 47-10), the 1-year graft survival rates in the SPK, PAK, and PTA categories were 86% ($n$ = 2737), 81% ($n$ = 544), and 86% ($n$ = 271), respectively. A sirolimus-based regimen was used as a maintenance immunosuppressive drug

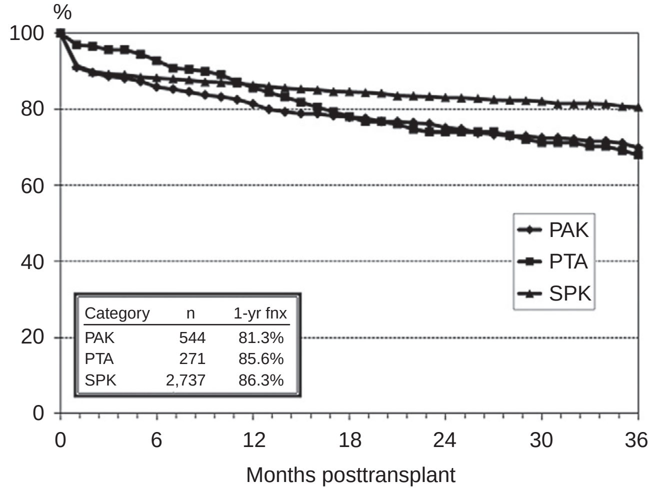


**FIGURE 47-10** Pancreas graft functional survival rates (insulin independence) for 2005 to 2009 U.S. deceased donor primary transplantations by category in diabetic recipients given anti–T-cell agents for induction and tacrolimus (TAC) and mycophenolate mofetil (MMF) for maintenance immunosuppression. Fxn, function; PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation.

in more than 13% of recipients in each category (Fig. 47-11), with excellent outcomes: The 1-year pancreas graft survival rates in the SPK, PAK, and PTA categories were 90% ($n$ = 407), 89% ($n$ = 94), and 89% ($n$ = 84), respectively. In contrast, the remaining recipients given alternative immunosuppressive regimens had distinctly lower pancreas graft survival rates in each category: at 1 year, 74% in SPK ($n$ = 153), 61% in PAK ($n$ = 71), and 29% in PTA ($n$ = 35) cases. A center effect may play a role in the outcomes of the Registry analysis according to immunosuppressive regimens.

Regarding the logistics of pancreas transplantation, the recent Registry data[55] showed a significant increase in technical

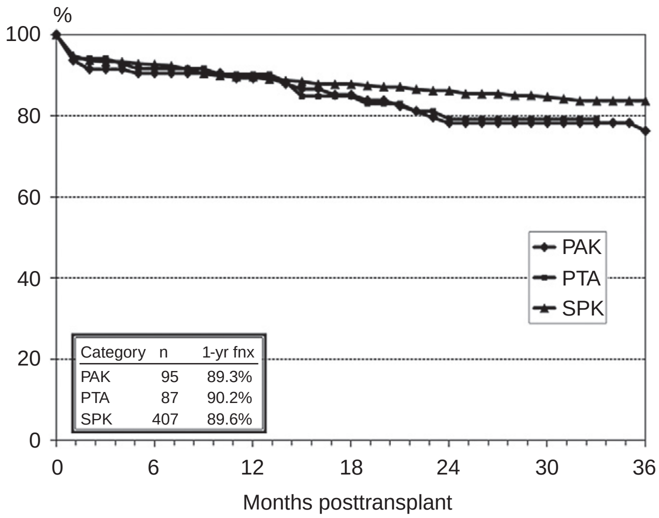


**FIGURE 47-11** Pancreas graft functional survival rates (insulin independence) for 2005 to 2009 U.S. deceased donor primary transplantations by category in diabetic recipients given sirolimus-based maintenance immunosuppression. Fxn, function; PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation.

failure rates and a decrease in graft survival rates with increasing preservation time. The relative risk (RR) to lose the graft doubled for SPK grafts with a preservation time greater than 24 hours compared with a preservation time of 12 to 24 hours. Shorter SPK preservation time showed a decreased risk of one third. HLA matching had virtually no impact on SPK graft survival rates, but matching at least at the class I loci had a beneficial effect in the PAK and the PTA categories.

Regarding pancreas recipient age, the recent Registry analysis of the 2005 to 2009 cases showed an effect on outcome mainly in solitary recipients, with rejection more likely in younger patients. In the SPK category, only 3 patients were younger than 15 years of age, and 312 recipients (7%) were between 15 and 29 years of age. In PAK, 5% ($n = 60$) were between the age of 15 and 29 years of age, and 15% ($n = 75$) in PTA. The relative risk for graft loss was not significantly increased for younger SPK recipients ($P = 0.21$) but clearly higher for PAK recipients (RR = 1.75, $P = 0.003$) and PTA recipients (RR = 1.99, $P = 0.009$) compared with recipients 30 to 45 years of age. Thus the young nonuremic diabetic is highly immunocompetent and more prone to reject a pancreas graft, consistent with an earlier analysis of outcomes in U.S. pediatric pancreas transplantation recipients from 1988 to 1999.[90] In that analysis, of slightly more than 8000 pancreas transplantations, only 49 were in recipients younger than 21 years of age (<1%), 34 in the SPK, 2 in the PAK, and 13 in the PTA category; all were deceased donor pancreas transplantations, except for two PTA segmental grafts from living donors. Less than half of the pediatric pancreas recipients were younger than 19. In the PTA recipients, the 1-year graft survival rate was only 15%, with all but one loss being from rejection in less than 1 year. The Registry data do not include the indications for a PTA in the pediatric recipients, but presumably they had extremely labile diabetes, justifying placement on immunosuppression in an attempt to gain control. In the pediatric SPK recipients, however, the 1-year patient, pancreas, and kidney graft survival rates were 96%, 78%, and 71%, respectively, which were outcomes comparable to those of adult SPK recipients for the entire period. Of the pediatric SPK recipients, most had a renal disease other than diabetic nephropathy.

Thus pancreas transplantations in the pediatric age group are uncommon, and most are in diabetic children who also have renal failure and thus need a kidney transplantation, obligating them to immunosuppression. At least in this group, the outcomes are such that it seems reasonable to recommend the addition of the pancreas so that the child can become insulin independent as well as dialysis free for the price of immunosuppression.[13] For nonuremic diabetic children with extreme lability, in whom a successful pancreas transplantation would be appropriate treatment, the antirejection strategies need to be optimized to improve the graft survival rates versus what has been achieved in the past.

With respect to outcome measures other than insulin independence, prevention and reversal of secondary complications, improvement in quality of life, extension of life span, and reduction of health care costs per quality-adjusted life-year have all been positively demonstrated in type 1 diabetic pancreas transplant recipients.[91–97] In patients with labile diabetes and hypoglycemic unawareness, a pancreas transplantation can resolve an otherwise intractable and life-threatening course.[98–100]

Whether a pancreas transplantation has an effect on survival probabilities for the diabetic population selected for the procedure is controversial. Two separate analyses of U.S. data from UNOS and the Organ Procurement Transplant Network (OPTN) for pancreas transplantation candidates and recipients between 1995 and 2000 compared the survival probabilities for patients who remained on the waiting list with those receiving a transplant by category.[103,104] In the first analysis,[103] SPK recipients had a significantly higher probability of survival than those remaining on the waiting list for the procedure, but, for solitary (PAK or PTA) recipients, just the opposite was the case. In the second analysis,[104] the higher survival probability for SPK recipients was confirmed, and, in addition, the overall survival probabilities of solitary pancreas transplant recipients compared with those waiting, and even after 1 year, were favorable for transplantation. In the second analysis, patients who listed at multiple centers were identified and were counted only once from the time of first listing, corrections were made for patients who changed categories, and longer follow-up was available. Thus pancreas transplantation does not entail a higher risk than staying on exogenous insulin for those on the waiting list and may improve survival probabilities for solitary as well as SPK recipients.[105]

In regard to secondary complications of diabetes,[106] numerous studies show a beneficial effect on neuropathy,[94,107–113] retinopathy[114–118] and nephropathy[92,119–122] as well as on cardiovascular disease,[123–128] and quality of life.[129,130] In regard to nephropathy, specifically in PTA recipients, even though the diabetic lesions in the native kidneys can improve,[131] this can be offset by the nephrotoxicity of the calcineurin inhibitors given for immunosuppression.[132]

It should be noted that pancreas retransplantation can be done if the first graft fails, with only slightly lower graft survival rates than for primary transplants.[66,67,133,134] Indeed, even third transplants can do well.[134]

Also of note, pancreas allografts are often procured by one center and transplanted at another, and there are studies showing no difference in outcomes compared with locally procured organs.[135]

Surgical complications of pancreas transplantation are numerous and are the subject of an extensive review recently published.[136] The most frequent complication leading to graft loss is venous or arterial thrombosis (5% to 10%). Anastomotic leaks are also common, but if diagnosed early, graft salvage is possible.

# Islet Transplantation

Human islet transplantation, the less invasive islet beta cell replacement alternative to transplantation of the vascularized pancreas, has been investigated for more than 3 decades[137–140] after the first clinical islet allograft was performed in 1974.[141] Since then, nearly 1000 islet allotransplantations have been performed worldwide.[142,143]

Islet autotransplantations have had a relatively high success rate in preventing diabetes after total pancreatectomy for more than 2 decades; so, they are briefly described before reviewing the current status of islet allografts for type 1 as well as for surgical diabetes.

## ISLET AUTOTRANSPLANTATIONS AFTER PANCREATECTOMY FOR BENIGN DISEASE

Islet autotransplantations to prevent diabetes after a total pancreatectomy for benign disease, primarily painful chronic pancreatitis, have been successful since the first case was performed in the 1970s[144,145] but depend on the number of islets transplanted.[146–151] Children with chronic pancreatitis and intractable pain who require pancreatectomy for relief of the pain and resolution of narcotic dependence nearly always have some beta cell function preserved by an islet autotransplantation, and they are either nondiabetic (more than a third) or can maintain euglycemia with once-daily long-acting insulin or near euglycemia with standard basal-bolus insulin.[152–155] Total pancreatectomy is highly successful in relieving the pain of chronic pancreatitis in both adults and children, particularly if done early before years of narcotic dependence.[148,150,153] The islet yield is also better if the pancreatectomy is not delayed, because the number of islets isolated correlates with the degree of pancreatic damage in both adults[156] and children.[157]

The surgical technique of pylorus-sparing total pancreatectomy and duodenectomy is shown in Figure 47-12. The procedure can be staged, but when the body and tail of the pancreas are removed, they should always be processed for islet isolation for an intraportal autotransplant (Fig. 47-13, *A*).

If a distal pancreatectomy is the primary procedure and a Whipple (completion) pancreatectomy becomes necessary, diabetes will have been prophylactically prevented by the initial islet autograft. If a Whipple procedure was the primary procedure, but pain persists and a distal (body and tail) completion pancreatectomy is required, it should be done in an institution capable of isolating islets from the excised gland for an autotransplantation.[158]

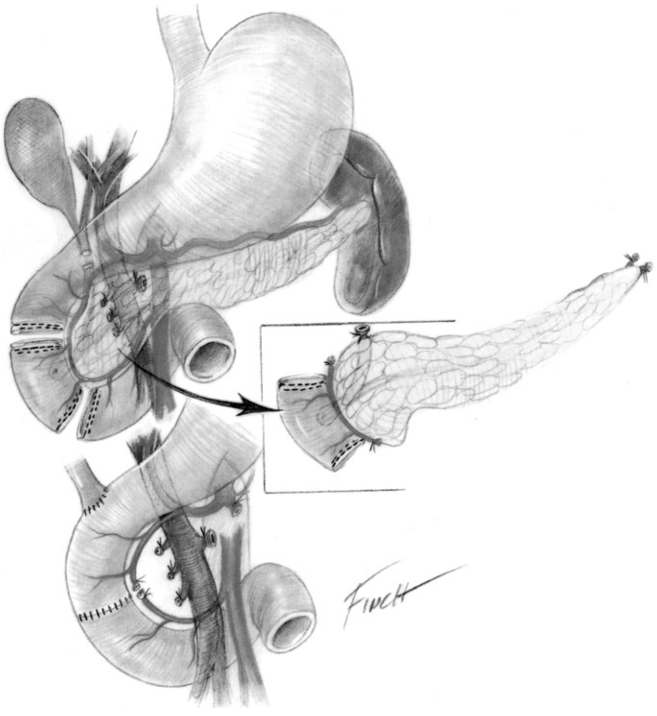

**FIGURE 47-12** Pylorus-sparing total pancreatectomy and partial duodenectomy technique for patients with chronic pancreatitis undergoing islet autotransplantations. The bile duct is transected and reimplanted into the duodenum, shown here proximal to a duodenoduodenostomy or duodenojejunostomy, but, more commonly, it is placed distal to the enteric anastomosis, with the site depending on the individual anatomy. When possible, only the second portion of the duodenum is resected, and an end-to-end duodenoduodenostomy is created; but if viability is not maintained, the entire distal duodenum must be resected and an end-to-end or end-to-side duodenojejunostomy performed. The short gastric vessels are preserved, as well as the gastroepiploic artery if possible, and the spleen is not removed if its viability is maintained. (Reproduced from Gruessner RWG, Sutherland DER [eds]: Transplantation of the Pancreas. New York, Springer-Verlag, 2004.)

## ISLET ALLOTRANSPLANTATIONS

Islet allotransplantations have been performed for the treatment of surgical and type 1 diabetes. As with autotransplantations, islet allotransplantations are usually done with embolization of the islets to the liver via the portal vein, where at least some islets will survive by nutrient diffusion until revascularization occurs (Fig. 47-13, *B*). A drawback of islet allotransplantations, as compared with pancreas transplantations, is the reduced beta cell mass; much attention has been given to compensating for the attrition that occurs. Islet allografts in patients with surgical diabetes have been associated with a very high success rate,[159,160] possibly because of the avoidance of diabetogenic steroids and the lack of an autoimmunity.

Islet allograft transplantations in patients with autoimmune type 1 diabetes have initially been performed simultaneously with a kidney transplant or in patients with established kidney transplants.[142] Insulin independence in this recipient group, even on an anecdotal basis, was not achieved until the early 1990s.[161–165]

Islet allografts have also been performed in patients in whom type 1 diabetes (T1D) is complicated by hypoglycemia unawareness and defective hormonal glucose counter-regulation resulting in recurrent episodes of severe hypoglycemia.[166] Today, the majority of human islet allografts are performed in this recipient group.[143] Acute complications are frequent in the 12.5% of T1D patients who have become aware of hypoglycemia 20 years after diabetes onset.[167] Iatrogenic hypoglycemia is the most limiting factor in the glycemic management of T1D;[168] it causes recurrent physical and psychological morbidity, including coma, seizures, and significant social embarrassment, and 7% to 10% of all deaths in patients with T1D are the result of hypoglycemia.[169,170] Hypoglycemia-related problems have not abated during the more than 18 years since they were first highlighted by the landmark report of the DCCT in 1993.[168,171] New glucose monitoring technologies are being developed; however, continuous glucose monitoring did not lower the rate of severe hypoglycemia in patients with T1D.[173,174]

A major milestone was reached in 2000 when Dr. Shapiro and colleagues at the University of Alberta in Edmonton achieved diabetes reversal in seven of seven recipients by using islets from more than one donor pancreas and by using corticosteroid-free, less diabetogenic immunosuppression.[175] Since then, several groups around the world have reported restoration of insulin independence after human islet allotransplantation in type 1 diabetic recipients.[11,176–194]

Furthermore, remarkable additional progress has been made in the past decade toward developing islet transplantation into a vital treatment option for T1D. First, new protocols

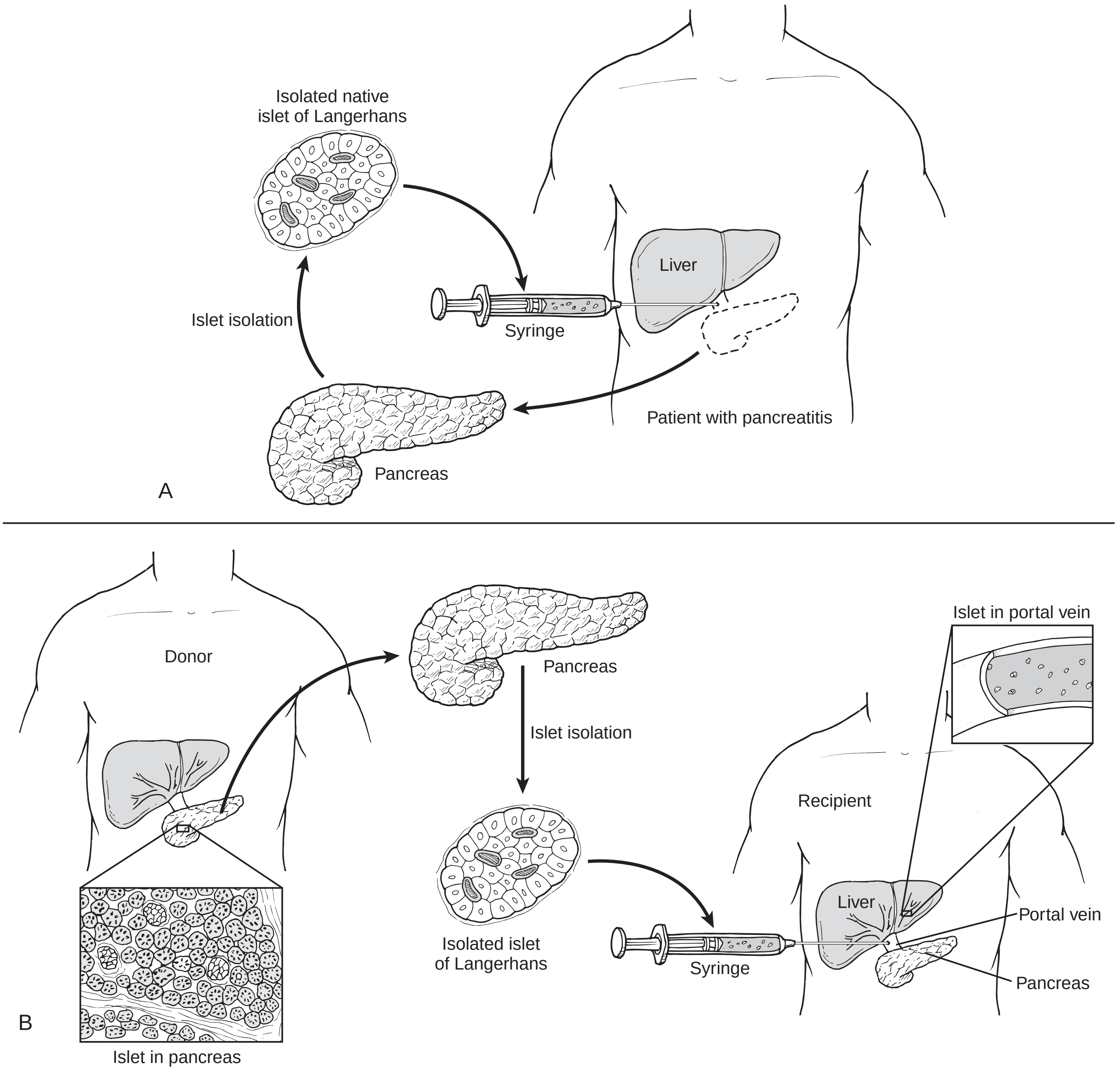


**FIGURE 47-13** Islet transplantation using the portal vein for embolization to the liver where revascularization will occur, either as an autograft of islets isolated from the excised specimen after pancreatectomy for benign disease **(A)** or as an allograft of cells isolated from a donor for treatment of a patient with type 1 diabetes **(B)**.

succeeded in achieving insulin independence with islets from a single donor pancreas.[179,180,187–191] Many of these protocols include adjunctive peritransplant anti-inflammatory and/or cytoprotective therapy, likely facilitating improved islet engraftment. Second, recent data indicate that islet allograft survival in T1D can be sustained with calcineurin inhibitor–free protocols.[188–190] Two immunosuppressive regimens, based on the costimulation blocker belatacept or the antileukocyte functional antigen-1 antibody efalizumab, were effective, well tolerated, and involved the first calcineurin inhibitor/steroid-sparing islet protocols resulting in long-term insulin independence. Although efalizumab is no longer available for clinical use, these early results demonstrate that calcineurin inhibitor–free regimens may be an effective alternative to improve graft function and longevity while minimizing renal and islet beta cell toxicity. Third, Berney and colleagues reported on the first type 1 diabetic patient who remained insulin independent for more than 10 years after islet allotransplantation.[195] Preliminary data now suggest that long-term insulin independence (>5 years) can be achieved in 50% of recipients given T-cell–depleting induction immunotherapy, matching insulin independence rates of solitary pancreas transplantation.[196] Early studies examining long-term islet function suggested a rapid loss of insulin independence beyond 1 year in many patients.[183,197] One possible factor contributing to islet loss is recurrent beta cell autoimmunity.[198,199]

Anti-CD3 antibodies and T-cell–depleting therapies, including anti-Thymoglobulin, have proved promising agents for minimizing autoimmunity in murine models of autoimmune diabetes and in clinical trials for new-onset T1D.[200–204] A recent analysis of University of Minnesota data and data reported to the Collaborative Islet Transplant Registry indicated that patients receiving an induction immunosuppression regimen that includes T-cell–depleting agents, either anti-CD3 antibody alone or either antithymocyte globulin (ATG) or alemtuzumab plus short-term TNF-α inhibition, for alloislet transplantation are more than twice as likely to maintain long-term insulin independence for at least 5 years post-transplant.[196] Three-year and 5-year insulin independence rates in these recipients are comparable with rates previously only attainable in recipients of pancreas transplants alone. Fourth, numerous reports have confirmed that human islet transplants are remarkably effective in protecting recipients with full and even partial islet graft function from severe hypoglycemia.[166,205,206] Finally, a prospective clinical trial demonstrated reduced progression of diabetic microvascular complications after islet transplantation compared with intensive medical therapy.[207] These data extend previous reports by the Milan group[208,209] and highlight the immense potential of cell-based diabetes therapy.

The unlimited and on-demand availability of xenogeneic pig islets would boost access to islet beta cell replacement. The quality of islet products from healthy, young, and living donor pigs would be predictably high and not compromised, as with human islet products, by comorbidity, brain death, age, and cold ischemia. The actual risks of infectious disease transmission from designated pathogen-free (DPF) source pigs are lower compared with risks associated with the use of deceased human donor organs.[210] Finally, genetic modification of source pigs would present opportunities for minimizing recipient immunosuppression not available to recipients of human islet allografts.[211] Thus exploiting the unique possibilities associated with porcine islet products would increase the availability and benefit-risk ratio of islet replacement therapies when compared with human islet products. The impact of such medical products on addressing unmet clinical needs in diabetes would be profound.

During the past few years, prolonged diabetes reversal exceeding 6 months has been demonstrated after porcine islet xenotransplantation in immunosuppressed nonhuman primates (NHPs) and for up to 6 months in nonimmunosuppressed NHPs.[212] Porcine C-peptide has been positive in the plasma of these recipients, and their fasting and, in some studies, also their non-fasting blood glucose levels have been in the normoglycemic to near-normoglycemic range. Perhaps most intriguing is that success has been achieved by five independent groups involving the use of various tissue sources (adult, neonatal, and embryonic pig islet tissue; wild-type and transgenic), implantation sites (portal vein, omental pouch, subcutaneous space), immunosuppressive protocols (with and without anti-CD154 monoclonal antibodies or encapsulation, avoiding immunosuppression), and animal models (streptozotocin-induced and surgical diabetes; in cynomolgus and rhesus monkeys).[213–216] Collectively, the demonstration of prolonged functional islet xenograft survival in nonhuman primates with several distinct xenotransplantation strategies suggests that porcine islet products could potentially be developed into a more widely available cellular therapeutic for T1D.

Although a transition from pancreas to islet transplantations as the dominant form of beta cell replacement therapy may occur during the next few years, pancreas transplantations will not disappear entirely. Patients with high pretransplantation insulin requirements, in whom diabetes reversal with islet transplantations is less likely, would best be served with a vascularized pancreas transplant, at least as long as other more unlimited sources of beta cells, such as porcine islets, are not available for clinical therapy. Furthermore, diabetic patients with exocrine deficiency would best be served by an enteric-drained pancreas transplant. In addition, in patients who have very high insulin requirements or insulin resistance (type 2 diabetes), an intact organ may be needed to obtain a sufficient islet mass to restore insulin independence from a single donor in the presence of insulin resistance.

Tissue availability will be the limiting factor in determining the magnitude of the impact of beta cell replacement therapy. Six thousand deceased donors are available each year in the United States, but it is estimated that only half have a pancreas suitable for transplantation. Thus the maximal number of pancreas transplantations that could be done in the United States is 12,000 per year, assuming that each deceased pancreas could be split for use in two recipients,[217] and that living donors would be used for segmental pancreas transplantations[61] to the extent that they have been for kidney transplantations (currently about 6000 per year in the United States). This scenario has not yet materialized, but the potential is there to transplant at a rate approaching half of the annual incidence of new-onset cases of type 1 diabetes (30,000/year in the United States). The numbers could be increased further if enough islets could be isolated from one donor for transplantations into more than two recipients. Although the efficacy of islet transplantation protocols will continue to improve, and the procedural and immunosuppressive risks now associated with islet transplantations will continue to diminish, islet transplantations will not be the ultimate approach to diabetes care. Just as pancreas transplantations set the stage for islet transplantations, the real value of islet transplantations will be to create and build momentum for the development of xenogeneic and stem/precursor cell–derived islet beta cell therapy[218] that will then make cell replacement therapy routine and commonplace in diabetes care.

Pancreas transplantations, and eventually islet transplantations, should be in the armamentarium of every transplantation center for the treatment of diabetic patients. Likewise, every endocrinologist should consider beta cell replacement in the treatment of patients in whom type 1 diabetes is complicated by hypoglycemia-associated autonomic failure[219] and/or progressive microvascular complications. Continued clinical research on pancreas and islet transplantations is needed to identify the most appropriate recipient population, the optimal timing in the course of diabetes, and the most suitable donor tissue and transplantation protocol for a given patient. Both pancreas and islet transplants need to be made as economical as possible.[220] Studies such as those done in pancreas-kidney transplant recipients, showing the efficiency in the treatment of complicated diabetes,[221] are needed in islet recipients as well. Currently, beta cell replacement has a well-defined clinical role for adult patients with

incapacitating hypoglycemic unawareness and is also appropriate in children and adults who otherwise need immunosuppression, such as for a kidney transplantation. As antirejection strategies become safer and with fewer side effects, the indications for pediatric beta cell replacement therapy can be liberalized.


## Acknowledgments

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*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 48

# Liver Transplantation

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and Ronald W. Busuttil

The treatment of liver disease in children with transplantation has its roots in the origin of liver transplantation itself, with the initial cases performed by Thomas E. Starzl on two children in 1963 and 1968.[1] Although the initial results were disappointing, during the ensuing 2 decades, liver transplantation developed into the standard therapy for decompensated cirrhosis, certain malignancies of the liver and biliary tract, acute liver failure, and many metabolic derangements. The National Institutes of Health Development Conference designated it as such in 1983, and the National Organ Transplantation Act created a nationally regulated system of organ allocation in 1987. The United Network for Organ Sharing (UNOS) was subsequently created and currently regulates the field through a peer review process. In 2009, 6320 liver transplantation procedures were performed in the United States, and of these, 572 were in the pediatric population.[2] This number of transplantation procedures has remained relatively stable since the late 1990s, although an increasing number of "partial" liver grafts from cadaveric and living donors are now being used. Pediatric liver transplantation offers unique challenges because of size, perhaps enhanced immune responsiveness, and the paucity of donor organs. Although nearly 65% of pediatric liver transplantation recipients are less than 6 years of age, only 25% of the pediatric cadaveric donor population comes from this same age group (Fig. 48-1).[2] As a consequence, achieving success in this arena requires technical perfection, both from the standpoint of obtaining a suitable graft and performing a meticulous transplantation operation. With reduction in transplantation waiting time and with improvements in immunosuppression, surgical technique, and long-term post-transplantation care, survival has markedly improved and now exceeds 90% at 1 year and 80% at 5 years, with many children surviving into adolescence and adulthood with a good quality of life.[3,4] In this chapter, we review the major indications for liver transplantation in children, the basic pathophysiology and clinical presentation of liver failure, operative strategies with emphasis on the unique surgical options available to children, postoperative management with emphasis on management of surgical complications, and outcome analysis.

## Indications and Pretransplant Care

### INDICATIONS FOR LIVER TRANSPLANTATION

Liver transplantation is currently indicated for children with decompensated cirrhosis because of cholestatic and noncholestatic causes, acute hepatic failure, some metabolic liver diseases, select tumors, and a variety of miscellaneous indications (Fig. 48-2). The general indication for liver transplantation in children is liver disease that limits long-term survival or quality of life, or markedly impairs normal growth and development. Cirrhosis alone is not an indication for transplantation, because many patients can be medically managed for a prolonged period prior to decompensation. In acute liver failure, the development of clear symptomatology, such as refractory coagulopathy, acidosis, and encephalopathy that correlate with a poor prognosis for spontaneous recovery of liver function, is an indication for transplantation. Otherwise, medical support in those with a better prognosis is provided until liver function returns to normal.[5,6] Finally, metabolic inborn errors of metabolism are a unique and not uncommon indication for transplantation in children, making up 9% of transplantation in children compared with approximately 2% in adults. Parenteral nutrition–associated liver disease accounts for 8% of liver transplantations, and less than 1% of adults are transplanted for this reason. Most of these transplantations are combined with an intestinal graft (Chapter 49).

With long-standing cirrhosis, the development of a constellation of symptoms and signs that represent decompensation of hepatocellular function or portal hypertension herald a need for transplantation. These include progressive jaundice, coagulopathy, protein-calorie malnutrition and growth retardation, impaired cognitive development, encephalopathy, hypersplenism, variceal hemorrhage, and advanced or refractory ascites. The majority of patients undergoing transplantation in this population are deeply jaundiced because of secondary or primary biliary cirrhosis from long-standing intrahepatic and/or extrahepatic biliary obstruction. On physical examination, these patients often have muscle wasting, an enlarged spleen, a hard palpable liver, abdominal distention

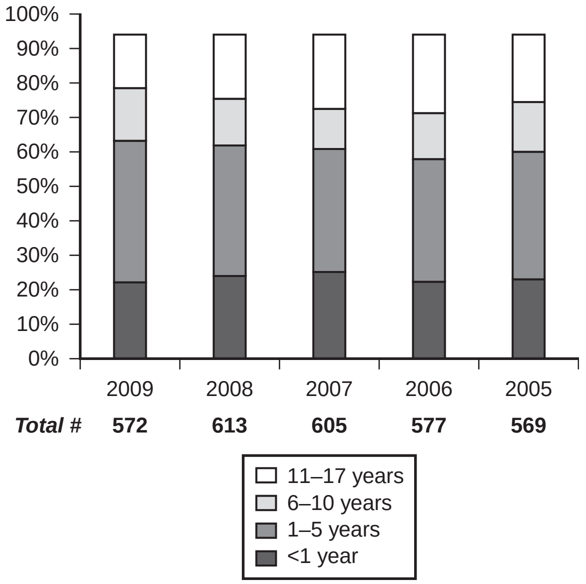



FIGURE 48-1 Distribution of pediatric liver transplantations by age. Data obtained from www.unos.org.

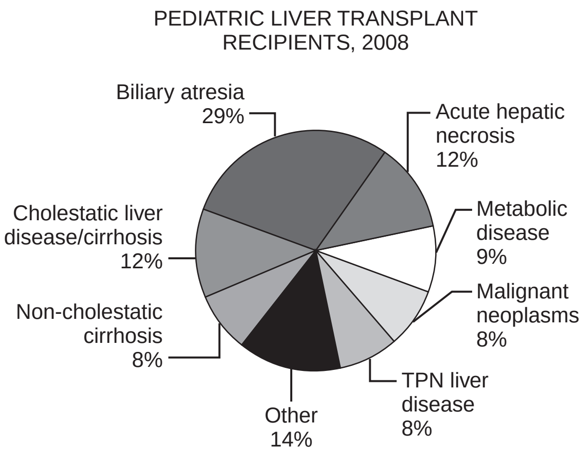



FIGURE 48-2 Indications for pediatric liver transplantation. Data obtained from www.unos.org, based on 2008 transplantations. TPN, total parenteral nutrition.

from ascites, and peripheral edema. With decompensation, long-term survival without liver transplantation is limited, and referral for transplantation must be made prior to decompensation.[3,7–9]

## CHOLESTATIC LIVER DISORDERS

The most common indications for liver transplantation are the cholestatic liver disorders, with the most common being biliary atresia (BA). This group accounts for roughly 40% of the transplantation performed on children in 2008, and BA accounts for 70% of this cholestatic group (see Fig. 48-2).[2] The management of BA rests on early diagnosis, using surgical exploration with biopsy as the central confirmatory test in most cases. The diagnostic workup is detailed in Chapter 105. Portoenterostomy (PE) is the preferred treatment if diagnosis precedes the development of cirrhosis, usually before 3 months of age, though long-term results from PE are optimal if it is done prior to 8 weeks.[10] This procedure is essential for slowing, and, in some cases, arresting, the progression of liver disease to cirrhosis and portal hypertension. Unfortunately, despite effective biliary drainage, more than 70% of patients will go on to develop decompensated cirrhosis by the age of 5 years and require transplantation.[10,11] However, in many cases, PE allows reasonable growth so that transplantation is forestalled until the child is older and larger. Primary PE performed late in the course of BA and reexploration for a failing biliary drainage procedure are both usually unsuccessful and only complicate transplantation outcomes. Instead, once a PE has failed, patients should be evaluated for transplantation. Liver transplantation is indicated when the diagnosis is made beyond 3 months of age, when decompensated cirrhosis is clearly present at any age, or after a PE has failed. Patients with BA should be managed by a pediatric hepatologist experienced in transplantation to ensure early referral for transplantation. This should occur prior to severe liver decompensation when signs are obvious on physical examination, especially with an advanced presentation at a late stage (Fig. 48-3).

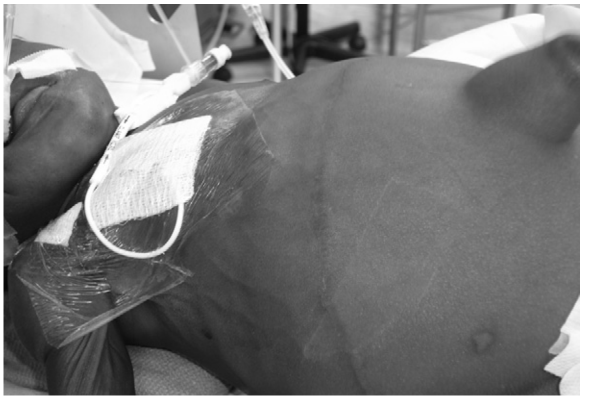


FIGURE 48-3 Decompensated cirrhosis after a Kasai portoenterostomy. This 6-month-old, 5-kg child presented for liver transplant with the advanced findings of hepatosplenomegaly, extensive abdominal wall venous collaterals, tense ascites, jaundice, and profound malnutrition.

Other uncommon etiologies of cholestatic liver injury and cirrhosis include familial paucity of intrahepatic bile ducts, which exists in a syndromic (Alagille syndrome) and nonsyndromic form, familial cholestatic syndromes, primary or secondary sclerosing cholangitis, and uncorrectable choledochal cyst disease, including Caroli disease. The cystic diseases have a component of uncorrectable extrahepatic obstruction while the others are the result of malformation or destruction of intrahepatic bile ducts and/or arterial systems. All these share in common a variable and unpredictable progression to advanced fibrosis, cirrhosis, and portal hypertension. These patients typically present with progressive jaundice at an older age than patients with BA. Although their management does not entail a PE, the indications for transplantation in these patients follow the same rationale as that for BA.

## NONCHOLESTATIC CIRRHOSIS

Noncholestatic cirrhosis is an uncommon indication for liver replacement in children, accounting for less than 10% of all procedures performed in 2008 (see Fig. 48-2).[2] These children usually present later in life than the cholestatic disorders.

Etiologies of cirrhosis and decompensated cirrhosis in these patients include chronic autoimmune hepatitis, neonatal hepatitis, chronic viral (B or C) hepatitis, and cryptogenic cirrhosis.

### ACUTE LIVER FAILURE

Fulminant hepatic failure is usually defined as the onset of encephalopathy within 28 days after the onset of jaundice in a patient with acute liver failure without evidence of chronic liver disease. The hallmarks of acute liver failure include profound coagulopathy, acidosis, hypoglycemia, and progressive hyperbilirubinemia. Acute liver failure patients can develop acute renal failure, systemic inflammatory response with multiorgan failure syndrome, or cerebral edema progressing to herniation. Early referral is essential to avoid progression to a condition that contraindicates transplantation. A variety of criteria to determine the need for transplantation have been devised in European centers, where these patients are managed in a highly structured and centralized manner.[12] The most common established etiology in children is viral hepatitis, followed by acetaminophen and other drug toxicities and Wilson disease. However, in nearly two thirds, an etiology cannot be identified. Liver transplantation is the only acceptable therapy in patients who meet the criteria of fulminant hepatic failure, and early referral of all patients with acute liver failure is essential.[5,6]

### METABOLIC LIVER DISEASE

These disorders have in common an enzyme deficiency or some other defect in hepatocellular function. This impairment can result in progressive fibrosis or cirrhosis (e.g., cystic fibrosis, chronic Wilson disease, and neonatal iron storage disease), with a typical presentation of decompensated cirrhosis. In other cases, the liver is structurally normal, but harmful byproducts of metabolism accumulate to cause neurologic injury (e.g., Crigler-Najjar syndrome, ornithine transcarbamylase deficiency, and acute Wilson disease), cardiovascular disease (e.g., familial hypercholesterolemia), or renal injury (familial hyperoxaluria). Some disorders are associated with the development of malignancies (e.g., tyrosinemia), and transplantation should be considered preemptively. Transplant evaluation of all patients with known metabolic disorders of the liver involves a thorough evaluation of extrahepatic function. This will ensure transplantation of only those patients who can benefit from liver transplantation and prevents progression of extrahepatic disease. In some patients, simultaneous or sequential or dual organ transplantation may be necessary (e.g., lung, kidney, heart).

### TUMORS

The most common liver malignancy in children is hepatoblastoma.[13,14] Although sporadic cases have been reported, hepatocellular carcinoma (HCC) is primarily seen in children with viral hepatitis, tyrosinemia, some of the glycogen storage diseases, or in association with cirrhosis from other causes. Primary liver malignancies in pediatric patients are managed by surgical resection unless tumor size and/or location preclude resection. The benefit of neoadjuvant and/or adjuvant chemotherapy and radiation for hepatoblastoma has been well documented.[15–17] In HCC, multimodal therapy can be used to prevent further cancer progression or perhaps to improve the outcome of highly selected patients with advanced HCC. Both may benefit from preoperative transarterial chemoembolization and/or radiofrequency ablation.[18] If the lesion is unresectable, transplantation can be considered after excluding extrahepatic disease.[15,17] With multimodal therapy to include liver transplantation, the long-term survival with hepatoblastoma now exceeds 50%, while outcomes from HCC are in excess of 70%.[15,17,19] The major controversy that exists is whether transplantation should be attempted for large hepatoblastomas primarily or as a salvage after recurrence following resection, and whether focal lung metastases contraindicate transplantation if they can be resected The most common benign tumor of the liver is hemangioendothelioma, and although the vast majority regress with growth and medical therapy, occasionally, progression of heart failure or mass effect warrants transplantation.[13,19]

### MISCELLANEOUS CONDITIONS

These conditions include diagnoses such as Budd-Chiari syndrome, trauma, biliary cirrhosis secondary to intestinal failure, and long-term total parenteral nutrition (TPN) use. The latter is detailed in Chapter 49.

## Organ Allocation and Pretransplant Care

Patients who have evidence of decompensated cirrhosis are candidates for liver transplantation. However, the small size of the pediatric patient combined with a nationwide shortage of organs relative to wait-listed patients makes achieving transplantation in a timely fashion problematic. In 2008, there were 613 pediatric liver transplantations performed. In that same year, there were 773 pediatric-aged cadaveric liver donors. The problem with a discrepancy between donors and recipients is primarily a problem in the less-than-6-year age category, where there were 423 liver recipients but only 274 donors.[2] Another problem is, of course, timing: When a pediatric donor is available, there is not necessarily a size-matched pediatric recipient available. This creates a relative shortage of organs that necessitates a system to allocate these scarce organs to those who will derive the most benefit. Since 2002, the Pediatric End-Stage Liver Disease (PELD) score was implemented to allocate organs based on this "sickest first" paradigm.[9] The PELD score consists of five variables: international normalized ratio (INR), total bilirubin, serum albumin, growth retardation ($\geq$2 standard deviations below the median height or weight for age), and young age ($<$1 or 1 to 2 years). Status I-A is used to designate patients with fulminant hepatic failure, primary graft nonfunction after transplantation, early hepatic artery thrombosis, and miscellaneous acute conditions. Unlike adults, pediatric patients with decompensated cirrhosis requiring intensive care unit (ICU) stay for accepted reasons, and occasional exceptions can be listed as status I-B. This is because their mortality is high despite an often minimal change in PELD score with a decompensation requiring ICU stay. In an effort to ameliorate the shortage of potential organs, the livers of all donors 18 years of age and younger are preferentially allocated to pediatric recipients before being offered to adults.

Also, in 2006, organ allocation policy was changed so that rather than allocating livers from donors less than age 18 years locally, they are allocated at a regional level to children to increase the probability of use of the organ in pediatric patients and to facilitate liver splitting. These changes in organ allocation combined with the widespread use of split-liver transplantation (see later) has markedly reduced waiting times and positively impacted wait list mortality.[3,20]

# Donor Procurement and Hepatobiliary Anatomy

## HEPATOBILIARY ANATOMY

The performance of a donor hepatectomy or transplant operation requires a thorough understanding of foregut anatomy. In addition, a very detailed understanding of this anatomy is essential to the field of segmental liver transplantation and has impacted hepatobiliary surgery. The blood supply to the liver is based on a highly variable arterial and portal system. Venous drainage is through the right, mid-, and left hepatic veins that join the inferior vena cava, which traverses the dorsal surface of the liver (the retrohepatic cava). The liver is composed of the major right and left lobes that are separated by external landmarks and further subdivided into the right anterior and posterior sectors and left medial and lateral sectors. This nomenclature is still used to describe major anatomic liver resections. However, through the elegant anatomic techniques of the pioneering surgical anatomist Claude Couinaud, hepatic anatomy was found to be much more intricate (Fig. 48-4). The "Couinaud nomenclature" describes nine hepatic segments based on portal vein branching in relationship to the transverse plane (a cross-sectional plane located at "midpoints" of the hepatic veins) and the longitudinal planes of the individual hepatic veins (see Fig. 48-4). Each of the segments is supplied by an independent portal and hepatic arterial branch and drained by an independent biliary radicle. The biliary tree is second only to the arterial system in its variability. The hepatic venous drainage is intersegmental.

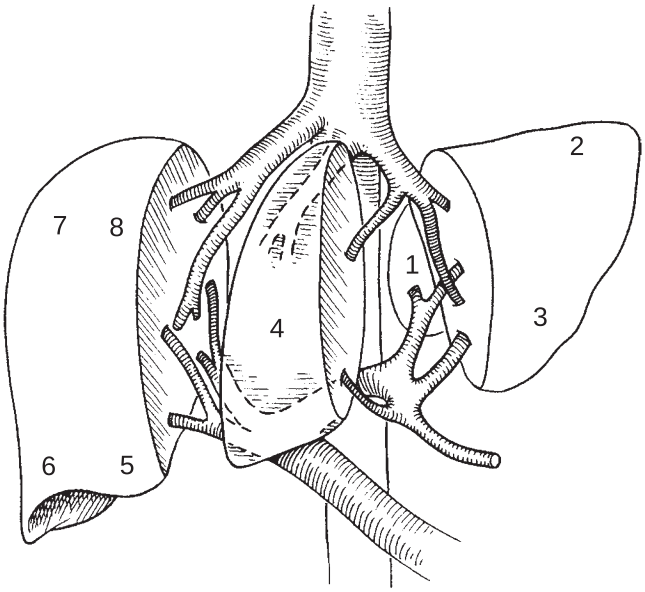



FIGURE 48-4 Segmental liver anatomy. The division of the liver into independently vascularized and drained segments is based on the parallel bifurcation of the portal vein and hepatic artery.

# Donor Operation

The use of organs from cadaveric donors in pediatric liver transplantation involves selecting an appropriate quality and size-matched donor, organizing an experienced transplantation harvest team, and performing a precise technical operation that recognizes arterial anatomical variants and allows for multiorgan procurement. The advent of segmental liver transplantation has expanded the acceptable donor age to approximately 40 years. Preharvest donor management should focus on maintenance of hemodynamic stability with adequate but not excessive volume loading, the minimization of vasopressors, optimization of oxygenation without excessive use of positive end-expiratory pressure (PEEP), and correction of hypernatremia that results from diabetes insipidus. In the stable donor, once these goals are achieved, the procurement operation can be performed. In the properly selected unstable donor, unnecessary delays are to be avoided, because expedient hypothermic perfusion and cold storage only help minimize the ongoing organ ischemia.

The donor operation begins with midline laparotomy and median sternotomy for wide exposure (Fig. 48-5). The abdominal great vessels are exposed by a medial visceral rotation of the right colon and small intestine, and the aorta and inferior mesenteric vein are cannulated. The liver quality is assessed, and the biliary tree is flushed via the gallbladder. After full systemic heparinization, the supraceliac aorta is cross-clamped, and the intrapericardial inferior vena cava is incised to exsanguinate the donor. Then cold-organ perfusion is begun through the previously placed cannulas, and the abdominal cavity is immersed in ice to attempt achieving a liver core temperature of 4°C. University of Wisconsin (UW) solution has been used as the standard solution in the United States since 1987 when it was developed by Belzer and Southhard. This solution extended the limit of preservation to as long as 12 to 18 hours, after which the incidence of primary

FIGURE 48-5 Cadaveric organ procurement. A wide exposure with median sternotomy extending to midline laparotomy is made for multiorgan procurement. This harvest resulted in the procurement of six organ grafts from a single recipient, benefiting six different recipients.

graft failure increases substantially. However, the acceptable preservation time depends on numerous donor and recipient variables and should still be minimized when possible. This is particularly the case with reduced-size or split-liver transplantation. The UW solution is a hyperkalemic, hyperosmolar solution that prevents cell swelling, maintains stable transmembrane electrical gradients upon reperfusion, by preventing efflux of intracellular potassium during storage, and contains a variety of oxygen free radical scavengers. Many centers are now using a histidine-tryptophan-ketoglutarate solution because of its lower potassium content and viscosity.[21] Once procured, the harvest team typically transports the liver graft to the transplantation center and prepares it for engraftment for a separate recipient team.

## Segmental Liver Transplantation: Living Donor, Reduced Size, and Split

The shortage of pediatric organs coupled with a significant wait-list death rate has driven the development of alternative organ sources. Three alternatives to use of a whole organ graft are available to these patients: living donor, reduced-size and split-liver grafts.[7,20,22,23] Living donor transplantation was developed as an alternative to scarce whole organ grafts and typically uses a segment 2 and 3 (left-lateral sector, LLS) graft. Because of the small but real risk of safety in a healthy donor, reduced-size transplantation was simultaneously developed as an alternative and involves resecting the LLS graft prior to or after cold-organ perfusion and discarding the remaining liver. Obviously, this benefits the pediatric recipient but wastes an organ that could be used by an adult recipient. Splitting the whole organ into a right trisegment and LLS graft to use in an adult and pediatric recipient, respectively, was first reported by Pichlmayr in Hanover in 1988. This can be done either prior to cold organ perfusion (in-situ technique) (Fig. 48-6) or after cold-organ perfusion and removal of the liver from the donor (ex-vivo technique).[22] This provides a suitable graft for the pediatric population without worsening the already severe organ shortage in the adult population. Although the initial results were discouraging, with increased experience, the survival rates of patients and grafts are nearly equal to whole organ and living donor transplantation, though the risk of vascular and biliary complications is somewhat higher.[27,23–25] At the University of California in Los Angeles (UCLA), we are only performing living donor transplantations when a whole or split graft is not available in a timely fashion or for special indications. There has been a marked reduction in transplant wait time since the routine use of segmental grafts with this strategy.[3,20,23]

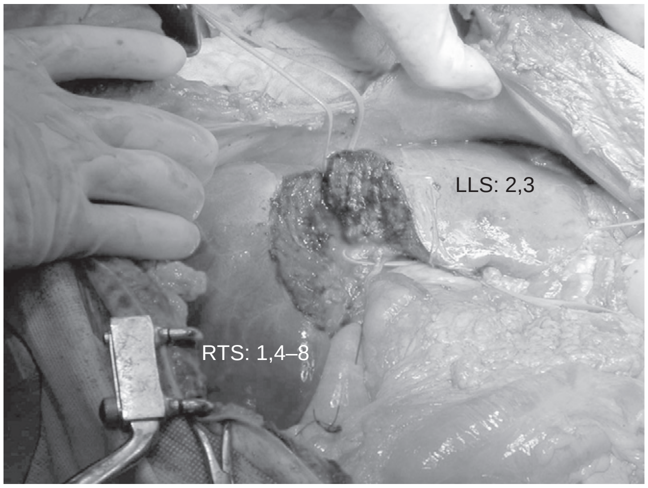



**FIGURE 48-6** Cadaveric in-situ split-liver procedure. The liver is separated just to the left of the umbilical fissure into a right trisegment (RTS) graft and a left-lateral segment (LLS) graft.

## Liver Transplant Operation

The performance of the whole organ cadaveric liver transplant procedure has changed little during the last 2 decades. Although there are tremendous individual and institutional differences in the subtleties and how certain techniques are used or not used, the basic steps in the procedure remain the same. What follows is a description of how the procedure is generally performed at UCLA today and has been applied in more than 3000 cases.[26] The procedure can be roughly divided into four major phases, each with its own anatomic and physiologic challenges: hepatectomy phase, anhepatic phase with engraftment, reperfusion with arterialization, and biliary reconstruction. Perhaps the most challenging step during liver transplantation is the hepatectomy. Coagulopathy, portal hypertension, and poor hepatic and renal function create a surgical environment wherein continuous bleeding is possible. During this phase, the anesthesiologist plays a key role in maintaining volume by rapid transfusion, correcting coagulopathy and fibrinolysis, and maintaining body temperature. The goal of this phase is to devascularize the liver by ligating and dividing the hepatic artery and portal vein as well as to mobilize the suprahepatic and infrahepatic vena cava to enable removal. These goals are achieved while leaving in the recipient adequate lengths of each vessel for later implantation of the donor graft. In the majority of pediatric liver transplant operations, the retrohepatic vena cava is retained as the liver is dissected off the vena cava by dividing the tributaries from the right and caudate lobes, and often only partial occlusion of the vena cava is necessary. Meticulous but expedient surgical technique is essential during the hepatectomy to ensure optimal patient outcome. During the anhepatic phase, the anesthesiologist must support certain aspects of hepatic function to prevent or treat acidosis, hypothermia, coagulopathy, and occasionally fibrinolysis. In addition, they must ensure adequate circulating volume and maintain hemodynamic stability. In children, venovenous bypass is rarely used.

While the patient is anhepatic, the liver graft is taken out of hypothermic storage and engrafted. This begins with the suprahepatic caval, followed by the infrahepatic caval and the portal anastomoses. If the retrohepatic cava was retained, the “piggyback” technique is used, in which the suprahepatic cava of the graft is sewn to the cloacae created from the confluence of the recipient hepatic veins, and the donor infrahepatic cava is ligated (Fig. 48-7). Prior to reperfusion, the liver is flushed with a cold colloid and albumin solution through the donor portal vein to lessen the potential reperfusion-associated complications.

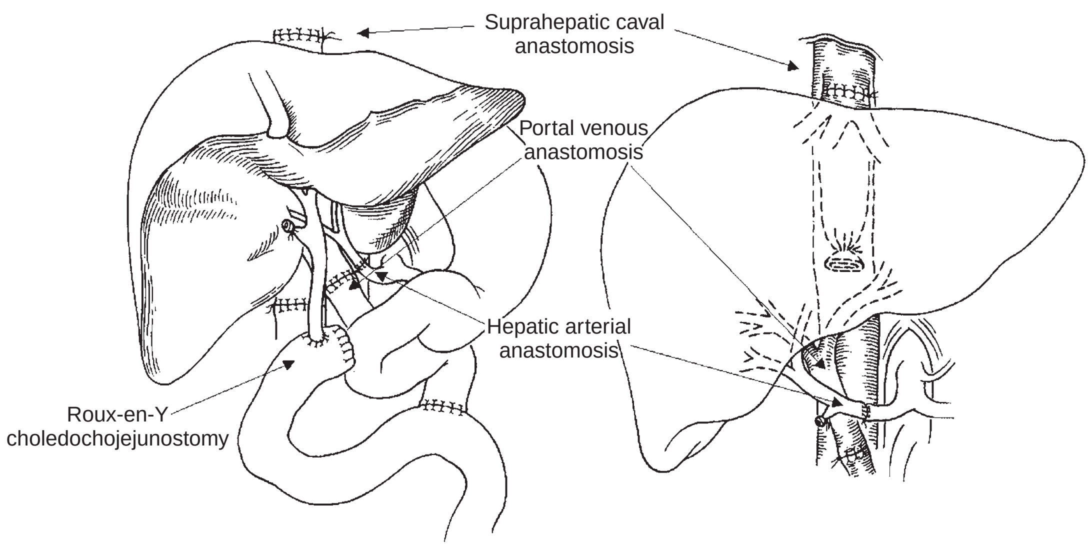



**FIGURE 48-7** Whole organ engraftment. Both the standard orthotopic and "piggyback" techniques are depicted.

Reperfusion is then undertaken in a controlled manner. Communication between the surgical and anesthesia teams is essential to allow the anesthesiologist time to institute preparative and preventive measures. Reperfusion is undertaken by first removing the suprahepatic vena cava clamp, then the infrahepatic vena cava clamp and, lastly, the portal venous clamp. As blood is reintroduced into the liver allograft and allowed to drain into the right atria, many serious and life-threatening complications can develop. The major challenges encountered by the anesthesiologist at this point are life-threatening hyperkalemia, acidosis, arrhythmias, and hemodynamic instability with or without surgical or coagulopathic bleeding. Factors that contribute are the return of cold, acidotic, and hyperkalemic blood directly into the right atrium. It is at this point that maintenance of physiologic stability by the surgeon and anesthesiologist in the preceding phases, the preoperative state of the recipient, and the intrinsic quality of the graft converge to determine early graft function as well as the course of the remainder of the operation. Without a doubt, this is one of the most hazardous portions of the liver transplant process.

The hepatic arterial anastomosis is then performed. In general, arterial inflow is obtained from one of the branches of the celiac trunk. However, in some instances, inflow from these vessels is not adequate, thus necessitating the use of aortic conduits. A conduit can be placed either on the supraceliac or infrarenal aorta. In some cases, when the arteries are of very small caliber (<3 mm), the arterial anastomosis is performed prior to reperfusion. The biliary tree is then reconstructed by choledochocholedochostomy or by Roux-en-Y choledochojejunostomy, the latter being more common in small children and used exclusively in partial liver grafts because of the size of the donor duct (Fig. 48-8). After ensuring sufficient hemostasis, drains are placed and the abdominal cavity is closed. The patient is then transferred directly to the ICU. Segmental transplantation, using split, reduced-size, or living donor grafts, involves variations in the manner in which the anastomoses are performed, but the general steps are the same (see Fig. 48-8).

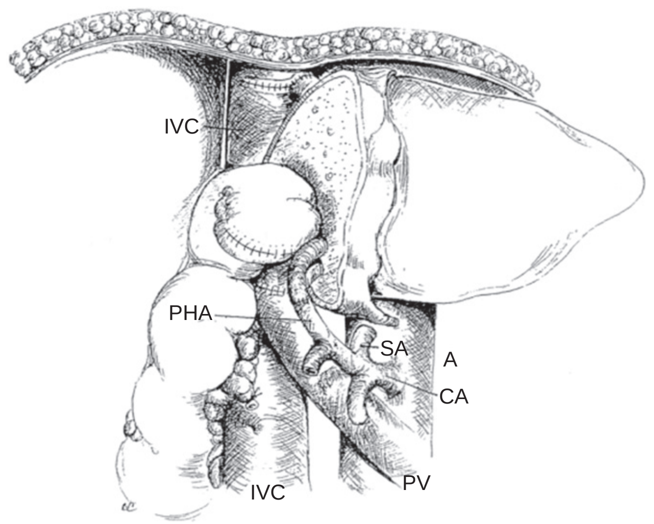



**FIGURE 48-8** Left-lateral segment engraftment. A, aorta; CA, celiac artery; IVC, inferior vena cava; PHA, proper hepatic artery; PV, portal vein; SA, splenic artery. (Reprinted with permission from Goss J, Yerziz H, Shackelton H, et al: In situ splitting of the cadaveric liver for transplantation. Transplantation 1997;64:871-877.)

# Post-transplant Care

## EARLY POSTOPERATIVE CARE

The early and long-term postoperative care of the liver transplant recipient is almost as important as the performance of the operation in ensuring optimal outcomes. The immediate postoperative care is aimed at assessing graft function, providing supportive care for the recipient, and early detection of complications. Graft function can be assessed in many ways. Physiologic and clinical assessment can be done almost immediately with a warm, arousable, hemostatic, and hemodynamically stable patient whose liver is making "golden-brown" bile (in the infrequent case where a biliary drainage tube is placed),

characteristics that are the hallmarks of a functional graft. Graft function is then confirmed biochemically by evidence of synthetic and metabolic function (e.g., correcting prothrombin time, reversal of acidosis). The degree of preservation injury, as measured by liver enzyme levels, does not linearly correlate with graft function, but grafts with severe injury are more likely to exhibit delayed function or nonfunction. Failure of a graft without vascular compromise (primary nonfunction [PNF]) is treated by retransplantation in almost all cases, with outcome directly related to the time to retransplantation. The incidence of PNF in pediatric patients is 5% to 10%.[7,8,23,24,27]

# Technical Complications

Technical complications can be divided into vascular, biliary, and general surgical complications. In the early postoperative period, infectious and general surgical complications of liver transplantation today are similar to those that occur after any major abdominal operation. However, the incidence of fungal infection is higher, and the incidence of bowel perforation in pediatric recipients is as high as 19% in some series. Also, early exploration or computed tomography (CT) imaging should be considered when sepsis is suspected and no other etiology can be found.

### VASCULAR COMPLICATIONS

Major vascular complications include hepatic artery thrombosis (HAT), portal vein thrombosis, and caval thrombosis or stenosis. Intravenous low-dose unfractionated heparin with or without low-molecular-weight dextran is routinely used for prophylaxis against vascular thromboses. Duplex ultrasonography and computerized tomographic or conventional angiography are accepted means of diagnosis. HAT is the most common complication, and its incidence varies from 5% to 18% depending on patient age and type of graft.[7,8,23,24,27,28] Early vascular complications are usually technical in nature, while immunologic and infectious (e.g., cytomegalovirus [CMV]) etiologies have been ascribed to those occurring months after transplantation. HAT occurring in the first week is commonly associated with graft nonfunction and biliary necrosis or leak, while those occurring later do not necessarily affect graft function immediately, but usually produce biliary complications. These include intrahepatic biliary abscesses, biliary anastomotic stricture, and sclerosing cholangitis with sepsis, all of which lead to significant morbidity. If diagnosed early, some patients can be managed by thrombectomy and surgical revision. However, most early HATs require urgent retransplantation. Late HATs with preserved graft function can be managed by radiologic interventional techniques and retransplanted remote from initial transplantation. Thrombosis of the portal vein occurs in 2% to 4% of pediatric liver transplantations and is usually associated with loss of the graft. Prompt retransplantation is required for patient salvage. Late portal vein thrombosis usually presents with recurrent variceal bleeding or ascites and can be managed medically, endoscopically, or surgically with shunting or retransplantation. Vena caval or hepatic vein thrombosis or stenosis occurs in 3% to 6% of pediatric patients and presents with variceal bleeding and/or ascites and is usually best managed with balloon dilation in interventional radiology[7,8,23,24,27,28]

### BILIARY COMPLICATIONS

Biliary complications that are not associated with HAT occur in 3% to 20% of patients depending on the type of graft and whether a choledochojejunostomy was used. These usually result from technical factors, but occasionally warm ischemia or immunologic and infectious factors can be implicated (e.g., CMV). Diagnosis is by cholangiography and treatment can be by endoscopic or radiologic intervention or by surgical revision.[7,23–25,27]

# Immunosuppressive Therapy and Rejection

Immunosuppression for liver transplantation in the modern era rests on a class of drugs known as calcineurin inhibitors (CNI), the prototype being cyclosporine (Table 48-1). Cyclosporine, especially its microemulsion formulation, which allows better bioavailability and more consistent therapeutic levels, revolutionized organ transplantation by reducing the incidence of rejection in all solid organs. The second-generation CNI, tacrolimus, was first used clinically in 1990. The greater potency of tacrolimus allowed for a further reduction in the early incidence of rejection following liver transplantation, while also allowing the earlier weaning of steroid therapy. Also, the incidence of chronic rejection has significantly decreased with the use of tacrolimus, which can also effectively treat episodes of acute rejection. Currently, most liver transplant centers use a tacrolimus-based regimen combined with steroid therapy with or without adjunctive agents. Cyclosporine and tacrolimus share certain acute and long-term side effects while having some that are unique to the agent. The most important of these is nephrotoxicity, which occurs in an acute variety from vasoconstriction of the afferent renal arterioles and is reversible, as well as a more chronic variety marked by tubular atrophy, interstitial fibrosis, and glomerulosclerosis. The latter is variably reversible depending on the degree of disease. To minimize acute toxicity and to allow lower early CNI levels, especially with pretransplant renal insufficiency, a purine antimetabolite, mycophenolate mofetil, is sometimes used as an adjunctive agent (see Table 48-1). The newest class of immunosuppressants is the inhibitors of mammalian target of rapamycin, the prototype being sirolimus. This agent has been used sparingly in pediatric liver transplantation, and only preliminary data exist. Although this drug has no nephrotoxicity, it has other long-term sequelae, such as hypercholesterolemia. No perfect immunosuppression (i.e., one with minimal side effects) has been developed yet.

Acute rejection (AR) is common in pediatric liver transplantation, with the peak incidence being within the first 6 months, during which 30% to 50% of patients experience at least one episode.[7,8,23,27] It is less common after the first post-transplant year, occurring in 10% or less of patients. AR is suspected with elevated aspartate or alanine transaminase levels or by elevated alkaline phosphatase levels and gamma-glutamyl transferase levels. AR is an alloantigen specific, T-cell–mediated inflammatory process that targets

**TABLE 48-1**
**Modern Immunosuppressants Used in Liver Transplantation**

| *Name* | *Mechanism of Action* | *Principal Use* | *Common Toxicities* |
|---|---|---|---|
| Calcineurin inhibitors (CNI) cyclosporine tacrolimus | Exact and complete mechanism unknown; inhibits IL-2 and other cytokine gene transcription, thus preventing T-helper cell expansion | Induction and maintenance of immunosuppression long term; tacrolimus is the only agent approved for monotherapy, while cyclosporine must generally be used with another agent long term | Shared: nephrotoxicity, hypertension, hyperglycemia, neurotoxicity (seizures, myoclonus, essential tremors) Cyclosporine: hirsutism, gingival hyperplasia, more diabetes Tacrolimus: diarrhea, anorexia, more neurotoxicity, more hypertension |
| Glucocorticoids methylprednisolone prednisone | Diffuse action on immune system by its anti-inflammatory properties, especially inhibition of IL-1 | Induction of immunosuppression and maintenance; may be weaned off long term in some patients | Hyperlipidemia, osteopenia, hypertension, diabetes, impaired wound healing, growth retardation, Cushingoid features, striae, acne |
| Mycophenolate mofetil | Purine antimetabolite, semiselective for salvage pathway present primarily used in lymphocytes | Used as an adjunctive agent to reduce the dose of CNI or steroid | Myelosuppression, diarrhea, anorexia, nausea, vomiting, GI mucosal ulceration |
| Mammalian target of rapamycin inhibitors rapamycin | Inhibits cell cycle progression in stimulated cells, thus preventing clonal expansion of stimulated B and T cells | Unclear, use in pediatric patients preliminary; may be useful in minimizing CNI dose when toxicity exists or in refractory AR or chronic allograft rejection | Hyperlipidemia, impaired wound healing, pneumonitis, oral ulceration |
| OKT3 monoclonal antibody | Clonal deletion of (CD3+) T cells | Severe or refractory acute allograft rejection | SIRS and other infusional reactions, increased risk of viral infections and PTLD |
| Antilymphocyte globulin (Thymoglobulin) | Exact and complete mechanism unknown, but produces central and peripheral deletion of lymphoid cells | Severe or refractory acute allograft rejection | Increased risk of viral infections and PTLD, lower incidence of infusional reactions than OKT3, thrombocytopenia |
| IL-2 receptor antagonists basiliximab daclizumab | Competitive inhibition of IL-2 receptors | Induction of immunosuppression as an adjunct to CNI; used to minimize other immunosuppression (CNI, steroids) | Increased risk of viral infections, possible PTLD, rare infusional reactions |

AR, acute rejection; GI, gastrointestinal; IL-1, IL-2, interleukin-1, interleukin-2; PTLD, post-transplant lymphoproliferative disorder; SIRS, systemic inflammatory response syndrome.

vascular endothelium and biliary epithelium but not hepatocytes. This is based on the greater expression of donor human leukocyte antigens on the former cell types. The histologic hallmark of AR is a mixed cell inflammatory infiltrate (polymorphonuclear cells, lymphocytes, and eosinophils) in the portal triad, with evidence of inflammation of the endothelium and/or biliary epithelial injury. Rejection can be graded as mild, moderate, and severe depending on the proportion of involved portal triads, the degree of infiltrate and injury, and the presence of central vein endothelial inflammation, which is a sign of severe AR. Treatment of AR is centered on a high-dose methylprednisone bolus, but cases unresponsive to this may require use of antibody therapy (OKT3, antithymocyte globulin [ATG], see Table 48-1). Mild AR can often be treated by simply increasing the tacrolimus level, though steroid bolus should be considered if there is not a prompt response. AR does not influence long-term graft survival in adults or children, unless it occurs in multiple or steroid refractory episodes, or if it occurs beyond the first year post-transplant.[4,7,29] AR accounts for less than 3% of overall patient and graft loss. However, treatment for AR is an important risk factor for the development of cytomegalovirus and Epstein-Barr viral infections in children. The latter is a risk factor for the development of post-transplant lymphoproliferative disorder. Therefore a balance between adequate immunosuppression to prevent AR and over-immunosuppression to avoid toxicity is necessary. Currently, long-term morbidity from immunosuppressive drug therapy is the major challenge facing long-term survival and quality of life in the pediatric population.

Chronic rejection is a common cause of late graft loss in children, because disease recurrence is uncommon. It is not felt to be entirely alloantigen driven, and may be due to a number of factors that share final common pathway of graft injury. Its hallmark is the intrahepatic loss of bile ducts and has been termed "vanishing bile duct syndrome" in the past because of this histologic finding on biopsy. This diagnosis is suspected if progressive jaundice and rising levels of alkaline phosphatase occur. Currently, there is no prophylactic or therapeutic agent for chronic rejection, though progression of graft fibrosis may be forestalled by sirolimus, based on animal and preliminary clinical data.[30] Although maintenance immune suppression is often enhanced, the only definitive treatment when decompensated graft failure occurs is retransplantation.

# Infectious Complications

Post-transplant infections are the most common cause of morbidity and mortality after liver transplantation (Table 48-2). The highest incidence of bacterial and fungal infections is in the first month after transplantation. Fungal infections occurring months to years after transplantation are unusual and are more commonly the atypical or endemic organisms, such as *Cryptococcus* spp., *Mucormycosis* spp., *Blastomycosis* spp., or *Coccidiomycosis* spp. Viral infections are the most common infections after the early post-transplant period. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections account for the vast majority of opportunistic viral infections. Overall

**TABLE 48-2**
**Infectious Complications after Liver Transplantation**

| *Organism* | *Presentation* | *Diagnosis* | *Antimicrobials* |
|---|---|---|---|
| Cytomegalovirus (CMV) | Infection results from reactivation of virus; blood transfusion; infected transplanted organ<br>Mild viral, "flulike" syndrome<br>Invasive tissue infection (retinitis, pneumonitis, myocarditis, enterocolitis, hepatitis, CNS) | Quantitative CMV-DNA PCR<br>pp65 antigen<br>Tissue cultures<br>Blood or fluid cultures<br>Biopsy with immunostains | Prophylaxis: IV ganciclovir, oral valganciclovir<br>Therapy: IV ganciclovir with or without CMV immunoglobulin |
| Epstein-Barr virus (EBV) | Spectrum: infectious mononucleosis to lymphoproliferative disease to lymphoma to EBV-associated soft tissue tumors<br>Occurs with EBV and immunosuppression, 10%-15% infant liver transplantation<br>GI tract, neck, thorax, CNS | Quantitative EBV-DNA PCR<br>Blood smear<br>Biopsy with immunostains<br>CT scans of suspected sites | Prophylaxis: IV ganciclovir, oral valganciclovir<br>Therapy: Acyclovir, reduction or withdrawal of immunosuppression; possible use of systemic chemotherapy for lymphoproliferative disorders or lymphoma |
| Herpes simplex virus (HSV) | Skin lesions, GI tract disseminated herpes—fever, fatigue, abnormal liver functions, hepatitis, pneumonia | HSV-1 and HSV-2 antibodies<br>Biopsy with viral cultures | Acyclovir |
| Pneumocystis | Atypical pneumonia, can progress to life-threatening pneumonitis | BAL, lung biopsy | Prophylaxis: low-dose oral sulfamethoxazole/trimethoprim, Dapsone, or pentamidine<br>Therapy: high-dose IV sulfamethoxazole/trimethoprim |
| *Candida* | Local mucous membrane, invasive tissue infection, fungemia | Blood, fluid, and tissue cultures, fundoscopic exam | Prophylaxis: fluconazole, possibly lipid formulation of amphotericin B in very-high-risk patients<br>Therapy: fluconazole (for sensitive candidal species) or lipid formulation of amphotericin B, caspofungin, or voriconazole (insensitive *Candida* or *Aspergillus*) |
| *Aspergillus* | Entry via upper or lower respiratory tract with metastatic spread (CNS, intra-abdominal, solid-organ) | Blood, fluid, and tissue cultures, BAL, CT scans | |
| Bacteria | Gram negative: enterobacteria, *E. coli, Pseudomonas*<br>Gram positive: *Enterococcus, Staphylococcus* | Blood, fluid and tissue cultures, BAL, CT scans, surgical exploration | Varies |

BAL, bronchoalveolar lavage; CNS, central nervous system; CT, computed tomography; GI, gastrointestinal; IV, intravenous; PCR, polymerase chain reaction.

reduction and more selective immunosuppression and prophylaxis with ganciclovir have reduced the incidence and morbidity of these infections. The other agents responsible for infectious morbidity, their presentation, diagnosis, and treatment are included in Table 48-2. Of particular importance in children is the prophylaxis and effective treatment of EBV. This is associated with the development of numerous malignant consequences. The most common of these is a diffuse proliferation of lymphoid tissue known as post-transplant lymphoproliferative disorder (PTLD). PTLD can present as a mononucleosis-like syndrome with diffuse lymphadenopathy or as lymphoma involving any organ. A variety of other tumors are also associated with EBV infections.[29] The general therapy for PTLD is reduction or elimination of immunosuppression, and, occasionally, surgical intervention and/or chemotherapy. The complete discussion of these disorders is beyond the scope of this chapter but is extensively covered elsewhere.[29]

# Outcome and the Future

Numerous factors are known to impact patient and graft survival in this population of liver transplant patients.* Overall, survival has improved with 1-year and 5-year patient survival exceeding 90% and 80%, respectively, in patients less than 18 years of age.[3,4] Age, nutritional status, urgency of transplantation, the indication for transplantation, and presence of renal dysfunction are all major factors that determine the outcome in any individual patient. Although early data suggested that patients with BA have worse outcomes because of their often-malnourished state, young age, and previous surgical intervention, more recent data suggest that this difference is not significant.[11,31] Patients with metabolic disease do exceedingly well, because they often are older, do not have liver failure and its sequelae, and have not previously undergone abdominal operation. Finally, transplantation for malignancy in children is associated with survival that is substantially less than that of transplantation for other indications but much better than the natural history of the disease. Numerous large series exist in the literature detailing the improvement in outcome with experience.[4,7,8]

Although outcomes have improved, many issues still remain to be resolved. The first and foremost is the organ shortage. The number of listed patients is increasing, while the number of suitable donors (even with segmental liver transplantation and improved organ allocation policies) has plateaued. Strategies aimed at expanding the donor pool and allocating organs to those patients that not only have the greatest survival benefit compared with pretransplant survival, but also the greatest chance of optimal post-transplant outcome are essential. National policies aimed at effectively identifying donors for splitting and development of local, regional, and national sharing of split grafts still await refinement. Finally, the development of gene therapy or optimization of hepatocyte transplantation as alternatives

* References 3, 4, 7, 8, 23, 24, 27, 31.

to transplantation for metabolic diseases may alleviate some of the organ shortage.

Another important challenge for the liver transplant community is the perfection of immunosuppression. Currently, all immunosuppressants have long-term side effects that result in impaired growth and development, infectious morbidity, malignancies, and numerous medical complications such as renal failure. The development of drug therapy that minimizes or eliminates these is essential. Furthermore, a better understanding of the immunology of peripheral T-cell tolerance and chronic rejection is essential. Although the last decade saw improvements in many technical and immunosuppressive aspects of liver transplantation, improvements in survival and quality of life in the next decade will rest firmly on a better understanding of our immune system on a cellular and molecular level.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 49

# Pediatric Intestinal Transplantation

Yann Révillon and Christophe Chardot

Intestinal failure (IF) is characterized by the inability of the gastrointestinal tract to provide sufficient digestion and absorption capacities to cover the nutritional requirements for maintenance in adults and for growth in children.[1] The first-line treatment for IF is parenteral nutrition (PN). In patients with life-threatening complications of PN, intestinal transplantation (IT)—isolated or combined with the liver and/or other organs—provides children with a second chance for survival. Since the early days of IT in the 1980s (treatment with cyclosporine-based immunosuppressive regimens), significant progress has been made in the medical and surgical management of children requiring IT, with short-term results (1-year patient survival) now approaching those of liver transplantation.

## Indications for Intestinal Transplantation

The causes of intestinal failure in children can be divided into five groups[2] (Fig. 49-1): (1) short bowel, mainly resulting from gastroschisis, midgut volvulus, necrotizing enterocolitis, and intestinal atresia; (2) motility disorders: long-segment Hirschsprung disease and chronic intestinal pseudo-obstruction; (3) epithelial disorders with intractable diarrhea, such as microvillous inclusion disease and tufting enteropathy; (4) children with a failed intestinal transplant; and (5) miscellaneous, including tumors.

Parenteral nutrition, including home PN, is the first-line treatment for children with intestinal failure and allows satisfactory growth and acceptable (although not normal) quality of life in most patients.[1,3] However, life-threatening complications of PN may occur, primarily line sepsis, loss of venous access resulting from thrombosis, and liver disease leading to cirrhosis. In such cases, intestinal transplantation may be the only lifesaving alternative. Depending on the underlying disease and the complications of PN, transplantation of additional organs may be required: liver in patients with cirrhosis, stomach and duodenopancreas in patients with extended motility disorders, and kidney(s) in patients with renal failure.[4]

The management of children with intestinal failure requires a multidisciplinary approach and is a continuous process that may last the whole life of the child. In most patients, the disease starts in the neonatal period and requires initial surgery. The possibility that the child may need other operations in the future should be considered at each surgical intervention. Adequate parenteral nutrition and prevention of line infections have paramount importance for the long-term prognosis of children with intestinal failure.[3,5] If long-term dependence on PN is expected, early contact with a team specializing in the management of children with intestinal failure is recommended before the onset of PN-related complications, to optimize the overall management of the child: adaptation of long-term PN and prevention of its complications, education of parents about home PN, and anticipation and preparation of further steps of the medicosurgical management, which may include nontransplant surgery or transplantation. This early contact with the intestinal failure team is recommended for every child whose requirements for PN are anticipated to be more than 50% at 3 months after initiating PN.[6] In a retrospective study, including 302 children followed for home PN in our center between 1980 and 1999, the median duration of home PN was 1.3 years. By January 2000, 54% had been weaned from PN, 26% were still receiving PN, 16% had died, and 4% had undergone intestinal transplantation. Patient survival rates at 5, 10, and 15 years were 89%, 81%, and 72%, respectively. Nine percent of children with primary digestive disease died versus 38% of children with nonprimary digestive disease.[3] In a multicenter prospective European study, including 688 adults and 166 children on home PN, the candidacy rate for transplantation was estimated at 16% in adults and 34% in children, and it varied greatly among home PN centers.[7,8] The 5-year survival rate on home PN was 87% in noncandidates for transplantation, 73% in candidates with home PN failure, 84% in those with high risk of death attributable to the underlying disease, 100% in those with IF with high morbidity or low acceptance of PN, and 54% in IT recipients ($P < 0.001$). Nontransplant surgery may have a place in the rehabilitation program of such children, especially bowel lengthening procedures in those with a short bowel and limited hepatic or vascular complications.[9,10]

The appropriate timing of intestinal transplantation sometimes is not easy to determine, because it is difficult to predict the ability of the native intestine to adapt, as well as the course of PN-related complications. On the one hand, intestinal adaptation may allow digestive autonomy in some patients with

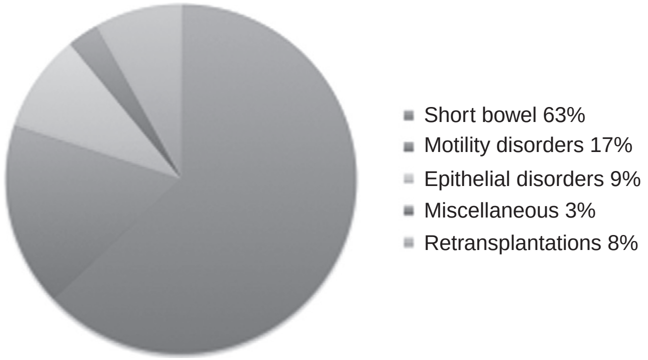



**FIGURE 49-1** Indications for intestinal transplantation. From the Intestine Transplant Registry 2003 report[2]: 606 grafts (223 isolated bowel, 306 liver and intestine, 77 multivisceral) in 563 children (age $\leq$ 18 years).

a short bowel,[9] and PN-associated liver disease may regress after optimization of PN, especially regarding the quality of lipid intake.[11–13] On the other hand, transplantation results are better in children who are in good general condition, as opposed to children with end-stage disease.[2] However, early referral to a specialized center for intestinal failure does not necessarily result in finding an indication for transplantation. In a series of 118 patients referred to our center for transplantation assessment, 10 could be weaned off PN, 12 patients were unsuitable for transplantation, 65 patients were listed for transplantation, and 31 remained potential candidates.

The two following examples of children treated by our team illustrate how the same condition (short bowel syndrome) may require very different therapies, based on the specifics of the patient.

*Yasmine* was born in 1971. In 1981, she presented with a midgut volvulus and complete necrosis of the small bowel and right colon. She underwent a duodenocolic anastomosis, and she has been on PN since then. Because of loss of venous access, an arteriovenous fistula was created in 1983. Today, she eats normally and receives home PN 5 nights per week. She has three bowel movements per day. Her general condition is good. She sometimes complains of anal burns or abdominal distension. She has an ovarian cyst and renal stones. She works in business, was married in 2002, and gave birth to two children. She enjoys dancing, skiing, and diving. She does not wish to receive an intestinal transplant.

*Virginie* was born in 1988, and underwent an extensive intestinal resection at birth after midgut volvulus. Because of complications of PN, she underwent intestinal transplantation, in 1989, with cyclosporine-based immunosuppression. Today, she eats normally and is off PN, with normal intestinal biopsies. Her weight and height are normal. She has mild intellectual retardation and does not work. Her renal function is moderately impaired. She is the world's longest survivor (22 years) with a functional intestinal graft. However, it is still impossible to predict whether this situation will last for a normal lifespan.

## Assessment and Preparation for Intestinal Transplantation

Potential candidates for IT usually have a complex medical history and may have undergone several prior operations. A detailed workup is needed to precisely evaluate (1) the level of IF and its potential reversibility; (2) the history of PN and central-line complications—number of catheters, number of episodes of line sepsis, and bacteria involved (antibiotic resistance profiles); (3) thrombotic complications and current cartography of patent vascular access; (4) intestinal failure–associated liver disease (IFALD)—liver fibrosis or cirrhosis, jaundice, ascites, portal hypertension (esophageal and/or gastric and/or peristomal varices, thrombocytopenia), liver insufficiency; (5) surgical status of the abdomen—previous operations, length and function of remaining bowel, stomas; (6) function of other organs, especially heart, lungs (pulmonary shunts or pulmonary hypertension), and kidneys; (7) neurologic development and potential neurologic impairment; (8) serologic status and immunizations; (9) immunologic status (anti-HLA antibodies); and (10) sociofamilial and psychological assessment and ability of the family to manage the child before and after transplantation. The indications for transplantation as well as all of these issues and alternate therapies are discussed in a multidisciplinary meeting. Whatever the proposal for treatment, the child will require careful follow-up, with further reassessments, because the indication for transplantation and the type of graft needed may change with time.

The general condition of the child has a strong impact on the results of transplant surgery; therefore careful preparation is required, focusing especially on (1) optimization of PN to improve nutritional status and reduce its toxicity; (2) prevention and treatment of infections (optimization of central venous-line management) and immunizations; (3) treatment of the complications of liver disease, primarily ascites and portal hypertension (sclerosis or ligation of esophageal varices, transjugular intrahepatic portosystemic shunt). Education of the child and family about transplantation is done simultaneously.

## Transplantation Surgery

The donor is usually a deceased donor, although a few living-related donations have been reported for isolated small bowel transplants.[14] The volume of the graft must correlate with the abdominal cavity of the recipient; this depends on (1) the donor to recipient weight ratio, (2) the native organs removed and the type of graft implanted, and (3) whether the abdominal cavity is small (IT for short bowel) or distended (IT for intestinal motility disorders with chronic intestinal distention).

A wide variety of grafts can be implanted, from isolated small bowel to multivisceral grafts, including stomach, pancreas and duodenum, small bowel, right colon, liver, and kidneys (Fig. 49-2). These grafts can be classified as

1. Isolated intestinal transplantation: small bowel $\pm$ right colon. This type of graft is generally indicated for IF with normal motility of the stomach and duodenum, and without significant liver disease. The native stomach, duodenum, pancreas, spleen, and liver are preserved. The superior mesenteric artery of the graft is connected to the recipient infrarenal aorta, and the mesentericoportal axis of the graft is joined to the native infrarenal vena cava. The proximal jejunum of the graft is connected to the native jejunum.

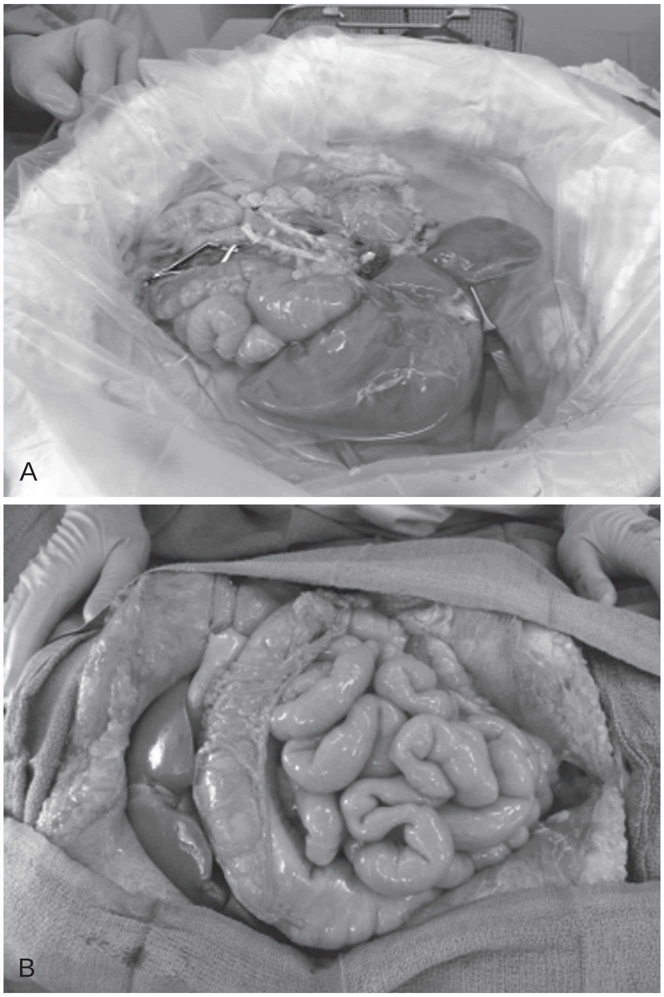



**FIGURE 49-2** **A,** Multivisceral transplantation: the graft before implantation. The graft includes stomach, pancreas, duodenum, small bowel, right colon, liver, and two kidneys. **B,** Multivisceral transplantation: the graft after implantation and reperfusion.

2. Modified multivisceral transplantation: stomach, pancreas and duodenum, small bowel ± right colon. This type of graft is indicated for IF with impaired motility of the native stomach and duodenum (i.e., pan-intestinal Hirschsprung disease and chronic intestinal pseudo-obstruction), without significant liver disease. The upper part of the native stomach, duodenum, pancreas, spleen, and liver are preserved. The arterial axis of the graft (including celiac trunk and superior mesenteric artery) is connected to the recipient infrarenal aorta, and the mesentericoportal axis of the graft is joined to the recipient infrarenal vena cava. The native and transplanted hemistomachs are connected, the native first portion of duodenum is closed, and the native jejunum is connected to the transplanted jejunum as a Roux loop.
3. Combined liver and intestinal transplantation: liver, pancreas and duodenum, small bowel, ± right colon. This type of graft is indicated for IF with normal motility of the stomach and duodenum, and with significant liver disease. The native liver is removed, and a portocaval anastomosis is fashioned between the native portal vein and vena cava. The native stomach, duodenum, pancreas, and spleen are preserved. The arterial axis of the graft (including celiac trunk and superior mesenteric artery) is connected to the recipient infrarenal aorta, and the suprahepatic vena cava of the graft is connected to the native suprahepatic vena cava in a "piggyback" fashion. The first portion of the duodenum of the graft is closed, and the graft jejunum is connected to the native jejunum as a Roux loop.
4. Multivisceral transplantation: liver, stomach, duodenum and pancreas, small bowel, ± right colon, ± kidneys. This type of graft is indicated for (1) IF with impaired motility of the stomach and duodenum (pan-intestinal Hirschsprung disease and chronic intestinal pseudo-obstruction), with significant liver disease; (2) when en-bloc ablation of native organs (liver, pancreas, duodenum, and intestine) is needed,[4] either due to previous surgeries and portal hypertension, making selective dissection of native abdominal organs impossible, or (rarely) because of a tumor. All abdominal organs anterior to the aorta and vena cava are removed. The arterial axis of the graft (including celiac trunk and superior mesenteric artery) is connected to the recipient aorta, and the suprahepatic vena cava of the graft is connected to the native suprahepatic vena cava in a "piggyback" fashion. The native lower esophagus is connected to the transplanted stomach.

In all cases, a distal ileostomy is performed to provide easy access to the graft for intestinal biopsies. When the right colon is transplanted, its distal end is either anastomosed to the remaining native rectum (patients with short gut or mucosal diseases) or a temporary distal colostomy is created (Hirschsprung disease). Cholecystectomy and gastrostomy (for continuous enteral feeding) are generally performed if not done previously.

Abdominal wall closure is an issue after intestinal transplantation, because of the size discrepancy between the graft and the abdominal cavity of the recipient and post-reperfusion edema of the graft. Reduction of the liver and/or intestinal graft is possible.[15,16] Staged abdominal closure, using a temporary Silastic sheet and a vacuum dressing, avoids abdominal compartment syndrome. The final abdominal closure is usually possible after 5 to 7 days (Fig. 49-3).

# Postoperative Care

The intestinal transit generally resumes quickly after surgery, and enteral feeding is progressively introduced 2 to 7 days after the operation. Transit time is accelerated because of the graft's denervation, and if dysfunction of the graft (mainly rejection or infection) has been ruled out, antimotility agents, such as loperamide or codeine, can be used to slow down the intestinal motility. In an uncomplicated postoperative course, full enteral feeding can be achieved 1 month after the operation.

Various surgical complications may occur (obstructions, peritonitis, fistulas, and pancreatitis), and may be difficult to detect under steroid therapy. Vascular monitoring of the graft relies on observation of the color of the stoma and, if the graft includes the liver, repeated ultrasonography (US) of the liver.

The intestine is highly immunogenic, and IT requires high-level immunosuppression. As understanding of the mechanisms of rejection progresses and new immunosuppressive

**FIGURE 49-3** **A,** Intestinal transplantation, end of operation. The edema of the graft after reperfusion prevents primary abdominal closure. A Silastic silo is performed. **B,** Staged abdominal closure. The Silastic silo is covered with a vacuum dressing. The silo is progressively tightened over the next days at the bedside, as edema progressively resolves and graft reintegrates the abdomen. **C,** Final abdominal closure. After 5 to 7 days, the edema of the graft has diminished, and final abdominal closure can be achieved; the musculoaponeurotic layer can be closed either completely or with a wound prosthesis (for instance, a GORE-TEX sheet).

drugs become available, immunosuppressive protocols evolve. The current standard immunosuppressive regimen is a combination of tacrolimus, steroids, and basiliximab or daclizumab (anti–IL-2 receptor antibodies). Monitoring of intestinal rejection is based on stoma output, protein concentration in the stools, and repeated intestinal biopsies through the stoma. Other markers, such as stool calprotectin or serum citrulline, have also been used. In case of biopsy-proven rejection, first-line treatment relies on high-dose steroid pulses. Second-line treatments are available but expose the child to complications of overimmunosuppression, primarily opportunistic infections, and post-transplant lymphoproliferative disease (PTLD). In case of uncontrolled rejection, removal of the transplanted intestine may be needed. Recently, humoral rejection has increasingly been studied: Donor-specific anti-HLA antibodies are monitored, and high levels can be treated by high-dose intravenous (IV) immunoglobulins, rituximab (anti-CD20 antibody), and plasmapheresis.

Because of the high level of immunosuppression, opportunistic infections are a constant threat after IT. Various infectious agents can be involved, the most common being cytomegalovirus (CMV) and Epstein Barr virus (EBV). CMV can cause severe graft enteritis and trigger rejection. EBV can trigger lymphoproliferation. Monitoring of the viral loads is currently determined by polymerase chain reaction (PCR), which guides the prophylactic or curative treatments.

Post-transplant lymphoproliferative disease is nowadays detected at earlier stages. First-line treatment relies on reduction of immunosuppression and rituximab.

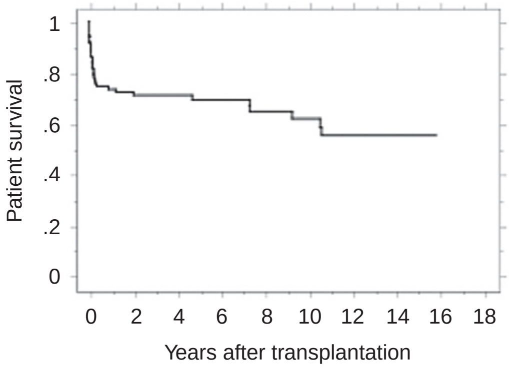
Drug toxicity is an issue after IT, because these children receive many drugs, some of them at high doses. Impairment of renal function, hypertension, and seizures are the most common side effects, which are usually reversible after dose reduction or a switch to alternate therapies.

Progressively, all treatments are decreased or withdrawn. Stoma closure can be considered when the child has been stable, without rejection, under maintenance immunosuppression for several months.

## Results of Intestinal Transplantation

Short-term results of intestinal transplantation have improved with increasing experience.[2] In the United States, current 1-year patient and graft survival is 89% and 79%, respectively, for isolated bowel recipients, and 72% and 69%, respectively, for liver-intestine recipients. However, medium-term results remain unsatisfactory; by 10 years, patient and graft survival falls to 46% and 29%, respectively, for isolated bowel recipients, and 42% and 39%, respectively, for liver-intestine recipients.[17,18] According to the International Intestine Transplant Registry (1985 to 2003 data: 989 grafts in 923 patients),[2] causes of death were sepsis (46.0%), multiorgan failure (2.5%), graft thrombosis (3.2%), graft rejection (11.2%), post-transplant lymphomas (6.2%), respiratory causes (6.6%), technical reasons (6.2%), and other causes (17.3%).

Our team in Paris performed 97 transplants in 90 children, between November 1994 and April 2011, using tacrolimus-based immunosuppression: isolated bowel in 55; stomach, pancreas, duodenum, and bowel (modified multivisceral) in 1; combined liver and bowel in 39; liver, stomach, pancreas,

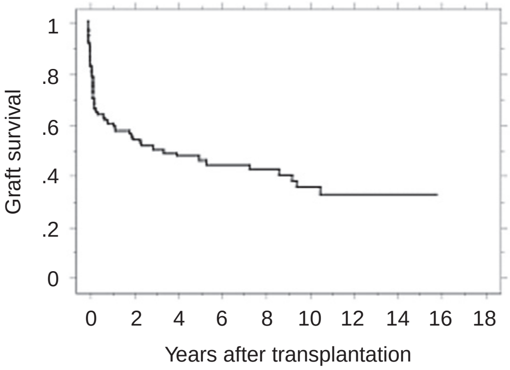



| 90 patients | 1-year | 5-year | 10-year | 15-year |
|---|---|---|---|---|
| Patient survival | 73.0% | 61.8% | 48.6% | 43.7% |
| Standard error | 4.5% | 5.2% | 6% | 6.3% |
| Number of patients reaching considered follow-up | 66 | 43 | 21 | 2 |

**FIGURE 49-4** Patient survival after intestinal transplantation in the tacrolimus era. Paris series from November 1994 to March 2011: 90 patients.

duodenum, and bowel in 1; liver, stomach, pancreas, duodenum, bowel, and two kidneys in 1 (see Fig. 49-2). In 63 of 97 transplants (65%), the graft included the right colon. One-year, 5-year, 10-year, and 15-year patient survival rates are 73.0%, 61.8%, 48.6%, and 43.7%, respectively, and 1-year, 5-year, 10-year, and 15-year graft survival rates are 59.5%, 45.0%, 33.6%, and 31.2%, respectively (Figs. 49-4 and 49-5). Early mortality is higher, but long-term graft survival is better after combined liver and intestine transplantation compared with isolated intestinal transplantation. This is probably due to the protective effect of the liver against intestinal rejection.[19,20]

In a study of 31 children treated by our group, and who are alive with their graft 2 to 18 years after transplantation,[21] all were weaned from PN after transplantation, and 26 of 31 (84%) remained PN-free at last follow-up. Enteral nutrition was still required for 14 of 31 (45%) patients 2 years after transplantation. All children had high dietary energy intakes. The degree of steatorrhoea was fairly constant, with fat and energy absorption rates of 84% to 89%. After transplantation, two thirds of children had normal growth, whereas in one third, growth remained delayed, concomitant to a delayed puberty. Endoscopy and histology analyses were normal in asymptomatic patients. Five intestinal grafts (16%) were removed 2.5 to 8 years after transplantation for acute or chronic rejection. Late complications also include impairment of renal function and malignancies.




| 97 grafts | 1-year | 5-year | 10-year | 15-year |
|---|---|---|---|---|
| Graft survival | 59.5% | 45% | 33.6% | 31.2% |
| Standard error | 5% | 5.3% | 5.7% | 5.8% |
| Number of grafts reaching considered follow-up | 53 | 31 | 14 | 2 |

**FIGURE 49-5** Graft survival after intestinal transplantation in the tacrolimus era. Paris series from November 1994 to July 2010: 97 grafts.

Results of intestinal transplantation have improved in the recent decades,[2,18] because of better preparation of patients and timing of transplantation, progress in surgical techniques, availability of new immunosuppressive drugs and improved immunosuppressive regimens, and better monitoring and treatments of postoperative complications. The scarcity of grafts remains an important issue, and patients still succumb while waiting for a graft. With expected improvements in the outcomes (especially in the long term), intestinal transplantation may move from a lifesaving procedure to an improving quality-of-life procedure,[22] which may also have economic advantages compared with PN.

# Conclusion

Home PN remains the first-line treatment of intestinal failure. Intestinal transplantation and its technical variants are indicated only in case of life-threatening complications of PN. Intestinal failure requires a multidisciplinary approach in specialized centers. Early assessment of the child in such a center, before the onset of complications of PN, is recommended. This does not mean early transplantation, but adequate planning of medicosurgical strategies to provide the child with the best chances of survival and an optimal quality of life.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The authors, Yann Révillon and Christophe Chardot, who are part of the surgical team, wish to thank the following pediatric multidisciplinary team members*:

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   *Anesthesiology:* Nadège Salvi, Nathalie Bourdeau, and Caroline Télion.
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*The complete reference list is available online at www.expertconsult.com.*

*All members are affiliated with Hôpital Necker-Enfants Malades, Paris, France, except Jean-Pierre Hugot and Jean-Pierre Cézard, who are affiliated with Hôpital Robert Debré, Paris, France.

CHAPTER 50

# Heart Transplantation

Stephanie M. P. Fuller and Thomas L. Spray

Thoracic organ transplantation has been successfully performed in pediatric patients since the mid-1980s and now serves as an important option in the treatment of both congenital and end-stage heart and lung disease in children. Approximately 400 pediatric heart transplantations are performed annually in the United States, or roughly 16% of all pediatric solid organ transplantations.[1] Despite the clinical success of heart and lung transplantation in children, limited donor availability has prevented broader application of this therapy. Infants awaiting heart transplantation face the highest wait-list mortality among all children and adults listed for a heart transplantation in the United States, with one in four infants dying before a donor heart can be identified.[2] Complications, such as acute and chronic rejection, graft coronary artery disease (CAD), and bronchiolitis obliterans, as well as the infectious and neoplastic complications of current methods of immunosuppression, threaten cardiac transplant longevity. This chapter focuses on the clinical aspects of heart transplantation in infants and children, including indications, preoperative evaluation, operative techniques, postoperative management, complications, and outcomes.

## Historical Notes

Kantrowitz and colleagues[2a] performed the first pediatric heart transplant in 1967 when they transplanted the heart of an infant with anencephaly into a 3-week-old infant with tricuspid atresia. The next year, Cooley[2b] transplanted the heart and lungs of a newborn with anencephaly into a 3-month-old with an atrioventricular septal defect and pulmonary hypertension. Although neither of the infants survived for more than a few hours because of allograft rejection, these pioneering procedures emphasized the technical feasibility of thoracic organ transplantation in children. It was only in 1980 with the introduction of cyclosporine as an immunosuppressive agent that meaningful clinical success became possible. In November 1985, Bailey performed the first successful cardiac transplantation on a 4-day-old neonate with hypoplastic left heart syndrome (HLHS) at Loma Linda.[3,4] During the last 2 decades, outcomes have been improved by technical advances, better immunosuppression, including reduced steroid use and the advent of induction therapy, a decreased incidence of rejection, increased attention to viral prophylaxis, and aggressive treatment of post-transplant lymphoma and other post-transplant complications.

## Indications

As published by the Registry for the International Society for Heart and Lung Transplantation in the Thirteenth Official Pediatric Report in 2010, the number of pediatric heart transplantations has remained relatively constant during the last 10 years (Fig. 50-1).[5] The most common indications for cardiac transplantation in the pediatric population remain congenital cardiac disease and cardiomyopathy, as demonstrated in Figures 50-2 and 50-3. Congenital heart disease is seen more commonly in infants, whereas cardiomyopathy is more prevalent in older children. As expected, the incidence of retransplantation increases with increasing patient age.

When examining the congenital heart disease population, the most common anomaly treated by transplantation is hypoplastic left heart syndrome (HLHS), a group of defects characterized by aortic or mitral atresia/stenosis with a diminutive left ventricle. Initial poor results with a staged palliative approach to HLHS led some centers to consider orthotopic heart transplantation as the primary treatment of this anomaly. Long transplantation waiting lists have led other institutions to advocate a stage I palliation (Norwood or Sano procedure) to help stabilize the patient and then list the patient for transplantation.[6] However, with improvement in early survival from the Norwood procedure followed by a Fontan repair, the majority of cardiac centers have abandoned primary transplantation as initial therapy for HLHS. Transplantation is an option now reserved for patients with unusually high risk, including aortic atresia with a diminutive ascending aorta and severe tricuspid or atrioventricular valve regurgitation.[7]

Other forms of congenital heart disease that have been treated by cardiac transplantation during infancy include an unbalanced atrioventricular canal, single ventricle, the Ebstein

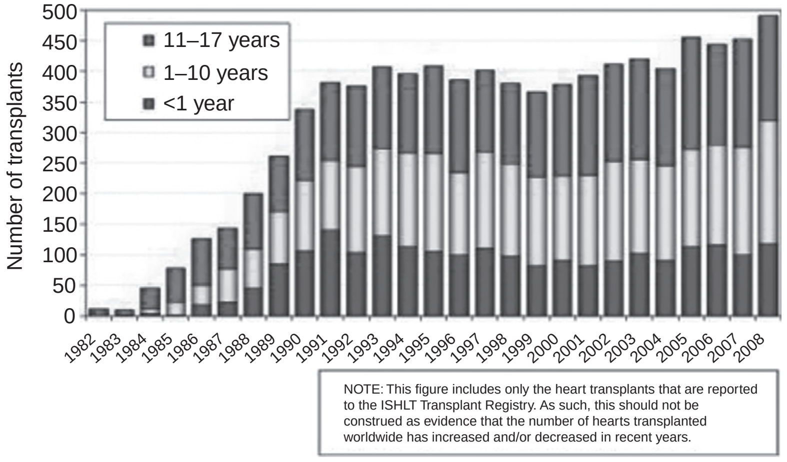


**FIGURE 50-1** Age distribution of heart recipients by year of transplantation. (From Kirk K, Edwards LB, Kucheryavaya AY, et al: The Registry of the International Society for Heart and Lung Transplantation: Thirteenth official pediatric heart transplantation report—2010. J Heart Lung Transplant 2010;29:1119-1128.)

anomaly, L-transposition of the great arteries, and pulmonary atresia with an intact ventricular septum (Table 50-1).[8,9] Even the most complex forms of congenital heart disease, such as heterotaxy syndromes with anomalies of systemic and venous drainage, are amenable to cardiac transplantation with suitable reconstruction.[10] Other pediatric candidates include infants with congenital heart disease who have undergone previous corrective or palliative procedures, yet who exhibit residual or progressive cardiac dysfunction manifested by left ventricular failure that ultimately requires transplantation. Postoperative cardiac dysfunction is often related to atrioventricular or semilunar valvar insufficiency that eventually results in dilated cardiomyopathy. In some cases, ventricular function may be preserved, but the indication for transplantation is for hemodynamic compromise secondary to anatomic abnormalities not amenable to surgical intervention, intractable arrhythmias, or complications that arise following the Fontan operation, such as protein-losing enteropathy. Of note, multiple previous palliative procedures do not preclude successful transplantation.[11] In the current era, despite the need for repeat sternotomy, the tendency toward diffuse coagulopathy and potentially prolonged ischemic times, patients undergoing transplantation for congenital heart disease experience no actuarial difference in survival compared with those patients undergoing transplantation for cardiomyopathy who undergo first-time sternotomy and dissection of mediastinal structures.[8,12]

Cardiomyopathy is the other most common indication for heart transplantation in infancy and childhood. Most pediatric heart transplantations outside infancy are performed for dilated, idiopathic cardiomyopathy. Other causes of cardiomyopathy include viral, familial, and hypertrophic. Despite the diverse causes of cardiomyopathy, several variables have been associated with poor outcome, including a very high left ventricular end-diastolic pressure, a left ventricular ejection fraction less than 20%, ventricular arrhythmia, and a family

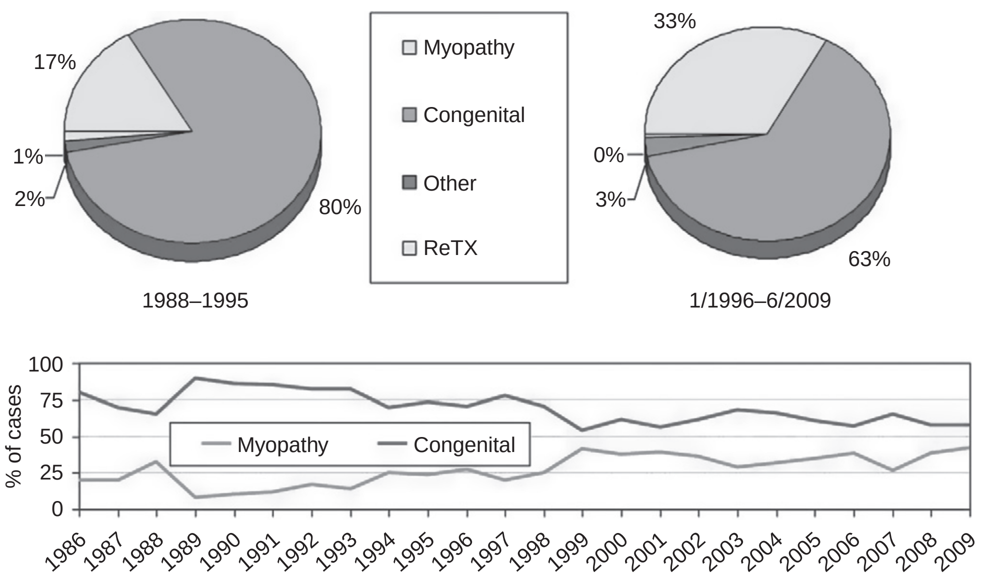


**FIGURE 50-2** Infant heart recipient diagnosis according to year of transplantation. ReTx, retransplant. (From Kirk K, Edwards LB, Kucheryavaya AY, et al: The Registry of the International Society for Heart and Lung Transplantation: Thirteenth official pediatric heart transplantation report—2010. J Heart Lung Transplant 2010;29:1119-1128.)

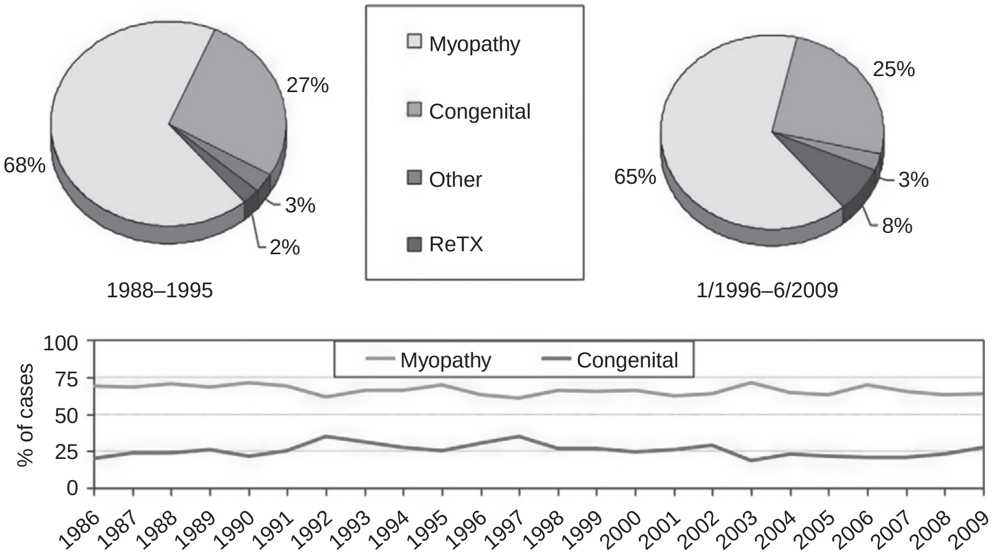


**FIGURE 50-3** Diagnosis of heart recipients aged 11 to 17 years according to year of transplantation. ReTx, retransplant. (From Kirk K, Edwards LB, Kucheryavaya AY, et al: The Registry of the International Society for Heart and Lung Transplantation: Thirteenth official pediatric heart transplantation report—2010. J Heart Lung Transplant 2010;29:1119-1128.)

history of cardiomyopathy.[13,14] Cardiomyopathy attributable to inflammation or arrhythmia tends to have a more favorable outcome, and these patients should be supported as long as possible before transplantation to allow for the possibility of spontaneous recovery. Other less common indications for cardiac transplantation are doxorubicin-induced cardiotoxicity from chemotherapy for malignancy and obstructive cardiac tumors, such as fibromas and rhabdomyomas that are not amenable to surgical resection.

Regardless of the diagnosis, there are several clinical indications for heart transplantation in children, many of which have been borrowed from the adult population. These include the need for ongoing intravenous inotropic support or mechanical circulatory support. Transplantation is indicated in those patients who experience a progressive deterioration of ventricular function despite optimal medical care or those with life-threatening arrhythmias unresponsive to medical treatment, ablation, or automatic implantable defibrillator. Progressive pulmonary hypertension secondary to systemic ventricular failure is an indication for cardiac transplantation, whereas pulmonary hypertension may otherwise be an indication for lung transplantation. Growth failure secondary to severe heart failure and unacceptably poor quality of life are considered indications as well as certain high-risk conditions following the Fontan procedure, such as protein-losing enteropathy and plastic bronchitis.[15]

**TABLE 50-1**

**Distribution of Anatomic Diagnoses in Children Older Than 6 Months of Age and Adults Undergoing Transplantation for Congenital Heart Disease in the Pediatric Heart Transplant Study and Cardiac Transplant Research Databases**

| *Diagnosis* | N | *% of Patients* |
|---|---|---|
| Single ventricle | 176 | 36 |
| Dextrotransposition of the great arteries | 58 | 12 |
| Right ventricular outflow tract lesions | 49 | 10 |
| Ventricular/atrial septal defects | 38 | 8 |
| Left ventricular outflow tract lesions | 38 | 8 |
| Levotransposition of the great arteries | 39 | 8 |
| Complete atrioventricular canal | 37 | 8 |
| Other | 53 | 11 |
| Total | 488 | 100 |

Modified from Chen JM, Davies RR, Mital SR, et al: Trends and outcomes in transplantation in complex congenital heart disease: 1984-2004. Ann Thorac Surg 2004;78:1352-1361.

# Preoperative Evaluation

The pretransplant evaluation is a multidisciplinary screening process that serves as the key to successful organ transplantation (Table 50-2). Potential recipients go through a thorough

**TABLE 50-2**

**Pretransplant Recipient Evaluation**

| | |
|---|---|
| Cardiac catheterization | Assess pulmonary vascular resistance and reactivity<br>Delineate complex anatomy |
| Exercise testing | Obtain $mVo_2$ |
| Assessment of end-organ function | Pulmonary function tests to evaluate lung function<br>Liver and kidney function |
| HLA sensitization | Panel reactive antibody |
| Psychosocial evaluation | Social work assessment of family dynamic<br>Psychiatric evaluation |
| Financial evaluation | Insurance evaluation |
| Blood work | Complete blood count with differential chemistry<br>Lipid profile<br>Thyroid function<br>Hepatic function test<br>Blood type<br>Urinalysis<br>Viral testing for cytomegalovirus, Epstein-Barr virus, herpesvirus, HIV, varicella, toxoplasmosis, hepatitis virus, tuberculosis |

HIV, human immunodeficiency virus; HLA, human leukocyte antigen; $mVo_2$ myocardial oxygen consumption.

physical and psychosocial evaluation with careful examination of the cardiac, pulmonary, neurologic, renal, infectious, and socioeconomic systems. The presence of an adequate family support system is of paramount importance to survival postoperatively. Parents must demonstrate the ability and resources to comply with the complex medical regimens required and to cope with the potential for long or frequent hospitalizations even years after transplantation. As part of this multidisciplinary evaluation, patients undergo screening laboratory tests, including a viral serology panel (e.g., human immunodeficiency virus [HIV], cytomegalovirus [CMV], human Epstein-Barr virus [EBV], hepatitis).

Cardiac evaluation is performed mainly by echocardiography and cardiac catheterization in which the anatomy of the systemic and pulmonary venous connections of the heart and lungs are precisely identified. Important hemodynamic data, including systemic cardiac output and pulmonary vascular resistance (PVR), both indexed to the patient's body area, are obtained at cardiac catheterization and used to screen candidates. These numbers become significant, because the major contraindication to transplantation is fixed pulmonary hypertension unresponsive to pulmonary vasodilators. Patients with elevated PVR (>4 to 6 Wood units) are tested with pulmonary vasodilators, including sodium nitroprusside, oxygen ($FiO_2$ 100%), and inhaled nitric oxide, to establish whether the pulmonary vascular bed is reactive. In general, the presence of a fixed PVR in excess of 6 to 8 Wood units is a contraindication to orthotopic heart transplantation, because the donor heart is unable to tolerate right-sided dilation caused by high pulmonary vascular resistance. Patients who demonstrate improvement with vasodilators may undergo transplantation with a survival rate comparable to that in patients with normal resistance.[11] Although patients with fixed pulmonary hypertension have successfully undergone transplantation, they have a much higher mortality rate, usually because of postoperative right ventricular failure. Other contraindications to cardiac transplantation include multiple noncardiac congenital anomalies, active malignancy, infection, severe metabolic disease (i.e., diabetes mellitus), multiple organ failure, multiple congenital anomalies, and the lack of an adequate family support system, in addition to socioeconomic factors that lead to noncompliance with drug regimen and follow-up care (Table 50-3).

**TABLE 50-3**

**Potential Contraindications to Cardiac Transplantation**

| | |
|---|---|
| General | Presence of any noncardiac condition that significantly shortens life expectancy |
| Specific | Active infection |
| | Active ulcer disease |
| | Active neoplasm |
| | Morbid obesity (BMI > 32) |
| | Renal insufficiency with creatinine greater than 2 times normal |
| | Hepatic dysfunction with elevated transaminases or cirrhosis |
| | Elevated, nonreactive pulmonary vascular resistance |
| | Recent pulmonary embolic event with infarction |
| | Recreational drug use |
| | Recurrent medical noncompliance |

BMI, body mass index.

Children suffering from cardiomyopathy and manifesting symptoms of chronic congestive heart failure that limit activity or uncontrollable arrhythmias are often referred for transplantation, particularly if they are unresponsive to medications. The timing for transplantation, especially for those children with hypertrophic cardiomyopathy, is less clear because some patients may improve with medication and conservative therapy. As previously stated, the mortality for idiopathic dilated cardiomyopathy in children is highest in the first year after diagnosis and is mainly determined by the degree of left ventricular failure.

Children listed for heart transplantation should be closely monitored until their transplantation, either as outpatients, if their condition permits, or while hospitalized. Good nutritional status should be maintained, and supplementation, such as tube feedings or total parenteral nutrition, is used as needed. A close watch for infectious complications is important, and any subtle indications of infection should be thoroughly investigated. Major infections require patients to have their transplantation status put on hold until they are treated adequately. Anticongestive therapy should be optimized with digoxin, diuretics, and afterload reduction with captopril or other angiotensin-converting enzyme inhibitors. If heart failure worsens, hospitalization may be required for inotropic support with dobutamine or phosphodiesterase inhibitors such as milrinone. Long-term therapy may require the placement of an intravenous access device such as a Broviac catheter.

The use of mechanical support as a bridge to cardiac transplantation in critically ill children had been limited mostly to those with postcardiotomy ventricular failure. In general, the results have been poor, although several studies show survival rates ranging from 45% to 73% when extracorporeal membrane oxygenation (ECMO) is used as a bridge to cardiac transplantation.[16,17] ECMO is restricted to short-term use. Additional limitations are the inability to ambulate and undergo effective physical therapy while on ECMO, as well as the damage to circulating red blood cells and platelets requiring persistent transfusion. In the current era, children have excellent survival with the use of long-term ventricular assist devices (VADS) as a bridge to transplantation. Although adult systems can be used in adolescent patients, the Berlin Heart VAD (Berlin Heart AG, Berlin, Germany) is a pulsatile, paracorporeal VAD that is suitable in neonates and infants for both single and biventricular support. The North American experience from 2000 to February 2007 details approximately 80 patients supported for more than 200 days, with the smallest patient being 3.0 kg. Overall, approximately 55% of the patients have undergone transplantation, 13% were weaned, and 25% died during device support.[18]

A neonate referred for cardiac transplantation requires several other unique considerations. Infants with complex congenital heart disease, such as HLHS, are commonly confined to a neonatal intensive care unit and are usually maintained on a continuous infusion of prostaglandin $E_1$ to prevent closure of the ductus arteriosus if there is ductal-dependent physiology. Implantation of expansile stents in the ductus may allow for discontinuation of prostaglandin therapy while waiting. Initial palliative procedures, such as the Norwood procedure for HLHS or a Blalock-Taussig shunt for lesions with ductal-dependent pulmonary blood flow, can be performed in the face of a prolonged wait for a

donor. Balloon atrial septostomy, with or without stenting to improve mixing of saturated and desaturated blood and to decompress the left atrium, can be helpful if there is a restrictive patent foramen ovale. Other important issues are the maintenance of adequate nutritional support, avoidance of renal and metabolic complications, and prompt and thorough treatment of any infectious complications, especially line sepsis, in these fragile infants. Common neonatal problems, such as seizures, necrotizing enterocolitis, and intraventricular hemorrhage are also seen. At the minimum, 10% to 20% of infants die while awaiting a donor heart.

In all cases, important consideration is given toward pretransplantation recipient human leukocyte antigen (HLA) sensitization. Circulating antidonor antibodies may result in either cellular or humoral rejection culminating in early graft failure.[19] The presence of HLA antibodies is reported as a panel reactive antibody (PRA), and a panel percentage of greater than 10% is considered elevated. Patients prone to developing anti-HLA antibodies include those who have received blood and platelet transfusions during prior surgeries, postgravid adolescent girls, children who have undergone implantation of cryopreserved tissue valves or allograft conduits, and patients with previous organ transplants. Strategies for reduction in PRA include the use of intravenous immunoglobulin as well as agents that may inhibit antibody production by B cells. Candidates who are high risk are managed with pretransplantation plasmapheresis that is continued postoperatively, resulting in good short-term outcomes. However, long-term outcomes are unknown. The United Network for Organ Sharing determines organ allocation and, in 2002, revised their classification for pediatric patients awaiting heart transplantation. Status 1A applies to patients requiring ventilatory or mechanical circulatory support (i.e., left ventricular assist device, ECMO, or a balloon pump) or multiple- or high-dose inotropes, infants younger than 6 months with pulmonary pressure greater than 50% of systemic levels, or any patient with a life expectancy of less than 14 days without a heart transplantation. Status 1B applies to patients requiring single-dose inotropic support or infants younger than 6 months who have significant failure to thrive (less than the 5th percentile for weight or height or loss of 1.5 standard deviations [SD] of expected growth). All other patients with less acuity are classified as status 2. A patient's status may change depending on changes in clinical condition, or the patient may be placed on hold (status 7) because of an infectious, malignant, or other complication and then reactivated.

## Donor Evaluation and Organ Procurement

The criteria for an ideal organ donor are as follows: meets requirements for brain death, consent from next of kin, ABO compatibility in older children, weight compatibility (1 to 3 times that of the recipient), normal echocardiogram, age younger than 35 years, and normal heart by visual inspection at the time of harvest. A history of cardiopulmonary resuscitation is not an absolute contraindication to cardiac donation for pediatric recipients. All potential donors are evaluated carefully for the cause of death, including the presence of chest trauma, need for cardiopulmonary resuscitation, and cardiac function before death. For neonates, most donors have suffered sudden infant death syndrome or birth asphyxia, whereas older donors are victims of violence and car accidents.

The shortage of suitable organ donors, especially for neonatal recipients, has led to many attempts at expanding the donor pool. Hearts from donors with moderately impaired ventricular function by echocardiography (left ventricular shortening fraction greater than 25% without major wall motion abnormalities) have been successfully transplanted into infant recipients.[10] Donor-to-recipient weight ratios of up to 4:1 have been used in infants. Tamisier and colleagues demonstrated that the higher the PVR, the larger the donor heart needed for successful transplantation and that hearts with PVR values thought to be in excess of normal can also be used.[20] Although ideal donor ischemia time is from 2 to 4 hours, ischemic times have been successfully extended beyond 9 hours. Deviations from the "ideal" donor criteria should be individualized, and even though the use of a marginal donor for a dying infant maintained on ECMO may be justified, use of the same heart for a child who is stable as an outpatient might not.

ABO-incompatible transplantation has been introduced as a method to decrease recipient waiting time and associated waiting list mortality.[19] Because neonates do not have the ability to produce antibodies to T-cell antigens, including major blood group antigens, ABO incompatibility becomes a negligible complication. ABO-incompatible transplantation has been infrequently used in the United States, and the age at which it is no longer feasible is still not clearly defined. Despite ABO-incompatible listing, it has not yielded lower wait-list mortality under the current UNOS allocation algorithm.[21]

Good donor management is a vital part of successful organ transplantation. The main goals are maintenance of normothermia, euvolemia, and adequate tissue perfusion and prevention of infection. Often, donors with poor cardiac function on initial evaluation will respond to volume loading and low-dose inotropic support with a significant improvement in function after heart retrieval, usually as part of a multiorgan retrieval procedure. Similar to recipients, all donors are screened for agents that might cause serious infection in an immunocompromised host, such as CMV, EBV, HIV, hepatitis, and *Toxoplasma*. The presence of antibodies is not a contraindication to transplantation but helps guide post-transplant therapy.

The four major goals in procurement of a donor heart are to (1) work effectively with the other teams to ensure the optimal condition of each recovered organ, (2) evaluate the hemodynamic status of the patient and the gross function of the heart by inspection, (3) use an effective cardioplegia and venting procedure that maximizes preservation of the heart, and (4) expertly remove the heart and adjoining vascular connections to ensure optimal anatomy for implantation. Procurement is performed through a median sternotomy. Donor blood is obtained for viral titers and retrospective HLA typing. The initial dissection involves separating the aorta from the main pulmonary artery to allow cross-clamping. Careful inspection of the heart is performed, and the patient is systemically heparinized. Procurement commences when the aorta is cross-clamped. Cardioplegia solution is infused through the aortic root, and the heart is vented through the right atrial

appendage or superior or inferior vena cava for the right side and through the superior pulmonary vein or left atrial appendage for the left side. The superior vena cava is dissected free of its pericardial attachments up to the innominate vein, and the azygous vein is ligated and divided. The pericardial reflections around the right superior pulmonary vein and the inferior vena cava are sharply divided. The cardiectomy begins with inferior vena cava transection at the pericardial reflection. The main pulmonary artery is divided and then the posterior pericardial attachments and the superior vena cava. Last, the aorta is transected at the level of the innominate artery or more distally if the aorta is needed for the recipient. The donor heart is immersed in cold (4° C), sterile saline and then triple-bagged in a sterile manner for transport. In general, the cold ischemia time should be limited to a maximum of 4 to 5 hours.

## Recipient Preparation and Techniques of Implantation

The standard technique for orthotopic heart transplantation was first described by Lower and Shumway in 1960 and consists of biatrial anastomoses, thus avoiding individual caval and pulmonary vein connections (Fig. 50-4).[22] Currently, however, the majority of cardiac transplant centers now use the bicaval technique, because it preserves atrial morphology and kinesis and is simpler when reconstruction after previous congenital heart repair is necessary. Once adequate hemodynamic monitoring is in place and the recipient is properly anesthetized, a median sternotomy is performed and the heart is suspended in a pericardial cradle. If previous sternotomies have been performed, appropriate precautions should be taken, including exposing the groins in the sterile field for access for femoral bypass. Once in the chest, the main pulmonary artery is dissected off the aorta past the bifurcation, and the pericardial reflection is mobilized off the aortic arch. Normally, aortic and bicaval cannulation is used.

In the case of a neonatal recipient with HLHS, the aortic arch vessels are mobilized proximally and controlled with snares, and the descending thoracic aorta is dissected to a level 2 to 3 cm below the insertion of the ductus arteriosus. The right and left pulmonary arteries are mobilized and controlled with snares in preparation for cardiopulmonary bypass. After heparinization, the main pulmonary artery is cannulated for arterial inflow, and a single venous cannula is placed in the right atrium, because circulatory arrest will be used. Immediately on instituting cardiopulmonary bypass, the pulmonary arteries are snared tight and the body perfused though a patent ductus arteriosus. The recipient is cooled to 18° C for circulatory arrest.

Once the donor organ is available in the operating room and the patient has been adequately cooled, circulatory arrest is established, the arch vessels are snared tightly, and the patient is exsanguinated into the venous reservoir. The aorta is divided just above the valve and incised longitudinally along the lesser curve of the aortic arch to a level 1 to 2 cm below the ductal insertion site on the descending aorta. The ductus is ligated next to the pulmonary artery and divided, and then the main pulmonary artery is transected just below the bifurcation. The right atrial incision is started superiorly at the base of the appendage. This incision is then carried down into the coronary sinus and across the atrial septum into the left atrium. The superior aspect of the right atrial incision is next carried across the septum to open the roof of the left atrium. The lateral wall of he left atrium is incised above the left pulmonary veins with the left atrial appendage included with the specimen.

The donor organ is prepared on the back table in cold saline solution. The right atrium is incised from the inferior vena

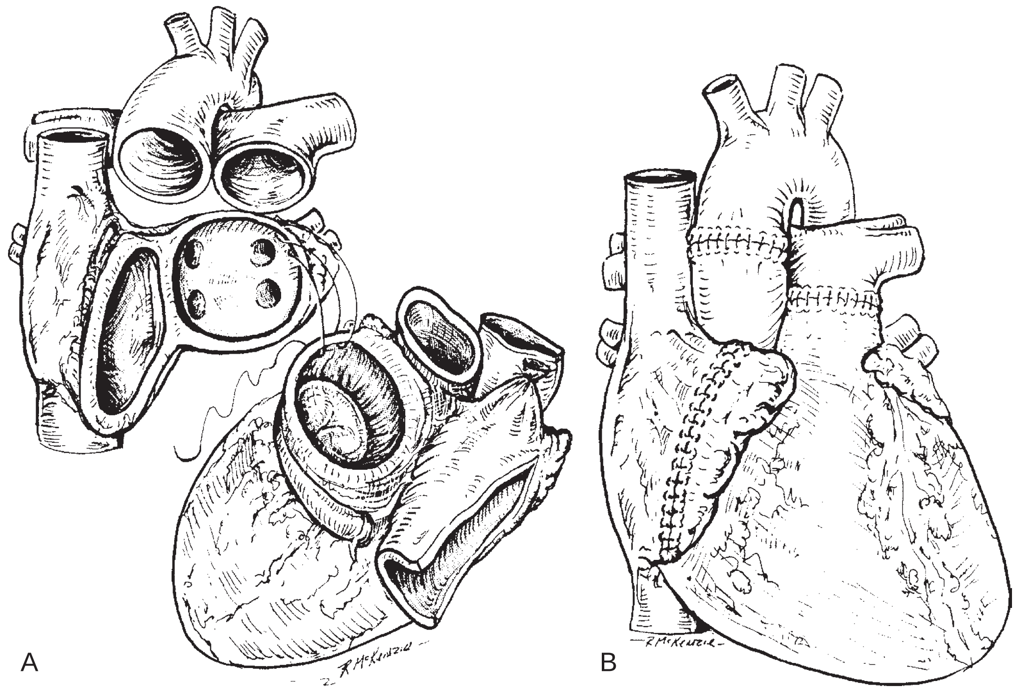


FIGURE 50-4 Standard heart transplantation using biatrial anastomosis. **A,** A recipient ventricular mass has been removed, and the left atrial anastomosis has been started. **B,** Final appearance after all anastomoses are completed.

cava laterally to the base of the appendage; the area of the sinoatrial node is avoided if atrial anastomoses rather than caval anastomoses are to be performed. The pulmonary vein confluence is excised off the back of the left atrium, leaving an opening comparable in size to the recipient left atrial cuff. The pulmonary artery is transected just below the bifurcation to provide a wide anastomosis. The aorta is trimmed, depending on the level required in the recipient. Care must be taken to check for and adequately close a patent foramen ovale, which is frequently present, especially in infant hearts. Failure to do so may result in significant postoperative right-to-left shunting in the face of pulmonary hypertension.

The implantation is begun by forming an anastomosis between the lateral wall of the left atrium from the level of the left atrial appendage inferiorly. A left ventricular vent is placed through the right superior pulmonary vein, and the left atrial anastomosis is completed by reconstructing the intra-atrial septum. The arch of the aorta is then reconstructed. The right atrial anastomosis is begun at the inferior vena cava orifice and then taken superiorly along the intra-atrial septum. The ascending aorta is then cannulated by a new purse-string suture, air is evacuated, and cardiopulmonary bypass is resumed. The snares are released from the head vessels and warming is commenced. The pulmonary anastomosis is then performed in an end-to-end fashion. If time permits, this step may be done during circulatory arrest in a drier field. After adequate warming, the patient is weaned from cardiopulmonary bypass and the cannulas removed (Fig. 50-5).[22] Right atrial, left atrial, and, occasionally, pulmonary artery pressure catheters are placed before discontinuing bypass and brought out through the skin below the incision.

In older children with cardiomyopathy or infants without aortic arch abnormalities, the recipient procedure is similar to that performed in adults. The ascending aorta is mobilized to the pericardial reflection and used for arterial cannulation. The child is cooled to 28° C to 34° C, because the implantation is performed under aortic cross-clamp rather than circulatory arrest. After the left atrial anastomosis has been completed, the right atrial connection can be sewn either directly or by using a bicaval technique if a previous cavopulmonary connection has been performed. This may decrease the incidence of tricuspid regurgitation in certain patients. The aortic anastomosis is then completed in an end-to-end fashion in the midascending aorta. The pulmonary artery anastomosis may or may not be performed during aortic cross-clamp, depending on how long the implant procedure takes.

Numerous other variations of the implantation procedure can be used, depending on the recipient anatomy. Modifications accounting for a persistent left superior vena cava, previous cavopulmonary shunt or Fontan procedure, corrected transposition of the great arteries, and situs inversus totalis have been described.

## Postoperative Management

The recipient is returned from the operating room to an isolation room in the intensive care unit. Mechanical ventilation is required initially but is weaned as rapidly as possible. Antibiotics are continued until all monitoring lines and chest tubes have been removed.

Some level of inotropic support is required in virtually all heart transplant recipients. Isoproterenol is often an ideal choice because of its pulmonary vasodilatory effects, as well as its inotropic and chronotropic effects, because many patients have a slower than optimal heart rate initially. This transient sinus node dysfunction is rarely permanent. Dobutamine and dopamine, especially at "renal doses," are also frequently used to augment ventricular contractility. Epinephrine and norepinephrine are usually reserved for poor graft function. Sodium nitroprusside infusion or phosphodiesterase inhibitors are used for afterload reduction in the early postoperative period. Right ventricular dysfunction secondary to pulmonary hypertension may respond to phosphodiesterase inhibitors, which are used for afterload reduction in the early postoperative period. Right ventricular dysfunction secondary to pulmonary hypertension may respond to phosphodiesterase inhibitors such as milrinone. Inhaled nitric oxide has been shown to be an effective selective pulmonary vasodilator with few systemic side effects and is useful in cardiac transplant recipients with pulmonary hypertension.

## Transplant Immunosuppression

A combination of immunosuppressive agents is used for the prevention and treatment of rejection. Standard triple-drug immunosuppression therapy consisting of prednisone, cyclosporine, and azathioprine has been successfully used in pediatric cardiac transplant recipients and remains the most common regimen.[23] In 2009, more than 70% of transplant recipients received induction immunotherapy. The induction and maintenance doses of medications used for immunosuppression at the Children's Hospital of Philadelphia are listed in Table 50-4. Because of the adverse effects of corticosteroids, withdrawal from prednisone is usually attempted 6 months after transplantation.[24] Up to 80% of recipients may be successfully weaned from steroids; only a quarter of these patients have an episode of rejection in the first 6 months.[25]

Most patients are maintained on an immunosuppressive regimen that is a combination of calcineurin inhibitor and cell-cycle inhibitor. Tacrolimus (formerly called FK-506) has been shown to be an effective immunosuppressive agent in children, and its use has increased over the last 5 years, with approximately 66% of all pediatric cardiac transplant patients receiving it for maintenance immunosuppression 1 year after transplantation in the place of cyclosporine. Overall, patients taking tacrolimus appear to have a lower incidence of rejection. Side effects of azathioprine therapy, such as bone marrow depression, have precipitated the use of mycophenolate mofetil (MMF) in its place. It is estimated that approximately 66% of patients use MMF as a cell-cycle inhibitor. It is well tolerated with few side effects and has been shown in large clinical trials to have benefits in survival and treated rejection episodes.[26]

An increasing number of centers use induction immunosuppression in pediatric cardiac recipients, with nearly 70% of patients now receiving a polyclonal anti–T-cell preparation, OKT3 (a murine monoclonal CD3 antibody), or an interleukin-2 receptor antibody immediately after transplantation. However, there have been no significant

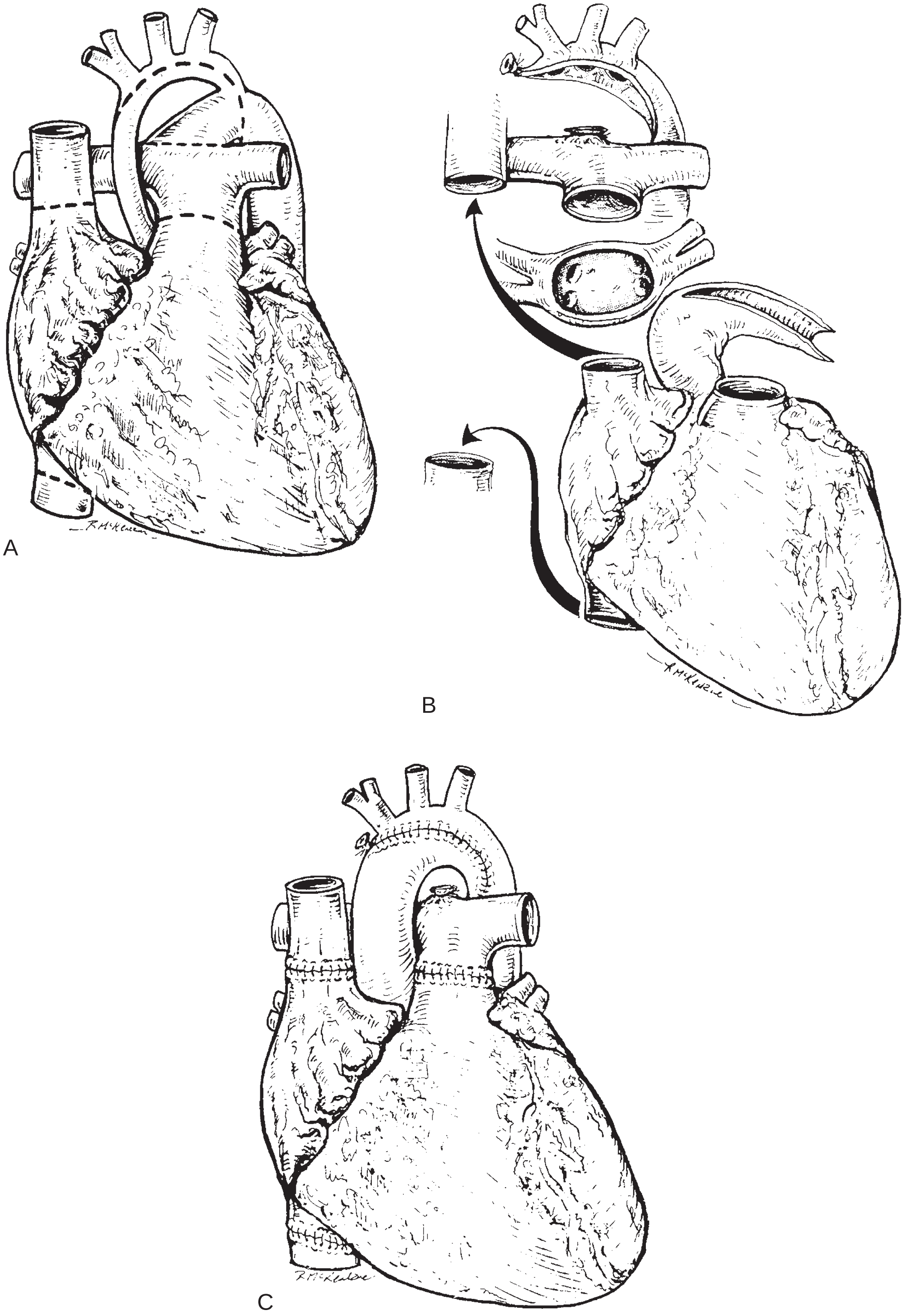


**FIGURE 50-5** Technique for transplantation in hypoplastic left heart syndrome (with the use of bicaval anastomosis). **A,** Recipient anatomy before cardiectomy. **B,** Appearance of the recipient after cardiectomy. Note that the aortic incision must be extended into the descending aorta beyond the level of the arterial duct. **C,** Final appearance after all anastomoses are completed.

differences in the average number of rejection episodes in patients treated for rejection regardless of the type of induction used. In addition, there is no significant difference in survival between the induction groups or between use of induction versus no induction. Induction therapy does not increase the risk of CMV disease or post-transplant lymphoproliferative disease.

Infectious prophylaxis includes oral nystatin for fungal prophylaxis and oral trimethoprim-sulfamethoxazole 3 times per week. Pentamidine inhalation treatment is an effective

**TABLE 50-4**

**Heart Transplantation Immunosuppression Regimen at the Children's Hospital of Philadelphia**

| ***Drug*** | ***Dosage*** |
|---|---|
| Rabbit antithymocyte globulin (ATG) | 1.5 mg/kg IV given in operating room before transplantation for sensitized patients and once daily for 5 days; titrated to CD3 count |
| Azathioprine/mycophenolate mofetil (MMF) | 2 mg/kg IV given in the operating room before transplantation<br>Then 2 mg/kg IV given once daily for 5 days (neonates), 7 days (infants), 9 days (adolescents)<br>Change to MMF 600 mg/m$^2$ IV given twice daily<br>Change to MMF orally once intestinal function resumes |
| Tacrolimus | 0.05 mg/kg every 12 hours orally |
| Cyclosporine | 0.02 mg/kg/hr IV infusion beginning in the operating room before transplantation<br>Then 0.02 mg/kg/hr IV infusion for 24 hours<br>Change to ATG on postoperative day 3 and give 1.5 mg/kg IV once daily for 3 days (neonates), 5 days (infants), or 7 days (adolescents)<br>Change back to cyclosporine orally once ATG course completed<br>Dosing should be carefully adjusted to maintain levels of 125-150 mg in neonates, 175-200 mg in children, 250 mg in 6- to 12-year-olds, and 250-300 mg in adolescents |
| Solumedrol | 15 mg/kg in operating room before transplantation<br>3 mg/kg IV twice daily for 3 doses<br>0.5 mg/kg twice daily for sensitized patients followed by oral prednisone taper |

alternative to trimethoprim-sulfamethoxazole for *Pneumocystis carinii* prophylaxis if bone marrow suppression is a problem. Routine CMV prophylaxis is used in cardiac transplant recipients at our institution.

## Early Complications

Acute rejection and infection are the most common early complications after cardiac transplantation. Nearly 60% to 75% of patients have at least one episode of rejection, and it should be expected that about a third will have an episode in the first 3 months and 50% within the first year after transplantation.[27] Some studies suggest that infants may be less prone to rejection than older children. Rejection surveillance is based on clinical evaluation, echocardiography, and endomyocardial biopsy. Clinical assessment includes observation of changes in a patient's activity or appetite. Atrial or ventricular ectopy, including tachycardia, is suspicious for rejection and mandates evaluation. Echocardiography is particularly useful in neonates, in whom biopsy is technically difficult and carries significant risk because of patient size. Echocardiographic evaluation is typically performed weekly for the first month and then monthly for the first year after transplantation. Echocardiography-guided transjugular endomyocardial biopsy has been shown to be an effective means of monitoring pediatric transplant recipients for rejection and remains the gold standard for detection of rejection.[28] An aggressive approach, consisting of routine endomyocardial biopsy weekly for the first month after transplantation, every second week for the second month, and then once monthly for the remainder of the first year, has been adopted at the Children's Hospital of Philadelphia for rejection surveillance. Subsequent biopsies are obtained twice annually or whenever rejection is clinically suspected. Most biopsies are performed on an outpatient basis. The international grading system for cardiac transplant rejection is shown in Table 50-5.

Episodes of acute rejection are usually treated with a 3-day course of intravenous methylprednisolone (10 mg/kg). OKT3 and antithymocyte globulin are reserved for an incomplete response or rejection refractory to steroids. Response is confirmed by follow-up biopsy 1 to 2 weeks after treatment.

**TABLE 50-5**

**International Society of Heart and Lung Transplantation Grading System for Evaluation of Cellular Rejection**

| | |
|---|---|
| 2005 Classification | |
| 0 | No acute rejection |
| 1R | Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage |
| 2R | Two or more foci of infiltrate with associated myocyte damage |
| 3R | Diffuse infiltrate with multifocal myocyte damage, edema, hemorrhage, vasculitis |
| 1990 Classification | |
| 0 | No acute rejection |
| 1A | Focal, mild acute rejection |
| 1B | Diffuse, mild acute rejection |
| 2 | Focal, moderate acute rejection |
| 3A | Multifocal moderate rejection |
| 3B | Diffuse, borderline severe rejection |
| 4 | Severe acute rejection |

Modified from Billingham ME, Cary NRB, Hammond ME, et al: A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. J Heart Lung Transplant 1990;9:587-593; Stewart S, Winters GL, Fishbein MC, et al: Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005;24:1710-1720.

Although infectious complications are common in cardiac transplant recipients, infection-related deaths do not appear to be. Bacterial infections are most frequent in the early post-transplant period, but can occur late after transplantation and usually respond to proper antibiotic therapy. Of viral infections, CMV appears to be the most common and is treated with intravenous ganciclovir. Viral respiratory infections usually occur at a frequency similar to that in normal children and appear to be well tolerated by the recipient.

Aside from rejection and infection, the immediate postoperative complications after heart transplantation are hypertension, seizures, renal dysfunction, and diabetes. Nearly 10% of infant heart transplant recipients require perioperative peritoneal dialysis. Among neonates, 10% to 15% require phenobarbital therapy for postoperative seizures.

## Late Complications

The primary late complications in pediatric cardiac transplant recipients are chronic rejection, post-transplant lymphoproliferative disease (PTLD), and transplantation CAD. Rejection may account for up to 40% of deaths after cardiac transplantation. Lymphoproliferative disease is associated with EBV infection and is currently treated by a reduction in immunosuppressants, acyclovir, and chemotherapy.[29]

The onset of transplant CAD has a prevalence of 10% to 15% and may be suggested by symptoms of congestive heart failure in recipients. Echocardiograms are performed routinely during follow-up visits of heart transplant recipients, and worsening ventricular function is a sign of graft CAD. A new onset of arrhythmias after transplantation, especially ventricular arrhythmias, may also be an indication of underlying CAD. Additionally, CAD may be found on routine follow-up catheterization or intracoronary ultrasonography, without any previous suggestion of disease. A number of causes have been implicated in the development of graft CAD, including chronic cellular rejection, hyperlipidemia, vascular rejection, and CMV infection. Unlike adult cardiac transplant recipients, CAD appears to develop in pediatric patients relatively early after transplantation, with one series demonstrating an incidence of 35% by 2 years after transplantation. A review of 815 pediatric transplant patients found nearly 8% to have significant CAD by angiogram or autopsy findings. The mean time after transplantation to diagnosis was 2.2 years, with one patient having significant CAD 2 months after transplantation. Only 20% of patients in whom graft CAD was diagnosed were still alive, and most of the deaths were sudden or unexpected. Retransplantation appears to be the only viable option for these patients, although the results in general are not encouraging, with 1- and 3-year survival rates of 71% and 47%, respectively, and CAD developing in the second grafts in 20% of retransplantation patients. However, the Loma Linda group has reported a significantly better retransplantation experience in infants who were first transplanted when younger than 6 months. In this group, a 10-year actuarial survival rate of 91% was observed after retransplantation. Potential medical treatment targeted at cholesterol and lipid-lowering therapies are currently under investigation.

## Results

The largest group of infant cardiac transplant recipients reported in the literature is from Loma Linda, where 233 heart transplantations in infants younger than 6 months have been performed. Nearly 65% were for HLHS, and the rest were for other complex congenital anomalies (29%) or cardiomyopathy or tumor (8%). The operative (30-day) survival rate was 89%, with the primary causes of mortality being primary graft failure, technical problems, pneumonia, or acute rejection. The overall 1-year survival rate was 84%, with a 5- and 10-year actuarial survival rate of 73% and 68%, respectively. In addition, patients undergoing transplantation when younger than 30 days had a significantly better outcome than did older infants, with an actuarial survival rate of 80% and 77% at 5 and 10 years, respectively, potentially related to improved immune tolerance in the younger subgroup.

Stanford University reported its series of 72 patients younger than 18 years who have undergone heart transplantation since 1977. Only 25% were younger than 1 year (mean of 9 years), and nearly two thirds had cardiomyopathy unrelated to congenital heart disease. The operative survival rate was 87.5%, with deaths mainly caused by pulmonary hypertension/right ventricular failure and acute rejection. There were 20 late deaths, 24% were due to rejection, and 17% were due to graft CAD. Actuarial survival rates at 1, 5, and 10 years were 75%, 60%, and 50%, respectively.

At St. Louis Children's Hospital, 45 heart transplants were performed from 1983 to 1993, more than half in infants with HLHS. The infant group had a survival rate (92%) similar to that of the Loma Linda series, whereas the pediatric group (older than 1 year) had an 80% early survival rate. Morales and colleagues published results of their experience spanning more 2 decades at Texas Children's Hospital and reported no change in mortality in survivors after the first post-transplant year.[30]

Results from the Registry of the International Society for Heart and Lung Transplantation reveal a perioperative mortality rate higher for infants than for older children (Fig. 50-6). Despite the much greater early mortality, however, the half-life of 18.3 years is longer than that of the childhood or adolescent survivors. For the childhood age group of 1 to 10 years, the half-life was 17.5 years versus 11.3 years for the adolescent age group, thus conferring the younger patients a significant survival advantage. If those patients who died within the first year after transplant were excluded, the median conditional survival was 21.4 years for those who underwent transplantation in the first year of life, 19.3 years for those aged between 1 and 10 years, and 15.2 years for older children (Fig. 50-7). Survival has been improving in relation to the era of transplantation, with the median survival increased

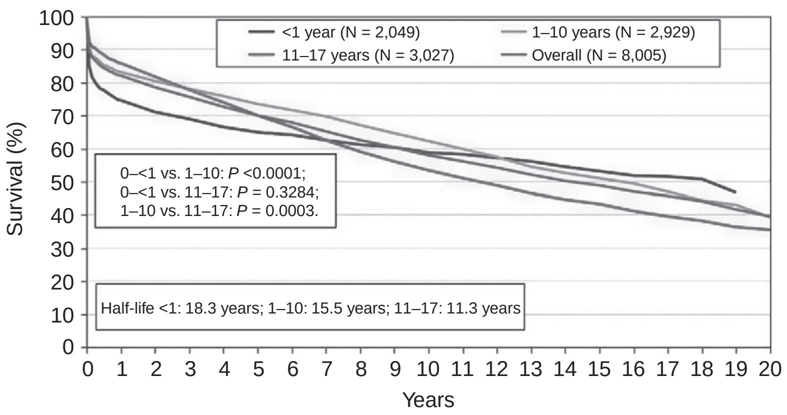


**FIGURE 50-6** Survival analysis for transplantations performed January 1982 to June 2008. (From Kirk K, Edwards LB, Kucheryavaya AY, et al: The Registry of the International Society for Heart and Lung Transplantation: Thirteenth official pediatric heart transplantation report—2010. J Heart Lung Transplant 2010;29:1119-1128.)

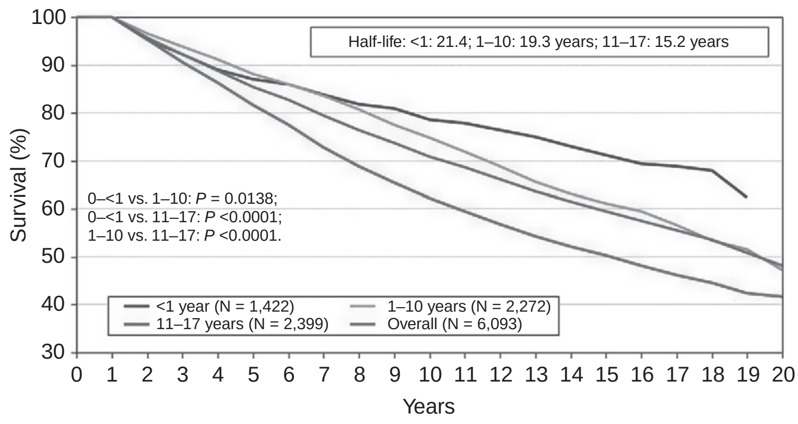


**FIGURE 50-7** Survival analysis for transplants performed January 1982 to June 2008 and surviving to 1 year after transplantation. (From Kirk K, Edwards LB, Kucheryavaya AY, et al: The Registry of the International Society for Heart and Lung Transplantation: Thirteenth official pediatric heart transplantation report—2010. J Heart Lung Transplant 2010;29:1119-1128.)

from 9.5 years for the period 1982 to 1989, to 11.7 years for the period 1990 to 1994, to 14.3 years for the period 1995 to 1999 (Fig. 50-8). Averaged over 15 years, an infant recipient would have an approximate 2% per year risk of mortality, whereas for older children, it remains approximately 4%, again indicating a longer-term survival advantage for younger cardiac transplant recipients.

The most predictive risk factors for 1-year mortality in the pediatric population remain congenital heart disease, donor age, pulmonary artery systolic pressure greater than 35 mm Hg, and the need for mechanical ventilation and hospitalization while awaiting transplantation. Among the most significant risk factors for 5-year mortality are dialysis, congenital heart disease, and female gender (Fig. 50-9). Causes of death include CAD, acute rejection, lymphoma, graft failure, and infection. Retransplantations now account for 5% of all transplantation operations. Survival for retransplantation is decreased when the intertransplantation interval was less than 3 years and is relative to indication for primary transplantation (Fig. 50-10).[31,32]

Aside from survival, it has been demonstrated that transplanted hearts in children appear to grow normally, and the left ventricle increases muscle mass to maintain the normal left ventricular mass-to-volume ratio with time. Exercise testing in older children has shown peak heart rate and oxygen consumption to be consistently two thirds of that predicted in heart transplant recipients. Somatic growth appears to be normal in infants after heart transplantation, and neurologic development is generally preserved, although some neuro-

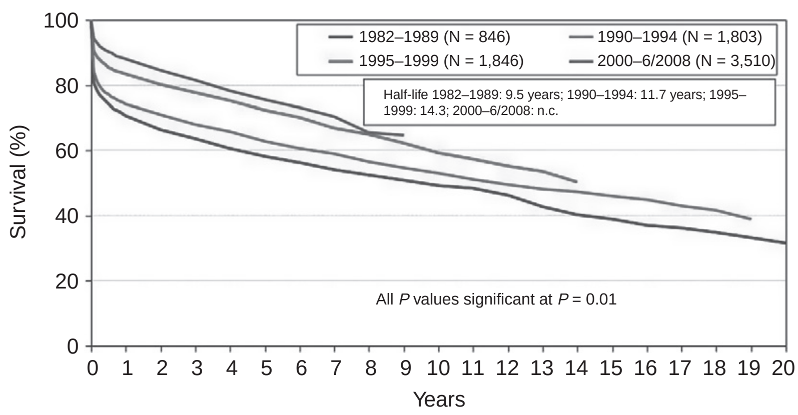


**FIGURE 50-8** Survival analysis by era for transplantations performed January 1982 to June 2008. (From Kirk K, Edwards LB, Kucheryavaya AY, et al: The Registry of the International Society for Heart and Lung Transplantation: Thirteenth official pediatric heart transplantation report—2010. J Heart Lung Transplant 2010;29:1119-1128.)

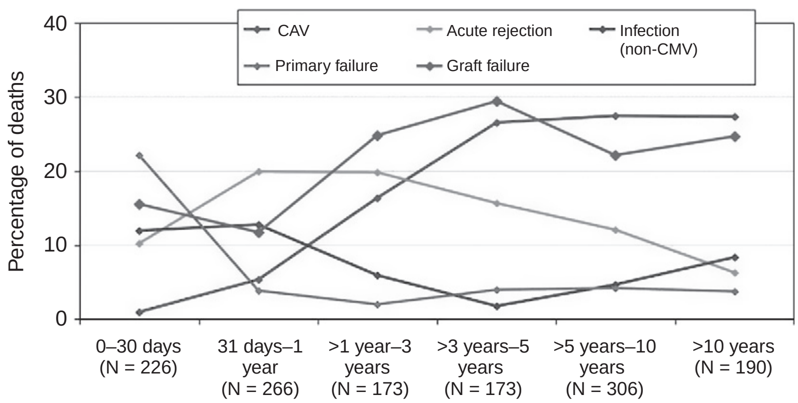


**FIGURE 50-9** Relative incidence of leading causes of death for deaths occurring January 1998 to June 2009. CAV, coronary artery vasculopathy; CMV, cytomegalovirus. (From Kirk K, Edwards LB, Kucheryavaya AY, et al: The Registry of the International Society for Heart and Lung Transplantation: Thirteenth official pediatric heart transplantation report—2010. J Heart Lung Transplant 2010;29:1119-1128.)

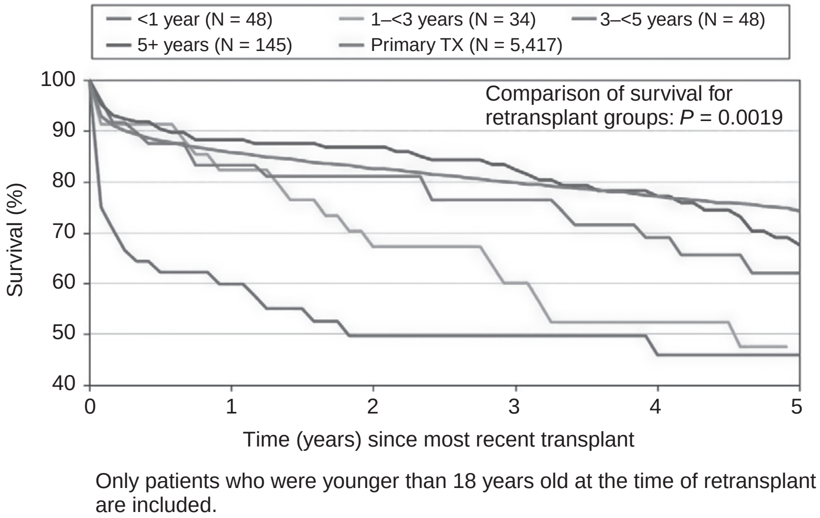


**FIGURE 50-10** Survival rates for retransplantations, stratified by intertransplantation interval, for retransplantations performed January 1994 to June 2008. (From Kirk K, Edwards LB, Kucheryavaya AY, et al: The Registry of the International Society for Heart and Lung Transplantation: Thirteenth official pediatric heart transplantation report—2010. J Heart Lung Transplant 2010;29:1119-1128.)

logic abnormalities may be seen in up to 20% of neonatal recipients on long-term follow-up.

## Conclusion

Despite further improvements in surgical technique, immunosuppression, perioperative management, and rejection surveillance, long-term results of pediatric heart transplantation have shown little change, with a 15-year survival rate of approximately 50%. Chronic rejection, graft CAD, and the long-term effects of steroids on growth continue to cloud the development of cardiac transplantation as the primary treatment of complex congenital heart disease. However, for many children with end-stage cardiomyopathy and structural heart disease not amenable to corrective surgery, transplantation is the only option. Future areas of research include the use of xenografts, ABO incompatibility, permanent mechanical support, and widening the bridge to transplantation with smaller and more adaptable assist devices.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 51

# Pediatric Lung Transplantation

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The first reported attempt at lung transplantation occurred in 1963 and was performed by Dr. James Hardy at the University of Mississippi Medical Center.[1] The patient did not survive the hospitalization, dying 18 days after the transplant. There were a number of additional attempts at this during the next few years, with most failures related to poor healing of the airway anastomosis. Approximately 20 years after Dr. Hardy's ill-fated effort, the first truly successful lung transplant was performed in Toronto, Canada, by a team led by Dr. Joel Cooper. This patient had a single-lung transplant for pulmonary fibrosis and survived for more than 6 years, ultimately dying of renal failure.[2] During the subsequent years, and particularly in the late 1990s, pediatric lung transplantation has emerged as a viable treatment option for children with end-stage pulmonary parenchymal and vascular diseases. However, the number of children undergoing transplantations throughout the world since 1989 remains relatively small, representing only 4% of all lung transplantations performed.[3] In this chapter, pediatric lung transplantation is described as an isolated procedure, and heart-lung transplantation is not included.

## Organ Allocation

In 2005, a new system to allocate lungs to recipients was established across the United States. Previously, lungs were allocated based on the amount of time the recipient had accrued on the waiting list (first come, first served). In an attempt to make distribution of lungs more equitable, a lung allocation score (LAS) was devised and implemented.[4] This score attempts to prioritize organs to patients on the list most in need of the organ (the sickest) as well as to those most likely to do well post-transplantation. This score is used in children 12 years and older. For those younger than 12 years, the old system still remains in effect at present.

## Indications

Isolated lung transplantation is applicable to any child with life-threatening and progressive disability because of pulmonary parenchymal or vascular disease. In general, this treatment modality is indicated for increasing the duration of life and for improvement in the quality of life. The current long-term survival after lung transplantation is approximately 50% at 5 years. Thus the selection of patients for transplantation and the timing of the procedure are critically important. One would like to be able to predict when a child would be within 2 years of dying without any form of medical treatment. Obviously, this may be very difficult. The major diagnostic groups for pediatric lung transplantation are cystic fibrosis (CF), interstitial lung disease with pulmonary fibrosis, primary pulmonary hypertension, pulmonary hypertension associated with congenital heart disease, retransplantation, and a "miscellaneous" category (Table 51-1). Chronic obstructive lung disease, the most common indication for transplantation in adults, is remarkably absent from this list.[3]

### CYSTIC FIBROSIS

This disease, the most common lethal hereditary disease in North America, comprises the largest diagnostic group of children younger than age 18 years who undergo lung transplantation. Although the median survival now exceeds 38 years, one eighth of the deaths from CF in 2008 still occurred in the pediatric age group. Without question, the most common cause of death is respiratory related. About 250 to 300 transplantations are performed annually in the United States for CF, and, although this number is growing slowly each year, donor availability still remains a major limiting factor.[5]

As with other diagnostic groups, timing of transplantation in the course of a chronic disease is a crucial issue. Kerem, in the early 1990s, demonstrated that a 1-second forced expiratory volume ($FEV_1$) less than 30% of predicted, a $PaO_2$ less than 55 mm Hg, and/or a $PCO_2$ greater than 50 mm Hg were associated with a survival beyond 2 years of less than 50%.[6] The impact of these factors is magnified in the pediatric age group, particularly in girls. However, more recent studies on the natural history of CF patients, once they have severely compromised lung function, show that an isolated measure of the $FEV_1$ alone may not be sufficiently predictive. The rate of

**TABLE 51-1**

| Indications for Lung Transplantation in Children |
| --- |
| Cystic fibrosis |
| Pulmonary fibrosis |
| Pulmonary vascular disease |
| Primary pulmonary hypertension |
| Eisenmenger syndrome |
| Bronchiolitis obliterans |
| Retransplantation |
| Other |

decline in the $FEV_1$ may be a more accurate determinant of survival.[7,8] Other factors that may serve as relative indicators in deciding to proceed toward transplantation include the need for continuous supplemental oxygen, increased frequency of hospitalizations, and diminished weight for height (below the 80th percentile).[6] More recently, Liou and colleagues validated a formula that included microbiological data, body mass index measures, and presence of diabetes, in addition to lung function and gender, as important determinants in prognosticating 5-year survival.[9] The presence of antibiotic-resistant organisms in the sputum is a relative contraindication to lung transplantation. The synergistic effectiveness of antibiotic combinations is not useful in treating pulmonary exacerbations and is no longer readily available. Chronic infection with *Burkholderia cenocepacia,* pretransplantation, is associated with a particularly poor post-transplantation prognosis and therefore is of particular concern.[10,11] Portal hypertension with hepatic cirrhosis occurs in 5% to 10% of patients with CF. These children are at risk for variceal bleeding as well as derangements of synthetic function. In general, if the synthetic function is preserved, decompression of the portal venous system with percutaneous procedures will lower the risk to a level satisfactory for lung transplantation.[12] However, when there is also synthetic dysfunction of the liver, combined liver-lung transplantation may be the only appropriate option.[13,14] Diabetes mellitus is generally not considered a contraindication to transplantation unless there is evidence of vasculopathy, bearing in mind that control of serum glucose will be more difficult after transplantation.[15] As many as 10% to 15% of CF lung transplantation candidates will have had prior thoracotomies for either pneumothorax or pulmonary resection. Most centers do not consider this a contraindication to transplantation, although the resultant adhesions from these prior operations do increase the difficulty and the risk of bleeding.[16] Mechanical ventilation or presence of a tracheostomy are not in and of themselves contraindications to transplantation, but the overall medical condition of patients requiring this level of support must be carefully considered.[17]

## PULMONARY VASCULAR DISEASE

This rather broad classification of patients includes those with primary pulmonary hypertension (PPH) and those with pulmonary hypertension associated with congenital heart disease (PH/CHD). The latter category includes patients with Eisenmenger syndrome but is not limited to this. These patients die of either progressive right-sided heart failure, arrhythmias, or a lethal episode of hemoptysis. It is difficult to predict when a patient might have a fatal arrhythmia or episode of hemoptysis. However, most patients with pulmonary vascular disease will die of progressive right-sided heart failure over a protracted period of time.[18] In the past several years, a number of somewhat selective pulmonary vasodilators have become available for use in these patients. These include intravenous prostacyclin,[19] prostacyclin analogues iloprost (inhaled)[20] and betaprost (oral),[21] and bosentan,[22] an endothelin receptor antagonist. These drugs have enabled patients to delay the need for transplantation for years. In fact, the number of patients undergoing transplantation for pulmonary vascular disease has significantly dropped in recent years. The timing of transplantation for patients with pulmonary vascular disease is influenced significantly by the response to medical therapy and the underlying cause of the pulmonary vascular disease. Although primary pulmonary hypertension and Eisenmenger syndrome result in identical histologic changes in the pulmonary vascular bed, the latter of these two is associated with a much more favorable long-term prognosis. A retrospective analysis by Hopkins of 100 adults with severe pulmonary hypertension resulting from either Eisenmenger syndrome or PPH revealed that, in the former group, actuarial survival without transplantation was 97% at 1 year, 89% at 2 years, and 77% at 3 years. In contrast, survival was 77%, 69%, and 35% during the same respective time intervals in the PPH cohort.[23] It is presumed that the intracardiac defect allows the right ventricle to “decompress” via the defect when the afterload in the pulmonary vascular bed becomes prohibitively high. On the basis of this and other observations, atrial septostomy performed in the cardiac catheterization suite has been demonstrated to provide clinical benefit in patients with PPH.[24] Results from a multicenter study of patients with PPH performed before the advent of long-term intravenous prostacyclin therapy demonstrated a median survival from time of diagnosis of 2.8 years. In that study, a formula was developed incorporating hemodynamic variables to assist in predicting the 2-year mortality,[18] and it was recommended that patients should be listed when this figure is less than or equal to 50%. Studies regarding natural history in adults have been applied to children, but it is unclear whether this disease behaves the same in a younger population. Clabby and co-workers reviewed 50 patients from many centers to provide a means of estimating survival in children with PPH.[25] There was a direct correlation of mortality with the product of the mean right atrial pressure and the pulmonary vascular resistance.[25] With progress in the medical therapy of PPH to identify selective pulmonary vasodilators as well as the underlying mechanisms of this disease, these formulas predicting survival may be obsolete. The durability of medical therapy is unclear. How this therapy might be applied to secondary pulmonary hypertension, such as Eisenmenger syndrome, is speculative.

The two main issues in considering patients with Eisenmenger syndrome or PH/CHD for lung transplantation are the timing of listing and the complexity of the cardiac lesion to be repaired. As noted earlier, it is clear that, once the diagnosis is made, these patients can live much longer than those with PPH.[23] The mode of death in these patients is by progressive heart failure, pulmonary hemorrhage, stroke, or sudden death, presumably due to arrhythmias.[25] Patients should be listed when symptoms develop, when there has been a single pulmonary hemorrhage, or perhaps arbitrarily when they reach their late 30s. Most patients with PH/CHD have an atrial septal defect, ventricular septal defect, or patent ductus arteriosus. All of these require relatively simple cardiac repairs. However, there

are patients with unrepaired atrioventricular canal defects, transposition of the great arteries, and truncus arteriosus who would require more complex procedures. An alternative for these patients would be heart-lung transplantation. The likelihood of obtaining a donor heart-lung block for anyone more than 40 kg is low because of the distribution policy for thoracic donor organs. In addition, the long-term survival after heart-lung transplantation is particularly poor (approximately 40% at 5 years post-transplantation).[3] These two issues must be factored into the decision as to whether one should perform the higher-risk procedure of lung transplantation in combination with repair of a complex cardiac lesion or heart-lung transplantation. Some patients with congenital heart disease who have undergone repair may not experience the expected decline in pulmonary vascular resistance after appropriate correction. Occasionally the repair has been performed relatively late in life, but there are children who have undergone timely repair and still present later with severe pulmonary hypertension. It is not clear how to classify these patients. In general, this is a less uniform group than either the patients with PPH or those with Eisenmenger syndrome. They seem to follow a clinical course similar to that seen in patients with PPH and should be treated in a similar fashion.[23]

Another diagnostic group with pulmonary vascular disease are patients with an inadequate pulmonary vascular bed. Examples of this include pulmonary atresia, ventricular septal defect and multiple aortopulmonary collaterals, and congenital diaphragmatic hernia, where there is primarily a general deficiency of pulmonary parenchyma. In the former group, complete correction (repair of the ventricular septal defect combined with reconstruction of the right ventricular outflow tract with a conduit to the unifocalized aortopulmonary collaterals) represents a high-risk but viable option for the majority of these patients. However, when the anatomy of the aortopulmonary collaterals is not amenable to unifocalization or when unifocalization has not produced satisfactory growth of the pulmonary vascular tree, the result is progressive cyanosis or progressive pulmonary hypertension or both. Lung transplantation with repair of the residual cardiac defect may be the only feasible option for survival. Children with congenital diaphragmatic hernias, despite having undergone a successful hernia repair, may still be left with inadequate pulmonary parenchyma and vascular bed to handle the full cardiac output. The resultant severe pulmonary hypertension is the usual cause of death in these infants and is an indication for transplantation. The problem here is that these infants often will require extracorporeal membrane oxygenation (ECMO) support during the perioperative period. This reduces the time that patients such as this can wait for a donor offer once listed for lung transplantation. It is possible that a single-lung transplant on the affected side would be sufficient in this circumstance. In this scenario, once the patient has grown, it may be possible to remove the transplanted lung altogether, leaving the patient with a presumably normal contralateral lung to maintain normal respiratory function. In reality, those patients with insufficient pulmonary reserve will have to be identified very early in the course for lung transplantation to be a realistic option. The mortality is quite high even when donor organs are identified.

In all the previous situations, isolated lung transplantation is appropriate only when left ventricular function is normal. Poor left ventricular function will result in elevated left ventricular end-diastolic pressure post-transplantation, which will add significantly to problems with pulmonary edema and early graft failure. Right ventricular function is frequently poor, particularly in the patient group with PPH. That should not be a deterrent to isolated lung transplantation, because the right ventricular function always returns to normal within a relatively short period of time.[26]

Although a prior thoracotomy is generally not a contraindication to lung transplantation in patients with pulmonary parenchymal disease, this is not true for those with pulmonary vascular disease, especially when secondary to congenital heart disease and associated with cyanosis. The adhesions that develop after a thoracotomy for palliation of cyanotic congenital heart disease are extremely vascular. Intercostal and internal mammary arteries will form direct connections through the pleura into the parenchyma of the lung in a compensatory attempt to enhance pulmonary blood flow. The bleeding that occurs during the recipient pneumonectomy portion of the transplantation procedure is often horrendous and life threatening.

## PULMONARY FIBROSIS

These patients account for 5% to 10% of pediatric patients undergoing lung transplantation.[3] Placed in this category are those patients with “usual” interstitial fibrosis, radiation-induced fibrosis, bronchopulmonary dysplasia, and pulmonary fibrosis secondary to chronic aspiration. The progression of these disease processes is quite variable. Generally, patients should be listed when normal activities are markedly limited and minor viral illnesses lead to significant deterioration. Most patients will be oxygen dependent and may well have evidence of coexistent pulmonary hypertension. For those in whom aspiration is the underlying problem, the source of the aspiration must be eliminated.

The prognosis of children with idiopathic pulmonary fibrosis is not altogether clear. This may be because there is not a “usual interstitial pulmonary fibrosis” disease in children; the underlying causes are frequently unique and unusual. Decisions regarding listing for transplantation are somewhat difficult because of this. Pulmonary fibrosis presenting during infancy was once believed to have a poor prognosis; however, some studies have demonstrated improved survival with high doses of corticosteroid therapy.[27] The prognosis for adults with total lung capacity less than 60% predicted is still poor; nearly all are dead within 2 years.[28] It is difficult to translate this information into the pediatric experience. Pulmonary hypertension frequently accompanies this disease as it progresses. These patients should be evaluated and listed for transplantation when they become symptomatic. If there is a favorable response to corticosteroids, they can be followed with standard (age $>$ 5 years) or infant (length $<$ 90 centimeters) pulmonary function tests. One problem with managing this disease is that patients with progression of their disease tend to remain on relatively high doses of corticosteroids and come to transplantation in a rather cushingoid state. This should not exclude them from transplantation.

## BRONCHIOLITIS OBLITERANS AND RETRANSPLANTATION

Bronchiolitis obliterans is not a specific disease but rather a histologic description characterized by the obstruction and destruction of the distal airways. It may occur as a

consequence of any severe lung injury, including viral pneumonia, graft-versus-host disease after bone marrow transplantation, autoimmune diseases, chemical injury, Stevens-Johnson syndrome, and others. Of course, it is a relatively common late complication of lung transplantation (see later). The underlying etiology is unknown. “Primary” bronchiolitis obliterans (not related to prior lung transplantation) is a perfectly legitimate indication for lung transplantation: It is a slowly progressive disease in virtually all cases with no known effective treatment. When this disorder occurs as a consequence of an isolated lung injury, transplantation is a fairly straightforward decision process. However, those patients with prior bone marrow transplantations (usually for leukemia) offer special considerations.[29] Although the standard definition of “cure” is remission of the malignancy for more than 5 years, most of these patients present within 2 or 3 years of treatment. Another problem is the deranged immune competency seen after bone marrow transplantation and how the immunosuppressant agents used after lung transplantation might further affect this. We have found that these patients have less acute rejection than most other lung transplantation recipients but may be more prone to opportunistic infections.[29] However, the number of patients transplanted in this setting is low. For patients who acquire bronchiolitis obliterans through other immunologic injuries, such as autoimmune disorders, there are concerns about the likelihood of recurrence in transplanted lungs. One would have to ascertain that the primary process has completely abated before transplantation.

Retransplantation for acute graft failure after transplantation has an extremely poor prognosis.[30] Retransplantation for bronchiolitis obliterans is a controversial issue. Bronchiolitis obliterans accounts for the majority of deaths occurring more than 90 days post-transplantation.[3] This figure is borne out in our pediatric series.[31] Although early mortality after retransplantation is higher than for “first-time” lung transplantations, those who do survive this early phase have long-term survival similar to the non-redo transplantations.[30] Risk factors for poor early outcome include nonambulatory status, short period of time since the first transplantation, transplantation at a center with limited experience, and dependence on mechanical ventilation. We have further noted that a low glomerular filtration rate is an independent risk factor. Because patients continue to die on the waiting list, one could argue that no patient should ever be retransplanted because this might deprive an otherwise lower-risk patient from receiving organs in a timely fashion. At present this issue is unresolved. One can only advise use of proper judgment in selecting only the best candidates when the issue of retransplantation arises.

### MISCELLANEOUS

A variety of diagnoses fall into this group. Congenitally based pulmonary parenchymal diseases constitute one of the more interesting broad categories. Typically, these full-term newborns present with severe respiratory distress and no obvious cause, such as meconium aspiration, sepsis, or persistent fetal circulation. The diagnoses falling into this category include surfactant protein B deficiency, other forms of pulmonary alveolar proteinosis, alveolar-capillary dysplasia, pulmonary dysmaturity, congenital interstitial pneumonitis, and others. These infants usually have severe respiratory failure and require a high level of ventilatory support. Often extracorporeal membrane oxygenation has been or is currently being used. An open-lung biopsy is often necessary to either make the diagnosis or to exclude other diagnoses. Surfactant protein (SP) B or C deficiency and the ABCA 3 mutation can now be diagnosed by looking for the specific genetic mutation in peripheral blood or cheek swabs and assaying tracheal effluent for the presence of this surfactant protein.[32] All children will survive less than 3 months even with aggressive therapy. Abnormalities in SP-C and ABCA3 can have more varied presentations. Additionally, because the surfactant proteins are expressed only in the lungs, extrapulmonary organ dysfunction is rare.[33] Until other therapies become available, lung transplantation is the only viable therapeutic option. In general, the waiting time for an organ offer is relatively short in infants. Therefore one might realistically believe that an infant with a 3-month life expectancy could undergo transplantation and survive. When an infant is on ECMO, every effort should be made to wean from it, using whatever means possible, including a high-frequency oscillating ventilator and/or nitric oxide. Although ECMO is not an absolute contraindication to transplantation, one should be very cautious in this setting because of the relatively high incidence of other organ dysfunction.

## Contraindications

Contraindications to transplantation in children are also based on experience obtained in adults (Table 51-2). Absolute contraindications include systemic disease with major extrapulmonary manifestations or severe dysfunction of other organ systems. Thus widespread malignancy, collagen vascular disease, human immunodeficiency virus infection, and severe neuromuscular disease are absolute contraindications. The acceptable degree of renal insufficiency is open to some interpretation. Given the nephrotoxicity of cyclosporine and tacrolimus, the drugs that form the basis of nearly all immunosuppressant regimens, a serum creatinine value greater than 2.0 mg/dL and a probable need for post-transplantation dialysis are clinical parameters that would mitigate strongly against proceeding with transplantation. A glomerular

**TABLE 51-2**
**Contraindications to Lung Transplantation**

| |
|---|
| **Absolute** |
| Malignancy |
| Human immunodeficiency virus infection |
| Multisystem organ failure |
| Left ventricular dysfunction |
| Active collagen vascular disease |
| Severe neuromuscular disease |
| **Relative** |
| Renal insufficiency |
| Liver function impairment |
| Malnutrition |
| Resistant organisms in the sputum |
| Poorly controlled diabetes mellitus |
| Osteopenia |
| Prior thoracotomies in the presence of pulmonary vascular disease |
| Prior pneumonectomy with mediastinal shift |
| Extreme prematurity |
| Inadequate psychosocial support system |
| Poor compliance |

filtration rate less than 50 mL/min has been associated with a poor outcome in some patients. Significantly deranged hepatic synthetic function precludes transplantation unless concomitant liver transplantation is also being undertaken. More complex issues include severe malnutrition, poorly controlled diabetes mellitus, osteopenia, vertebral compression fractures, and the need for mechanical ventilation. None of these factors in and of themselves serves as an absolute contraindication. Nonetheless, all such concerning aspects of the clinical presentation must be evaluated and carefully considered in the scope of the patient's overall state of health to assess the likelihood for successful recovery after transplantation. Chronic administration of corticosteroids before transplantation is considered to be undesirable, and, when possible, one should reduce the total daily dose or change to an every-other-day dosage schedule. Previously, corticosteroids were believed to have a significant negative impact on airway healing, particularly in the case of double-lung transplantation with a tracheal anastomosis. Bilateral sequential lung transplantation with bronchial anastomoses has obviated this problem to a large degree. Severe psychiatric disorder in either the patient or, in the case of a young child, the care provider, is a strong relative contraindication. Finally, a history of poor compliance with either a medical regimen or in keeping follow-up appointments is considered by most to be a strong relative contraindication to transplantation. Graft failure due to lack of proper care not only results in death to the recipient involved, but also results in either a delayed or denied transplantation for a more appropriate candidate.[34]

### SPECIAL CIRCUMSTANCES

Some infants born extremely prematurely survive the early days of their lives only to develop severe bronchopulmonary dysplasia with respiratory failure within the first year of life. The incidence of significant cerebral injury in this group is high; approximately 50% of those surviving have some disability.[35] We can only assume that the incidence is higher in those with severe residual lung disease requiring transplantation. It is often difficult to assess the neurologic status in these infants because of their small size and often the need for sedation and neuromuscular paralysis for maintenance of satisfactory ventilation. It is probably unwise to submit an infant born at less than 28 weeks' estimated gestational age to lung transplantation, unless there has been an opportunity for an accurate neurologic examination. Imaging studies may offer some reassurance but are inconclusive. Another unusual situation that arises where lung transplantation may be considered appropriate is the child with severe acute respiratory distress syndrome. Those children still in the acute phase of this illness often have other organ dysfunction, and their condition is too unstable for them to wait the obligatory time once listed for transplantation, given the current organ allocation system for children less than 12 years of age. Those who survive the early phase of acute respiratory distress syndrome and are left with fibrotic lungs and stable ventilatory requirements should be evaluated. Finally, occasionally a patient with a history of prior pneumonectomy will be referred for lung transplantation. After pneumonectomy in children, the mediastinum shifts to the affected side. This distorts the hilar structures to the point that bilateral or single lung transplantation is virtually impossible. When possible, a patient undergoing pneumonectomy who might require lung transplantation in the future should have a prosthetic spacer placed in that side of the chest to maintain normal mediastinal geometry.

## Donor Evaluation and Organ Procurement

Donor availability remains a major limitation to the applicability of transplantation for end-stage lung disease. Donors must be matched by ABO blood type compatibility and within a reasonable size range of the recipient. Height is used as the most accurate correlate to lung size. Height that falls within 15% to 20% of the recipient height is probably suitable. Extending this range upward is certainly feasible, because it is not difficult to reduce the size of the lungs by trimming off the edge or even using only the lower lobes. However, extending the lower limit should be done with great caution, because the transplanted lungs may not fill the chest and may be more prone to pulmonary edema. Donors are excluded in the presence of positive HIV serology, active hepatitis, history of asthma, tuberculosis, or other significant pulmonary disease. A history of limited cigarette smoking is probably acceptable if other parameters of the evaluation fall within the guidelines. In general, the upper limit of donor age is approximately 55 years. The chest radiograph should be free of infiltrates, and the arterial oxygen tension should be more than 300 mm Hg on an inspired oxygen fraction of 1.0 with an appropriate tidal volume and 5 cm $H_2O$ positive end-expiratory pressure. Mild pulmonary contusions and subsegmental atelectasis would not necessarily exclude a donor as long as these criteria are met. Flexible bronchoscopy should be performed to examine the airways for erythema suggestive of aspiration of gastric contents. In addition, this provides an opportunity to assess the nature and quantity of pulmonary secretions. The presence of purulent secretions that do not clear well with suctioning should exclude the donor even if the chest radiograph is clear and the oxygenation is adequate.

The surgical part of the procurement process is performed through a median sternotomy. Both pleural spaces are opened widely to allow visual inspection of the lungs and also the topical application of cold saline and slush. The trachea is dissected out between the superior vena cava and aorta. It may be helpful to develop the interatrial groove, also, to allow a more accurate division of the left atrial tissue that must be shared with the cardiac donor team in most situations. The principles of the procurement process beyond this are (1) anticoagulation with high-dose (300 units/kg) heparin; (2) bolus injection of prostaglandin $E_1$ (50 to 70 mcg/kg) directly into the main pulmonary artery; (3) decompressing the right side of the heart by incising the inferior vena cava; (4) decompressing the left side of the heart by amputating the left atrial appendage; (5) high-volume (50 mL/kg), low-pressure flush of cold (4° C) pulmonary preservation solution of choice; (6) topical application of cold saline and slush to the lungs; and (7) continued ventilation of the lungs with low volumes and low pressures using an $FiO_2$ of 0.4. When all the preservation solution has been administered, the lungs are excised en bloc. The trachea is divided while the lungs are held in gentle inflation (pressure of $\approx$ 20 cm $H_2O$) with the $FiO_2$ at 0.4. The lungs are then extracted, placed in a bag containing the preservation solution used for the flush, and then placed in cold storage for transport.

Much research has been devoted to finding the "ideal" preservation solution to extend potential ischemic times and avoid reperfusion injury.[36] A full discussion of this complex topic goes beyond the scope of this chapter. The most commonly used preservation solutions at this time are modified Euro-Collins solution, University of Wisconsin solution, Perfadex, and Celsior. None of these is clearly superior to the others, and all work reasonably well. However, none reliably allows for preservation times greater than 8 hours, and none completely avoids reperfusion injury.

# Technique of Transplantation

The surgical technique used for children is like that for adults, except that virtually all children will require cardiopulmonary bypass, whereas that is not always necessary in adults. Transplantation without cardiopulmonary bypass would require single-lung ventilation during the procedure. Maintaining single-lung ventilation in these small children is extremely difficult, because the airways are too small to accommodate double-lumen endobronchial tubes. Bilateral lung transplantation is performed for nearly all children because of concerns over the growth potential of the transplanted lungs. Trans-sternal bilateral anterior thoracotomy incision (the so-called "clamshell incision") through the fourth intercostal space provides excellent exposure of the heart and hilar regions. Though absorbable suture theoretically provides the greatest potential for growth, some surgeons use nonabsorbable suture material for the anastomoses.[37] We recommend a simple end-to-end rather than a telescoping anastomosis for the airway because of the high incidence of stenosis in the latter.[38,39] If the patient requires concomitant repair of an intracardiac lesion (e.g., with Eisenmenger syndrome), that is best performed after the recipient pneumonectomies and before implanting the donor lungs. Many of these patients have significant aortopulmonary collaterals resulting in significant pulmonary venous return to the heart while on cardiopulmonary bypass. After the recipient lungs have been removed, the absence of pulmonary venous return to the heart from bronchial arteries and other collateral vessels will allow for a bloodless operative field for the intracardiac repair. The subsequent period during which allograft implantation is performed provides sufficient time for cardiac reperfusion before weaning from cardiopulmonary bypass.

Living donor lobar transplantation and the use of cadaveric lobes, has become less commonplace as an alternative to standard cadaveric "whole lung" transplantation, since implementation of the LAS.[40] Although the upper lobes have been used, lower lobes seem better suited anatomically, with each lobe serving as an entire lung. When lobes come from a living donor, there is less bronchial and vascular tissue with which to work and thus longer cuffs of the bronchus, pulmonary artery, and pulmonary vein of the recipient will facilitate the procedure. A technique has been devised whereby a single left lung can be partitioned such that the upper lobe is used on the right and the lower lobe on the left.[41] The circumstances under which one might use this technique would be quite unusual—a single left lung from a large donor being made available to a desperately ill child. Nonetheless, it is another attempt at solving the ongoing problem of inadequate donor organ supply.

# Immunosuppression

Although the precise protocols differ from one center to another, most use the so-called triple-drug immunosuppression approach (Table 51-3). Combinations of these immunosuppressant drugs allow for a better overall effect with a relatively less toxic dose of any one agent. Drug regimens generally include cyclosporine or tacrolimus in combination with azathioprine or mycophenolate mofetil (MMF) and prednisone. Most pediatric lung transplantation centers now use tacrolimus because of the cosmetic advantages it offers versus cyclosporine and therefore perhaps improving adherence, especially among adolescent recipients. The use of induction cytolytic therapy using antithymocyte globulin is somewhat controversial because of the potential of infectious complications associated with their use. Basiliximab, a specific monoclonal antibody to interleukin 2, is an alternative to cytolytic agents to "induce" tolerance.[42] Rather than being cytolytic, these drugs work by blocking a critical pathway in the activation of lymphocytes involved in cellular rejection. The low infection rate using these monoclonal antibodies has stimulated the reemergence of induction therapy early after lung transplantation.[43] The initial target trough cyclosporine blood level is 300 to 400 ng/mL by whole blood monoclonal assay. When tacrolimus is used, that target trough level is 10 to 15 ng/mL. The initial corticosteroid dose is 0.5 mg/kg daily of prednisone or methylprednisolone. MMF is given at a dose of 600 mg/m$^2$ twice daily while azathioprine is given in a dose of 2.5 to 3.0 mg/kg daily. Acute rejection is treated with 3 consecutive days of intravenous methylprednisolone at a dose of 10 mg/kg/day. Rejection refractory to methylprednisolone is treated with antithymocyte globulin for 7 to 10 days. Recurrent (greater than three) bouts of acute rejection may also prompt a change of the baseline immunosuppression. Although the corticosteroid dose is gradually tapered with

**TABLE 51-3**
**Immunosuppressant Agents**

| *Class of Drug* | *Side Effects* |
|---|---|
| **Interleukin-2 Synthesis Inhibitors** | |
| Cyclosporine | Hypertension, seizures, nephrotoxicity, hirsutism, gingival hyperplasia |
| Tacrolimus | Hyperglycemia, seizures, nephrotoxic |
| **Lymphocyte Proliferation Inhibitors** | |
| Azathioprine | Leukopenia, nausea |
| Mycophenolate mofetil | Leukopenia, nausea, diarrhea, elevated liver enzymes |
| Sirolimus | Hypertriglyceridemia, delayed wound healing |
| Corticosteroids | Hypertension, hyperglycemia, cushingoid appearance |
| **Induction Agents** | |
| Antithymocyte globulin | Fever, chills, leukopenia, cytomegalovirus infections, post-transplantation lymphoproliferative disorder |
| OKT3 | Fever, chills, cytomegalovirus infections, post-transplantation lymphoproliferative disorder |
| Daclizumab, basiliximab | Nausea, diarrhea |

time, we do not believe it is appropriate to stop this drug altogether. The side effects of immunosuppressive drugs in children are similar to those seen in adults. Sirolimus (rapamycin) is chemically similar to tacrolimus but inhibits the proliferative response of lymphocytes to interleukin-2.[44] It does not share the nephrotoxic potential of tacrolimus. It is currently reserved for situations of failure of other immunosuppressant drugs. Some caution should be exercised in using sirolimus as initial immunosuppression early after transplantation because there has been evidence of impaired wound and airway healing resulting in serious complications.[45]

All patients receive prophylaxis against pneumocystis jiroveci pneumonia with either sulfamethoxazole-trimethoprim orally 3 times per week or when sulfa allergy or intolerance is present one may consider monthly treatment with aerosolized pentamidine or daily therapy with atovaquone. Prophylaxis against mucocutaneous *Candida* infections is also used.

# Post-transplantation Surveillance

Surveillance after transplantation is based on periodic spirometry and bronchoscopy with biopsies and bronchoalveolar lavage. Before discharge from the hospital, patients are provided with a home spirometer and are asked to perform spirometry at least once daily. A decrease in $FEV_1$ of greater than 10% from baseline is considered an indication for evaluation. All patients, regardless of size, undergo regularly scheduled surveillance bronchoscopy to diagnose lower respiratory infections, subclinical graft rejection, and airway anastomotic complications. Virtually all episodes of suspected rejection should be confirmed with transbronchial biopsies. The main challenge occurs in small infants in whom a mini-forceps is used through either the 2.8-mm or the 3.5-mm pediatric flexible fiberoptic bronchoscope. However, obtaining an adequate specimen with these forceps can be challenging. Recently a 4.0 mm bronchoscope with a 2.2-mm suction channel was introduced into clinical practice, thus allowing the use of adult-sized forceps for many young children. At our institution, bronchoscopy with biopsy is performed at 7 to 10 days and at 1, 2, 3, 6, 9, 12, and 18 months after transplantation as a surveillance procedure. Worsening pulmonary function, infiltrates on a chest radiograph, or deterioration in clinical status, such as fever or an oxygen requirement, also prompt bronchoscopy and biopsy. Bronchoalveolar lavage is performed at these procedures for quantitative bacterial, routine viral, and fungal cultures.

# Post-transplantation Complications

## AIRWAY ANASTOMOTIC COMPLICATIONS

Anastomotic complications can involve either the airway or the vascular anastomoses. Airway dehiscence was the major source of postoperative morbidity and mortality in the early days of lung transplantation when tracheal anastomoses were performed. Not until this problem was solved by using an omental wrap for the airway anastomosis could clinical lung transplantation progress.[46] Currently, dehiscence is rare in spite of the fact that most surgeons do not use the omental wrap any longer, but rather approximate donor and recipient peribronchial tissue over the anastomosis. Dehiscence of the airway may be either partial or total. Partial dehiscence can usually be treated expectantly but puts the airway at increased risk of late stenosis.[47] Complete dehiscence requires emergent therapy and is generally a lethal complication. Although reanastomosis should be attempted when possible, it is associated with a high rate of failure, and transplantation pneumonectomy is required. Smaller airway size in children prompted concerns about whether the incidence of bronchial anastomotic stenosis would be higher and also whether the anastomoses would grow. Current evidence suggests that the airways at the anastomoses grow and that the incidence of bronchial stenosis is not affected by age or size at the time of transplantation.[48,49] Bronchial stenosis is usually treated with dilatation initially with either progressively larger rigid bronchoscopes or with an angioplasty balloon. Balloon dilatation of a stricture may be preferable, because it is less likely than a rigid bronchoscope to injure the distal airway. Repeat bronchoscopy 10 to 14 days after initial dilatation of a bronchial stenosis is necessary to judge the overall effectiveness and to assess the likelihood of recurrence. Depending on the severity of the initial stricture or the rapidity with which it recurs, one might consider placing a stent. There are two basic types of stents applicable to this situation: Silastic and wire mesh. In general, wire mesh stents are easier to insert but much more difficult to remove, and Silastic stents are harder to place and easier to remove. Alternatives to stent placement include sleeve resection (of the bronchus or upper lobe) or retransplantation. Resection has been performed with good results in adults but would be a very difficult procedure in children.[50] Retransplantation should be reserved for situations in which the stricture extends beyond the bronchial bifurcation on either side and cannot be managed with either endobronchial techniques or local resection.

## VASCULAR ANASTOMOTIC COMPLICATIONS

Problems with either the arterial or venous anastomoses are rare. In most instances, a stenosis in either of these is secondary to excessive length on the donor pulmonary artery or left atrial cuff or torsion of either of these structures when performing the anastomosis. Stenosis in one of the pulmonary artery anastomoses may or may not be manifest by right ventricular hypertension. Because pulmonary artery catheters are not often placed in children, one should check the right ventricular pressure by direct puncture once off cardiopulmonary bypass. If elevated, the pressure distal to each anastomosis should be checked also by direct puncture. Unilateral mild to moderate pulmonary arterial anastomotic stenosis may not result in significant elevation of right ventricular pressure. A perfusion lung scan is routinely performed within 24 hours of the transplantation to screen for technical problems with the vascular anastomoses. Any significant discrepancy between right- and left-sided perfusion should be immediately evaluated with either direct visualization in the operating room or angiography. Stenosis in either or both pulmonary venous anastomoses is manifest by pulmonary hypertension, profuse pink frothy sputum, and diffuse infiltrates on a chest radiograph. These findings may also be present with a severe

reperfusion injury or diffuse alveolar damage. However, the pulmonary capillary wedge pressure is generally normal in the latter two instances and elevated with a stenosis in the pulmonary venous anastomosis. Transesophageal echocardiography is particularly helpful in the diagnosis of pulmonary venous anastomotic problems. Confirmation of the diagnosis usually requires direct measurement of the pulmonary venous and left atrial pressures, particularly in small children. Early correction is mandatory.

## BLEEDING

A number of factors place these patients at increased risk for bleeding after transplantation. Nearly all transplantations in children require prolonged cardiopulmonary bypass for recipient pneumonectomies and implantation of donor organs. Additionally, many of these patients have undergone prior thoracotomies or sternotomies. Patients with cyanotic heart disease and a prior thoracotomy have the greatest risk of serious bleeding, as mentioned earlier.

## PHRENIC NERVE INJURY

This complication occurs in about 20% of lung transplantations and is secondary to trauma because of stretch while retracting to expose the hilar regions; it is more common on the right side.[51] Recovery of diaphragmatic function within 6 months of transplantation is the general rule. The reason for the right side being injured more commonly probably relates to the proximity of the nerve to the pulmonary artery and the superior vena cava on that side. The superior vena cava (and thus the phrenic nerve) must be retracted to expose the proximal right pulmonary artery. Prior thoracotomy puts the nerve at greater risk for injury, because it may be obscured by adhesions.

## HOARSENESS

Vocal cord paralysis caused by recurrent laryngeal nerve injury has an incidence of approximately 10%. This diagnosis is made at the time of flexible fiberoptic bronchoscopy with direct examination of the cords. In most cases, anatomic asymmetry improves without directed therapy within 6 months of transplantation. The left vocal cord is nearly always the one involved, and the injury presumably occurs as a result of dissection of the left pulmonary artery in the region of the ligamentum arteriosum.

## GASTROINTESTINAL COMPLICATIONS

Many centers now routinely assess for the presence of gastroesophageal reflux because of its potential association with the development of bronchiolitis obliterans (BO).[52] Since instituting routine 24-hour pH probe monitoring at the 2-month post-transplantation evaluation, we have found that almost 70% of our patients have evidence of acid reflux. The etiology of this high incidence of gastroesophageal reflux is not clear but may be due to injury to the vagus nerves bilaterally in the process of performing the recipient pneumonectomies. Decreased intestinal motility is also a common problem in all age groups. Patients with CF are at risk for distal intestinal obstruction syndrome. This can be avoided by aggressively treating with osmotic cathartics after transplantation. Gastrografin enemas may be necessary if there is no response to oral cathartics.

## ATRIAL FLUTTER

Atrial arrhythmias are relatively common with significant episodes of atrial flutter occurring in 10% of pediatric lung transplantation recipients. Many require long-term treatment.[53] Investigation into this entity using a model of lung transplantation has shown that the suture lines for the left atrial anastomoses provide sufficient substrate for the maintenance of atrial flutter when initiated by programmed extrastimulus.[54]

## GRAFT COMPLICATIONS

Reperfusion injury manifesting as graft failure with diffuse infiltrates on chest radiography, frothy sputum, and poor oxygenation is the most common graft complication early after lung transplantation, occurring in 20% to 30% of transplantation recipients.[55] It is the most common cause of death within the first 30 days after transplantation.[3] The underlying cause is probably multifactorial, with both donor and recipient conditions contributing to this problem. The best preventive measures include careful evaluation and procurement of the donor organs as well as having a recipient free of active infection or other acute problems. A well-conducted transplantation procedure is also of utmost importance. The treatment of reperfusion injury is mostly supportive, although nitric oxide[56] and prostaglandin $E_1$[57] may be of some primary benefit.

Rejection is a common occurrence after lung transplantation, perhaps more so than in other solid organ transplantations (Fig. 51-1). The lung has a much larger endothelial surface than other organs. Because the major histocompatibility antigen expression on endothelial surfaces is the primary signal for local immune recognition, the lung would seem to be the least easily camouflaged organ in the body. In addition, the lung graft comes with its own parenchymal bronchial lymphocytes and macrophages. Gradually, these are replaced by the recipient lymphocytes and macrophages. This rather intense immunologic activity adds to the risk of rejection. Acute graft rejection early after transplantation presents in such a nonspecific fashion that each suspected episode should be documented with histologic evidence obtained by either transbronchial biopsy or open-lung biopsy. The great majority of episodes of acute rejection occur in the first 6 months after transplantation. Although the incidence of acute rejection in all children is about the same as that seen in adults, it appears that infants have a much lower incidence.[58,59] The precise reason for this is unclear but may have to do with the relative immaturity of the immunologic system in infants.

Antibody-mediated rejection (AMR) is now recognized as a serious and relatively common complication of lung transplantation. With the advent of better detection assays, one can now quantitate the amount of circulating donor-specific antibody in the recipient. However, it is also becoming increasingly clear that non–human leukocyte antigen (HLA) antibodies may also be responsible and that, in fact, autoantibodies to previously sequestered antigens may play a vital role

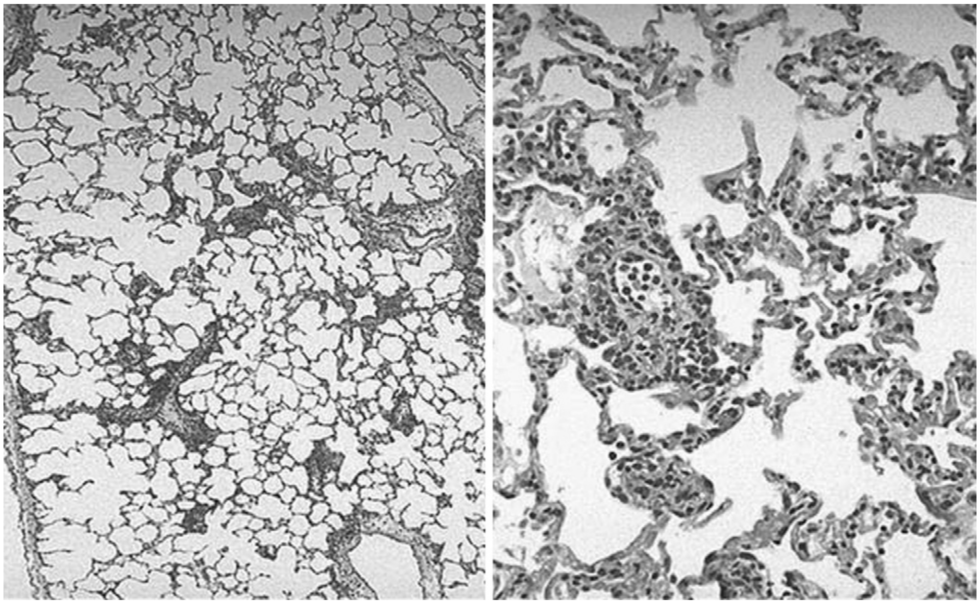

**FIGURE 51-1** Acute rejection. Multiple lymphocytes are present in a perivascular position involving many blood vessels, which can be seen better on higher power. This was interpreted as grade A2 acute rejection.

in the development of bronchiolitis obliterans. Increasing experience with C4d immunostaining of biopsy specimens and C4d and C3d immunofluorescence permit histologic confirmation of AMR. The exact frequency of this complication in lung transplantation recipients is not yet known. AMR has shown itself to be fairly refractory to therapy. We use a protocol that includes plasmapheresis, intravenous bortezomib, intravenous immunoglobulin (IVIG), and rituximab.

Bronchiolitis obliterans is viewed by most clinicians to be a manifestation of chronic rejection and occurs in nearly 50% of all long-term survivors.[60] The precise cause is unknown, although donor ischemic time, episodes of early acute rejection, and history of lymphocytic bronchitis have been identified as risk factors.[61,62] Bronchiolitis obliterans presents as a significant fall in $FEV_1$ without other obvious cause. The chest radiograph is generally clear, and the computed tomographic examination of the chest usually demonstrates evidence of air trapping with mosaicism and occasionally bronchiectasis. Ventilation/perfusion lung scanning may demonstrate air trapping with xenon retention. Bronchoscopy with transbronchial biopsy and bronchoalveolar lavage should be done as part of the evaluation to rule out other potential causes, such as acute rejection or infection, and to assess the degree of active lymphocytic infiltration of the airways. The histologic picture of bronchiolitis obliterans is one of dense scarring of the membranous and respiratory bronchioles (Fig. 51-2). It may be inferred by the absence of identifiable bronchioles on biopsy material. Diagnosis of bronchiolitis obliterans by histologic examination of transbronchial biopsy material may be very difficult, however, and many do not consider it necessary to establish the diagnosis. A staging system has been established based on the degree of decline of $FEV_1$ or forced expiratory flow $(FEF)_{25\text{-}75}$ from the peak value: post-transplantation stage 0p = 10% ($FEV_1$) or 25% ($FEF_{25\text{-}75}$), stage 1 = 20% to 35%, stage 2 = 35% to 50% decline, and stage 3 = more than 50% decline.[63] The usual treatment for bronchiolitis obliterans in the United States is to augment immunosuppression, usually beginning with antithymocyte globulin daily for 7 to 10 days; the clinical response has been variable. A change in the maintenance immunosuppression may also be appropriate. Antiproliferative agents may provide a more effective approach, but that has yet to be proved. Results from small studies suggest that azithromycin may be effective in stabilizing and perhaps even improving lung function.[64,65] Researchers at Duke University demonstrated that fundoplication in patients with BO and gastroesophageal reflux may potentially improve BO grade if performed early.[52] Total lymphoid irradiation and photopheresis are other modalities that have been proposed.[66] Patients not responding to these measures may be suitable candidates for retransplantation. As mentioned earlier, this is a somewhat controversial topic, because there is a shortage of donor organs, and the results with retransplantation overall are not quite as good as with first-time transplantations. However, if the candidates are ambulatory, not ventilator dependent, and at an experienced lung transplantation center, the survival results are not significantly different from first-time transplantations.[30]

Post-transplantation lymphoproliferative disease (PTLD) occurs in 10% to 19% of pediatric patients undergoing lung transplantation. PTLD occurs more frequently in association with a primary Epstein-Barr virus (EBV) infection.[67] Children may be somewhat more prone to this complication, because they are frequently seronegative for EBV infection at the time of transplantation and are therefore likely to acquire a primary EBV infection during their post-transplantation life. Reduction in immunosuppression is the mainstay of early therapy, although this may be insufficient and not uncommonly leads to the subsequent development of bronchiolitis obliterans. Rituximab, an anti-CD20 monoclonal antibody, has been used effectively in the treatment of PTLD.[60] Other treatment modalities include conventional chemotherapy,[68] irradiation, and infusion of human leukocyte antigen–matched T lymphocytes.[69]

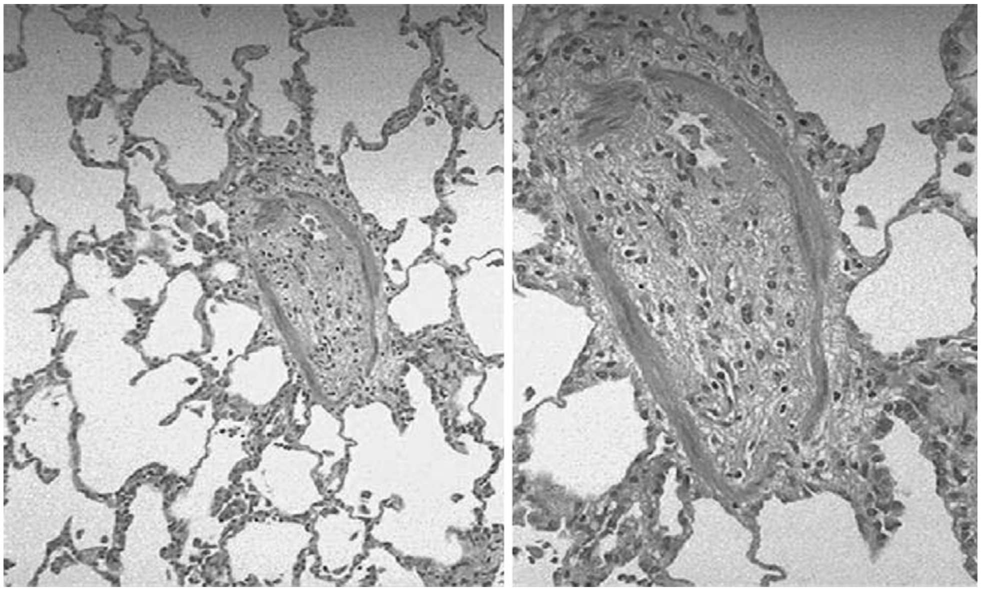

**FIGURE 51-2** Histologic slide taken from the lung of a patient undergoing retransplantation for bronchiolitis obliterans. Small airways are obliterated by fibrous tissue.

## INFECTION

Although infection is generally common after any solid organ transplantation, lung transplantation recipients are at greater risk. Donors are all on mechanical ventilation, resulting in colonization of the airway with bacteria from an intensive care unit. The lung is the only solid organ constantly in contact with the nonsterile outside world. An endotracheal tube necessary early after the transplantation bypasses some of the natural defenses available to the respiratory tract. Obligate denervation of the lung that occurs with transplantation results in the cough reflex being markedly diminished or absent altogether. These and numerous other factors demand that the caregivers maintain constant vigilance in the diagnosis and treatment of respiratory infections and also emphasize to the recipient the importance of pulmonary toilet.

All potential candidates are screened for the presence of organisms in the airway and evidence of previous infections. Evidence of prior viral infections is evaluated by serologic testing for antibodies to cytomegalovirus; herpes simplex virus; varicella; EBV; hepatitis A, B, and C; and human immunodeficiency virus. Viral serologic screening is less informative in young infants whose immunoglobulin pool reflects passively transferred maternal antibodies. The initial antimicrobial therapy given in the early post-transplantation period is directed in part by the results of pretransplantation studies. Ganciclovir is given at a dose of 5 mg/kg/day for 6 weeks for any positive donor or recipient serology for cytomegalovirus. If patients have evidence of present or past *Aspergillus* infection, antifungal therapy with either intravenous anidulafungin or voriconazole followed by oral voriconazole is used, depending on the clinical situation.

A number of viral respiratory infections are quite common in pediatric patients. Adenovirus and parainfluenza viruses are particularly bothersome in children. As for cytomegalovirus, primary disease is generally more likely to be severe than reactivation disease.[2] As mentioned earlier, primary infection with EBV is an important risk factor for the development of PTLD.

Fungal infections are uncommon but potentially devastating. Nystatin oral suspension is employed to reduce the risk of infection from *Candida* species. Virtually all infections caused by *Candida* species can be successfully treated with oral or intravenous triazole antifungal agents. Invasive *Aspergillus* infections, however, are much more difficult to treat and may result in widespread dissemination if appropriate antifungal therapy is delayed.

Bacterial infections are common after lung transplantation. Bacterial lower respiratory tract infections, which include both purulent bronchitis and pneumonia, occur in most patients at some point after transplantation. Patients with CF are more likely to experience this complication, with the organism usually the same as that colonizing the airway before transplantation. Prophylaxis against lower respiratory tract infections in CF lung transplantation recipients may be accomplished by administering aerosolized antibiotics (tobramycin or colistin) just as one might for end-stage CF.

## OTHER COMPLICATIONS

Hypertension is a common problem after transplantation and is presumably due to treatment with the calcineurin inhibitors cyclosporine and tacrolimus, as well as prednisone. Renal insufficiency occurs with increasing time after transplantation and is also related to treatment with cyclosporine and tacrolimus. Diabetes mellitus occurs in approximately 15% of patients after transplantation, primarily in patients with CF.[2] Tacrolimus predictably increases the likelihood for the development of hyperglycemia.

# Survival

The 3- and 5-year actuarial survival for children undergoing lung transplantation is approximately 54% and 45%, respectively, according to the International Society for Heart and

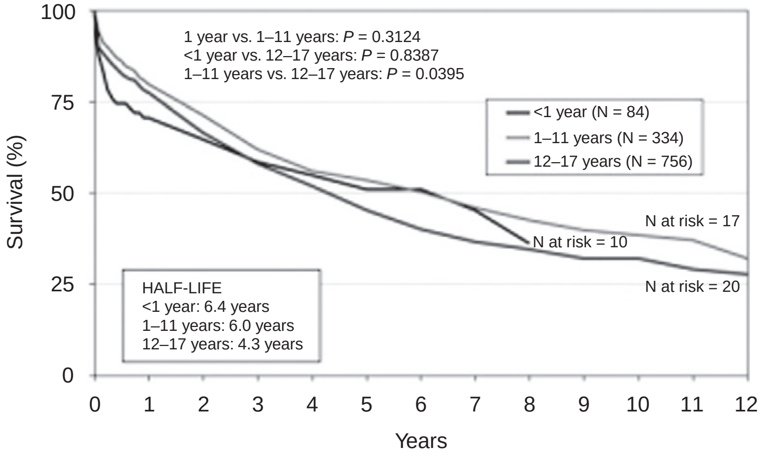


**FIGURE 51-3** Kaplan-Meier survival curve for pediatric lung transplantation. (From Aurora P, Edwards LB, Kucheryavaya AY, et al: The Registry of the International Society for Heart and Lung Transplantation: Thirteenth Official Pediatric Lung and Heart/Lung Transplantation Report—2010. J Heart Lung Transplant 2010;29:1129-1141.)

Lung Transplantation registry (Fig. 51-3).[3] Acute graft failure accounts for the majority of deaths in the first 30 days. Infection is the cause of death in approximately 50% of those dying in the first year beyond the transplantation hospitalization. Bronchiolitis obliterans is the cause of death in 50% of patients beyond 1 year after transplantation and is clearly the major impediment to long-term survival.[30]

## Pulmonary Function and Growth

It is unclear whether transplanted lungs grow in terms of number and size of alveoli, and experimental data are inconclusive.[70,71] Measurement of lung growth is fraught with a number of complicating factors. One cannot use pulmonary function tests and lung volume size as measured by either chest radiograph or computed tomography, because there are a number of elements that affect these studies that would not accurately reflect the number or size of alveoli. The impact of lung growth is particularly critical in small infants, because their transplanted lungs will have to grow substantially over the rest of their lives to handle the physiologic load presented to them. Those children in our series too young to undergo standard pulmonary function testing underwent infant pulmonary function tests that provide a measurement of functional residual capacity, a reasonable surrogate for lung volume. The average functional residual capacity per centimeter in height at 3 months after transplantation was 2.3 mL/cm and remained between 2.1 and 2.8 mL/cm through 15 months after transplantation. During this time, substantial somatic growth occurred in these infants.[72] Thus in the absence of central or peripheral airway obstruction, these data suggest that lung growth appropriate for size is occurring. However, we do not know whether this represents an increase in the number of alveoli and/or an increase in the size of existing alveoli.

## Future Considerations

Factors that limit the success of lung transplantation in children are similar to those in adults: donor shortage, balance of immunosuppression and prevention of infection, and development of bronchiolitis obliterans. Xenotransplantation may eventually offer another solution, but realistically, this is many years from application. Transplantation across ABO blood groups, now commonplace in infant cardiac transplantation, is another possibility in small children, though the overall impact of this would be minor. Newer immunosuppressive agents aimed at more specific areas of the immune response involved with organ recognition are necessary. Bronchiolitis obliterans remains the "Achilles heel" of long-term survival after lung transplantation. Although still not completely characterized as to its precise cause, most investigators ascribe this development to airway injury leading to chronic rejection. To that end, clinical and basic research aimed at understanding the vectors of injury and disease progression in bronchiolitis obliterans are of paramount importance to the field of lung transplantation. Because the airway as the site of injury is accessible for assessment and therapy, bronchiolitis obliterans may provide a model system whereby chronic rejection, which also affects long-term success in heart, kidney, and liver transplantation, can be understood and overcome.

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 52

# Surgical Implications Associated with Pediatric Bone Marrow Transplantation

Thomas E. Hamilton and Robert C. Shamberger

Fifty-three years after the seminal report of hematopoietic stem cell transplantation (HSCT) in children and adolescents by Thomas and colleagues,[1] pediatric surgeons have retained an important role in successful implementation of this therapy. The expansion of HSCT to a variety of malignant and nonmalignant diseases has grown based on successful use of multiple stem cell sources and innovative conditioning regimens.[2] A fundamental understanding of these processes will assist pediatric surgeons when called upon for access or complications associated with patients undergoing HSCT.

Stem cells can be derived primarily from bone marrow, umbilical cord blood, or peripheral blood stem cells (PBSC). Along with advances in infection prophylaxis and supportive care, the switch to PBSC has led to mortality rates of less than 5% for autologous transplantation in many studies. One of the major advances of PBSC compared with autologous marrow is more rapid engraftment of the recipient. Faster hematopoietic recovery results in an abbreviated period of neutropenia, thrombocytopenia, and anemia, resulting in lower rates of infection and hemorrhage, less risk of transfusions, and earlier discharge. Harvest and storage of a patient's own hematopoietic stem cells (HSC), followed by reinfusion after high-dose chemotherapy (HDC), is commonly referred to as autologous HSCT or stem cell rescue. HDC is generally administered beyond the tolerance of the patient's marrow (myeloablative), meaning no recovery is possible without stored HSC.[3]

The transplantation process is divided into five phases: (1) conditioning, (2) stem cell infusion, (3) neutropenia, (4) engraftment, and (5) postengraftment phase. The conditioning phase involves intensive chemotherapy with or without total body irradiation to eliminate the disease. This period lasts between 7 and 10 days. The stem cell processing and infusion time varies based upon the size of the patient and source of the stem cells. The neutropenic phase lasts 2 to 4 weeks and is an interval when the patient is extremely vulnerable to infections because of the lack of an effective immune system. Wound healing is impaired, and empiric antibiotics are generally administered to minimize infectious complications. Mucus membranes are rapidly dividing tissues, and therefore susceptible to ulceration and the risk for nosocomial infections is high. Total parenteral nutrition is widely used in children during this phase.

The engraftment phase takes several weeks as transplanted cells incorporate into recipient tissues. The development of graft versus host disease (GVHD) and viral infections are the greatest clinical obstacles of this phase. The postengraftment phase lasts months to years as the gradual development of tolerance, weaning of immunosuppression, and immune reconstitution occur.[4] Pediatric surgeons are consulted frequently for access or associated complications in all phases of the transplantation process.

## Stem Cell Harvest and Vascular Access

Multiple ports of access are required for peripheral stem cell harvest. Unlike adults, where large-bore antecubital catheters can be used for both harvest and infusion, pediatric patients generally require indwelling central venous catheters. The extracorporeal separation of blood components from patients or donors has spawned an entire field termed apheresis. As technologies of separation evolve, the one constant is the need for adequate access to withdraw and return blood components. Standard Broviac catheters collapse with the negative pressure required for apheresis (approximately 1 to 2 mL/kg/minute). Specially designed apheresis catheters allow faster flow rates because of larger-diameter stiffer walls and shorter catheter length. Most apheresis catheters are dual lumen offset with multiple ports to avoid mixing processed and unprocessed blood. Children weighing more than 10 kg will accommodate 8-Fr or larger (MedComp, Harleysville, Pa.) catheters. When children weigh less than 10 kg, temporary femoral or

subclavian catheters may be used.[3] Because of the larger size and stiffness of the apheresis catheters and dilators, fluoroscopic guidance and respect for tissue is paramount. As one of my surgical mentors always said, "placing the line in is never as interesting to the surgeon as taking out the tumor, but it is just as important to the care of the child."

# Complications of Immune System Ablation and Immunosuppression

## INTESTINAL COMPLICATIONS

Abdominal pain and diarrhea are common post-HSCT. A substantial component of the initial inflammatory cascade is thought to occur in the gastrointestinal tract, and patients with higher volumes of diarrhea at the time of the preparative regimen have an increased risk of acute GVHD.[5] Barker and associates[6] performed a retrospective study of 132 consecutive pediatric HSCT patients, and diarrhea occurred in 67% of patients. Common etiologic agents included GVHD (27%), viral (6%), *Clostridium difficile* (8%), and unknown (28%). When stool cultures are negative, endoscopy is considered to differentiate infectious etiologies from GVHD. Gastric antral biopsies and small bowel biopsies may be preferred, because duodenal hematomas have been reported by Ramakrishna and Treem.[7] They recommended avoiding the duodenum if possible and maintaining platelet counts greater than 55,000/mm$^3$ for 48 hours postbiopsy when a duodenal biopsy is necessary. A prospective multicenter study of pediatric bone marrow transplantation (BMT) patients who underwent 1120 small bowel biopsies did not report hematoma as a complication.[8,9] Silbermintz and co-workers[10] reported successful identification of small bowel graft versus host disease by capsule endoscopy in a child with refractory hemorrhage, when upper and lower endoscopies were nondiagnostic. Identification of small intestinal cytomegalovirus (CMV) disease has also been reported by capsule endoscopy.[11] The future role for capsule endoscopy is increasing as the intestinal complications after HSCT predominate in the small intestine.[12] Accurate visualization may help guide the need for more intensive immunosuppressive therapy or to avoid immunosuppressive therapy.

Neutropenic enterocolitis (typhlitis) is characterized by necrotizing inflammation of the colon in a severely immunocompromised patient (Table 52-1). Clinically, fever, abdominal pain, tenderness, and neutropenia are present (Fig. 52-1). The incidence is low in children after HSCT. Barker's retrospective review of 132 consecutive pediatric HSCT patients reported an incidence of 3.5%.[6] Early experience with neutropenic enterocolitis was marked by controversy regarding the timing of surgical intervention, and mortality exceeded 50%.[13–16] Delineation of the criteria for surgical intervention reserved for clearly identified surgical complications has contributed to a substantial decrease in mortality and morbidity.[15,17]

Multiple contemporary series now report excellent outcomes using a strategy of bowel rest, prompt institution of appropriate intravenous fluid resuscitation, broad-spectrum antibiotics and antifungal therapy, nutritional support with total parenteral nutrition (TPN), and the use of granulocyte colony-stimulating factor (GCSF).[18–21] In 2002, Otaibi reported a series of 142 HSCT transplantations performed in Alberta Children's Hospital. Ninety-seven patients developed abdominal pain, and only five developed radiographically proven typhlitis. No patients required surgical intervention.[20] Mullassery, from The Royal Liverpool Children's Hospital reported a 5-year retrospective series in 2009 in which 18 of 596 patients had radiographically confirmed typhlitis and three required surgical intervention. One child, each, had extensive colonic necrosis, perforated gastric ulcer, and perforated appendix. A single mortality was also reported from fulminant gram-negative sepsis without intervention.[19]

**TABLE 52-1**
**Neutropenic Enterocolitis: Criteria for Appropriate Surgical Intervention**

1. Persistent gastrointestinal bleeding after resolution of neutropenia and thrombocytopenia and correction of clotting abnormalities
2. Evidence of free intraperitoneal perforation
3. Clinical deterioration requiring support with vasopressors or large volumes of fluid, suggesting uncontrolled sepsis
4. Development of symptoms of an intra-abdominal process, in the absence of neutropenia, which would normally require surgery

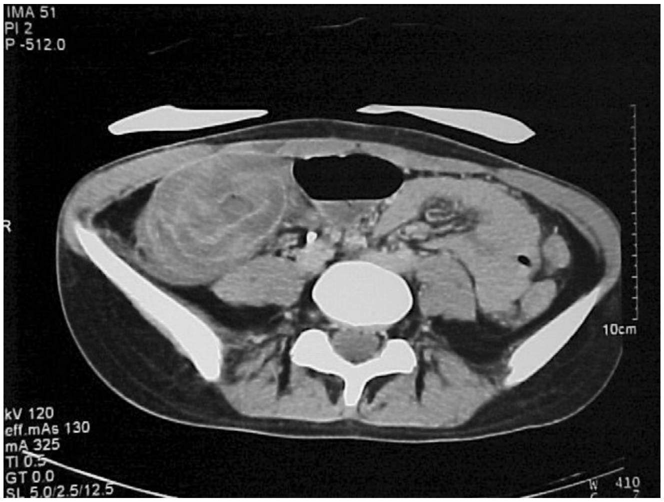


**FIGURE 52-1** Typhlitis in a teenager with acute myelocytic leukemia who had undergone bone marrow transplantation (BMT). Note the thickened, onionskin appearance of the cecal wall and the pinpoint lumen. This patient underwent right hemicolectomy with ileostomy and mucous fistula; 1 year later, still in clinical remission from her leukemia, her condition was successfully reversed. Most cases of typhlitis are handled nonoperatively.

## HEPATOBILIARY COMPLICATIONS

Abnormal liver function studies are commonly identified in HSCT patients. An extensive 40-year review of hepatobiliary complications in HSCT has recently been published by McDonald.[22] Liver complications have become far less frequent as the understanding of how to prevent and treat severe hepatobiliary problems has emerged. Surgeons are frequently consulted to discern whether abnormal liver function studies are secondary to obstruction or parenchymal dysfunction. Biliary obstruction occurs secondary to calculous disease.

Safford and colleagues[23] reported a series of 575 patients, of which 235 received ultrasonography of the abdomen for pain, jaundice, sepsis, or metastases. Cholelithiasis was identified in 20 cases (8.5%). The overall incidence of cholelithiasis reported in the study was far greater than the 0.13% to 0.21%. incidence in children.[24] When the reason for HSCT was considered in Safford's series, 27% of patients who had HSCT for bone marrow failure versus 7.4% for neoplasia developed cholelithiasis ($P < 0.01$). This suggests a role for hemolysis. Despite the high incidence of cholelithiasis, 85% of children did not require surgical intervention. Nine (45%) died from primary disease, five (25%) showed sonographic resolution, and three (15%) had nonoperative follow-up for persistent cholelithiasis. Surgical interventions included one cholecystostomy, one open cholecystectomy, and one laparoscopic cholecystectomy in three (15%) patients who developed acute cholecystitis, with a mean time to operative intervention of 1.9 years without complication. There was no morbidity or mortality associated with conservative management of cholelithiasis in any child.[23]

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS) is a serious and frequent complication after HSCT. It is clinically heralded by a triad of (1) painful hepatomegaly, (2) hyperbilirubinemia, and (3) unexplained fluid retention. Milder cases resolve spontaneously, but severe cases may become rapidly fatal. Prognosis varies with extent of injury and the development of multiorgan system failure.[25] The pathogenesis involves sinusoidal endothelial cell and hepatocyte damage from high-dose alkylating chemotherapeutic agents.[22,25] Plasminogen activator inhibitor (PAI-1) serum levels have both diagnostic and prognostic value as a marker for VOD.[26] The intensity of the conditioning regimen and type of transplantation are important determinants for risk of VOD. Pediatric patients younger than 6.5 years at transplantation appear to be at increased risk of hepatic VOD.[27] Defibrotide (DF) is a polydisperse mixture of single-stranded oligonucleotide with local antithrombotic, anti-ischemic, and anti-inflammatory activity that has clinical efficacy in severe VOD. DF appears to modulate endothelial cell injury without enhancing systemic bleeding and protects the hepatic sinusoids without compromising the antitumor cytotoxic effects of therapy.[28] Ho and associates[25] reviewed hepatic VOD and multiple clinical trials with DF, where 30% to 60% complete remission rates are reported, even in patients with severe VOD and multiorgan system failure. Corbacioglu and colleagues[29] reported that 34 (76%) patients with severe VOD post-HSCT, treated with DF, achieved a complete response, and in multivariate analysis, early intervention (1 day vs. 5.5 days in nonresponders) was the only significant factor. Richardson and coworkers[30] recently reported a phase II multicenter randomized trial in adult and pediatric patients that established the safety and efficacy of defibrotide. Early stabilization or decreased bilirubin was associated with better response and day +100 post-HSCT survival, and decreased plasminogen activator inhibitor type 1 (PAI-1) during treatment was associated with better outcome; changes were similar in both treatment arms. A dosage of 25 mg/kg/day was selected for ongoing phase III trials of the treatment of VOD.

Focal nodular hyperplasia following pediatric HSCT has been identified in 17 of 137 patients prospectively studied, with a median delay of 6.4 years from a series reported by Sudour and associates.[31] The authors postulate an iatrogenic vascular origin, because 16 patients received myeloablative preconditioning, and only three had evidence of SOS. No complication or malignant transformation was reported; clinical and diagnostic imaging follow-up is recommended.

## HEMORRHAGIC CYSTITIS

Hemorrhagic cystitis (HC) occurs in 10% to 20% of pediatric HSCT patients. Decker and colleagues[32] have recently reviewed the pediatric experience. HC is characterized by diffuse vesical bleeding which ranges from microscopic hematuria to gross hemorrhage with clot formation and urinary obstruction requiring instrumentation for evacuation. With severe HC, prolonged hospitalization with significant morbidity may occur. High-dose chemotherapy and immunosuppression that accompany HSCT make the pediatric patient particularly susceptible. Investigations point to a multifactorial pathophysiology of HC. Damage to the transitional epithelium by radiation, chemotherapy, and infectious agents have been postulated. BK virus is now a known pathogen with increasing evidence for a major role in HC. High-dose cyclophosphamide and bisulfan are well studied alkylating agents used in conditioning protocols for HSCT that are known to cause HC. Three main strategies for HC prophylaxis include mesna, hyperhydration with forced diuresis, and continuous bladder irrigation (CBI). Three-way catheter drainage is often difficult in pediatric populations and may require a suprapubic tube. Ultrasonography may underestimate the clot burden, and cystoscopy provides visualization with the opportunity for clot evacuation and fulguration of the bladder epithelium. Escalation to more intensive therapies, such as instillation of drugs into the bladder (intravesical therapy), carry increased risk. Many agents, including aluminum potassium sulfate, prostaglandins, and ϵ-aminocaproic acid and cidofovir have been used for intravesical therapy, but none are well studied in a pediatric population. HC is a self-limiting condition once engraftment and immune reconstitution occur, effective defense barriers of the bladder mucosa are reconstituted, and viral replication is controlled. More intensive therapies should be undertaken under the auspices of a multidisciplinary team.[33]

## PULMONARY COMPLICATIONS

Opportunistic infections are common in HSCT patients. Pneumonia is the most common infectious complication but must be distinguished from noninfectious causes, such as bronchiolitis obliterans, diffuse alveolar hemorrhage (DAH), and a constellation of noninfectious fever accompanied by either skin rash, pulmonary infiltrates, or diarrhea—termed engraftment syndrome.[34] Early recognition and treatment of post-HSCT pneumonia favorably impacts survival.[35,36] A recent article from Shannon and co-workers[37] from M.D. Anderson Cancer Center has examined the utility of early versus late fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) post-HSCT in 501 consecutive adult patients. Five hundred and ninety-eight fiberoptic bronchoscopies (FOB) with bronchoalveolar lavage (BAL) were performed for the evaluation of pulmonary infiltrates. The overall diagnostic yield was 55%. The diagnostic yield was 2.5-fold higher when the FOB was performed within the first 4 days

and highest (75%) when performed within 24 hours of clinical presentation. The rates of adjustment in antimicrobial therapy were not different with early versus late treatment (51%); however, late FOB-guided antibiotic adjustments were associated with 30-day pulmonary-associated deaths that were threefold higher (6% vs. 18%, $P = 0.035$). The authors conclude early referral for FOB may yield a higher diagnostic yield and favorably impact survival in adult patients.

The utility of lung biopsy in pediatric patients post-HSCT is controversial. Shorter and colleagues[38] reported a 10-year experience of 126 HSCT patients from Children's Hospital of Philadelphia from 1976 to 1986. Twenty-one patients had open lung biopsies; 14 showed no causative organisms. One patient had CMV, and three patients had *Pneumocystis carinii*. Thirteen patients died because of continued deterioration postbiopsy. Hayes-Jordan and associates[39] reported a retrospective series of 528 patients post-HSCT from St. Jude's Children's Research Center from 1991 to 1998. Eighty-three patients developed pulmonary infiltrate within 6 months; 43 (52%) had BAL and 19 (23%) had open lung biopsies, 6 (7%) underwent needle biopsy, and 5 (7%) underwent transbronchial biopsy. Histology identified infections in 6 (30%), bronchiolitis obliterans organizing pneumonia (BOOP) in 5 (26%), interstitial pneumonia in 4 (21%), gangliosidosis in 1, and lymphocytic infiltrate in 1. Despite changing the clinical plan, based on histology in 17 of 19 (90%) patients, improvement in outcome was only seen in 8 (47%). Postoperative morbidity at 30 days was 47%, including prolonged intubation (7 patients), pneumothorax (2 patients), and pleural effusion (1 patient). Thirty-day survival was 63.2%, and no patient with multiorgan system failure, ventilator dependence, or postoperative complication survived post–open lung biopsy. Careful patient selection and consideration of less-invasive modalities should be strongly considered in these extremely high-risk patients. Minimally invasive surgical techniques have been applied both diagnostically and therapeutically in childhood cancer;[40] however, the decrease in pulmonary compliance and increase in cardiac afterload is often prohibitive for thoracoscopic techniques in the post-HSCT patient population.

Invasive pulmonary aspergillosis (IPA) is a common infection in the HSCT population. A potentially lethal complication of HSCT is pulmonary hemorrhage secondary to the angioinvasive nature of this agent. IPA is one specific opportunistic infection where surgical therapy remains beneficial. Gow and colleagues[41] reported on 43 patients with invasive pulmonary aspergillosis, spanning 9 years, from St. Jude's Children's Cancer Research Hospital. Eighteen patients had surgical intervention, (16 thoracotomies [89%] and 2 thoracoscopies). Fourteen had one operation; 4 patients had two. Surgical resection of the affected parenchyma significantly improved survival ($P < 0.001$). The four survivors had disease amenable to wedge resection, the longest interval at the time of report being 43.5 months. When feasible, a surgical approach should be strongly considered, because, left untreated, invasive pulmonary aspergillosis is almost always fatal.

### SOFT TISSUE INFECTIONS

Necrotizing soft tissue infections are rapidly progressive and carry a significant mortality and morbidity without prompt surgical intervention. Neutropenia makes the clinical picture even more challenging. As opposed to the otherwise healthy child, who typically has a solitary organism after a traumatic event, immunocompromised patients may have enteric translocation of gram-negative organisms. Extreme pain (often out of proportion to physical findings), fever, and tachycardia are the hallmarks of soft tissue infection. Johnston and colleagues[42] presented a retrospective series over an 11-year period, where seven neutropenic patients with deep soft tissue infections were identified. The median number of days postinitiation of chemotherapy was 14, pain was present in all patients, and 86% had fever and tachycardia. The pathogenic organism was from the gastrointestinal tract in four of seven patients. Five patients survived and were treated with urgent surgical debridement, intravenous antibiotics, GCSF, and hyperbaric oxygen. Butterworth and associates[43] reported an 11-year retrospective series of 19 patients with necrotizing soft tissue infections in healthy and immunocompromised children. An interesting finding in this series was that the immunocompromised patients were less likely to have severe tenderness and more likely to have polymicrobial perineal/buttock infections. When diagnostic uncertainty exists, judicious use of magnetic resonance imaging (MRI) may prove beneficial if tolerated by the patient's clinical status.

#### Post-transplantation Malignancies

As survival increases post-HSCT, attention has become directed toward late effects, including post-tranplant malignancies (PTMs). New malignancies post-HSCT fall into three broad categories: post-tranplant lymphoproliferative disorders (PTLD), hematologic malignancies (primarily treatment-related myelodysplastic syndrome and acute myeloid leukemia [MDS/AML]) and solid tumors. Baker and co-workers,[44] from the University of Minnesota, reported 147 PTMs in 137 pediatric and adult patients of 3,372 patients post–stem cell transplantation. The majority of PTMs were PTLD (44), with MDS/AML in 36 patients. Sixty-two solid tumors were reported in 57 patients. A significant finding was the risk of solid tumor malignancy continues to increase with each successive year of follow-up. The cumulative incidence of developing a solid tumor did not plateau and was 3.8% (95% confidence interval [CI], 2.2 to 5.4) at 20 years post-HSCT. The most common solid tumors reported were 11 basal cell and 8 squamous cell carcinomas of the skin, 4 breast, 5 carcinoma in situ, 8 melanoma, and 4 soft tissue sarcomas. Age greater than or equal to 20 years at the time of HSCT was the only significant predictor for development of a solid tumor (relative risk [RR] 2.0; 95% CI, 1.1 to 3.5; $P = 0.03$).[44] Forty-two percent of patients died from their post-transplantation solid tumor. Future efforts at long-term surveillance are warranted.

## Conclusion

HSCT has evolved into a well-established clinical modality with increasing utility for multiple malignant and nonmalignant disease processes in children. Pediatric general surgeons are integral members of the multidisciplinary team required for HSCT because of the multitude of organ systems involved.

Pulmonary, gastrointestinal, hepatic, genitourinary, and soft tissues are all subject to surgical complications. Vascular access will continue to be required for medications, apheresis, and transfusions. Pediatric surgeons must have knowledge of the HSCT process and the surgical complications during all phases of transplantation, including long-term survivors, in order to provide expert advice for treatment and to contribute to the understanding of this rapidly expanding field.

*The complete reference list is available online at www.expertconsult.com.*

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# HEAD AND NECK

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CHAPTER 53

# Craniofacial Anomalies

Jason J. Hall and H. Peter Lorenz

In 1967, Dr. Paul Tessier presented his modifications of Gilles' previously little known and underutilized techniques to correct congenital or post-traumatic bony anomalies to the International Society of Plastic Surgeons in Rome. Over the next 30 years, his teachings formed the basis of a new subspecialty of plastic surgery—craniofacial surgery. Tessier developed precisely placed osteotomies, autologous nonvascularized bone and soft tissue grafts, and intracranial approaches to the facial skeleton. His techniques gave children and adults with previously "unfixable" craniofacial anomalies a chance for a more normal appearance. Currently, most major medical centers have a multidisciplinary team dedicated to the care of this special subset of patients. The craniofacial anomaly teams span many different specialties, which include plastic surgery, pediatric otolaryngology, pediatric neurosurgery, speech pathology, audiology, oral surgery, dentistry and orthodontics, social work, pediatrics, and genetics.

Fortunately, many of the anomalies discussed in this chapter are relatively rare, but for surgeons in a pediatric tertiary care center, these patients are seen as daily occurrences. This chapter is not meant as a definitive tome on the diagnosis and treatment of these disorders, but is meant to paint a picture of the spectrum of craniofacial anomalies with broad brushstrokes.

The first two sections discuss two of the more common skeletal anomalies treated by craniofacial surgeons: craniosynostosis and jaw anomalies that require orthognathic surgical correction. The final section deals with facial asymmetry and hypoplasia disorders that are rare and complex to treat.

## The Craniosynostoses

Craniosynostosis refers to the premature closure of one or more cranial sutures and encompasses a wide range of anatomic derangements. Isolated, premature fusion of a single suture causes a predictable cranial deformity that can typically be recognized without the need for radiologic imaging by an experienced practitioner. However, complex craniosynostosis, consisting of multiple suture fusions, can be difficult to diagnose without radiologic imaging. Despite the wide range of clinical presentation, treatment for craniosynostosis cases is similar to any other surgical problem in children: accurate diagnosis, appropriate treatment planning, proper timing of surgery with respect to current and future growth, and surgical technique that gives a predictable correction and minimizes adverse long-term sequelae.

### ETIOLOGY AND PATHOLOGIC ANATOMY

The infant skull undergoes a period of rapid expansion during the first year of life, which is driven by brain growth. Bone growth at patent cranial sutures causes calvarial expansion in a distinct morphologic pattern. Typically, suture fusion occurs from anterior to posterior and lateral to medial.[1] The metopic suture, which normally closes by 8 to 9 months of age, is the only suture to close completely during infancy; the remaining sutures do not completely fuse until adulthood. Most patients presenting with craniosynostosis have prenatal onset of suture fusion. However, in severe cases of syndromic craniosynostosis, progressive, multiple suture fusion can occur over the first 3 to 4 years of life.[2] In this situation, the calvarial deformity is typically not detected at birth except when quite severe. After a few months of rapid growth, the deformity typically becomes more apparent.

In 1851, Virchow published his landmark paper that laid the foundation for our understanding of craniofacial deformities associated with craniosynostosis. He described the growth pattern of the skull as being restricted in a plane perpendicular to the fused suture while being amplified in a plane parallel to the direction of the suture. This compensatory growth pattern causes predictable deformities in patients with single suture synostosis. The growth constriction, however, is not confined to the cranial vault, but also affects the cranial base to varying degrees. Moss proposed that the cranial base pathology was the inciting event, and that the calvarial fusion occurred as a secondary phenomenon.[3] However, cranial base anomalies are not corrected by calvarial vault surgery and are now not thought to be the inciting event.

Recent research has focused on the role of the dura and its influence on suture patency in the growing skull. A number of dural-related cytokines, such as heparin-binding factor, fibroblast growth factors (FGFs), bone morphogenic proteins (BMPs), transforming growth factor(s)-β (TGF(s)-β), and transcription factors Msx2 and TWIST, have a role in the regulation and coordination of suture patency.[4] A mutation of the *TWIST*

gene on chromosome 7p21 has been linked with Saethre-Chotzen syndrome.[5,4] FGF receptor mutations causing constitutive activation of the receptor occur in many of the human craniosynostosis syndromes, including Apert, Crouzon, Muenke, and Pfeiffer syndromes.[4] Interestingly, one mechanism of bony fusion across the suture occurring with the *FGF-R* mutation is the loss of Noggin expression in the involved suture mesenchyme. Noggin is a BMP-inhibitor that prevents bony fusion in the mesenchyme. When Noggin is not present, bone forms across the mesenchyme, and the suture fuses.[6] Most incidences of craniosynostosis are the result of sporadic genetic anomalies. Yet, a number of both autosomal dominant and autosomal recessive syndromes, whose most striking phenotype is the pattern of craniosynostosis, are known. Patients with a family history of craniosynostosis should thus be referred to a dedicated craniofacial team and be evaluated by a skilled geneticist, as new genetic mutations linked to the craniosynostosis syndromes are being discovered frequently.

The treatment for craniosynostosis is surgical calvarial vault remodeling, which is performed to avoid future adverse sequelae. Chief among these is the avoidance of intracranial hypertension, which has been linked to brain damage, optic nerve compression, and cognitive impairment.[7] Early surgical correction (between 3 to 6 months of age) has the advantages of prevention of elevated intracranial pressure and its attendant consequences, improved reossification of calvarial bone defects, and the need for a less extensive surgical correction. Correction at a more advanced age (6 to 9 months) is reported to have more stable long-term results and lower rates of reoperation. These factors are taken into account by the craniofacial surgeon and pediatric neurosurgeon during the treatment planning process.

**FIGURE 53-1** A lateral view of a patient with scaphocephaly resulting from sagittal synostosis. Note the frontal bossing, elongation along the anteroposterior (AP) axis, and prominent occiput, all of which are characteristic of this condition.

**FIGURE 53-2** A child with left unicoronal synostosis. Characteristic findings include ipsilateral fronto-orbital retrusion, prominent contralateral forehead bossing, and nasal root deviation toward the affected side. The C-shaped facial deformity is notable here.

## Common Patterns of Single Suture Craniosynostosis

The most common form of craniosynostosis is sagittal synostosis, with an incidence of approximately 2 per 10,000 live births. In concordance with Virchow's law, premature fusion of the sagittal suture leads to compensatory growth in the anteroposterior dimension, resulting in *scaphocephaly* (Fig. 53-1).

Unilateral coronal synostosis is less common, with an incidence of approximately 0.9 per 10,000 live births. The growth pattern in unicoronal synostosis is more complex, albeit leading to a stereotypical calvarial phenotype. Ipsilateral to the fused coronal suture, the supraorbital rim is flattened and recessed, and the forehead is flattened. As calvarial growth occurs, the contralateral forehead becomes bossed and the nasal bridge starts to twist, producing a C-shaped facial deformity (Fig. 53-2).

Premature fusion of the metopic suture results in constriction of growth in an axial plane centered on the caudal forehead. A palpable bony ridge is present in the midline of the forehead (described as a "keel-shaped forehead" or *trigonocephaly*). The forehead is narrow and pointed. The medial orbital rims are consequently closer to the midline, giving the appearance of hypotelorism. Bilateral lateral brow recession and temporal hollowing also occurs and exaggerates this appearance.

The least common form of single suture craniosynostosis affects the lambdoid suture. Common findings are posterior plagiocephaly, ipsilateral mastoid bossing, and both anterior and inferior ipsilateral ear displacement. A posterior skull base cant and contralateral forehead bossing occur in more advanced cases.

Multiple suture craniosynostoses are rare, and may present with a variety of skull-shaped deformities.

## Syndromic Craniosynostosis

Children born with craniofacial dysostosis syndromes require multiple staged procedures to correct their bony deformities during their childhood years and extending into early adulthood. These patients have a higher relapse rate because

multiple affected midface and skull base sutures are usually present. The syndromic craniosynostoses carry a greater risk of intracranial hypertension, as well.

Many of the craniofacial dysostosis syndromes are inherited in an autosomal dominant pattern and are the result of mutations in the *FGF*-receptor genes, which alter the signaling pathway. Although penetrance is complete in most syndromes, the expression of the mutation is highly variable. Examples of these include Crouzon, Apert, and Pfeiffer syndromes, the three most common craniofacial dysostosis syndromes, all of which have mutations in the *FGF*-receptor genes.

Crouzon syndrome is the most common syndromic craniofacial dysostosis, with an estimated incidence of 1 in 25,000 live births.[8] Crouzon syndrome is caused by a mutation in the *FGFR2* gene, causing increased receptor activation.[9] The syndrome is characterized by the triad of bicoronal craniosynostosis, exorbitism, and midface retrusion (Fig. 53-3). Exorbitism is the feature of this syndrome, which results in prominent globes. As such, ocular protection is a key feature the clinician must keep in mind when assessing these children. Exposure keratitis and conjunctivitis may prompt earlier surgical intervention to avoid permanent visual impairment.

Apert syndrome has an incidence of 1 per 160,000 live births and is also caused by an *FGFR2* mutation.[10] Unlike Crouzon syndrome, the genetic defect in Apert syndrome is a missense mutation, and the vast majority of Apert patients are the result of a sporadic mutation. The triad of bicoronal craniosynostosis, midface hypoplasia, and syndactyly of the hands and feet characterize Apert syndrome. The craniofacial findings include bicoronal suture fusion, a large anterior fontanelle, midface retrusion, and varying degrees of exorbitism.

**FIGURE 53-3** Brachycephaly, exorbitism, and midface retrusion, which are common findings in both Apert and Crouzon syndromes.

Neonatal respiratory distress from a narrowed nasal vault, sometimes severe enough to warrant tracheostomy, may occasionally occur.[11] A specialist in congenital hand anomalies typically addresses complex syndactyly of the hands and feet. Unlike Crouzon syndrome, mental retardation is common, and affects nearly 50% of children with Apert syndrome.

Other craniofacial dysostosis syndromes include Pfeiffer syndrome, Saethre-Chotzen syndrome, and Carpenter syndrome. These are much less common than either Crouzon or Apert syndrome and share varying degrees of craniosynostosis, midface retrusion, digital anomalies, and mental retardation. Management priorities in these children are similar to that of children with either of the previously mentioned syndromes.

## DIAGNOSIS

A thorough history and physical examination is the cornerstone of diagnosing synostosis of the calvarial sutures. Single suture fusion results in the characteristic patterns of calvarial morphology described previously and are readily diagnosed by physical examination.

Measurement of head circumference with plotting on a standard growth curve gives an indication of head growth relative to the child's body. Physical examination should accurately define asymmetries in the infant skull. Head shape should be assessed from anterior, posterior, and top-down views to identify areas of relative bossing or recession. Ear position in both anterior-posterior and craniocaudal planes should be examined. Lateral examination of the forehead and face will identify forehead bossing and the position of the midface and orbits. Facial examination is especially important in identifying children with the craniofacial syndromes that have midface retrusion as part of their phenotype. Stigmata of intracranial hypertension should be investigated. For infants, these include a history of irritability, "burrowing" behavior, or repetitive head slapping.

Since the advent in the early 1990s of the American Academy of Pediatrics "Back to Sleep" campaign, designed to decrease the incidence of sudden infant death syndrome (SIDS), a sharp increase in the incidence of *positional plagiocephaly* has occurred. Positional plagiocephaly is the deformation of the calvarium despite the presence of widely patent cranial sutures. This condition may be difficult to differentiate from unilateral coronal or lambdoid craniosynostosis, which both result in forms of plagiocephaly. Usually, an experienced craniofacial surgeon can make the correct diagnosis based on physical examination findings alone. However, sometimes computed tomography (CT) imaging is needed. The correct diagnosis is critical, however, because children with positional plagiocephaly are treated with changes in sleeping position or, in more severe cases, a custom orthotic molding helmet.

Children who are suspected of having craniosynostosis should be referred to a craniofacial team for evaluation. This evaluation includes detailed cranial measurements and a thorough physical examination. CT scanning is rarely needed for diagnosis, but is obtained by many craniofacial surgeons prior to calvarial vault remodeling to assess for intracranial abnormalities. Given the additional cost, risks of sedation, and potential harmful effects of ionizing radiation on the growing child, radiologic imaging should be undertaken on a case-by-case basis as determined by the craniofacial surgeon.[12]

In addition to findings of suture fusion, stigmata of intracranial hypertension, such as a "moth-eaten" appearance of the calvarium on CT images or a "copper-beaten" appearance on plain radiographs will be seen. Papilledema may be seen on fundoscopic examination and is an indication for urgent cranial vault expansion.

### TREATMENT

The mainstay of treatment for premature fusion of cranial sutures is surgical cranial vault remodeling. The two goals of surgery are to release the involved suture through resection and reconstruction of the cranial vault to a more normal shape. Surgery is a combined procedure between a craniofacial plastic surgeon and a pediatric neurosurgeon. In general, the pediatric neurosurgeon performs the initial craniotomy, and the craniofacial surgeon performs the bony reshaping. However, the procedure is mainly "bone surgery" and not "brain surgery." Cranial vault remodeling is accomplished by removing the abnormally shaped calvarial bones and recontouring them. The plasticity of the infant calvarium is utilized as the bones are bent and shaped to a more anatomic contour. Barrel stave osteotomies are commonly performed to expand the cranial vault. Wedge osteotomies are done to reduce the vault in areas of bony excess or bossing. Except in cases of isolated sagittal or lambdoid synostosis, the orbits are deformed, which necessitates advancement of the supraorbital rim in addition to reshaping of the forehead and anterior cranial vault. Bones are fixed into their new position with resorbable hardware consisting of polyglactic/polyglycolic acid plates and screws. This type of hardware undergoes degradation over the course of a year, and is not prone to intracranial migration, which can occur with traditional titanium hardware. After initial reconstruction in infants, bony defects remain after surgery. The unique osteogenic potential of the dura and overlying periosteum in infants results in primary bone formation and complete healing of these large bone defects. Bone defects that remain after 2 years of age typically require secondary bone grafting. Endoscopic techniques have been described for correction of both sagittal and coronal synostosis.[13,14] Although resection of the involved suture is performed, these techniques rely on a long period of postoperative molding helmet therapy to achieve final head shape. Despite their reported benefit of reduced blood loss and transfusion requirements, endoscopic techniques have not gained wide acceptance, primarily due to their poor head shape outcomes.

Timing of surgery is somewhat controversial among craniofacial surgeons. Some surgeons advocate "early" correction at 3 to 6 months of age, believing that the rapidly growing brain will assist in remodeling the skull if the fused suture is released and the calvarium reshaped. This theoretically reduces the amount of correction that needs to be performed in the operating room. Delaying surgery until 9 to 12 months of age allows the infant skull growth to begin to plateau prior to surgery. Although this reduces the amount of intrinsic bone shape normalization resulting from brain growth, the thicker calvarial bone may provide a more stable skeletal correction with less relapse. In reality, a large window exists when the surgery can be performed with acceptable risks and outcomes. Children who present late for corrective surgery present unique challenges to the craniofacial surgeon. Bone in these children is typically thicker and more difficult to contour with bone-bending forceps and simple barrel stave osteotomies. The asymmetric skull base is more developed and resistant to normalization, which increases the chances of a permanent deformity. Also, the diploic space between the inner and outer table has begun to form, subjecting the child to increased blood loss during surgical exposure and bony resection. The entire reconstructive procedure is more extensive, as even subcentimeter bone defects must be grafted in order to heal. Extracranial bone grafts (rib and/or iliac) are needed when the diploic space has not yet formed (before 5 years of age).

In children with syndromic craniosynostosis and midface retrusion, further reconstruction is frequently needed. A midface advancement consisting of either a Le Fort III or a monobloc osteotomy is performed between the ages of 5 and 8 years, unless the need for ocular protection forces earlier correction. The choice between procedures depends on forehead projection—a subcranial Le Fort III is performed if forehead projection is adequate, whereas a monobloc frontofacial advancement is needed if forehead retrusion has occurred. At the age of skeletal maturity (typically between the ages of 14 and 16), a Le Fort I maxillary osteotomy, with or without mandibular osteotomies, is usually needed to formally correct any malocclusion that commonly exists in these patients.

## Orthognathic Surgery

The term *orthognathic* is derived from the Greek "orthos," meaning to straighten, and "gnathos" meaning jaw. Orthognathic surgery is a discipline that crosses the boundaries of many different specialties, principally oral and maxillofacial surgery and craniofacial surgery (a distinct subspecialty of plastic surgery). Orthognathic surgery repositions the dentofacial skeleton to correct either congenital or acquired malocclusions and restore a harmonious balance to the underlying bony facial form. These movements can involve both the maxilla and the mandible, either in segments or in conjunction with varying portions of the craniofacial skeleton. Certain procedures mandate the assistance of a pediatric neurosurgeon, because they require intracranial osteotomies to fully mobilize the bony segments for repositioning. An orthodontist who is familiar with the necessary dental movements is also needed to prepare a patient for surgery. The orthodontist also "fine-tunes" the dental occlusal relationships postoperatively, which is imperative for a successful outcome.

Although secondary trauma can lead to orthognathic surgery, the field predominantly addresses congenital and developmental deformities leading to malocclusion that cannot be corrected orthodontically. Nearly 25% of all patients who have undergone correction of a cleft lip and palate will develop severe maxillary hypoplasia that warrants surgical correction. Whether this is due to an intrinsic growth disturbance or restriction of growth of the midface due to postcleft surgical scarring is a hotly debated topic among craniofacial surgeons.

The age at which orthognathic procedures are performed is an important consideration in planning subsequent surgeries. Any skeletal facial advancement procedure performed prior to the age of bony maturity carries a significant rate of relapse as the remainder of the face grows; merely advancing the hypoplastic segments will not "unlock" their growth potential. For this reason, definitive orthognathic procedures are carried out

in mid- to late adolescence, once the majority of facial skeletal growth is complete. Thus orthognathic surgery is usually done between 14 and 16 years for girls and 15 and 17 years for boys. Epiphyseal closure on anteroposterior hand radiographs is a good indicator of overall skeletal maturity.

Preoperative evaluation of patients with congenital dentofacial deformities usually occurs in the setting of a cleft/craniofacial team visit. An orthodontist is present for discussion of treatment options and will be intimately involved in both the preoperative and postoperative care of these patients. The patient's occlusion is determined according to the Angle classification, with class 1 being a "normal" occlusal relationship, class 2 as the typical "overbite," and class 3 being an "underbite." The facial profile and aesthetics are analyzed with special attention paid to the soft tissue bony landmarks. A lateral cephalometric radiograph, which is a standardized view with the head aligned in the neutral position, is used for treatment planning. The positions of the maxilla and mandible are determined with respect to the cranial base. Dental models are cast and mounted on an articulator in their anatomic relationship. Model surgery is performed wherein the models are precisely moved to place the teeth in proper planned postoperative occlusion. An acrylic splint is made from the models after each jaw is repositioned, which will be wired into place in the operating room to assure the bony segments are in proper position. This splint can be a final interdental splint for wear postoperatively.

In 1901, René Le Fort, a French surgeon and anatomist, carried out a series of rather grotesque experiments and defined a classification system for facial fractures that bears his name.[15,16] These "fault lines" of the facial bony skeleton were then subsequently adapted for use in elective orthognathic surgery and have become the mainstay of therapy to correct midfacial skeletal anomalies. The most common is the *Le Fort I osteotomy*, which repositions the tooth-bearing segment of the maxilla in either the anteroposterior or craniocaudal planes, or both. This osteotomy can be modified to divide the maxilla into two or three tooth-bearing segments, which can be moved independently to provide a functional, Angle class 1 occlusion and correct both sagittal and transverse maxillary deficiency. The Le Fort I osteotomy is used to correct cleft lip and palate-related maxillary hypoplasia. It is also used to correct vertical maxillary excess or rotational abnormalities of the maxilla.

Another commonly used corrective procedure in craniofacial surgery is the *bilateral sagittal split osteotomy* (BSSO). In this technically demanding procedure, the mandible is split in the sagittal plane from midramus to proximal body, sparing the inferior alveolar nerve on both sides. The BSSO movements can be adjusted to correct mandibular asymmetry, level the occlusal plane, or correct overall facial disharmony caused by overgrowth or undergrowth of the mandible. The BSSO is often combined with the Le Fort I osteotomy to correct larger mandibular–maxillary discrepancies. *Genioplasty* refers to reduction, advancement, or lateral movements of the bony chin point. It is generally considered a purely aesthetic procedure that can be added to enhance the facial skeletal balance.

Although not usually considered an orthognathic procedure, but rather a "craniofacial" procedure, the *Le Fort III osteotomy* is performed to reposition the midface (maxilla and zygomas) relative to the cranial base. In this procedure, osteotomies are created across the ascending portion of the zygoma, the zygomatic arch, orbital floor and both medial and lateral walls, frontonasal junction, and pterygomaxillary junction. The nasal septum is divided in the coronal plane. This allows for complete separation of the facial skeleton from the cranial base and subsequent advancement of the Le Fort III segment to correct midface hypoplasia. The Le Fort III advancement is used to correct severe malocclusion or upper airway obstruction from overall midface growth restriction. The majority of patients who undergo a Le Fort III osteotomy have a named syndrome (Crouzon, Apert, and Pfeiffer being the most common), and have their first midface advancement at age 5 or 6 years. Because the growth of the midface is not complete until mid- to late adolescence, a second advancement is frequently necessary. When midface retrusion is accompanied by growth restriction of the supraorbital rim and forehead, a *monobloc frontofacial advancement* may be necessary. This is an intracranial and extracranial procedure and requires both a pediatric neurosurgeon and a craniofacial surgeon for intracranial access. A monobloc advancement is similar to a Le Fort III osteotomy, except that the supraorbital rim and forehead are advanced along with the midface. This procedure has fallen out of favor because of infectious complications arising from difficulty obtaining adequate separation of the intracranial space and nasal cavities.[17] Thus the monobloc is now usually performed as a staged procedure (fronto-orbital advancement, followed by a Le Fort III osteotomy a few months later) or is performed with the use of distraction osteogenesis to allow the soft tissues to grow along with bony skeletal expansion, which minimizes the risk of intracranial infectious complications.

*Distraction osteogenesis* was pioneered by Ilizarov (a Russian orthopedist) in 1958, and adapted for use in the mandible by McCarthy in 1992.[18,19] It is now commonly used for a number of applications in craniofacial surgery. The principle behind distraction osteogenesis is that gradual expansion of the bony skeletal gap left by a surgically placed osteotomy will allow lengthening of the bone by gradual osteoblastic activity and ingrowth of new bone. This results in lengthening of the skeleton in the direction of the vector of expansion. Distraction is useful in situations that would require extensive bone grafting to obtain adequate bone length, or in cases in which opposing soft tissue forces would result in skeletal relapse if the bone was rapidly advanced and grafted. Clinically, maxillary distraction is most commonly applied when a large discrepancy exists between the maxilla and mandible as a result of a complete cleft lip and palate and resultant maxillary hypoplasia. Scarring from the numerous previous procedures makes maxillary advancement alone prone to relapse; by applying the principle of distraction, the bone and soft tissue are gradually expanded, and the cleft maxilla can be advanced into a normal occlusal relationship (Angle class 1) with minimal chances of relapse resulting from soft tissue resistance. Distraction is also useful to correct severe mandibular hypoplasia accompanying conditions such as hemifacial microsomia or Pierre Robin sequence, which will be discussed in subsequent sections of this chapter.

## Craniofacial Clefts

Dr. Paul Tessier, the father of the field of craniofacial surgery, also developed a classification system for craniofacial clefts that is arguably the most widely used of those available today.

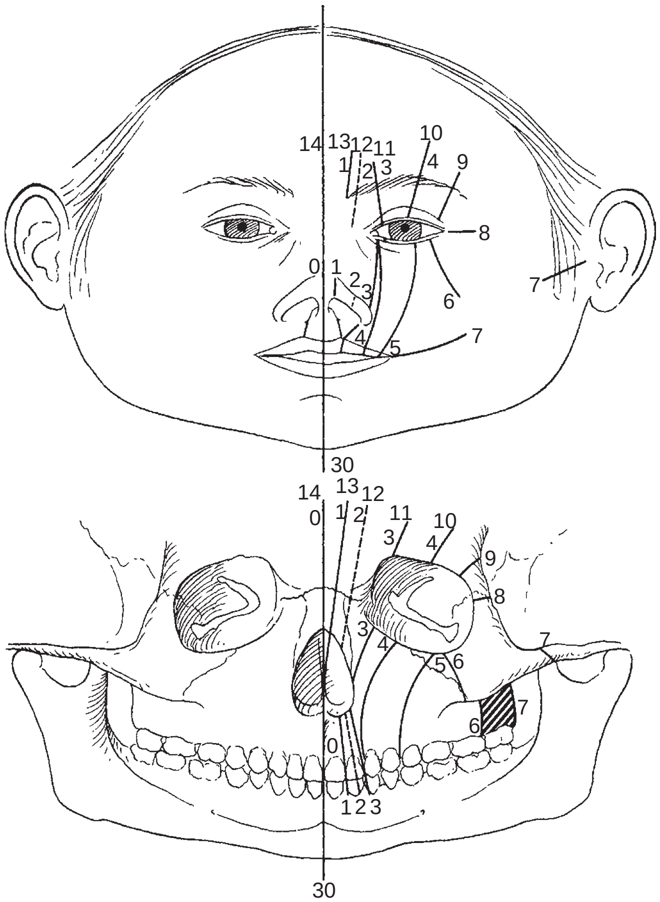


**FIGURE 53-4** Tessier's pre-computed tomography classification system of rare craniofacial clefts. The lower image represents the cleft location of the bony skeleton, while the upper illustrates the cutaneous manifestations of the various bony clefts.

The Tessier system is based on specific anatomic derangements that fall along embryonic lines of fusion within the face (although these were not known at the time they were initially described) (Fig. 53-4). Tessier's classification system is notated 0 to 14, with clefts 0 to 7 describing facial clefts and clefts 8 to 14 describing cranial vault clefts. Each cleft has unique soft tissue and bone lines of clefting. Also, the facial and cranial clefts coincide such that the sum of the two components is 14 (i.e., 0 and 14 clefts coincide, as do 3/11 and 5/9, etc.). A thorough search along the meridian of the cleft will usually elucidate subtle (or not-so-subtle) findings.

The majority of craniofacial clefts are rare and will be seen infrequently during an individual surgeon's career. As such, the remainder of this section of the chapter will be spent dealing with those more common Tessier clefts.

## CLEFT NUMBER 7

A number 7 cleft can be protean in physical manifestation and is known by a number of different names. Hemifacial microsomia, oculoauriculovertebral syndrome (OAV), first and second branchial arch syndrome, and otomandibular dysostosis syndrome all refer to the physical findings associated with a number 7 cleft. The number 7 cleft is thought to have an incidence of between 1 in 3000 and 1 in 5642[20] live births. A number 7 cleft is usually unilateral, but approximately

**FIGURE 53-5** A child with a typical Tessier number 7 soft tissue cleft.

10% of affected children will have symmetric, bilateral involvement.[21]

The derivatives of the first and second branchial arch are abnormal, albeit to varying degrees. Macrostomia is a common finding, with the commissure of the lip being displaced laterally toward the affected side, resulting in an enlarged oral opening (Fig. 53-5). Preauricular "ear tags," embryologic remnants of the developing ear, are present anterior to the external auditory canal and contain small "stalks" of cartilage remnants (Fig. 53-6). The external ear can likewise be affected and can range from mild hypoplasia to near complete absence. A conductive hearing loss on the ipsilateral side is commonplace. The mandible is commonly affected, and the defect of the ascending ramus and condyle may range from mild hypoplasia to complete absence (Fig. 53-7). The facial nerve may be affected to varying degrees, as well, which in turn contributes

**FIGURE 53-6** Multiple accessory external ear tags as seen in Tessier 7 clefts.

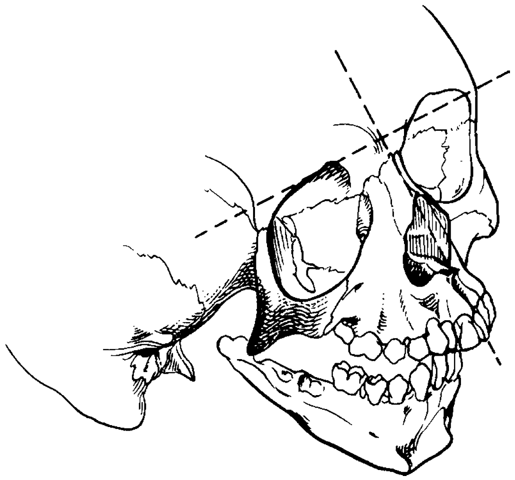

FIGURE 53-7 Skeletal findings in hemifacial microsomia. Note the absence of the ascending ramus and condyle of the mandible.

to weakness and underdevelopment of the muscles of facial expression that they supply.

Given that the manifestations of the number 7 cleft vary, so do the treatment options. In general, more severely affected children require earlier and more significant reconstruction. Cutaneous manifestations—macrostomia and branchial arch remnants—are usually treated with excision and local flap reconstruction during infancy. Underlying bony anomalies are treated based on severity. Children with mild hypoplasia of the ramus and condyle are followed throughout growth, and will usually develop an occlusal cant (Fig. 53-8) as they age. These children can be treated with orthognathic surgery after cessation of skeletal growth to reposition the hypoplastic mandible and maxilla with the combination of a Le Fort 1 osteotomy, bilateral sagittal split osteotomies, and an osseous genioplasty to align the chin point. Those with more severely hypoplastic rami will undergo distraction osteogenesis of the ramus during childhood, but will usually need formal orthognathic correction during late adolescence.[22] Children who are born with complete absence of an ascending ramus need an extensive reconstruction to achieve normal function of their mandible and a normal occlusal relationship. This is typically accomplished through the use of a free costochondral rib graft, which is performed around 7 years of age. Ear reconstruction with costal cartilage is performed at the same age, when necessary.

## TREACHER COLLINS SYNDROME

First described in 1847,[23] Treacher Collins syndrome (or mandibulofacial dysostosis) is a relatively common syndrome made up of Tessier clefts 6, 7, and 8. Its incidence is estimated at 1 in 10,000 live births. Treacher Collins is caused by a mutation on chromosome 5q31.3-33.3 (the *TCOF1* gene) and is an autosomal dominant disorder with variable penetrance.

Treacher Collins patients manifest bilateral anomalies of the eyelids, zygomas, maxilla, mandible, and ears (Fig. 53-9). There is typically an antimongoloid slant to the palpebral fissures, with lower lid notching present. Eyelashes are often absent on the medial two thirds of the lower eyelid. The zygomas are severely hypoplastic or absent. The maxilla is hypoplastic with a shortened vertical height, which can impede or block nasal airflow. Shortening of both the length and height of the mandible results in narrowing of the posterior pharyngeal airway and can contribute to upper airway obstruction in these children, which in the past necessitated placement of a tracheostomy. Within the past 20 years, however, distraction osteogenesis has been applied to these patients to relieve early upper airway obstruction and avoid the need for long-term tracheostomy dependence. Severe microtia is often accompanied by atresia of the middle and inner ear; placement of bone-anchored hearing aids (BAHA) is commonly necessary to allow for improved hearing and speech development. As is the case with either isolated or syndromic microtia, reconstruction of the external ears is usually undertaken at age 7 or 8 with autologous costal cartilage grafts. At around this same time, onlay bone grafting of the maxilla and zygoma is performed to add projection and give a more normal midfacial profile. Correction of the eyelid notching with local tissue transfers is also performed at this age should it not be needed earlier because of corneal protection issues. Definitive orthognathic surgical correction of the associated deformities of the occlusal plane is performed in late adolescence.

FIGURE 53-8 A child with hemifacial microsomia and an occlusal cant. Note the upward slant of the mandible caused by right-sided ramus hypoplasia.

FIGURE 53-9 Typical findings in a patient with Treacher Collins syndrome. Down-slanting palpebral fissures, malar hypoplasia, and microtia are common hallmarks of this syndrome. This child lacks true colobomas of the lower eyelid but has loss of lower eyelid support and excess scleral show.

### Acknowledgments

Special thanks to Henry K. Kawamoto, Jr., DDS, MD, for Figures 53-4 and 53-7.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 54

# Understanding and Caring for Children with Cleft Lip and Palate

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## Epidemiology

The incidence of orofacial clefting varies among racial backgrounds. Because of the close association between cleft lip and palate, the presence of cleft lip is often described as being with or without cleft palate. Worldwide prevalence of cleft lip and palate is 1 per 700 live births.[1] People of African descent have the lowest incidence of cleft lip with/without cleft palate at 0.5 per 1000 live births, followed by whites (1 per 1000 live births), and Asians (1.3 per 1000 per live births). Overall, an isolated cleft lip makes up approximately 21% of all patients with cleft lip and palate. Unilateral clefts are roughly 9 times more prevalent than bilateral cleft lips, and males are more affected than females. The U.S. incidence of cleft palate alone ranges from 0.3 to 0.5 per 1000 live births.[2] A child with a cleft lip with or without cleft palate has an approximately 30% chance of having an associated syndrome; interestingly, a child with an isolated cleft palate has a 50% incidence of an associated syndrome.[2,3] Because of this association, genetic workup and counseling is mandatory, as is heightened suspicion for other physical and physiologic anomalies.

## Etiology

Genetic and environmental factors have both been associated with clefting. If other family members are affected by a cleft, offspring have an increased chance of being affected. For example, if a family already has a child with a cleft, or one parent has a cleft, the chance that the next child will have a cleft is 4%; with two affected children, the chance that a third child will have a cleft increases to 9%. The probability increases to 17% in a family if both a child and parent have a cleft.[4] This increase in frequency is seen in spontaneous clefting not associated with syndromes. There are some syndromes in which clefting can be passed down in an autosomal dominant fashion, such as van der Woude syndrome, where presence of the cleft palate is an autosomal dominant trait.

Environmental causes of clefting include the use of anticonvulsants, including phenytoin, which is associated with 10-fold increase in clefting; maternal smoking increases the incidence twofold. Other environmental influences, such as alcohol use, the use of retinoic acid, and dietary causes, including zinc and folate deficiencies, can cause syndromes with clefting; however, these are not directly linked to isolated cleft lip/palate. People with certain genotypes are more susceptible to certain environmental exposures; hence, women with less efficient methyl tetrahydrofolate reductase enzymes are more prone to clefting in the face of folic acid deficiency.[5–12]

## Embryology

Basic understanding of midface and palatal embryologic development helps elucidate the pathoanatomy of cleft lip with or without palate. Orofacial clefting occurs when there is failure of fusion of maxillofacial structures migrating from lateral to medial during the initial 4 to 10 weeks of embryonic development. A key anterior–posterior embryologic and anatomic landmark in understanding clefts is the incisive foramen. The structures that form anterior to the foramen ultimately develop into the nose, lip, and alveolus; embryologically, these structures form first and are designated as the primary palate. The structures that form posterior to the foramen become the hard palate and soft palate, and are referred to as the secondary palate, because they fuse secondarily. Clefting of the lip (primary palate) occurs when the nasomedial and nasolateral prominences of the frontonasal prominence do not meet with the maxillary prominence (Fig. 54-1, *A*). Clefting of the palate (secondary palate) occurs when the lateral palatine shelves do not elevate and fuse at the midline to each other or to the primary palate (Fig. 54-1, *B*). Because the development of this craniofacial area is complex, deformities can occur at multiple points along the embryologic time line, resulting in a full spectrum or combination of anomalies.

## Anatomy

### UNILATERAL CLEFT LIP

A cleft lip affects the anatomy of the lip, philtrum, nose, as well as the alveolus, depending on the severity of the defect. Microform clefts are the mildest form of clefting, involving

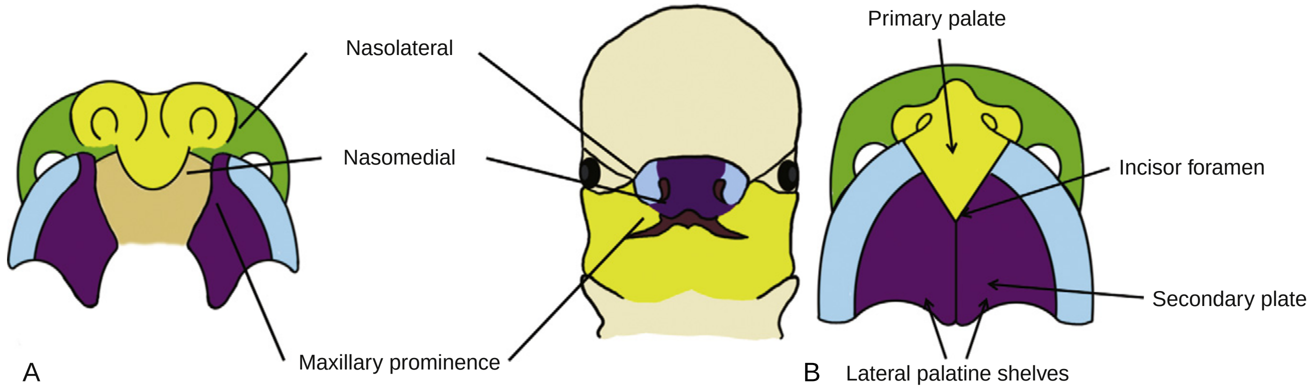


**FIGURE 54-1** **A,** The nasolateral and nasomedial prominence fuse to make the lip and nose. Lack of fusion between the maxillary nasal prominence with the nasomedial prominence will yield a cleft lip. **B,** The lateral palatine shelves fuse in the midline, thus forming the secondary palate. The primary palate fuses posteriorly with the palatine shelves to form a complete palate.

the vermillion and white roll, and can be quite subtle (Fig. 54-2, *A*). Incomplete clefts are associated with absence of skin, mucosa, and orbicularis muscle but have a retained webbing of skin across the floor of the nasal aperture, referred to as a Simonart band (Fig. 54-2, *B*). A complete unilateral cleft involves the alveolus, and can be associated with a cleft of the palate (Fig. 54-2, *C*).

The most obvious deformity involving a cleft lip is discontinuity of the lip itself. However further analysis of the defect demonstrates deviation of the nasal septum and columella, as well as widening or flattening of the cleft-side nasal cartilage. Other defects include the lack of nasal floor and discontinuity of the lip, muscle, and the alveolar ridge. Successful surgical correction of the lip must address all of these structures.

## BILATERAL CLEFT LIP

Bilateral clefts have a two-sided discontinuity of the lip, with a central portion, the premaxilla, which is discontinuous from either of the lateral segments. The premaxilla contains


**FIGURE 54-2** **A,** Microform cleft can be seen with mild notching of the lip's vermilion along with the minimal distortion of the nose. **B,** Incomplete cleft has some webbing across the cleft with some retention of the lateral nose; however, the skin across the cleft is devoid of orbicularis oris muscle and is functionless. This skin is also called a Simonart band. **C,** Complete cleft lip has lateralization of the lip and lateral nasal element. Notice the deviation of the nasal columella and philtrum away from the cleft, and the flattened nose on the cleft side. This picture also demonstrates the clefting of the palate, which allows an unobstructed view into the nasal airway.

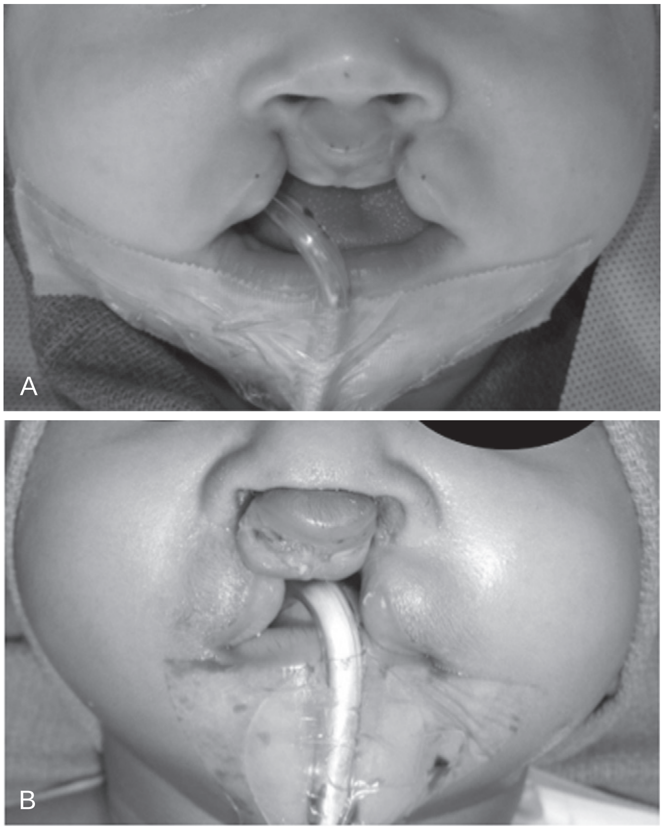


**FIGURE 54-3** **A,** Bilateral cleft lip with a Simonart band transversing both clefts. **B,** Complete bilateral cleft lip. The midline protuberance is called the premaxilla and is much more protruding than an incomplete bilateral cleft; tethering of the Simonart bands help in keeping the premaxilla in a more anatomic position. Absence, or shortening of the columella, widening of the alar bases, and anterior projection of the premaxilla are all trademarks of bilateral cleft lips.

elements of skin, mucosa and bone, which can be asymmetrically deviated to one side or the other, and can be anteriorly positioned, depending on the severity of the deformity. Bilateral clefts can be incomplete with Simonart bands (Fig. 54-3, *A*), or complete with defects that proceed through the alveolar ridges (Fig. 54-3, *B*). A central feature of the bilateral cleft lip deformity is depression of the nasal tip, a shortened columella, and widely splayed alae.

## CLEFT PALATE

Clefts of the palate can exist with clefts of the lip or may be present alone. Anatomically, the hard palate begins immediately posterior to the incisive foramen, with embryologic fusion of the palate from anterior to posterior. Hence, an isolated cleft of the soft palate may exist; however, an isolated cleft of the hard palate cannot. A complete cleft of the secondary palate includes both the hard and soft palate, extending anteriorly from the incisive foramen to the uvula, and this can be bilateral as well (Fig. 54-4). The primary function of the palate is to separate the oral cavity from the nasal cavity. This function is lost in the presence of a cleft. The function of the soft palate is primarily speech related and dependent on five paired muscles, the two most important of which are the levator veli palatini and the tensor veli palatini. Ordinarily, these muscles form a transverse sling enabling the palate to rise and move posteriorly to close the oropharynx from the nasopharynx. In a cleft palate, these muscles abnormally insert onto the posterior shelf of the hard palate, and as a consequence, the palate is deficient in its ability to seal off the oropharynx from the nasopharynx.

A submucous cleft is the most minor expression of the clefting spectrum. The soft palate mucosa is actually intact, but split posteriorly, resulting in a bifid uvula; there is a midline lucency in the soft palate, referred to as a zona pellucidum, which is a muscle diastasis, and a notch at the midline, posterior edge of the hard palate.[13] As in a full cleft, the levator and tensor veli palatine abnormally insert onto the posterior hard palate, preventing the soft palate from moving appropriately during speech, potentially leading to nasal sounding speech. The incidence of submucous clefts is roughly 1 in 1,200 to 2,000; however, this is likely an underestimation, because many patients may not seek treatment or even know of their submucous cleft unless there is functional speech deficit.[14]

# Treatment Protocols

The timing for cleft lip repair in the United States is generally between 3 to 6 months of age. Depending on the severity of the deformity, various forms of presurgical orthopedics can be used to prepare the child for lip surgery. In general, the goals of these techniques are to improve the alignment of the alveolar segments, decrease the size of the soft tissue cleft, and to

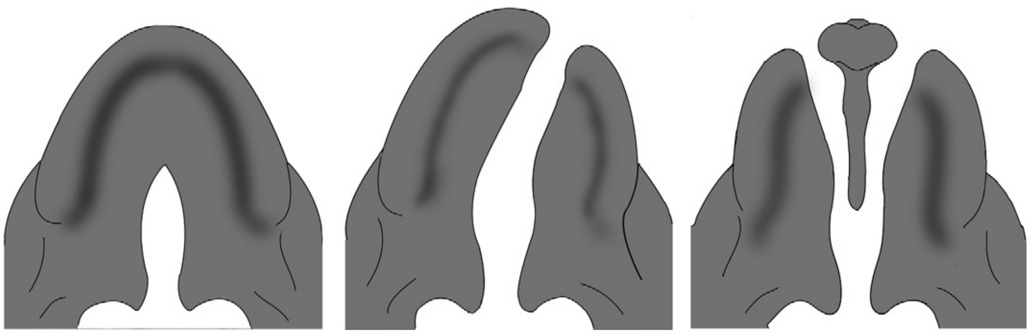

**FIGURE 54-4** The figure on the *left* depicts a cleft of the secondary palate only; there is an intact hard palate. The *middle* figure depicts a complete unilateral cleft. The figure on the *right* depicts a complete bilateral cleft.

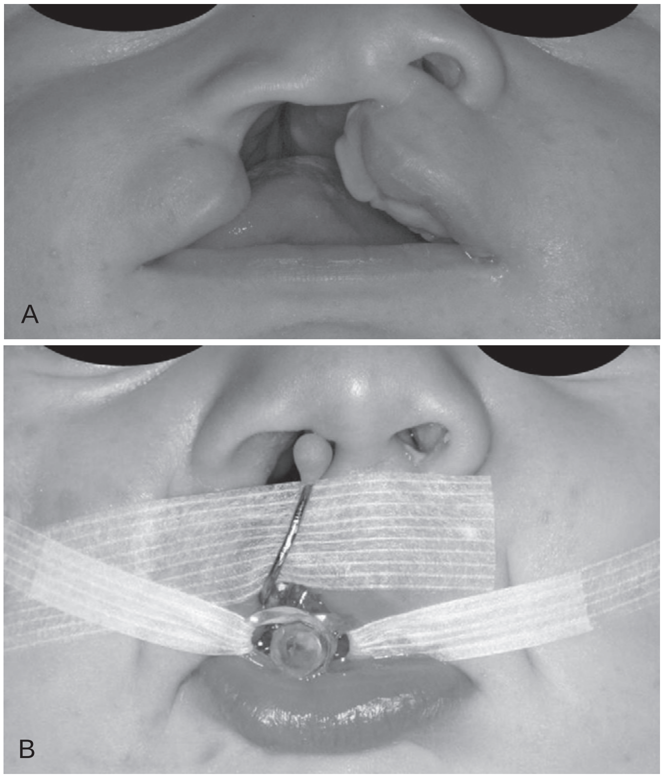


**FIGURE 54-5** **A,** A unilateral cleft lip prior to nasoalveolar molding (NAM) has a wide alveolar cleft, slumping of the nasal cartilage on the cleft side, and lateralization of the alar base of the cleft side. **B,** Nasoalveolar molding assists in realigning the alveolar segments, reshaping the slumping nasal cartilage of the cleft side, and medializing the alar base of the cleft side.

improve the symmetry of the nose. The simplest form is a taping regimen (literally from cheek to cheek) that helps to pull the two sides of the clefts together, with the goal of narrowing the cleft and realigning the tissues in an anterior-posterior dimension. Some centers also use a technique termed nasoalveolar molding (NAM) to address the three major components of the cleft deformity (Fig. 54-5). NAM addresses the slumping of the nasal alar cartilage, helps realign the alveolar ridges, and brings the soft tissue of the lips into closer proximity.[15,16]

## CLEFT LIP SURGICAL REPAIR

### Unilateral

There are multiple surgical techniques for cleft lip repair. A recent survey of U.S. cleft surgeons found three predominant surgical techniques for unilateral cleft lip repair: the Millard rotation-advancement technique (46%), the Millard rotation-advancement technique with modifications (38%), and triangular flap techniques (9%).[17] Techniques for bilateral cleft lip repair include variations of techniques introduced by Millard and by Mulliken.[18]

In a unilateral cleft lip, there is absence of central tissue of the lip and philtrum, as well as of the nasal columella, depending on the severity of the cleft. The overall goals of surgery are restoration of lip continuity, which starts with functional orbicularis oris muscle reapproximation, establishing symmetry of the lip (especially at the central cupid's bow) and nose, with aesthetic placement of scars in anatomic subunits. The rotation-advancement repair, as described by Dr. Ralph Millard


**FIGURE 54-6** Markings for the rotation-advancement lip repair (Millard lip repair).

in 1976, addresses all of these goals (Fig. 54-6). Because there is a paucity of tissue medial to the cleft, the downward *rotation* of the remaining philtrum helps to provide adequate tissue that matches the contralateral, noncleft side. *Advancement* of the lateral tissue reconstructs the affected philtrum, thus providing lip continuity. Medialization of the base of the nose, as well as further soft tissue dissection of the nose, results in a symmetric reconstruction. Reapproximation of the orbicularis oris muscle provides oral competence. Further soft tissue arrangement in the nasal floor allows final closure of the lip and nose. Surgical details are found in several references.[19–21] A potential shortcoming of the rotation-advancement technique is the inability to provide adequate philtral length despite aggressive downward rotation of this tissue. This may result in the high point of the cupid's bow on the cleft side being located in a position higher than on the noncleft side.

Some of the more commonly used modifications of the rotation-advancement technique are the Mohler repair, the Noordoff vermilion flap, and the triangular advancement flap, although the details of these techniques are beyond the scope of this chapter (see the referenced articles for more complete descriptions).[22–24]

Another technique for unilateral cleft lip repair is the triangular flap technique (also known as the Tennison repair), introduced by Charles Tennison in 1952. Tennison approached the lack of central soft tissue of the cleft in a very different fashion than Millard. In this technique lip length is achieved by designing a triangular flap of the lateral, cleft side, which then inserts into a cut of the medial, noncleft side, thus providing the extra tissue for appropriate lip height. The muscle is repaired, as in the rotation-advancement technique, followed by reconstruction of the floor of the nose (full surgical details are found in the references).[25,26] Shortcomings of the Tennison repair include placement of the scar in a nonanatomic location, thus drawing attention to the repair, as well as an overly long lip, depending on the size of the triangular flaps.

### Bilateral Cleft Lip Repair

Bilateral cleft lip repairs are especially challenging because of a central lack of soft tissue, and the anterior displacement of the premaxilla, which functionally increases the transverse width of cleft defect. Many surgeons use presurgical orthopedics to decrease premaxillary protrusion, thus increasing the columellar length and nasal tip projection. This technique also decreases the distance of the cleft, potentially making surgical repair easier for the surgeon (Fig. 54-7). The primary goals of surgery include lip and nasal symmetry, which is achieved through the creation of a philtral column, including the cupid's bow, reapproximation of the orbicularis oris, repositioning the nasal alar cartilages, lengthening the columella, and closure of the nasal floor (Fig. 54-8). The absence of the philtral column and cupid's bow is especially problematic since these structures are difficult to replicate in a repair. Postoperatively, these imperfections can be quite noticeable at conversational distances.[27] Realistically, patients with bilateral cleft lips will ultimately require revisional surgeries to correct the secondary stigmata of the repair, which include a shortened columella, blunted nasal tip, widened nasal ala, and a widened philtrum.

FIGURE 54-7 Nasoalveolar mold (presurgical orthopedics) for bilateral cleft lip, designed to align the alveolar segments, as well as realign the premaxilla into a more anatomic position.

## CLEFT PALATE SURGICAL REPAIR

Following surgical repair of the lip, repair of the palate is generally performed between 9 to 12 months of age. The choice of techniques for palate repair depends on the type of cleft. Recent surveys show that the most commonly used techniques are the Bardach two-flap palatoplasty (45%) (Fig. 54-9) and the Furlow palatoplasty (42%) (Fig. 54-10); the Veau-Ward-Kilner (VWK) pushback (Fig. 54-11) and the von Langenbeck (Fig. 54-12) techniques, although less common, are also used.[28] The common denominators for all of these techniques are repair in three layers (nasal mucosa, muscle layer of the soft palate, and the oral mucosa), and anatomic repositioning of the soft palate musculature. Bilateral cleft palate repair is similar in principle in that a three-layer repair is achieved (Fig. 54-13). See the references for complete descriptions of these techniques.[29]

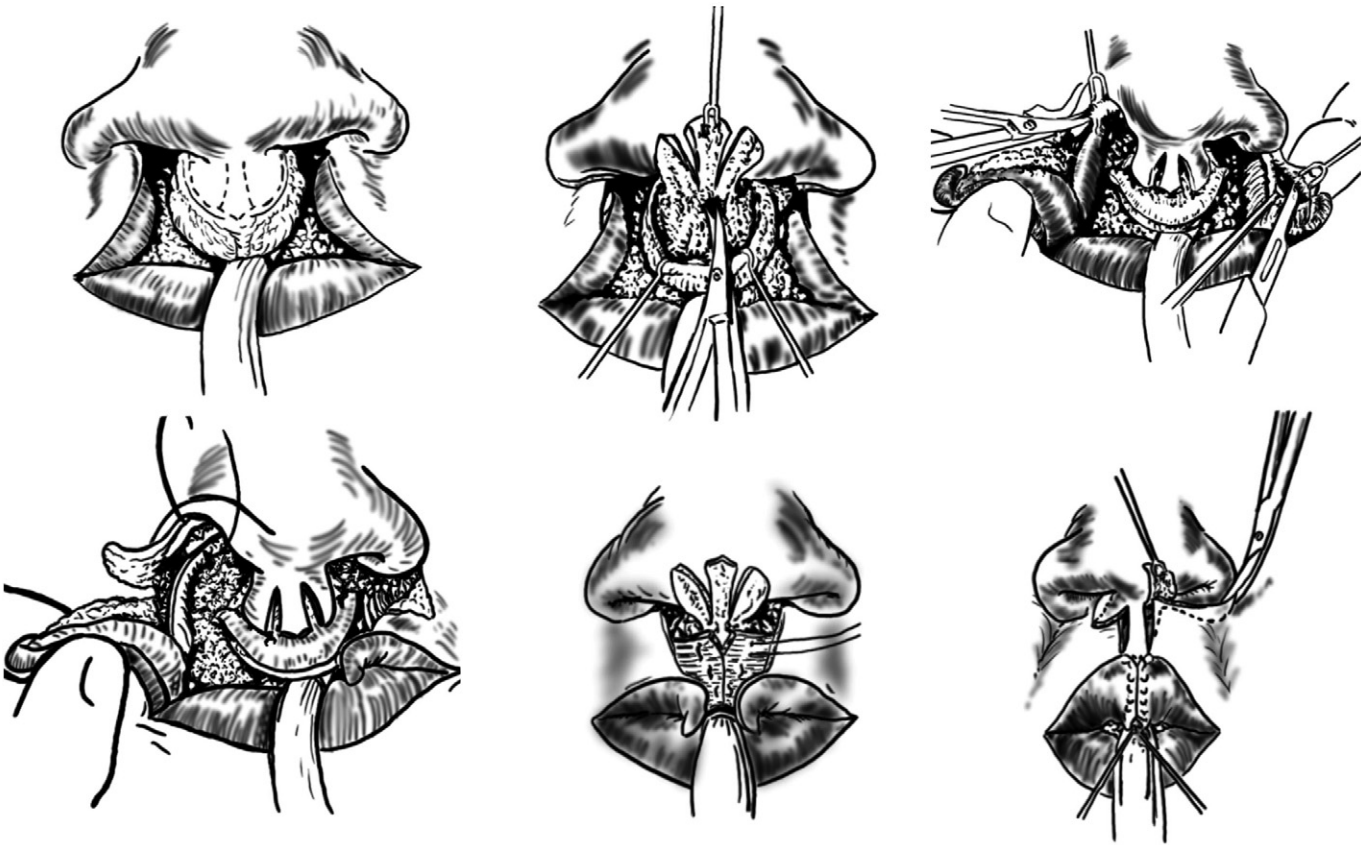

FIGURE 54-8 Schematic of the steps involved with a bilateral cleft lip repair. Re-creation of the columella, dissection of the muscle in the lateral lip elements, re-creation of the nasal floor, reapproximation of the lateral lip muscle, and insetting of the nasal alar bases with trimming of skin for final closure are all integral parts of bilateral cleft lip repair.

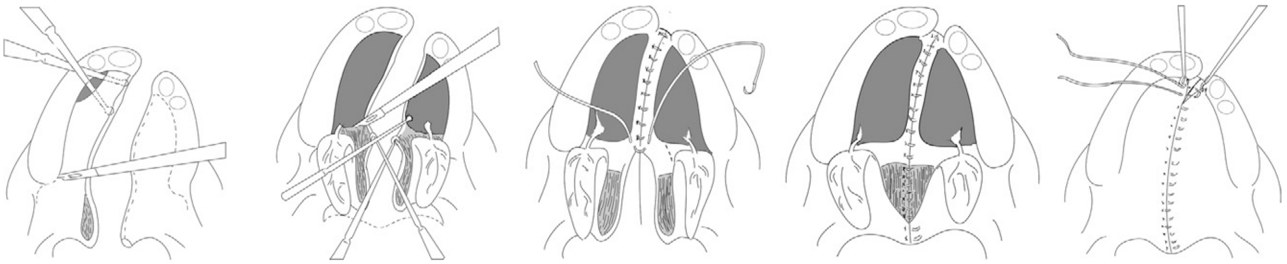

**FIGURE 54-9** The Bardach two-flap palatal reconstruction consists of elevating the palatal mucosa off the hard palate bone as a flap, elevation of the nasal mucosa, and closure of these two layers separately for the hard palate. Pedicles for the mucosal flaps come from the greater palatine arteries posteriorly. Closure of the soft palate is a three-layer repair, including a nasal mucosal layer, muscle layer (levator veli palatini and tensor veli palatini realignment), and oral mucosal layer.

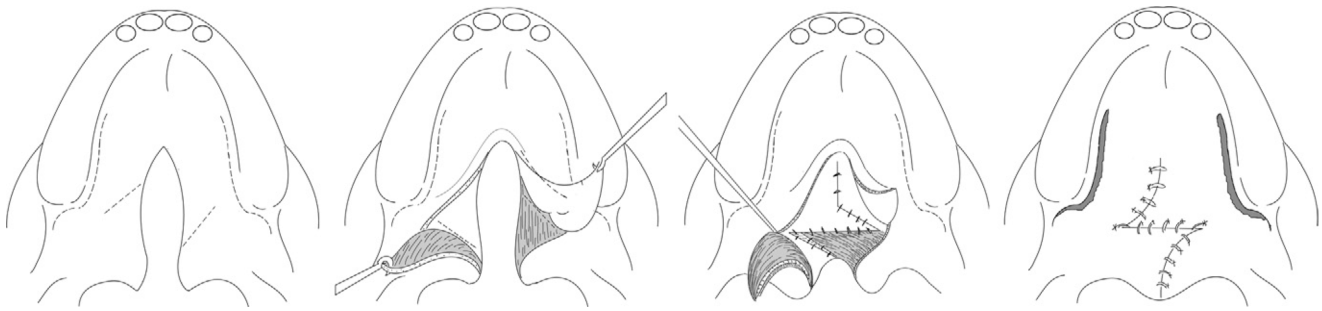

**FIGURE 54-10** The double opposing Z-plasty, (Furlow palatoplasty) of the soft palate includes realignment of the levator and tensor veli palatine muscles in the form of Z-plasty. One flap has oral mucosa only, whereas the contralateral side has oral mucosa and muscle. The nasal layer consists of a separate nasal mucosal layer, which is on the side with oral mucosa and muscle flap, and the contralateral side has nasal mucosa and muscle. Closure of both layers in a double opposing Z-plasty assists in elongating the soft palate, which should subsequently improve palatal speech function.

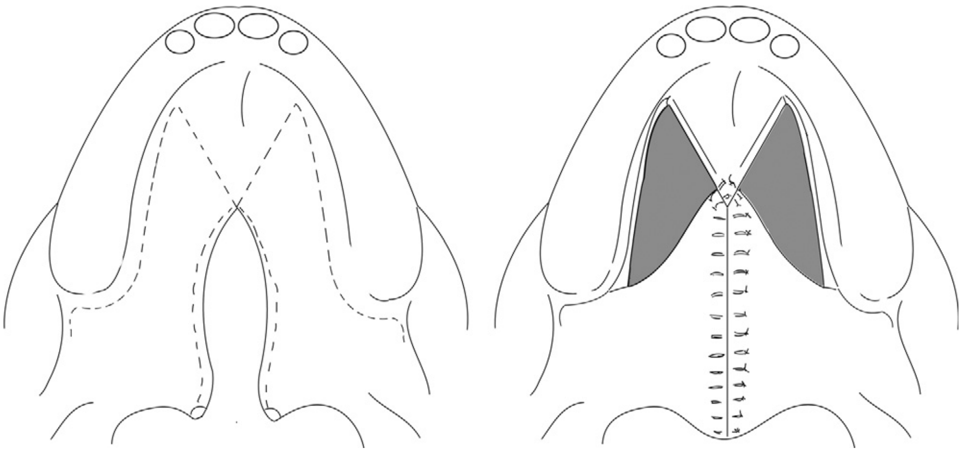

**FIGURE 54-11** The Veau-Ward-Kilner repair consists of advancing the oral mucosal flaps posteriorly to allow closure of the hard palate. Muscle realignment of the soft palate assists in palatal function.

Muscle repair is integral to the palate's primary function, namely speech. Any repair that does not address the muscle will fail in the development of normal speech.[30] As previously noted, the levator veli palatine and the tensor veli palatine are the two most integral muscles in producing a functional palate. Detaching these muscles from their abnormal insertions to the remnant shelves of the posterior hard palate, and then reapproximating them to each other in a transverse palatal sling, is referred to as an intravelar veloplasty. Failure to perform this step will result in a nonfunctional palate.

# Multidisciplinary Care

Patients with orofacial clefts require multidisciplinary care that is provided by plastic surgeons, otolaryngologists, dentists, orthodontists, oral surgeons, geneticists, audiologists, and speech and language pathologists. This team approach yields more comprehensive and coordinated care, which benefits the patient.[31–33] Longitudinal follow-up in a team environment is mandatory, because many issues, including the ability

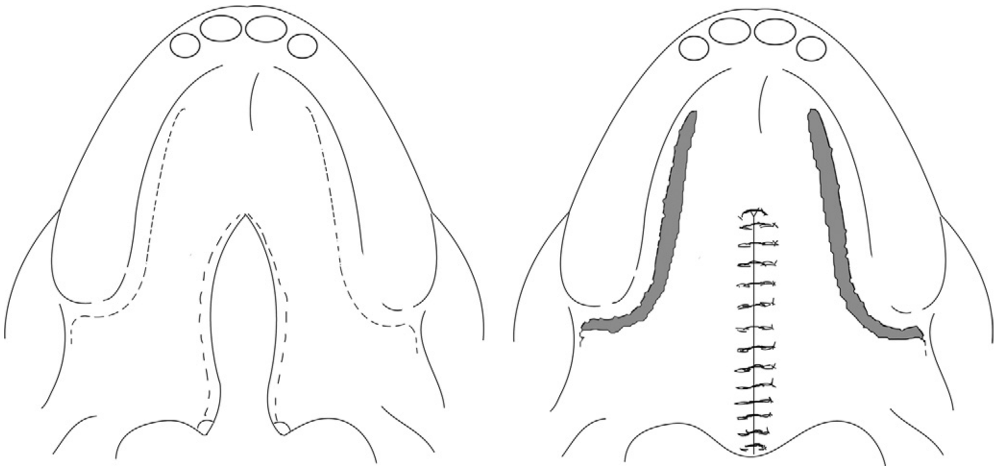

FIGURE 54-12 The von Langenbeck repair consists of relaxing incisions on the lateral palate with subsequent advancement to midline, allowing a palatal repair of both mucosa and muscle layers. Benefits include keeping a bipedicled flap; however, the advancement can be limited and inadequate with wider cleft defects.

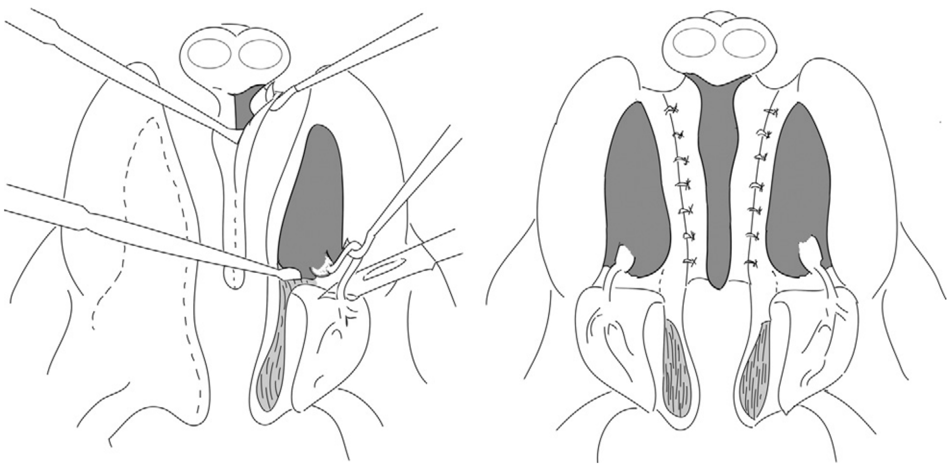

FIGURE 54-13 Closure of bilateral cleft palate follows in the same principles. Nasal mucosal layers are dissected off the vomer and palatine shelves and closed. Dissection of the hard palate oral mucosa allows closure separately, thus providing a two-layer closure. The soft palatal muscles are dissected and realigned to provide palatal function.

to produce normal speech, and dental eruption, continue to evolve as the patient grows.

Care of the cleft patient begins prenatally when a screening ultrasound makes the initial diagnosis. Ideally, counseling with the family begins during the perinatal period, and focuses on potential feeding concerns postnatally, the time line for surgical repair of the clefts, and team-centered care. In the neonatal period, feeding is the primary concern, especially in children with clefts of the palate. Appropriate weight gain must be monitored, as well as the family's overall psychological comfort with the child's cleft. A genetic evaluation, looking for evidence of associated anomalies and syndromes, and further counseling within a cleft team, prepare the family for the ongoing care of their child.

## Secondary Cleft Management

Although patients with cleft lip and palate undergo initial repair of their clefts in the first 12 to 18 months of life, these patients will ultimately require further surgical interventions. Nasal and lip revision, if needed, can be pursued at 5 years of age, which coincides with greater self-awareness of physical differences, and exposure to an expanding group of peers in school.

Between the ages of 7 and 9 years, during the period of mixed dentition (when the adult lateral incisor is ready to erupt through the area of the alveolar cleft), a bone graft generally harvested from the hip, is required in the alveolar cleft. The new bone allows eruption of the lateral incisor, and completes the continuity of the maxilla. Both before and after the bone graft, additional dental and orthodontic work may be required to align the teeth in normal anatomic position.

At facial skeletal maturity, generally at 15 years of age for females and 17 to 19 years of age for males, orthognathic surgery, with surgical movement of the maxilla, mandible, or both, may be required to achieve normal occlusion, overall facial appearance and profile. During the teenage years, further revisions of the lip and nose may be required to give these patients the desired aesthetic outcome that prepares them for adult life.

Velopharyngeal insufficiency (VPI) is the condition in which the repaired cleft palate is physically incapable of isolating the nasopharynx from the oropharynx, resulting in

air escape through the nose during speech. The patient with VPI has a nasal quality to his or her speech. Usually the most affected sounds are plosives, /p/ and /b/, in words such a "papa" and "buggy." In a patient with VPI, the pressure is dissipated through the nose, making these sounds more nasal in quality: "mama" and "muggy." Depending on the severity of the condition, VPI can range from being barely audible to rendering speech unintelligible. VPI usually occurs in patients whose palates are short and scarred or who have an inadequately functioning soft palate muscle sling. The advent of VPI is usually noticed as children become more verbal, between 3 and 5 years of age. Another time period during which VPI may arise is during tonsillar and adenoid regression. As these tissues atrophy, the nasopharyngeal and oropharyngeal spaces enlarge; a marginally functional soft palate may no longer be able to seal the nasopharynx from the oropharynx, resulting in VPI. Because of these ongoing changes, vigilance for VPI must be maintained throughout a child's growth and development.

In patients suspected of VPI, evaluation by a speech therapist is vital in determining whether additional speech therapy or surgical intervention is required. Nasoendoscopy and video-fluoroscopy may be required to determine the degree of soft palate incompetence, which in turn helps to determine the optimal surgical technique to correct the child's VPI.

## Conclusions

Cleft lip and palate can be visually and functionally devastating to a child. Multispecialty and interdisciplinary team care is both ideal and necessary for the care of these children because of the complexity of the anomalies and the longitudinal nature of cleft care. Establishing rapport with patients and their families, as well as among team specialists, can lead to life-changing differences in patients with clefts, allowing them to lead normal, productive lives, as well as making the formidable problems of cleft care rewarding to treat.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 55

# Otolaryngologic Disorders

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This chapter is divided according to anatomic structures: the ear, the nose, the oral cavity and pharynx, the larynx, and the neck. In each section we review anatomy, embryology, and examination, before discussing congenital and acquired disorders, including infections, trauma, and tumors.

## Ear

### ANATOMY

The ear is divided into three anatomic and functional areas: the external ear, the middle ear, and the inner ear. The external ear consists of the auricle, external auditory canal, and the lateral surface of the tympanic membrane. The auricle is a complex fibroelastic skeleton that is covered by skin and subcutaneous tissue that directs sound into the external ear canal.

The external auditory canal is oval with the long axis in the superior to inferior direction. In neonates, the external canal is almost entirely supported by soft, collapsible cartilage. As the temporal bone grows over several years, the bony portion of the canal enlarges to comprise the inner one third, leaving the outer two thirds supported by firm cartilage. Hair and cerumen glands are present in the outer two thirds of the external canal. The ear canal is lined by skin that is continuous with the lateral surface of the tympanic membrane, and it is innervated by cranial nerves V, VII, IX, and X and by the great auricular nerve.

The tympanic membrane separates the external ear canal from the middle ear. It has three layers: an outer layer of squamous epithelium (skin); a middle layer of fibrous tissue that is attached to the malleus, the most lateral middle ear ossicle; and an inner layer of mucosa that is continuous with the mucosa lining the middle ear. The fibrous layer is also attached to a thick fibrous annulus that anchors the tympanic membrane to the temporal bone.

The middle ear is an air-filled space within the temporal bone of the skull that is lined by ciliated, columnar respiratory epithelium. The middle ear communicates with the mastoid air cell system posteriorly and is lined by the same mucosa. It also communicates with the nasopharynx anteriorly through the eustachian tube. The mucociliary transport system of the middle ear moves mucus and debris into the nasopharynx, where it is swallowed. Secretory cells are not evenly distributed throughout the middle ear and mastoid complex and are more numerous anteriorly near the eustachian tube.

Three ossicles are present in the middle ear—the malleus, incus, and stapes—that transmit sound from the vibrating tympanic membrane to the stapes footplate. Stapes movement creates a fluid wave in the inner ear that travels to the round window membrane and is dissipated by reciprocal motion to the stapes.

There are two striated muscles in the middle ear. The tensor tympani muscle lies parallel to the eustachian tube, and its tendon attaches to the medial surface of the malleus. The stapedius muscle lies along the vertical portion of the facial nerve in the posterosuperior part of the middle ear. Its tendon attaches to the head of the stapes. These muscles stiffen the ossicular chain in the presence of sustained loud noise.

The facial nerve traverses the middle ear with its horizontal portion lying superior to the stapes. Posterior to the stapes, the facial nerve turns inferiorly in a vertical fashion to exit the stylomastoid foramen deep to the tip of the mastoid. The chorda tympani nerve is a branch of the facial nerve that innervates taste to the anterior two thirds of the tongue. It exits the facial nerve in the vertical segment and passes under the posterosuperior surface of the tympanic membrane, crossing the middle ear lateral to the long process of the incus and medial to the malleus. The facial nerve lies within a protective bony canal throughout its course in the middle ear. However, the bony canal may be absent (in the horizontal portion) in as many as 8% to 30% of patients.[1] Cranial nerve IX supplies sensation to the floor of the middle ear.

The inner ear consists of the cochlea, semicircular canals, and vestibule. The cochlea is a coiled fluid-filled tube consisting of 2½ to 2¾ turns surrounded by dense bone. It contains the membranes that support the organ of Corti and has hair cells that detect the fluid wave from vibration of the stapes footplate. The hair cells create the neural impulses that are transmitted from the auditory nerve (cranial nerve VIII) to the brain, providing the sensation of hearing.

The three paired semicircular canals (horizontal, superior, and inferior) are also fluid-filled tubes surrounded by dense bone. The semicircular canals each have a hair cell–containing structure (the ampulla) that detects motion. The utricle and saccule of the vestibule also have hair cell structures that detect acceleration.[2]

## EMBRYOLOGY

The external ear develops during the sixth week of gestation and is completely developed by the 20th week. Six hillocks fuse to form the basic units of the pinna. Defects in the fusion of the hillocks lead to preauricular tags and sinuses. The external auditory canal develops from the first branchial cleft. A solid epithelial plug forms during the beginning of the third month of gestation and canalizes in the seventh month to form the external auditory canal.

The middle ear space develops from the first pharyngeal pouch. The ossicles develop from the first and second pharyngeal arches. The inner ear arises from neuroectodermal tissue within the otic placode that forms the otic pit.[2]

Any combination of anomalies may occur. Abnormalities of the development of the ear may create anomalies of the pinna, external auditory canal, middle ear structures, and inner ear. One of the anomalies that involves the external and middle ear is aural atresia (absence of the external auditory canal). Absence of the external canal may occur with a deformed or normal external ear. The ossicles may be deformed and are usually fused to each other as well as the bony plate representing the undeveloped tympanic membrane. The facial nerve may also be altered in its course through the temporal bone. Reconstruction of the atretic canal, removal of the bony tympanic plate, release of the fused ossicles, and reconstruction of a new eardrum is a complex surgical procedure that may improve hearing. Rarely, there is incomplete development of the inner ear structures. The most common of these is dysplasia of the cochlea, and it may vary in severity. Dysplasia is associated with sensorineural hearing loss in most cases.[3,4]

## EXAMINATION

The examination of the ear should always start with inspection of the outer ear and surrounding structures. Deformities of the outer ear structure may suggest the presence of other anomalies, such as a first branchial cleft sinus. A first branchial cleft sinus usually presents below the ear lobe near the angle of the jaw. The sinus tract may connect to the ear canal or, rarely, the middle ear.

The external auditory canal and tympanic membrane are best examined with a handheld otoscope that has a bright fiberoptic light source and a pneumatic bulb attached to its head. The largest speculum that comfortably fits in the external canal should be used to maximize visualization and minimize pain. A very small speculum may be inserted deeply, but it might lacerate the ear canal as well as limit visibility of the tympanic membrane. The otoscope permits visualization of the ear canal and tympanic membrane. A translucent tympanic membrane will also permit visualization of the contents of the middle ear.

A healthy middle ear contains air and is ventilated via the eustachian tube that connects to the nasopharynx. Insufflation of air into the ear canal via the pneumatic bulb should cause the tympanic membrane to move if the middle ear is normal (aerated) and fail to move if it is filled with effusion (mucus or pus). Cerumen may be encountered in the ear canal that obstructs the view of the tympanic membrane or fails to allow insufflation to occur with pneumatic otoscopy. Removal of cerumen may be performed by using an operating otoscope head and an ear curette. However, the use of a headlight, such as the Lumiview (Welch Allyn, Skaneateles, NY) or operating microscope, permits the use of both hands and superior visualization. Care should be taken to secure the child to prevent sudden movement, and the ear curette should be used gently to avoid causing pain and a laceration of the ear canal. A mechanical test of tympanic compliance (tympanometry) may also be useful to help determine if the middle ear is normally aerated (type A, peaked tracing), fluid-filled (type B, flat tracing), or has negative pressure because it is poorly ventilated, suggesting eustachian tube dysfunction (type C, negative pressure tracing). Examination of a child with an apparent or suspected ear condition often requires objective assessment of hearing by audiometry. Current technology and expertise makes it possible to test a child at any age.

Behavioral audiometry can usually be accurately performed for a child who is older than 6 months of age by sound-field testing. Older children are presented with a tone through insert earphones and are tested across a range of frequencies between 250 and 8000 Hz for ear-specific testing. The hearing thresholds are recorded at each presented frequency, and this represents the air conduction threshold. The sound has to traverse the ear canal, tympanic membrane, and middle ear. The inner ear must respond by creating electrical impulses that are transmitted to the brain. Normal thresholds are less than 20 dB for children.

Bone conduction thresholds test the sensorineural component of hearing. A bone oscillator is used to test a range of frequencies by vibrating the skull, which stimulates the inner ear directly, bypassing the external and middle ear. Normally, air conduction thresholds require less energy than bone conduction thresholds. If bone conduction thresholds require less sound intensity to be heard than air conduction, the child has a conductive hearing loss. If air conduction and bone conduction thresholds are elevated but the same, the child has a sensorineural hearing loss. Most sensorineural hearing loss in children is a result of hair cell dysfunction in the organ of Corti. Hearing loss may be conductive, sensorineural, or mixed. Objective electrophysical tests, such as brainstem auditory-evoked response and sound emission tests that measure the intrinsic sounds from the inner ear (otoacoustic emissions), may be used in young infants and children who cannot participate in behavioral audiometry. All of these tools are used by pediatric audiologists.[5]

For purposes of describing hearing loss, a threshold of 20 to 40 dB is considered mild, 40 to 65 dB is moderate, 55 to 70 dB is moderately severe, 70 to 90 dB is severe, and greater than 90 dB is profound. Four of 1000 children are born with a hearing loss, and 1 of those children is born with a severe to profound hearing loss.

Conductive hearing loss may be corrected with otologic surgery. Hearing aids and frequency modulation (FM) amplification systems may be helpful to children with both conductive and sensorineural hearing loss. Assistance may be needed through auditory training, speech language therapy, and education to maximally develop communication skills. When a child has a sensorineural hearing loss that is too severe to be helped with hearing aids, a cochlear implant may be considered.

A cochlear implant is an electrical device that is implanted under the scalp behind the ear. Its processor converts sound to electrical impulses. A cable travels through the mastoid and facial recess to reach the middle ear, and the electrode array

is inserted into the scala tympani of the cochlea through an opening that is made in the cochlea.

Cochlear implants stimulate the neural elements of the cochlea directly and bypass the hair cells. Because the vast majority of sensorineural hearing loss in children is due to hair cell dysfunction, nearly all children get sound perception from a cochlear implant. Rare conditions, such as an absent auditory nerve or an absent cochlea, preclude the use of a cochlear implant.

A multidisciplinary evaluation by a cochlear implantation team is required to evaluate a child and determine family expectations before performing a cochlear implantation. A temporal bone computed tomographic (CT) scan and/or magnetic resonance imaging (MRI) is performed to assess the cochlea and auditory nerves.

Children who are born deaf and are younger than the age of 3 years, as well as children who have already developed communication skills, language, and speech before losing their hearing, derive the greatest benefit from cochlear implants. Cochlear implantation is approved for children 12 months of age or older by the U.S. Food and Drug Administration. Children with cochlear implants should be vaccinated against *Streptococcus pneumoniae,* according to high-risk schedules, and against *Haemophilus influenzae,* according to standard schedules, because the implant wire crosses from the middle ear into the cochlea, increasing the risk of meningitis if the child gets otitis media. After a cochlear implant is performed, considerable auditory oral training is required to maximize a child's benefit to develop skills of audition, speech, and language. A child who has been deaf and without sound perception for several years is expected to benefit to a lesser degree.[6]

## OTITIS MEDIA WITH EFFUSION AND INFLAMMATORY DISORDERS

Otitis media with effusion is the most common chronic condition of the ear during childhood. All children are born with small and horizontally oriented eustachian tubes that may at times be unable to clear mucus that is secreted in the mastoid and middle ear normally and when the child has an upper respiratory tract infection. The excess mucus usually clears within a few weeks as the upper respiratory tract infection resolves. Younger children (infants to 3 years of age) and children with craniofacial anomalies, such as cleft palate and Down syndrome, are more prone to having persistent middle ear effusions; there is no medication that is consistently effective in resolving such effusions.

Persistent effusion may cause a conductive hearing loss in the range of 20 to 40 dB. A middle ear effusion may also function as a culture medium and predispose children to recurrent acute otitis media (AOM).

When fluid persists in the middle ear for 3 to 4 months, causing a hearing loss or is associated with AOM, myringotomy and tympanostomy tube placement is helpful to resolve the hearing loss and reduce the frequency and severity of infection.

Myringotomy and placement of a tube is performed under general anesthesia using an operating microscope. A small incision is made in any quadrant of the tympanic membrane except the posterosuperior quadrant, where there would be risk of injuring the ossicles. The mucus is suctioned from the ear, and a Silastic tube is placed in the myringotomy to provide prolonged ventilation of the middle ear. The tube will usually extrude and the tympanostomy will heal in 6 months to 1 year. When the ear is no longer ventilated by a tube, the eustachian tube must ventilate the middle ear. If fluid recurs and persists, a repeat procedure may be needed. Most children outgrow this problem as their eustachian tube grows. Occasionally, adenoid tissue in the nasopharynx may contribute to the persistence of middle ear effusion and may also be removed at the time that a tube is placed. Children who have had multiple sets of tubes are candidates for adenoidectomy.

## ACUTE OTITIS MEDIA

Acute otitis media is the most common infection of childhood except for acute upper respiratory tract infections. It is the most common bacterial infection for which children seek medical care from their primary care physician. Usual pathogens causing AOM include *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.*[7]

AOM usually causes severe deep ear pain, fever, and a conductive hearing loss in the affected ear. The purulence in the middle ear is also present in the mastoid air cells because they are connected.

To prevent the overuse of antibiotics, the American Academy of Pediatrics (AAP) and the American Academy of Family Practitioners (AAFP) developed guidelines in 2004 to improve accuracy of diagnosis of AOM.[8] Three components should be present to diagnose AOM, including history of acute onset of symptoms within 48 hours of presentation, presence of middle ear effusion confirmed by pneumatic otoscopy or tympanometry, and signs of middle ear inflammation. The tympanic membrane typically is reddened and bulging, with obliteration of normal landmarks.[8]

Once an accurate diagnosis is made, the AAP/AAFP guidelines offer options for treatment in otherwise healthy children. They advocate that a period of observation (48 to 72 hours) is justified because AOM spontaneously resolves in many children (80% of episodes of AOM resolve within 2 to 7 days of symptom onset). Very young children (less than 6 months old) and those with Down syndrome, immune disorders, craniofacial anomalies, or chronic medical conditions should not be considered candidates for observation, because they are at higher risk of developing complications such as mastoiditis or meningitis.

Table 55-1 describes specific recommendations for treatment in otherwise healthy children aged 6 months to 12 years,

**TABLE 55-1**
**AAFP/AAP Guidelines for Treatment of Acute Otitis Media in Children Younger Than 12 Years**

| *Child Age* | *Certain Diagnosis* | *Uncertain Diagnosis* |
|---|---|---|
| Younger than 6 months | Antibiotics | Antibiotics |
| 6 months to 2 years | Antibiotics | Antibiotic if severe illness*; observe if nonsevere illness† |
| $>$ 2 years to 12 years | Antibiotic if severe illness*; observe if nonsevere illness† | Observe |

*Severe illness: fever $> 39°$ C and/or moderate to severe otalgia.
†Nonsevere illness: fever $< 39°$ C and/or mild otalgia.
AAFP, American Academy of Family Practitioners; AAP, American Academy of Pediatrics.

based on age, certainty of diagnosis, and severity of symptoms. All affected children should be given pain control, and children who are treated with observation should be followed up in 48 to 72 hours and treated if they continue to manifest symptoms.

Recommended first-line antibiotic therapy is higher-dose amoxicillin (80 mg per kilogram per day in two divided doses for 5 to 10 days). Higher dose therapy can effectively cover even intermediate and some highly resistant strains of *S. pneumoniae*. Infections caused by this organism are most likely to cause more serious complications and are least likely to spontaneously resolve. Azithromycin, erythromycin, or clarithromycin can be used as alternatives in patients with type 1 allergy (anaphylaxis or hives to amoxicillin). Second-line antibiotics should be considered in patients who fail to improve after several days of first-line antibiotics and includes higher-strength amoxicillin-clavulanate (90 mg per kilogram per day in two divided doses for 10 days) or oral cefdinir, cefuroxime, cefpodoxime, clindamycin, and, less commonly, intravenous or intramuscular ceftriaxone.

Occasionally, AOM does not respond as expected to standard antibiotic therapy. When this occurs, culture and sensitivity testing can be obtained by tympanocentesis. After sterilizing the ear canal with alcohol, a 22-gauge spinal needle can be placed through the posterior or anterior inferior quadrant of the tympanic membrane and fluid can be aspirated with a small syringe.

Complications of AOM are uncommon if appropriate antibiotic therapy is used. The conductive hearing loss resolves as the middle ear effusion clears. However, infection may necrose the tympanic membrane, causing a spontaneous perforation. Small perforations usually heal in less than 7 days, but larger perforations may persist, cause a conductive hearing loss, and require a tympanoplasty for closure. The ossicular chain may also be disrupted by necrosis of the long process of the incus requiring ossicular reconstruction to restore hearing.

Acute coalescent mastoiditis occurs when infection erodes the bony mastoid cortex and destroys bony septae within the mastoid. A subperiosteal abscess may also develop over the mastoid process. There is usually postauricular erythema and edema over the mastoid area. The auricle is displaced laterally and forward (Fig. 55-1). Otoscopy reveals forward displacement of the posterior superior skin of the ear canal.

In addition to antibiotics, treatment should include a wide-field myringotomy from the anterior inferior quadrant to the posterior inferior quadrant, a tympanostomy tube placement for middle ear drainage, and a postauricular mastoidectomy to drain the subperiosteal abscess and the mastoid.

Facial nerve paralysis may occur from inflammation of that portion of the facial nerve that is exposed in the middle ear during AOM. Treatment with parenteral antibiotics and ototopical antibiotic drops applied in the ear canal through a tympanostomy tube almost always results in complete recovery of facial function. A short course of oral steroids may also be helpful. Facial nerve recovery may take a few weeks to several months.

Intracranial complications of AOM include meningitis, epidural abscess, brain abscess, otitic hydrocephalus, and lateral sinus thrombosis. Meningitis is the most common intracranial complication of AOM and may be associated with profound sensorineural hearing loss and loss of vestibular function. Treatment of the intracranial complications of AOM is focused on appropriate treatment of the intracranial process, in addition to a wide-field myringotomy and tympanostomy tube placement in the affected ear.[9]

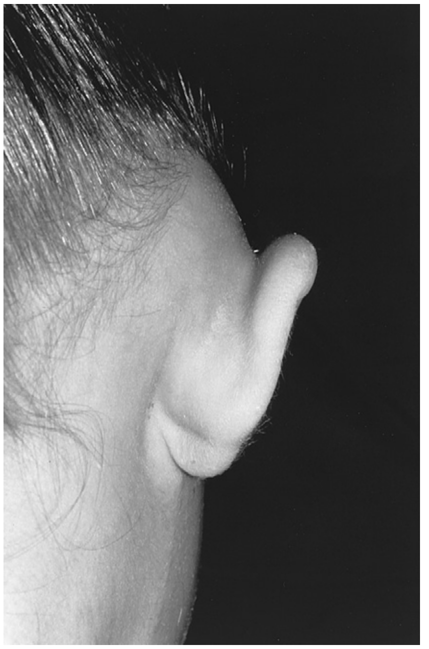

**FIGURE 55-1** Acute mastoiditis. Extension of the acute inflammatory process from the middle ear and mastoid air cell systems to the overlying soft tissues displaces the auricle in an inferior and lateral direction from the side of the head. Fluctuance may be palpated over the mastoid cortex, and a defect in the cortical bone can frequently be appreciated. Surgical drainage with mastoidectomy is required.

## OTITIS MEDIA WITH EFFUSION/CHRONIC OTITIS MEDIA/CHRONIC SUPPURATIVE OTITIS MEDIA

Otitis media with effusion is a descriptive term that refers to persistent middle ear effusion that usually is serous or mucoid in nature. Chronic otitis media is a term used to describe the effusion if it lasts longer than 3 months. Otitis media with effusion may occur following an ear infection, but can occur spontaneously, especially when the nose has been congested. It may be associated with hearing loss and the child may or may not be symptomatic with pain, irritability, or poor balance. Most effusions resolve spontaneously within weeks, and most children affected are younger than 5 years of age.

In otherwise healthy children, hearing tests or hearing screens should be performed once the effusion has been present for more than 3 months, and sooner if significant hearing loss is suspected or if the child is at high risk for developing significant speech and language delays. The associated hearing loss usually falls in the mild range (30 dB), but even in normal children, may contribute to the development of speech and language delays. Speech and language tests should be considered if hearing loss is documented. Children should be evaluated for surgical treatment with bilateral myringotomy and tube placement if they have ongoing pain or irritability attributable to the effusion, structural changes to the tympanic membrane (such as thinning or deep retractions), documented speech and language delays, or those who are at high risk for complications if observed (Down syndrome, those with

existing speech delay, autism, or neurocognitive delays). Adenoidectomy would be considered as well if the adenoids are found to be enlarged, especially if the child has symptoms of heavy snoring, sleep apnea, or chronic nasal congestion.[10]

Chronic suppurative otitis media occurs when otorrhea (drainage of pus or mucous) persists for more than 3 months, either through a perforation of the tympanic membrane or through a tube in the tympanic membrane. A cholesteatoma of the middle ear may also be present in patients who have perforated tympanic membranes. A cholesteatoma is a squamous epithelial-lined cyst that may be congenital or acquired. Congenital cholesteatomas are caused by epithelial rests that persist in the middle ear during temporal bone development. They present behind an intact tympanic membrane and appear as a white, smooth mass, most often located in the anterior superior quadrant of the middle ear. They expand over time and are filled with squamous debris and may erode the ossicular chain and extend into the mastoid.

Acquired cholesteatomas develop from skin entering the middle ear after a tympanic membrane perforation or a retraction pocket from eustachian tube dysfunction and are usually located in the posterior-superior quadrant of the middle ear space. Cholesteatomas are usually painless, cause a conductive hearing loss, and, in acquired cases, often present as otorrhea. The otorrhea should be treated with ototopical antibiotic eardrops, but the only treatment of cholesteatomas is complete surgical excision by tympanomastoid surgery and ossicular reconstruction.[11] The potential complications of cholesteatomas are the same as those for acute suppurative otitis media (ASOM).

## TRAUMA

Objects stuck deeply into the ear canal, such as a cotton-tipped applicator, may perforate the tympanic membrane. This usually causes acute pain, bleeding, and a conductive hearing loss. If the ossicular chain is not disrupted, the vast majority of these perforations will heal spontaneously in about 2 weeks. If the tympanic membrane is perforated and the middle ear is contaminated with water, topical antibiotics should be given.

Lacerations of the auricle should be cleaned to prevent tattooing and repaired by careful approximation of the skin and soft tissue to restore the contours of the ear. The cartilage itself does not usually need to be sutured. Partially or totally avulsed tissue should be replaced. If necrosis of tissue occurs, it can be debrided as needed. In severe injuries of the auricle, oral antibiotic treatment to cover *S. aureus* and *Pseudomonas* species is helpful to prevent chondritis and loss of the cartilage framework.

Blunt trauma to the ear is commonly seen in wrestlers, in children with poor neuromuscular tone, or in children with self-injurious behaviors. Blood or serum collects between the periosteum and the auricular cartilage. If the cartilage is fractured, the collection may occur on both sides of the ear. Evacuation of the collection is required to restore the contours of the ear, prevent infection, and prevent scarring with formation of a "cauliflower ear." Aspiration of the fluid and placement of a mastoid dressing for compression may be tried but is most often unsuccessful. Incision and drainage provides for complete evacuation of the blood or serum. Cotton dental rolls placed on each side of the auricle and held in place with bolster mattress sutures is the most effective management. The dental rolls should be left in place for 7 to 10 days while the patient also continues with a course of oral antibiotics. No outer dressing is required except in a child with cognitive impairment, who may pick at the bolsters.[11]

Blunt head trauma may disrupt the inner ear membranes causing sensorineural hearing loss and vertigo. No treatment is required, and the injury and symptoms may resolve spontaneously, but the sensorineural hearing loss may persist. Severe head trauma may cause fracture of the temporal bone of the skull. Temporal bone fractures can be classified as longitudinal, transverse, or mixed (Fig. 55-2) but are often


FIGURE 55-2 **A,** Longitudinal temporal bone fracture. These fractures run parallel to the petrous pyramid. The otic capsule is generally not affected by the fracture lines. Balance, hearing, and facial function are generally preserved. **B,** Transverse temporal bone fracture. These fractures generally extend through the cochlea and facial canal and result in deafness, vertigo, and facial nerve paralysis of immediate onset. Facial nerve exploration with repair should always be considered in these cases.

complex and do not neatly fit into one category or another. A high-resolution, thin-section CT scan of the temporal bone will define the extent of the fracture. The middle ear and mastoid are filled with blood when a fracture is present. The blood causes a conductive hearing loss that resolves when the ear clears.

Otoscopic evaluation of a child with a temporal bone fracture may reveal a laceration of the ear canal and tympanic membrane. Blood is usually present in the ear canal, and the tympanic membrane appears to be dark blue because the middle ear is filled with blood. There is often ecchymosis of the mastoid area (Battle's sign).

It is important during evaluation of a skull and temporal bone fracture to note and record the function of the facial nerve if the patient is not unconscious. Facial nerve paralysis may be immediate or delayed in onset. Delayed facial nerve paralysis has a good prognosis for spontaneous recovery. Immediate complete facial paralysis may indicate disruption of the nerve or compression by bone fragments. Immediate facial nerve paralysis requires exploration and repair once the patient is stable and sufficiently recovered from any associated trauma. The facial nerve should be decompressed in the mastoid, middle ear, and middle cranial fossa. Bone chips impinging on the nerve should be removed, and the nerve should be sutured or grafted if needed. All patients with temporal bone fractures should have an audiogram once their condition has stabilized. If the fracture disarticulates the ossicles, a conductive hearing loss will persist after the blood has cleared from the middle ear and mastoid.

Fractures of the temporal bone may transverse the cochlea and vestibular apparatus. These fractures usually cause a severe sensorineural hearing loss and loss of vestibular function on the affected side. Most children compensate for vestibular injuries within weeks, but sensorineural hearing loss is less likely to improve. A concussive injury of the cochlea may also simultaneously be present in the opposite ear in severe head trauma.

Temporal bone fractures may permit leakage of cerebrospinal fluid (CSF) into the middle ear and mastoid. CSF may also drain through the lacerated tympanic membrane, causing CSF otorrhea. These leaks usually stop spontaneously, but persistent CSF otorrhea may require a lumbar drain to reduce the pressure and permit healing. Rarely, tympanomastoid exploration is required to close the leak. Persistent CSF leaks in the ear are associated with meningitis.

### TUMORS

Benign and malignant tumors of the ear are rare. Glomus tympanicum tumors and neuromas of the facial nerve may present in the middle ear. Also, eosinophilic granuloma and rhabdomyosarcoma may involve the structures of the temporal bone.[12,13]

## Nose

### ANATOMY

The nose can be divided into three anatomic sections. The bony vault is the immobile portion of the nose. It consists of the paired nasal bones, the frontal process of the maxillary bone, and the nasal process of the frontal bone. The cartilaginous vault is supported by the upper lateral cartilages and the cartilaginous nasal septum. The nasal lobule is supported by the lower lateral cartilages and the cartilaginous septum. The nasal septum is formed by the quadrilateral cartilage anteriorly. The posterior septum is composed of bone from the vomer, perpendicular plate of the ethmoid, nasal crest of the maxillary bone, and palatine bone.

Both the internal and external carotid artery systems supply blood to the nose. The roof and lateral wall of the internal nasal cavity are supplied by the anterior and posterior ethmoidal arteries, sphenopalatine artery, and greater palatine artery. The septum is supplied by the anterior and posterior ethmoidal arteries, palatine artery, and the superior labial artery. The convergence of these vessels in the anterior segment of the nose is referred to as the Kiesselbach plexus or the Little area. Venous drainage is accomplished mainly by the ophthalmic, anterior facial, and sphenopalatine veins.

The olfactory bulb is positioned high in the roof of the nasal cavity and is responsible for the sense of smell. Sensory information is transported by nerves that penetrate the cribriform plate and traverse cranial nerve I (the olfactory nerve) to the brain. Smell is also an important component of what is perceived as taste.

Bony projections, called turbinates, form the lateral nasal wall and significantly increase the surface area of the nose, allowing for more efficient humidification and warming of the air to 36° C. Three turbinates are usually present (i.e., inferior, middle, and superior). A supreme turbinate, which is essentially a flap of mucosa, is occasionally present. The turbinates contribute to the turbulent airflow that creates approximately 50% of the total airflow resistance to the lungs.

Cleaning of air is accomplished through the nasal hairs (vibrissae) and the mucosal surface. Anteriorly, the nose is lined with stratified squamous epithelium, which changes to respiratory epithelium immediately anterior to the turbinates. Trapped debris is transported in a posterior direction into the nasopharynx by a mucociliary transport mechanism.

Speech is affected by nasal anatomy and pathologic conditions. Hyponasality from nasal obstruction or hypernasality from an excessive air leak can affect voice quality and intelligibility of speech.

### EMBRYOLOGY

The nose serves as a drainage port for the paranasal sinuses. The meati are spaces between the lateral aspect of the nasal turbinates and the medial aspects of the lateral nasal wall. Each meatus is named for the turbinate that surrounds it. The maxillary, frontal, and anterior ethmoidal sinuses drain into the middle meatus. The posterior ethmoidal sinuses drain into the superior meatus. The sphenoidal sinus drains into an area known as the sphenoethmoidal recess that is located posterior and superior to the superior turbinate. The nasolacrimal duct drains into the inferior meatus.

The nasal cavities develop from the nasal pits in the 4-week embryo. These pits deepen and move medially to form the nasal cavity. The oronasal membrane that separates the nose from the mouth resolves in the seventh week to permit communication between the nose and nasopharynx.

The paranasal sinuses develop from an outpouching of the lateral nasal walls during the third and fourth months of

development. The maxillary and ethmoidal sinuses are present at birth. The frontal and sphenoidal sinuses develop several years after birth. The frontal sinus begins to develop at 7 years of age but is not fully aerated until adulthood.[14]

## INFLAMMATORY CONDITIONS

Viral rhinosinusitis (the common cold) accounts for the majority of nose and sinus infections. It is caused by many strains of viruses and is a self-limited infection. Symptoms of fever, nasal congestion, headache, and clear rhinorrhea usually resolve over 5 to 7 days. Treatment is symptomatic.

## BACTERIAL RHINOSINUSITIS

Acute bacterial rhinosinusitis may often follow an acute viral upper respiratory tract infection. The most common bacteria causing rhinosinusitis are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*. Acute rhinosinusitis causes malaise, headache, and nasal congestion. There may also be pain localized to the sinus region or pain on palpation over the maxillary or frontal sinuses. Chronic sinus infection may persist after the acute phase, and symptoms often last longer than 30 days.

The gold standard for diagnosing sinusitis is CT of the sinuses, but a thorough history and nasal examination is usually sufficient to diagnose acute rhinosinusitis. The nasal cavity can be visualized by using a large speculum on an otoscopic head. The posterior nasal cavity can be visualized with either a straight-rod endoscope or a flexible fiberoptic nasopharyngoscope.

The treatment of rhinosinusitis includes oral antibiotics, short-term use of topical nasal decongestants (e.g., oxymetazoline), and saline nasal sprays. Topical nasal corticosteroid sprays may be helpful for the treatment of both acute and chronic sinusitis.

Chronic sinusitis in a child may be exacerbated by gastroesophageal reflux disease, immunodeficiencies, mucociliary dysfunction, and, more commonly, upper respiratory allergy. These predisposing conditions should be managed while treating the sinus infection. If the signs and symptoms of chronic sinus infection persist, a sinus CT is required to evaluate the condition of the sinus mucosa and the drainage pathways. Endoscopic sinus surgery may be necessary to open the involved sinuses to provide drainage.

Chronic inflammation of the nasal and sinus mucosa may lead to nasal and sinus polyp formation that chronically obstructs the nose and sinuses. Antrochoanal polyps are large polyps that originate from the walls of the maxillary sinus and extend through the nasal cavity into the nasopharynx. Nasal polyps may be removed endoscopically, but a large antrochoanal polyp may require removal through an open maxillary sinus procedure. Nasal polyps in a child should always prompt an evaluation for cystic fibrosis.

## COMPLICATIONS OF SINUSITIS

The sinuses surround the orbit so a common complication of acute rhinosinusitis in children is orbital cellulitis with erythema and edema of the eyelids. Chemosis (edema of the ocular conjunctiva) is usually absent. However, if a periorbital subperiosteal abscess forms adjacent to an infected sinus, there may be proptosis, chemosis, ophthalmoplegia, and loss of vision. Infection in the ethmoidal sinuses most commonly results in this complication. Subperiosteal periorbital abscess is demonstrated best by sinus CT (with axial and coronal cuts). Initial treatment should include intravenous antibiotics. Endoscopic or external drainage may be required in some cases.

Intracranial complications of sinusitis include cerebritis, meningitis, cavernous sinus thrombosis, as well as epidural, subdural, and brain abscesses. Treatment of impending or confirmed intracranial complications requires surgical drainage of the involved sinus and concurrent treatment of the intracranial lesion by a neurosurgeon.[15]

## FUNGAL SINUSITIS

Fungal sinusitis may occur in immunocompromised children, specifically severe diabetics, children undergoing chemotherapy, and bone marrow transplant recipients. The more common invasive fungi include *Mucor* and *Aspergillus* species. The treatment of fungal sinusitis involves surgical drainage and intravenous antifungal agents.

However, a chronic form of fungal sinusitis is allergic fungal sinusitis. The presence of fungi causes inflammatory cells to proliferate in the sinuses, causing symptoms of nasal plugging and facial pain, along with discharge or polyps. These patients usually have other signs of allergy, such as asthma. The treatment of this condition is corticosteroids and debridement of the involved sinuses. The diagnosis is made by sinus CT findings and the presence of eosinophils as well as fungi in the sinus secretions that are removed at the time of surgery.[16]

## CONGENITAL MALFORMATIONS

### Pyriform Aperture Stenosis

Congenital stenosis of the anterior bony aperture causes partial nasal obstruction that may be severe enough to cause difficulty feeding, respiratory distress, and failure to thrive. Anterior rhinoscopy demonstrates a very constricted nasal opening bilaterally. CT of the nose shows marked narrowing of the pyriform aperture.

Neonates are obligate nasal breathers, and severe stenosis must be surgically corrected. Because the stenotic segment is very anterior and the remainder of the nasal cavity is normal, removal of the constricting bone with drills is done through a sublabial approach. The nasal openings are stented with 3.0-mm endotracheal tube stents that are sutured in place and removed after a few days.

### Choanal Atresia

Choanal atresia may be unilateral or bilateral. The obstructing tissue is usually a bony plate, but a few cases will have only membranous atresia. Unilateral choanal atresia presents as chronic unilateral rhinorrhea. There is no significant respiratory distress. Because neonates are obligate nose breathers, bilateral choanal atresia is associated with severe respiratory distress, difficulty feeding, and failure to thrive. The diagnosis is suspected if catheters cannot be passed through the nose and into the pharynx. The obstruction may be visualized with a narrow flexible nasopharyngoscope after the nasal cavity has


FIGURE 55-3 Choanal atresia. This disorder frequently presents at birth with respiratory distress.

FIGURE 55-4 Nasal dermoid presenting in the midline as a pit.

been suctioned of mucus and the nasal mucosa has been constricted with a nasal decongestant (e.g., oxymetazoline). The diagnosis is best made with CT of the nasal cavity. CT will demonstrate the atresia, define the tissue (bony or membranous), and show the configuration of the entire nasal cavity.

Choanal atresia may be successfully treated by removing the obstructing tissue transnasally. Curettes, lasers, microdebriders, bone punches, and drills may all be effective to remove the atresia plate. However, when the bony plate is very thick and there is an extremely narrow posterior nasal cavity, a transpalatal repair is more direct. A transpalatal repair provides better access for more effective removal of the bony plate and posterior septum (Fig. 55-3). Stents fashioned from endotracheal tubes are placed and secured with sutures to the septum. They are removed after several weeks. The stents must be moistened with saline and suctioned several times daily to prevent mucus plugging and acute respiratory distress. Transpalatal repair of choanal atresia has a lower incidence of restenosis.[11]

## Nasal Dermoid

Nasal dermoid cysts or sinuses present in the midline of the nasal dorsum (Fig. 55-4). They usually appear as a round bump or a pit with hair present in the pit (Fig. 55-5). They also may become infected. Nasal dermoid sinuses may extend through the nasal bones into the nasofrontal area and have an intracranial component. Both CT and MRI may be necessary to demonstrate the extent of the dermoid. Surgical removal is required to prevent infection and recurrence. This may be done between ages 3 and 5 years if prior infection has not occurred. Dermoids confined to the nose are resected completely using a midline incision with an ellipse around the sinus tract. The tract is followed to its termination, and the nasal bones may need to be separated to reach the end of the tract.[11] If an intracranial component is present, a combined craniotomy and nasal approach with a neurosurgeon is recommended.

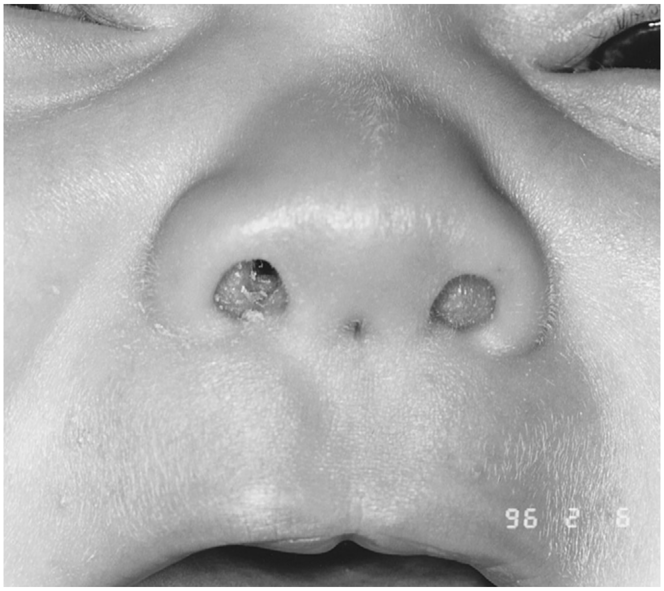


FIGURE 55-5 Nasal dermoid. These lesions typically present on the nasal dorsum as a single midline pit, often with a hair extruding from the depths of the pit. The pits may also be found on the columella. The dermoid will then tract through the septum toward the cranial base.

### Nasal Glioma and Encephalocele

A nasal glioma presents as an intranasal mass and may be confused with a nasal polyp. The mass contains dysplastic brain tissue and may have an intracranial connection. CT and MRI are important to define the extent of the glioma and intracranial component as well as to plan the surgical approach.

An encephalocele presents as a soft compressible mass and may also be confused with a nasal polyp or a nasal dermoid. Intranasal encephaloceles extend through a defect in the skull at the cribriform plate. CT and MRI define the extent of the encephalocele and are necessary to design the surgical approach. Surgical removal often includes a frontal craniotomy. Nasal encephaloceles may be associated with CSF rhinorrhea and meningitis.

## TRAUMA

### Anosmia

Head trauma can lead to temporary or permanent anosmia (lack of sense of smell). In one large study of head trauma patients ($n = 190$), 11% reported loss of sense of smell that persisted after their initial recovery and later was confirmed by smell tests. Those at higher risk had trauma that led to intracranial hematoma and/or hemorrhages or injury near the skull base.[17]

### Nasal Fracture

An infant may be born with the soft nasal bones and the septum deviated to one side either as a result of a difficult delivery or from persistent intrauterine compression of the nose. The nasal structures can most often be returned to the midline with digital manipulation. If the nasal deformity is partially reduced, the nose usually straightens with growth during the first 12 to 18 months of age.

Nasal bone and nasal septal fractures in older children usually occur from a blow to the face during sports. There is usually a brief period of epistaxis and deviation of the nasal dorsum to one side. Swelling occurs rapidly, and the degree of the cosmetic deformity or the need for fracture reduction may not be easily determined. At the fourth to sixth day after injury, the edema subsides and the need for reduction can be determined. Nasal bone radiographs are of little help in making this judgment; so, the need for nasal fracture reduction is usually based solely on clinical examination. Effective closed nasal fracture reduction may be done up to 2 weeks after the injury. Closed reduction under general anesthesia is the method of choice. Oral antibiotics prevent infection and are essential if nasal packing is used to support the nasal bone.

Although nasal fracture reduction is not urgent, a septal hematoma from a fractured septum should be excluded by the initial physician seeing the child. A septal hematoma that remains untreated may cause cartilage necrosis and loss of nasal support, with a resulting saddle-nose deformity. Treatment of a septal hematoma is with incision and evacuation of the clot. The mucoperichondrial flap should then be sutured in place by bolster sutures through the septum. A small rubber band drain may be required and, if used, should remain in place for 12 to 24 hours, and antibiotics be given for 10 to 14 days to prevent secondary infection while a drain is in place.

Epistaxis in children usually occurs in Little's area of the anterior septum and frequently results from digital trauma (nose picking). The bleeding usually stops with pressure by squeezing the nasal ala. Infrequently, cauterization of the vessels under general anesthesia is needed to reduce the frequency of bleeding. In cases that fail to stop with pressure, the nose should be packed with absorbable materials (such as Gelfoam or cellulose) or nonabsorbable gauze. Finally, in severe cases, embolization or emergent surgery has been used to control bleeding from the internal maxillary and anterior ethmoid arteries, which are the primary sources of nose bleeds. Hematology consultation should be considered in severe or recurrent cases to evaluate for coagulopathies.

### Nasal Foreign Bodies

Children may be observed inserting a foreign body into their nose, or they may inform their parents of the event. Most children, however, present with a foul-smelling unilateral purulent nasal discharge and deny putting anything into their nose.

Most nasal foreign bodies are painless and do no harm to the nose but cause a foul nasal discharge. Disc batteries, on the other hand, cause very rapid alkali burns of the nasal cavity and pain. Batteries must be removed from the nose quickly because the chemical burn occurs in minutes to hours. If extensive tissue necrosis occurs, it may cause a nasal stenosis or septal perforation.

Removal of a nasal foreign body is aided by decongesting the nasal mucosa and using a headlamp to visualize the foreign body. A variety of forceps or hooks may be used. If the object is deep in the nose, the removal is best performed under general anesthesia. The endotracheal tube prevents aspiration of the object into the tracheobronchial tree if it is pushed back into the nasopharynx. One must remember that multiple foreign bodies may be present on one or both sides of the nose.

### Nasal Lacerations

Nasal lacerations should be closed with care to match edges and restore the contours of the nose. Standard wound closure technique is used. The nasal mucosa does not need to be sutured unless a large flap is displaced.

## NASAL/NASOPHARYNGEAL TUMORS

Rhabdomyosarcoma, lymphoma, squamous cell carcinoma, and esthesioneuroblastoma may occur in the nose and sinuses of children. Fortunately, these malignant tumors are very rare in children. The treatment of children with malignant tumors of the nose and sinuses usually involves a multidisciplinary, multimodal approach.

Juvenile nasopharyngeal angiofibroma is a benign tumor of adolescent males that originates from the lateral wall of the nose and nasopharynx. The tumor may completely obstruct the nose and fill the nasopharynx. This type of angiofibroma may also extend intracranially through the base of the skull. Patients with these tumors present with nasal obstruction, recurrent epistaxis, and rhinorrhea.

The tumor may be seen with a flexible fiberoptic nasopharyngoscope or a rod lens telescope after decongesting the nasal mucosa. It appears as a smooth reddish mass. Biopsy of the mass should be avoided because of the potential for severe bleeding. CT and MRI define the extent and location of the tumor. On imaging, the mass originates in the pterygopalatine

fossa within the aperture of the pterygoid (vidian) canal. It causes anterior bowing of the posterior wall of the maxillary sinus and erosion of the greater wing of the sphenoid as it grows into the nose and nasopharynx. MR angiography helps to delineate the blood supply, which may originate from both the internal and external carotid arteries. Contrast angiography may be reserved for presurgical planning and embolization of the copious blood supply that is often present.

The treatment of juvenile nasopharyngeal angiofibroma is complete surgical resection after preoperative embolization. Depending on the material used, the embolization may be effective for days to weeks. A variety of surgical approaches may be used, including endoscopic resection of small tumors using instruments to reduce blood loss, such as suction cautery or coblation tools. Extensive tumors may require a combined midfacial and craniotomy approach.[18]

Some authors have proposed radiation therapy as the primary treatment of juvenile nasopharyngeal angiofibroma, but many surgeons are concerned about the long-term effects of radiation in children, including the induction of malignant tumors.

Nasopharyngeal carcinoma can occur in adolescents and is more common in those of Asian or African descent. It arises from the epithelium of the nasopharynx and histologically is composed of lymphoepithelial cells of variable stages of differentiation. Epstein-Barr viral infection has been implicated as a possible cause in some cases, but genetic factors appear to make some individuals more susceptible to developing this tumor. Most children present with advanced disease and tend to have undifferentiated subtypes. They usually have a history of unilateral nasal plugging and otalgia or hearing loss caused by a blocked eustachian tube. They may also present with metastasis in the posterior triangle lymph nodes. Treatment consists of radiotherapy and, in some cases, adjuvant chemotherapy.

# Oral Cavity/Pharynx

## ANATOMY

The boundaries of the oral cavity include the lips anteriorly, the cheeks laterally, and the palate superiorly. The posterior boundary is a plane that extends from the soft palate to the junction of the anterior two thirds and posterior one third of the tongue. The oral cavity is composed of the vestibule, the space between the lips and cheeks and alveolar ridges, and the oral cavity proper. The vestibule and oral cavity proper are separated by the alveolar ridge and teeth. The vestibule is divided in the midline by the frenula of the upper and lower lips. The alveolar ridge is contiguous superiorly with the hard palate. The parotid ducts (Stensen ducts) enter the vestibule opposite the second maxillary molars. The submandibular ducts (Wharton ducts) enter the floor of mouth near the lingual frenulum.

The palate is formed by a fusion of the primary palate anteriorly and medial growth of the palatal processes that form the secondary palate. The hard palate divides the nasal and oral cavities and is formed by the premaxilla and the horizontal plates of the palatine bones. The soft palate is formed by a muscular aponeurosis of the tensor veli palatini tendon. Five muscles insert into this aponeurosis and include the tensor veli palatini, levator veli palatini, palatoglossus, palatopharyngeus, and the musculus uvulae. Defects in formation of the hard and/or soft palate result in clefting. The sensory and motor innervation of the palate is through the trigeminal nerve and pharyngeal plexus.

The circumvallate papillae divide the tongue into the anterior two thirds that lies in the oral cavity and the posterior one third lying in the oropharynx. The innervation and vascular supply to the two major divisions of the tongue reflect their differences in origin—the anterior two thirds of the tongue being a first branchial arch derivative (trigeminal), whereas the posterior one third being a combination of third and fourth arch derivatives (pharyngeal plexus). The hypoglossal nerve supplies motor innervation to the intrinsic musculature. In addition to the intrinsic tongue musculature, the action of four extrinsic muscles combine to provide mobility. The genioglossus protrudes and depresses, the hyoglossus retracts and depresses, the styloglossus retracts, and the palatoglossus elevates. In addition to the circumvallate papillae, other taste buds on the tongue surface include conical, filiform, fungiform, and foliate papillae.

The pharynx is a fibromuscular tube that extends from the skull base to the level of the cricoid cartilage of the larynx and can be divided into three levels. The nasopharynx extends from the skull base to the level of the soft palate, the oropharynx extends from the soft palate to the tongue base, and the hypopharynx extends from the tongue base to the cricoid cartilage. Three muscular constrictors combine to form the muscular portion of the pharynx: superior, middle, and inferior constrictors. The Passavant ridge is a muscular segment of the superior constrictor that is involved in velopharyngeal closure. Lower fibers of the inferior constrictor help to form the upper esophageal sphincter. The motor and sensory innervation of the pharynx is from the glossopharyngeal and vagus nerves via the pharyngeal plexus.

A collection of lymphoid tissue within the pharynx forms the Waldeyer's ring, which includes the palatine tonsils, the adenoids (pharyngeal tonsil), and lymphoid follicles lining the lateral and posterior pharyngeal walls.

## ACUTE PHARYNGOTONSILLITIS

In addition to the acute onset of sore throat, viral pharyngitis typically presents with fever and malaise. Signs include erythema of the pharynx and cervical lymphadenopathy. Depending on the viral agent, associated symptoms of nasal obstruction and rhinorrhea may also be present. Rhinovirus, coronavirus, parainfluenza virus, respiratory syncytial virus, adenovirus, and influenza virus are agents responsible for viral pharyngitis.

Primary herpetic gingivostomatitis, caused by herpes simplex virus types 1 or 2, presents as fever, adenopathy, and vesicles and ulcers on the lips, tongue, buccal mucosa, soft palate, and pharyngeal mucosa. Herpangina and Coxsackie virus (hand-foot-and-mouth disease) are viral infections that involve the oropharynx. Epstein-Barr virus (EBV) infection (infectious mononucleosis) presents as acute pharyngotonsillitis (often with white sloughing debris on the tonsils), fever, generalized adenopathy, malaise, and splenomegaly. Although EBV infection is suspected by the appearance of 10% or more atypical lymphocytes on a complete blood cell count and the presence of a positive Monospot test, the definitive diagnosis is confirmed by elevated titers of EBV. A short course of

corticosteroids has been proven to reduce the lymphoid hypertrophy that can cause acute airway obstruction.

Group A beta-hemolytic streptococci (GABHS, i.e., *S. pyogenes*) commonly infect the pharynx. In addition to sore throat, associated symptoms include fever, headache, and abdominal pain. Associated signs include pharyngeal erythema, halitosis, tonsillar exudates, and tender lymphadenopathy. Lack of cough helps differentiate it from other upper respiratory tract infections. Diagnosis may be confirmed initially with a rapid streptococcal antigen test. Because rapid antigen testing is more sensitive than formal plating on blood agar, a negative test does not need confirmation, but positive rapid streptococcal tests should be confirmed with formal plating. Other bacterial pathogens that cause acute pharyngitis include *Haemophilus influenzae* and groups C and G beta-hemolytic streptococci. Occasionally, concurrent infection with penicillin-resistant *Staphylococcus aureus* may interfere with treatment of a GABHS infection.[19] Although many cases of GABHS infections respond to treatment with penicillin V or amoxicillin, emerging resistance to oropharyngeal pathogens mandates treatment of recalcitrant cases with an antibiotic having known effectiveness against beta-lactamase–producing organisms. In cases in which a lack of compliance is suspected, intramuscular benzathine penicillin or ceftriaxone may be used.

Acute pharyngitis may also be associated with acute bacterial infections of the nose, nasopharynx, and sinuses. These infections may be caused by a variety of viral and bacterial pathogens; in addition to a sore throat, symptoms include fever, mucopurulent nasal drainage, nasal obstruction, and facial pain.

## RECURRENT PHARYNGOTONSILLITIS

Recurrent infection of the pharynx may be either viral or bacterial. GABHS are the most worrisome bacterial organisms, because recurrent infection may lead to complications such as scarlet fever, acute rheumatic fever, septic arthritis, and acute glomerulonephritis. In addition to a history of multiple positive cultures for *S. pyogenes*, elevated antistreptolysin-O (ASO) titers may identify patients with chronic infection who are at risk for developing complications. Some asymptomatic children may be chronic carriers of GABHS, and elevated ASO titers may not be a reliable indicator for distinguishing between an active infection and the carrier state.

Treatment of recurrent streptococcal infection or the child who is a carrier should include a trial course of an antibiotic shown to reduce carriage (e.g., clindamycin, vancomycin, or rifampin). Children with recurrent pharyngotonsillitis unresponsive to medical therapy or those who suffer a complication should be considered for surgical management. Whereas treatment of each child should be individualized, suggested guidelines for surgical candidates include seven infections in 1 year, five or more infections per year for 2 years, or three or more infections per year for 3 years.[20] Other factors to be considered in using a surgical option include severity of infection, response to antibiotic therapy, loss of time from school, and need for hospitalization.

## CHRONIC PHARYNGOTONSILLITIS

The pharynx and, specifically, the tonsils may be the target of chronic infection. Affected children complain of chronic throat pain, halitosis, and production of white particles or tonsilliths. Signs include erythema of the tonsils, cryptic debris, and chronically enlarged cervical lymphadenopathy. A variety of viral and bacterial agents can be blamed for chronic infection of the pharynx. Cultures may or may not be positive in these patients because surface cultures may be negative while core tissue is positive. Antibiotic therapy directed at oral anaerobes or *S. aureus* may be helpful in resistant cases. Children with infections unresponsive to medical management are candidates for tonsillectomy.

Periodic fever, aphthous ulcers, pharyngitis, and cervical adenitis (PFAPA) is a syndrome that occurs most commonly in young children (mean age 39 months). The cause is unknown. It is characterized by recurrences of fevers that usually last 3 to 7 days, along with aphthous stomatitis, pharyngitis, cervical adenitis, and headache. The recurrences occur in cycles of every 1 to 2 months, and the child is well between episodes. Throat cultures are negative. Antibiotics are not effective in treating this condition, but steroids (prednisone 1 mg per kilogram in a single dose) have been shown to reduce the duration of fever in individual episodes (from 4 days to 1 day in one study); however, sometimes steroids may also reduce the duration of intervals between infections. Most children have spontaneous resolution of these fevers over several years (mean time to resolution is 32 months). Tonsillectomy has been shown to be effective in significantly reducing the duration of this syndrome and frequency of episodes.[21,22]

## ORAL TRAUMA

Injuries to the oropharynx and palate are relatively common in children, usually occurring when a child runs with a toy or stick in his mouth. Most result in mucosal lacerations that spontaneously heal, but larger lacerations may require sedation or anesthesia to repair. Use of prophylactic antibiotics is reserved for larger wounds. Although rare, blunt (and less often penetrating) injuries can occur when the object strikes the jugular vein or the carotid artery that can result in immediate neurovascular injury and poor neurologic outcomes. However, more subtle injuries to the intima of the carotid can lead to pseudoaneurysms that may later develop emboli. These emboli can cause brain infarcts with severe neurologic sequelae over the following several days. Ideally, if a vascular injury has been identified, then aspirin, or, less often, anticoagulant therapy could be used to prevent these emboli from forming. Unfortunately, no specific clinical factors (including size or location of wound) have been shown to correlate with the presence of a subtle vascular injury. Computed tomography angiography (CTA) has been used to rule out a significant vascular injury, but benefit from CTA remains controversial, because only 2.8% of studies are positive.[23]

## PERITONSILLAR CELLULITIS/ABSCESS

Localized extension of tonsillar infection may result in peritonsillar cellulitis. The same pathogens that cause acute pharyngotonsillitis are responsible for peritonsillar cellulitis. In addition to a severe sore throat, symptoms and signs include drooling, trismus, muffled voice, ipsilateral referred otalgia, and tender lymphadenopathy. The affected tonsil is usually displaced in a medial and inferior position. Peritonsillar cellulitis may progress to frank abscess formation (quinsy).

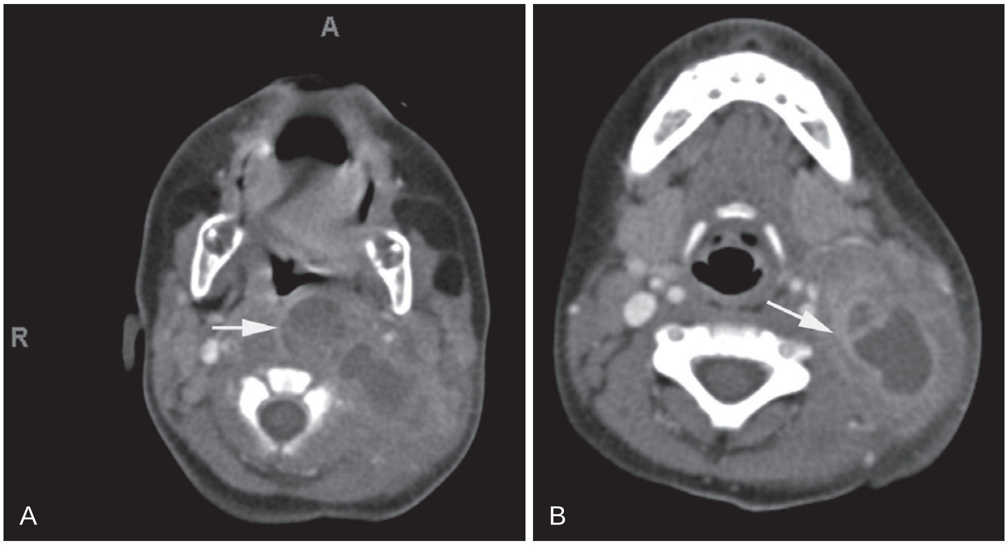


**FIGURE 55-6** **A,** Retropharyngeal abscess. Computed tomography of the cervical area demonstrates fluid loculated in the retropharyngeal space. The abscess is typically unilateral and frequently extends into the medial aspect of the peripharyngeal space. In the absence of associated complications, drainage can be done intraorally (*arrow*). **B,** Lateral neck abscess on the left side (*arrow*).

Early cases of peritonsillar cellulitis may respond to oral antibiotics, such as the penicillins, cephalosporins, erythromycins, or clindamycin. Unresponsive cases of cellulitis or abscess should be treated with intravenous antibiotics. In children with suspected abscess formation, a variety of surgical drainage procedures can be performed. Needle aspiration or incision and drainage have been shown to be equally effective.[24] In persistent cases or in those children who will require general anesthesia for drainage, consideration should be given to performing a tonsillectomy (quinsy tonsillectomy).

## RETROPHARYNGEAL/PARAPHARYNGEAL SPACE INFECTIONS

Signs and symptoms of deep neck space (retropharyngeal/parapharyngeal) infections that involve the pharynx typically are as fever, drooling, irritability, decreased oral intake, torticollis, and/or trismus. Often there is a history of a preceding viral illness. Stridor or symptoms of upper airway obstruction may be seen in half of patients.[25] A neck mass or enlarged cervical nodes may be present, depending on the location of the infection. Usual pathogens include coagulase-positive staphylococci and GABHS. Anaerobic bacteria have been found in as many as 50% of cases.[25] Complications of deep neck space infections include airway obstruction, bacteremia, rupture of the abscess into the pharynx with aspiration, mediastinal extension of infection, jugular thrombosis, and carotid artery rupture.

In suspected cases, the diagnosis of a retropharyngeal/parapharyngeal space infection is confirmed with either contrast medium–enhanced CT or MRI. Widening of the retropharynx on a lateral neck radiograph suggests a retropharyngeal infection. Although ultrasonography can detect the presence of an abscess cavity, CT or MRI are most helpful in demonstrating the extent of infection and the location of surrounding structures of importance, specifically the great vessels. Contrast medium–enhanced CT is particularly useful in distinguishing a phlegmon (cellulitis) from cases of frank suppuration. Demonstration of a hypodense region with surrounding rim enhancement has been shown to correlate with an abscess in 92% of cases (Fig. 55-6).

The initial management of a deep neck infection should begin with intravenous antibiotics, including clindamycin, cefazolin, beta-lactamase penicillins, or a combination thereof. Sixty-seven percent of children with these infections (including those presenting with cellulitis or early abscess) require eventual drainage. Surgical drainage should be reserved for those children who present with airway symptoms along with obvious abscess and for those who fail to show clinical improvement or progress to frank abscess formation on CT after 48 to 72 hours of intravenous (IV) antibiotics. The usual approach to surgical drainage is intraoral, if the abscess points medial to the great vessels, or extraoral, if the infection points lateral to the great vessels.

Complications of deep neck infections should be treated aggressively. Mediastinal spread requires prompt surgical drainage in most cases. An infected jugular thrombosis (Lemierre syndrome) can be a source of metastatic spread of infection as septic emboli. Signs and symptoms include spiking chills and fever (picket-fence fevers) and a neck mass despite appropriate antibiotic therapy. Anticoagulation or excision of the infected thrombus may be required to eradicate the infection.

## SLEEP-DISORDERED BREATHING

In the past decade, the impact of sleep-disordered breathing (SDB) on the health of children has been well described, beginning with the report of normative sleep data by Marcus and colleagues.[26] Children appear to have briefer but more frequent episodes of partial (hypopnea) and complete (apnea) obstruction. Because an apnea of less than 10 seconds may represent several missed breaths in a child, an apnea of any duration is abnormal. In most cases the site of obstruction during sleep is in the pharynx. In contrast to adults with this disorder, in whom the pharyngeal impingement is due to

adipose tissue surrounding the pharyngeal musculature, the major cause of airway obstruction in children results from adenotonsillar hypertrophy.

The apnea index (AI) represents the number of apneas in an hour, with a normal value being less than 1 in children. Because most children have an increased frequency of partial obstructions compared with adults, a measure of hypopneas may be more significant. A hypopnea is variably described as a reduction in airflow or respiratory effort or oxygen desaturation or combination thereof. The apnea/hypopnea index (AHI) is a measure of both apneas and hypopneas in an hour and may be a better reflection of SDB in children. An AHI greater than 5 is abnormal in adults, whereas, an AHI greater than 1.0 to 1.5 is abnormal in children. The upper airway resistance syndrome represents obstructed breathing with normal respiratory indices but with sleep fragmentation and electroencephalographic arousals that indicate disordered sleep.

The major group at risk for SDB includes children with adenotonsillar hypertrophy secondary to lymphoid hyperplasia (Figs. 55-7 and 55-8). Whereas the age of affected children ranges from 2 years through adolescence, the prevalence mirrors the age of greatest lymphoid hyperplasia, 2 to 6 years, the age the tonsils and adenoids are largest in size. Other at-risk groups include syndromic children with Down syndrome who also have relative macroglossia and tend to have larger tonsils and adenoids, children with craniofacial disorders, and patients with cleft palate or storage diseases (Hunter and Hurler syndromes). Adverse effects of obstructive sleep apnea on children include poor school performance, failure to thrive, facial and dental maldevelopment, and, rarely, severe cardiac impairment, including systemic hypertension, cardiac arrhythmias, and cor pulmonale with heart failure.

Daytime symptoms include noisy mouth-breathing, nasal obstruction and congestion, hyponasal speech, and dyspnea on exertion. In contrast to adults, hypersomnolence is uncommon in children because of the lower incidence of gas exchange abnormalities, specifically hypercarbia. Children may complain of headaches, seem irritable, and perform poorly in school. Nighttime symptoms are more obvious and include snoring, gasping, and choking respirations, apnea, coughing, and a variety of other behaviors, including sleepwalking, sleeptalking, rocking, head banging, and bruxism. Enuresis may appear in children with airway obstruction and then resolve after surgical treatment. In addition to enlarged tonsils, signs include the presence of a posterior pharyngeal flap in cleft palate patients, a craniofacial disorder, adenoid facies, and, rarely, evidence of right-sided heart failure.

FIGURE 55-8 Adenoid hypertrophy. Hypertrophy of the adenoids may cause the nasopharynx to be obstructed with tissue. Smaller amounts of tissue are also able to obstruct nasal respiration by growing into the posterior choana as shown in this photograph.

FIGURE 55-7 Tonsillar hypertrophy. Tonsillar hypertrophy is rated on a scale of 1 to 4. Grade 1+ tonsils are hypertrophic, grade 2+ tonsils extend slightly beyond the tonsillar pillars, grade 3+ tonsils extend in a medial direction beyond the anterior tonsillar pillars, and grade 4+ tonsils touch in the midline.

The diagnosis of SDB is suggested by history and physical examination. Confirmation of obstruction and apnea may be made with overnight pulse oximetry and video or audio monitoring of sleep. The gold standard in the diagnosis of obstructive sleep apnea remains formal polysomnography, including measures of nasal and oral airflow, transcutaneous oxygen and carbon dioxide, chest wall movements, electrocardiography, extraocular muscle movements, electroencephalography, leg movements, and gastric pH monitoring in selected cases. Depending on the suspected site of obstruction, adjuvant studies, such as a lateral neck radiograph, MRI of the head and neck, and flexible upper airway endoscopy, might be helpful.

The nonsurgical management of SDB consists of weight loss in obese patients and treatment of underlying allergies and gastroesophageal reflux. Nasal and dental appliances to maintain airway patency that may be useful in adults are usually poorly tolerated in children. Nasal continuous positive airway pressure, the mainstay of treatment in adults, is tolerated in many children and should be considered as a treatment option, especially in patients in whom other therapies have been exhausted or proven ineffective.

The initial surgical treatment for most children with SDB remains a tonsillectomy and adenoidectomy, a therapy that is usually curative. In patients with documented sleep apnea or a sleep disorder, both procedures should be used even if the tonsils appear small. Tonsillectomy and adenoidectomy techniques that have been standard for decades have been supplanted in some institutions by new technology, including use of coblation, harmonic scalpel, and the microdebrider. Efficacy of these newer techniques versus established methods remains unproven.

Complications after tonsillectomy and adenoidectomy usually consist of respiratory compromise and acute or delayed bleeding. Since the advent of modern pediatric anesthesia, respiratory complications, such as aspiration with resultant pneumonia and lung abscess, are rare. Humidification, intraoperative corticosteroids, and antibiotics have all been shown to improve the postoperative course after tonsil and adenoid surgery. Young children are most vulnerable to complications, and, in most institutions, children younger than 3 to 4 years of age are observed overnight for signs of dehydration and respiratory compromise.

Adjuvant surgery in the management of SDB includes craniofacial repair or posterior flap revision surgery in appropriate patients. Midface, mandibular, and hyoid advancement have proved useful in selected patients, along with nasal surgery such as septoplasty, partial inferior turbinectomy, or nasal polypectomy. Tracheostomy remains the treatment of last resort in patients who fail to respond to other forms of therapy.

## ANKYLOGLOSSIA

Ankyloglossia or tongue-tie is a common congenital disorder involving the lingual frenulum (Fig. 55-9). Neonates with diminished tongue mobility resulting from a foreshortened frenulum may have problems in sucking and feeding. Because the frenulum is thin and relatively avascular in neonates and young infants, it can often be incised as an office procedure. In older children the greatest effect of ankyloglossia is on speech and it can lead to dental caries because it may be difficult to clean the lower teeth. Because the tip of the tongue curls under on protrusion and has limited lateral and superior movement, speech articulation may be affected. Surgical treatment in these patients may require a short general anesthetic because the frenulum is thicker and more vascular, requiring surgical correction that includes simple division either with or without a Z-plasty repair.

## MACROGLOSSIA

Macroglossia is uncommon. Generalized macroglossia, as seen in association with Beckwith-Wiedemann syndrome, with glycogen storage diseases (Hunter and Hurler syndromes) or hypothyroidism, is rare. Relative macroglossia can be seen normally on occasion but is most common in Down syndrome. The most serious complication of this condition is airway obstruction. In infants, macroglossia should be distinguished from focal enlargement of the tongue seen in patients with a lymphatic malformation or hemangioma. Glossoptosis, posterior displacement of a normal-sized tongue, is seen in association with cleft palate and micrognathia in infants afflicted with the Pierre Robin sequence. The airway symptoms in most of these infants usually improve over the first year or two of life; so, supportive care is most often recommended (including oral airways and upright positioning with feeding). Infants with severe airway obstruction secondary to an enlarged or displaced tongue may require tongue reduction or a temporary tongue-to-lower lip adhesion suture, respectively. Tracheostomy is reserved for the worst cases. Macroglossia in older children that affects cosmesis, interferes with speech, or causes drooling may be treated with a variety of other tongue reduction techniques.

## BENIGN LESIONS

Epulis is a congenital granular cell tumor that typically presents as a soft, pink submucosal mass on the anterior alveolar ridge of the maxilla (Fig. 55-10). Females are more

**FIGURE 55-9** Ankyloglossia. Abnormal development of the lingual frenulum that limits extension of the tongue tip beyond the mandibular incisors frequently causes articulation disorders and should be corrected.

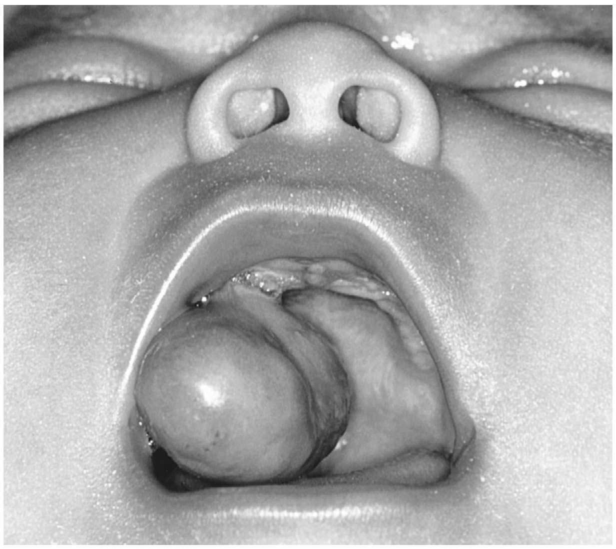

**FIGURE 55-10** Congenital epulis. The congenital epulis is an unusual benign lesion that frequently arises from the anterior maxillary alveolar ridge. Airway and feeding difficulties may develop secondary to large lesions. Surgical excision is required.

**FIGURE 55-11** A ranula is a pseudocyst caused by obstruction of a sublingual gland. It generally presents as a unilateral, painless swelling in the floor of the mouth.

commonly affected, and symptoms are usually confined to feeding problems. Surgical excision is curative.

Ranula is a pseudocyst located in the floor of the mouth that may occur congenitally or result from intraoral trauma (Fig. 55-11). Large ranulas may extend through the mylohyoid musculature and present in the neck as a "plunging ranula." Treatment of ranulas is by excision or marsupialization of the pseudocyst, often in conjunction with excision of the sublingual gland. Mucoceles are also pseudocysts of minor salivary gland origin and frequently rupture spontaneously. Recurrent or symptomatic mucoceles respond to surgical excision.

Hemangioma is a proliferative endothelial lesion found commonly in the head and neck. Their growth characteristics include enlargement during the first year of life, followed by spontaneous resolution. Surgical excision or treatment with corticosteroids may be necessary in lesions that cause ulceration and bleeding, airway obstruction, cardiovascular compromise, or platelet-trapping coagulopathy (Kasabach-Merritt syndrome). Longer-term systemic treatment with propranolol has recently been found to effectively reduce the size of symptomatic hemangiomas and may work by promoting vasoconstriction and downregulation of certain growth factors.[27] Vascular malformations, including venous, arterial, or arteriovenous malformations, rarely occur in the oral cavity and pharynx and necessitate intervention only if they cause pain, bleeding, ulceration, or heart failure. Management of complicated cases is by surgical excision or sclerotherapy for low-flow lesions (venous) and angiographic embolization for high-flow lesions. Lymphatic malformation, formerly known as lymphangioma or cystic hygroma, is congenital and usually presents before 2 years of age. Histologically, lymphatic malformations consist of multiple dilated lymphatic channels or may contain either capillary or venous elements (venolymphatic malformations). Lymphatic malformations have been characterized as microcystic, macrocystic, or mixed based on their histologic patterns. Lymphatic malformations can occur anywhere in the neck and may cause extensive cosmetic deformity and functional problems in cases with involvement of the tongue, floor of mouth, mandible, or larynx. Deep and macrocystic disease may be controlled with aspiration and sclerotherapy performed by interventional radiologists, whereas treatment of microcystic or more superficial disease usually is surgical. Surgical resection of lymphatic malformations may be fraught with difficulty because they lack a capsule and are infiltrative. During surgical excision, care should be taken to avoid damaging nearby vital structures, and debulking is an acceptable option to total radical excision in many cases. Postoperative suction drains can be helpful in preventing the recurrence of lymphatic drainage under skin flaps. Coblation therapy and carbon dioxide laser therapy have been used in superficial lymphatic malformations of the tongue.

Foregut cysts are true cysts, lined with respiratory epithelium, that present in the floor of mouth and should be distinguished from dermoid cysts, lined with stratified squamous epithelium and skin appendages, which may also be found in this location. A thyroglossal duct cyst may rarely present in the base of the tongue. Likewise, aberrant thyroid tissue, lingual thyroid, presents as a purple mass in the tongue base. Thyroid tissue in this location is usually hypofunctioning, and affected children require thyroid supplementation. Other aberrant rests of tissue, choristomas, consist of gastric, enteric, or neural tissue of normal histology in an abnormal location.

Second branchial cleft derivatives will rarely present as a cystic mass near the superior pole of the tonsil. Their extent and associated tracts can be demonstrated on MRI. A Tornwaldt cyst is a blind pouch in the nasopharynx that represents a persistence of an embryonic connection between the primitive notochord and the pharynx. Other benign nasopharyngeal masses include nasopharyngeal teratomas, dermoid lesions (hairy polyp), and nasopharyngeal encephaloceles. Most of these lesions are best evaluated by CT and/or MRI to determine their extent and the presence of an intracranial connection. Surgical excision is curative in most cases.

Squamous papillomas are benign slow-growing lesions typically found on the soft palate, uvula, and tonsillar pillars and are the result of infection with serotypes 6 and 11 of the human papillomavirus (HPV). Because of concern that these lesions could spread to the larynx or trachea, complete surgical excision is usually recommended. Pleomorphic adenoma (mixed tumor) is a benign neoplasm of minor salivary glands with a predilection for the palate, although it may also be found in the lip and buccal mucosa. Treatment is with surgical excision.

## MALIGNANT LESIONS

Rhabdomyosarcoma, the most frequent soft tissue malignancy of childhood, typically occurs in the 2- to 6-year-old group and is derived from embryonic skeletal muscle.[28,29] In the oral cavity and oropharynx, it presents as a rapidly growing mass in the tongue, palate, and uvula or cheek. These tumors metastasize early to local lymph nodes, lung, and bone. Surgical therapy is limited to biopsy, excision of small lesions, or surgical salvage of treatment failures. The usual therapy includes a combination of chemotherapy and radiation therapy.

Lymphoma of the oral cavity and oropharynx typically involves the lymphoid tissue of the Waldeyer ring and presents

as a mass of the tonsil or in the nasopharynx.[30] The diagnosis may be suspected by evidence of involved adenopathy in the neck but is confirmed by surgical biopsy. Treatment is with a combination of chemotherapy and radiation therapy.

Other rare malignant neoplasms of the oral cavity and pharynx include malignant salivary gland tumors (mucoepidermoid carcinoma) and epidermoid or squamous cell carcinoma. This latter tumor has been reported in organ transplant patients and adolescents who use snuff or chewing tobacco.[31] Treatment is usually surgical depending on the site and extent of involvement.

# Larynx

## ANATOMY

With the exception of the hyoid bone, the major structural framework of the larynx consists of cartilage and soft tissue. The hyoid bone lies superior to the larynx and is attached to it by the thyrohyoid membrane and strap muscles. The hyoid bone is derived from the second and third branchial arches. The cartilaginous structures of the larynx are composed of hyaline cartilage, with the exception of the epiglottis, which is composed of elastic cartilage. The cartilaginous structures of the larynx develop from the fourth, fifth, and sixth branchial arches. There are nine laryngeal cartilages, three that are single (thyroid, cricoid, and epiglottis) and six that are paired (arytenoid, cuneiform, and corniculate). The thyroid cartilage consists of two quadrilateral cartilages that form the anterior framework of the larynx. The cricoid cartilage is the only completely cartilaginous structure in the airway and provides posterior stability and a base of support for the cricoarytenoid and cricothyroid joints.

The cricothyroid muscles are paired extrinsic laryngeal muscles that serve to tilt the larynx down and forward, tensing the vocal folds. Paired intrinsic muscles—the thyroarytenoid, thyroepiglottic, and aryepiglottic muscles—act as a sphincter to close the larynx. The vocalis muscle comprises the internal fibers of the thyroarytenoid muscle and attaches to the vocal ligament. Action of this muscle serves to regulate the pitch of the vocal ligament. The other set of paired muscles includes the posterior cricoarytenoid, lateral cricoarytenoid, and interarytenoid muscles. The posterior cricoarytenoid muscles serve to abduct the vocal folds, whereas the cricoarytenoid and interarytenoid muscles adduct the vocal folds.

The quadrangular membrane is a connective tissue covering of the superior larynx that ends in a free margin along the vestibular ligament of the false cord. The conus elasticus is a membrane of elastic tissue that extends superiorly from the cricoid cartilage to form the paired vocal ligaments, the supporting structures of the vocal folds.

The blood supply of the larynx arises from the superior and inferior laryngeal arteries. The former is a branch of the superior thyroid artery, whereas the latter is a branch from the thyrocervical trunk. The intrinsic muscles of the larynx are innervated by the recurrent laryngeal nerve, which also supplies sensory branches to the inferior larynx. The superior laryngeal nerve has two branches: The external branch innervates the cricothyroid muscle, while the internal branch supplies sensation to the superior larynx.

The larynx has multiple functions within the upper airway. During respiration, it regulates airflow by opening during inspiration. The posterior cricoarytenoid muscle contracts with each inspiration to abduct the cords just before activation of the diaphragm. The protective function of the larynx produces two reflexes: cough and closure. Cough is important to expel mucus and foreign objects. The closure reflex serves to prevent aspiration of foreign matter. In addition to closure, the larynx elevates during swallowing. Both closure and elevation occur simultaneously along with relaxation of the cricopharyngeus muscle during the swallow of a bolus. Finally, the larynx plays an important role in speech production by generating sound. Vibration of the mucosa covering the vocalis structures produces sound whose pitch and register is altered by changes in tension, length, and mass of the underlying vocalis muscle and ligament.

The larynx of an infant sits much higher than that of an adult. The cricoid is located at the level of C4, whereas the tip of the epiglottis is at C1. The close approximation of the epiglottis to the soft palate makes the infant an obligate nose breather. By 2 years of age, the larynx has descended to the level of C5 and reaches the adult level of C6 to C7 by puberty. The glottis of the newborn is 7 mm in the anteroposterior dimension and 4 mm in the lateral dimension. The narrowest area of the infant airway, the subglottis, is approximately 4 mm in diameter.

## UPPER AIRWAY ASSESSMENT

Symptoms of acute airway obstruction include dyspnea, cough, vocal changes, dysphagia, and sore throat. Dyspnea and rapid or labored breathing are indications of inadequate ventilation and may be triggered by changes in $PCO_2$ and $PO_2$. A stimulus anywhere in the airway may produce cough. It is difficult to localize the site of the stimulus from the quality of the cough. Changes in the child's vocal character, such as hoarseness or a muffled or weak cry, may help in localizing the area of obstruction. Dysphagia for solids and/or liquids is often associated with airway obstruction. Depending on the cause of airway obstruction, affected patients may complain of sore throat.

The child's overall appearance is the first sign to be assessed in airway obstruction, because airway status often dictates how quickly further evaluation and intervention need to be performed. The level of consciousness should be determined, because the unconscious or obtunded patient may need immediate airway management. Along with cyanosis in a patient without cyanotic heart disease, the presence of anxiety, restlessness, and diaphoresis are all ominous signs of impending airway compromise. Other symptoms of airway obstruction include tachypnea and substernal retractions. The child with airway obstruction is often tachycardic. The presence of bradycardia is a late indicator of severe hypoxia. The presence of a muffled cry often suggests obstruction at the level of the pharynx, whereas a barking cough is associated with laryngeal inflammation and edema. Stertor is a snorting sound whose origin is often in the pharynx. Stridor is noise produced by turbulent airflow in the laryngeal or tracheal airway. Inspiratory stridor suggests turbulence at or above the glottis. Expiratory stridor results from turbulent airflow in the distal trachea or bronchi. Biphasic stridor suggests a tracheal or subglottic source. A barking or croupy cough usually occurs when the

subglottic trachea is involved. The degree and loudness of the sound is not always indicative of the severity of obstruction, because stridor can become softer just before complete obstruction. Other important signs of airway obstruction include drooling and use of accessory respiratory muscles.

In addition to determination of the child's physical status, assessment of the degree of airway obstruction should include an evaluation of the ventilatory status. Pulse oximetry provides an immediate record of arterial oxygenation, while transcutaneous monitoring of carbon dioxide is a good indicator of ventilation. The lateral neck radiograph remains the best study for the initial evaluation of a child with airway obstruction, because it demonstrates the anatomy from the tip of the nose to the thoracic inlet. It can demonstrate findings of retropharyngeal or subglottic swelling from edema or infection and identify free air in the soft tissue spaces. The anteroposterior view of the neck is also helpful, specifically in defining areas of narrowing, such as a steeple sign associated with subglottic edema. A chest radiograph is also important in the initial assessment to identify foreign bodies or other conditions such as unilateral emphysema, atelectasis, or pneumonia that may account for the child's respiratory compromise. If time permits, a barium swallow or airway fluoroscopy may provide additional information.

Additional airway evaluation may include a brief flexible endoscopic examination. The nose is first sprayed with a combination of 2% lidocaine and oxymetazoline, and the child is gently restrained. The airway can be examined from the nares to the glottis. Attempts to pass a flexible scope through the glottis in a child with airway obstruction should be avoided. Likewise, flexible endoscopy should be avoided in a child with supraglottitis because of the possibility of precipitating complete obstruction. Children with suspected airway pathology distal to the glottis or those in whom the possibility that flexible endoscopy could compromise the airway should undergo any airway examination in the operating room where rigid endoscopes and other airway equipment is immediately available to secure the airway if necessary.

Nonsurgical intervention in the child with acute airway obstruction may begin with just observation alone in a high surveillance unit. Humidified oxygen administered by face mask will improve $PO_2$ and clearance of secretions. Racemic epinephrine administered by nebulizer acts to reduce mucosal edema and is useful in conditions such as laryngotracheobronchitis (infectious croup). Because its length of action lasts 30 to 60 minutes, treated patients should be observed for signs of rebound for 4 to 6 hours after administration. Corticosteroids have been shown to have value in the management of postintubation croup, adenotonsillar hypertrophy that results from EBV infection, allergic edema, and spasmodic and viral croup. Corticosteroids and propranolol have been used successfully in infants to treat subglottic hemangiomas.[32,33]

Other adjuvant therapies include antibiotics and inhalation of helium/oxygen mixture (heliox). Although viral agents are often responsible for inflammation in the larynx and trachea, bacterial superinfection is also common. Because of the prevalence of penicillin-resistant organisms, broad-spectrum antibiotics, including a higher-generation cephalosporin, penicillinase-resistant penicillin, or beta-lactamase penicillin, are useful in preventing or eradicating infection. Heliox is a mixture of gas in which helium is used to replace nitrogen. The advantage of the helium-oxygen mixture is that its low density reduces air turbulence and gas resistance, allowing improved delivery of oxygen in patients with airway obstruction.

Nonsurgical airway management may include use of nasal or oral airways, endotracheal intubation, and, rarely, transtracheal ventilation. Nasal airways of rubber or other synthetic material can be easily inserted into the nose of most children after adequate lubrication with a water-soluble lubricant. Their best use is in cases where the pharynx is the site of obstruction. Oral airways are not as readily tolerated by children and only serve as a brief solution to an airway problem. During the 1970s, endotracheal intubation with polyvinyl chloride tubes revolutionized the management of supraglottitis, and even today intubation remains the mainstay of initial airway therapy in most children with severe airway obstruction. The size of the endotracheal tube used correlates with the age of the child. The subglottis, the narrowest part of the infant airway, typically admits a 3.5- or 4.0-mm inner-diameter tube. The tube used in children older than 1 year can be roughly estimated by using the following formula: tube size $=$ (age in years/4) $+$ 4. Once the airway has been established, the tube should be carefully secured and the child appropriately sedated and/or restrained, if necessary, to avoid accidental self-extubation. Another method of airway management should be considered in children with an unstable cervical spine or in whom oral or neck trauma makes visualization difficult. Transtracheal ventilation, insertion of a 16-gauge needle through the cricothyroid membrane for the delivery of oxygen, should be reserved for emergencies and used only until a more stable airway can be obtained.

The surgical management of the child with acute airway obstruction should begin with endoscopy. The larynx can be visualized with one of a variety of pediatric laryngoscopes and the airway secured with a rigid pediatric ventilating bronchoscope of appropriate size. Once the airway is secured, a more stable form of airway management can be used. Rarely, in a child with acute airway obstruction, an airway cannot be established, and a cricothyrotomy may need to be performed. As in adults, this procedure avoids some of the risks of bleeding and pneumothorax inherent in a formal emergency tracheostomy. A small endotracheal or tracheostomy tube can be inserted through the incision in the cricothyroid membrane, but conversion should be made to a more stable airway as soon as possible. Tracheostomy remains the preferred airway in cases of acute obstruction in which a translaryngeal approach is unsuccessful or must be avoided. The emergent tracheostomy should be avoided if at all possible to lessen complications of bleeding, pneumothorax, pneumomediastinum, subcutaneous emphysema, or damage to surrounding structures. The incidence of these complications can be reduced by careful attention to surgical technique, good lighting, and adequate assistance.

## CONGENITAL LARYNGEAL ANOMALIES

Laryngomalacia is the most common cause of newborn stridor and is caused by prolapse of the supraglottic structures (arytenoid cartilages, aryepiglottic folds) during inspiration (Fig. 55-12). Symptoms typically appear at birth or soon thereafter and include high-pitched inspiratory stridor, feeding difficulties, and, rarely, apnea or signs of severe airway obstruction. Gastroesophageal reflux disease (GERD) is common in children with laryngomalacia and tends to worsen the

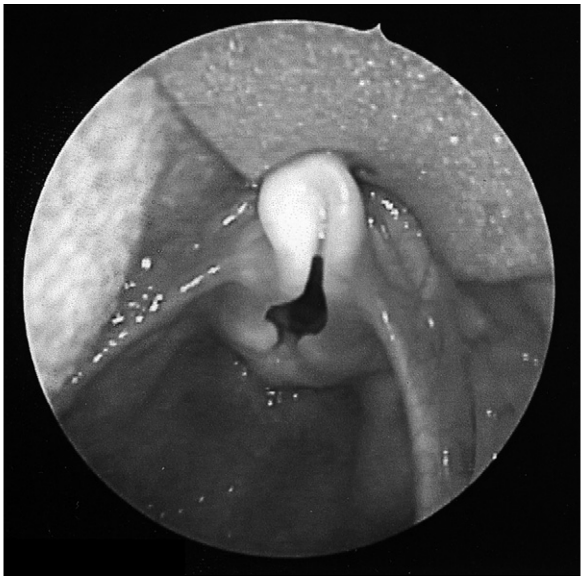

**FIGURE 55-12** Laryngomalacia. This disorder classically presents as an omega-shaped epiglottis. The arytenoid mucosa is redundant, and the aryepiglottic folds are foreshortened. The result is a hooding of tissue over the glottic inlet that leads to airway obstruction on inspiration.

airway symptoms, because it creates swelling of the posterior cricoid region of the larynx. The diagnosis of laryngomalacia is confirmed by flexible endoscopy of the larynx, and other airway pathology can be excluded with lateral neck, chest, and airway fluoroscopy. Barium swallow radiography is helpful to identify the presence of GERD. In most cases, laryngomalacia is self-limited and resolves by 18 months of age. Changes in positioning and feeding, treatment of reflux, and, in some neonates, use of monitoring may be necessary. In severe cases, surgical intervention with either a supraglottoplasty (surgical division with or without partial resection of the aryepiglottic folds) or a tracheostomy may be necessary.

Tracheobronchomalacia is defined as collapse of the tracheobronchial airway. It may be congenital or acquired (from long-standing intubation and infection) and may be segmental or involve the entire tracheobronchial tree. Depending on the extent and location, symptoms include low-pitched biphasic or expiratory stridor and signs of respiratory compromise. The diagnosis is usually made with endoscopy, although fluoroscopy of the airway may often demonstrate it. Treatment ranges from observation in most cases to airway management with a tracheostomy tube and positive-pressure ventilation in severe cases. Tracheomalacia may be localized, especially when associated with esophageal atresia, and aortopexy is occasionally the treatment of choice if due to extensive compression from vessels (see Chapter 69). Tracheal stents have also been used for more extensive tracheomalacia.

Vocal fold paralysis is the second most common congenital laryngeal anomaly (after laryngomalacia) and may be unilateral or bilateral. Congenital vocal fold paralysis may be caused by neurologic abnormalities (hydrocephalus, Arnold-Chiari malformation), birth trauma, or, rarely, in association with neoplasms of the larynx or neck. Acquired vocal fold paralysis may result from trauma or from neoplasms of the chest or neck, or it may be iatrogenic, typically after surgery of the neck, esophagus, or arch of the aorta. The risk of vocal cord paralysis is higher in premature babies who have surgery before they reach normal birth weights. Neonates with bilateral involvement typically present with high-pitched inspiratory or biphasic stridor but a good cry. Respiratory compromise and feeding difficulties may accompany the stridor because the vocal cords cannot abduct and the resultant airway is narrow. However, compensatory extralaryngeal muscles can help adduct the cords to produce a strong voice. In infants with unilateral involvement, the airway may be adequate because the affected vocal cord remains partly lateralized at rest. Unlike the case of bilateral vocal cord paralysis, the extralaryngeal muscles cannot cause the cord to adduct upon vocalization or during a swallow. As a result, these infants are at increased risk of aspiration and often have breathy, weak voices. The diagnosis of unilateral or bilateral vocal fold paralysis is confirmed with flexible or rigid endoscopy. Additional studies in the evaluation of patients with vocal fold paralysis include lateral neck and chest radiography, barium swallow, and CT or MRI of the head and neck. Most children with unilateral involvement can be observed. As they grow, they may be candidates for vocal cord medialization procedures, whereby, agents such as Gelfoam or Teflon are injected lateral to the cord to improve vocalization. Another treatment option is ansa cervicalis–to–recurrent laryngeal nerve anastomosis to reinnervate the affected cord. This increases the tone, bulk, and tension of the cord, but does not restore normal mobility.[34] Infants with bilateral vocal fold paralysis often require a tracheostomy. In addition, infants with associated feeding difficulties may need a gastrostomy. In older children (4 or 5 years of age) with bilateral vocal cord paralysis, a more permanent solution, such as a cordotomy or arytenoidectomy, can be considered to improve the glottic airway and to allow for decannulation of the tracheotomy tube.

Congenital subglottic stenosis is the third most common congenital laryngeal anomaly and is defined as a neonatal larynx in a term baby without a history of prior instrumentation or intubation who fails to admit a 3.5-mm endotracheal tube (Fig. 55-13). The underlying abnormality is a cricoid cartilage that is either small or deformed. Children with Down syndrome are at higher risk for this condition. Infants with congenital subglottic stenosis present with inspiratory

**FIGURE 55-13** Subglottic stenosis. Congenital and acquired stenosis create airway obstruction, depending on the severity and type of stenosis. Various forms of reconstruction are available (see Chapter 65).

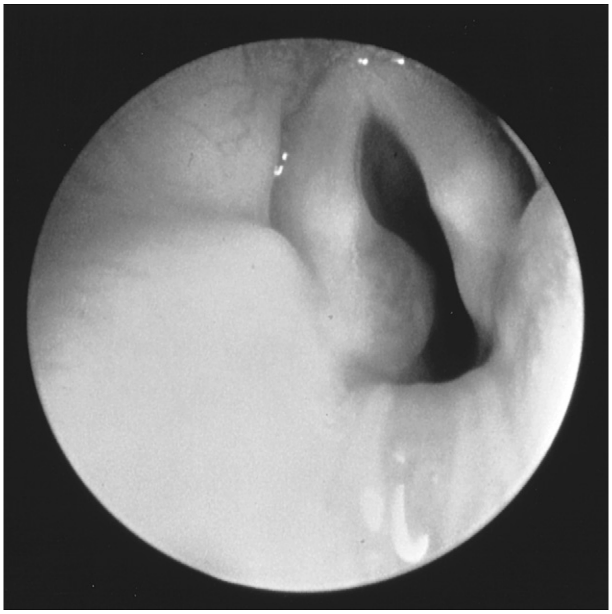

**FIGURE 55-14** Subglottic hemangiomas typically arise from the posterior lateral aspect of the larynx. Small lesions may be managed conservatively, whereas lesions with aggressive growth patterns that do not respond to propranolol or steroids require tracheotomy to bypass the laryngeal obstruction.

or biphasic stridor, barking cough, and other symptoms of airway obstruction. The diagnosis is often suggested by narrowing of the subglottis on a lateral neck radiograph and confirmed by endoscopy. Treatment depends on the severity of symptoms and ranges from observation to laryngeal reconstruction to tracheostomy.

A child with a subglottic hemangioma presents with the onset of progressive stridor during the first few months of life (Fig. 55-14). Hemangiomas are proliferative endothelial lesions that can form in the submucosa of the posterior and lateral subglottis. Occasionally, they may involve the subglottis in a circumferential pattern. Associated cutaneous hemangiomas may be found in approximately 50% of patients, but only 1% of patients with cutaneous lesions have airway lesions. Symptoms are dependent on the amount of airway compromise and include biphasic stridor, barking cough, difficulty feeding, and other symptoms and signs of airway obstruction. The diagnosis may be suggested on a lateral neck radiograph but is confirmed with endoscopy. Nonsurgical management of infants with a subglottic hemangioma includes observation or treatment with systemic corticosteroids or propranolol. Surgical therapy includes laser excision, open excision through a laryngofissure, or a tracheostomy.

A laryngocele is an air-filled dilatation of the saccule of the larynx that communicates with the laryngeal airway. It may present internally into the posterior superior false cord region or externally through the thyrohyoid membrane. A saccular cyst is fluid filled and protrudes between the true and false vocal folds. The diagnosis of this lesion is confirmed endoscopically, and CT of the larynx is helpful in assessing its extent and if it is fluid or air filled. Treatment is with endoscopic marsupialization or excision through a laryngofissure.

## INFLAMMATORY DISEASE OF THE UPPER AIRWAY

Laryngotracheobronchitis (viral croup) is an inflammation of the subglottic airway caused by a variety of parainfluenza and influenza viral agents. The infection may involve the entire glottis and extend into the trachea and bronchi. Affected children fall typically into the 1- to 3-year-old group; males are more commonly affected than females. Symptoms and signs of viral croup include biphasic stridor, barking cough, and hoarseness, often in association with a prodromal viral upper respiratory tract infection. The diagnosis of croup is made clinically, but endoscopic examination may help to exclude other pathologic processes. Care should be taken not to instrument the subglottis, causing more swelling and inflammation and precipitating acute obstruction. Lateral neck radiography demonstrates subglottic narrowing, whereas anteroposterior neck films show a "steeple sign," the result of subglottic edema. Treatment of viral croup is typically supportive with humidification. Treatment with nebulized racemic epinephrine in the emergency department or hospital setting often relieves symptoms; however, rebound of signs may occur several hours later, and children should be monitored accordingly. A meta-analysis of randomized controlled trials has shown treatment with glucocorticoids is effective in improving symptoms within 6 hours, for up to 12 hours, with significant improvement in croup scores, shorter hospital stays, and less use of epinephrine.[35] Severely affected children may require intubation for respiratory failure (less than 5% of affected patients). A smaller than normal tube should be chosen to avoid edema and scarring. In rare cases, a tracheostomy may be required if the inflammation fails to resolve.

A child younger than 1 year of age with recurrent bouts of "croup" should be suspected of having either congenital subglottic stenosis or a hemangioma. Spasmodic croup is the recurrence of crouplike symptoms in a child who is otherwise well. Fever is rarely present, and the attacks frequently occur at night. Gastroesophageal reflux disease has been suggested as a possible inciting process. Treatment of spasmodic croup is usually observant, although corticosteroids or antireflux medications may prove beneficial.

Supraglottitis (epiglottitis) is an infectious disease that involves the supraglottic larynx. In children, the most common pathogen is *Haemophilus influenzae* type B (HIB), followed by *S. pneumoniae* and *S. aureus*. The incidence of supraglottitis in children has diminished markedly since the introduction of the conjugated HIB vaccine in the early 1990s.[36] However, HIB-related supraglottitis continues to occur in children who have been vaccinated, with a reported 2% vaccine failure rate. Alternatively, *S. pneumoniae, S. aureus,* and viruses are more likely to cause supraglottitis in adolescents and adults.

Children who develop supraglottitis are somewhat older than those seen with croup in the 2- to 6-year-old group. Symptoms and signs have a rapid onset, progress quickly to frank airway obstruction, and include stridor, dysphagia, fever, muffled voice, and signs of systemic toxicity. Affected children frequently sit and assume the "sniffing" position in an attempt to maximize their airway. Intraoral or endoscopic examination should be avoided in suspected patients because of concern for precipitating complete obstruction. Lateral neck radiography demonstrates a classic "thumbprint sign" of the epiglottis but should only be obtained if facilities are present in close proximity to secure the airway.

Prompt airway management is essential in children with supraglottitis. In severe cases, the child's airway should be secured in either the emergency department or operating room with team members, including a pediatrician, anesthesiologist, critical care physician, otolaryngologist, or pediatric surgeon or others familiar with the pediatric airway. After inducing the child with general anesthesia, the airway should be intubated. Examination of the supraglottis may be made, and cultures of the larynx and blood are obtained. Equipment to perform a tracheostomy should be readily available. The child should remain intubated for 24 to 72 hours and should be supported with intravenous fluids and antibiotics that treat antibiotic-resistant *H. influenzae, S. pneumoniae*, and *S. aureus* (third-generation cephalosporins or ampicillin-sulbactam).

Bacterial tracheitis (membranous croup) often occurs as a complication of another infection, such as measles, varicella, or other viral agents. The most common organisms include *S. aureus,* GABHS, *M. catarrhalis,* or *H. influenzae*. It can occur in any age child and present with stridor, barking cough, and low-grade fever. Symptoms and signs then progress to include high fever and increasing obstruction and toxicity. The diagnosis may be suspected by diffuse narrowing of the tracheal air shadow on chest radiograph but is confirmed by endoscopic examination in the operating room. Purulent debris and crusts can be removed at this time. Cultures of secretions and crusts may be helpful in guiding intravenous antibiotic therapy that should be aimed initially at the usual pathogens. The airway should be secured with an endotracheal tube or, rarely, a tracheostomy. Repeat endoscopic examination of the airway may be warranted to continue debridement and to determine the feasibility of extubation.

## CHRONIC AIRWAY OBSTRUCTION

The chronic management of subglottic stenosis and other prolonged airway disorders is discussed in Chapter 65.

## BENIGN LARYNGEAL NEOPLASMS

Recurrent respiratory papillomatosis (RRP) is the most common benign neoplasm of the larynx in children. Squamous papillomas involve the larynx and, occasionally, the trachea and lower respiratory tract as exophytic lesions. Because of its recurrent nature, RRP causes morbidity and, rarely, mortality resulting from malignant degeneration. Patients may be almost any age, but the disease is more aggressive in children. Human papillomavirus (HPV) subtypes 6, 11, 16, and 18 have all been identified within papilloma tissue. The first two subtypes have been associated with genital warts, whereas the latter two have been associated with cervical and laryngeal cancers. The exact mechanism of HPV infection in the larynx remains unknown. In most cases, transmission of virus to the child is thought to occur via vaginal birth in a mother with cervical HPV infection or warts. However, children can still get RRP even when born by cesarean section.

Children afflicted with RRP present initially with hoarseness but may also have symptoms and signs of airway obstruction, including stridor. Lateral neck radiography may suggest laryngeal involvement, but the diagnosis is confirmed by direct laryngoscopy and biopsy (Fig. 55-15). In addition to the trachea and bronchi, squamous papillomas may also be found in the oral cavity.

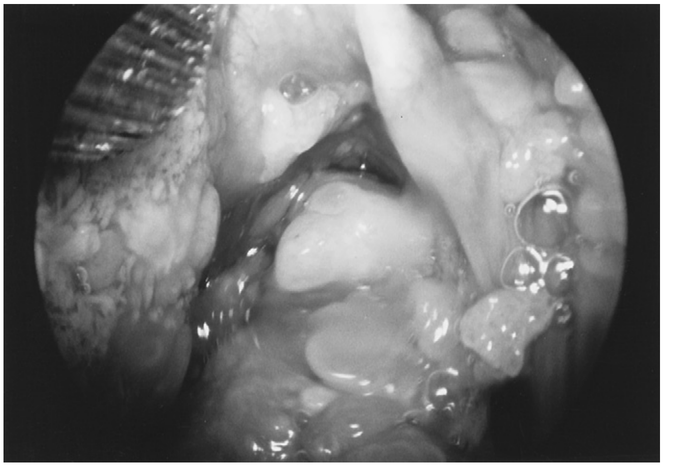

**FIGURE 55-15** Recurrent respiratory papillomatosis. Severe papillomatosis may completely obstruct the larynx. Papillomas are characterized by malignant degeneration and aggressive growth patterns.

Surgical excision is the mainstay of therapy in patients with RRP. In the past, papillomas were excised using the carbon dioxide laser. More recently, the laryngeal microdebrider has become the preferred method of excision in many centers. In aggressive cases with swift recurrence and accompanying airway obstruction, tracheostomy may be necessary for airway management, although tracheostomy has been implicated in the spread of disease to the trachea and lower respiratory tract. Medical adjuvant therapy that has been used with mixed results includes interferon, photodynamic therapy with dihematoporphyrin ether, indole-3-carbinol, or antiviral agents such as cidofovir.

Other benign laryngeal neoplasms are rare and include connective tissue tumors such as chondromas or fibromas, neurogenic tumors such as neurofibromas, or granular cell tumors and other cell types such as hamartomas or fibrous histiocytomas. Malignant tumors of the larynx are also rare and include squamous cell carcinoma and a variety of epithelial and connective tissue malignancies, such as spindle cell carcinoma, rhabdomyosarcoma, mucoepidermoid carcinoma, and chondrosarcoma. Metastatic tumors and lymphoma may also rarely involve the larynx in children. Diagnosis is suspected by the sudden appearance of stridor, hoarseness, and airway obstruction and confirmed by biopsy. Treatment is dependent on cell type and may include surgical excision, radiation therapy, and/or chemotherapy.

# Neck

## ANATOMY

The surgical anatomy and embryology of the neck is discussed in Chapter 59.

## CLINICAL EVALUATION

The initial examination of a disease or disorder of the neck begins with a thorough history. A detailed history can often serve to focus the differential diagnosis of a neck disorder. The age of the child is an important first consideration. The appearance of a neck mass in an infant often suggests a

congenital disorder, whereas the sudden appearance of a mass in an adolescent might suggest a malignant process. Inflammatory diseases of the neck may occur in any age group but typically mirror the incidence of upper respiratory tract infections in children. Growth and temporal relationships are often important clues to a diagnosis. Neck masses that grow rapidly suggest either an inflammatory or malignant process, whereas slow-growing masses are typically benign. A history of systemic infection elsewhere in the body or recent travel or exposure to farm animals often points to an infectious origin. A history of trauma to the neck may explain the sudden appearance of a neck mass. Likewise, changes in the size of a neck mass with eating may suggest a salivary gland origin. Vascular lesions enlarge with straining or crying. Finally, systemic symptoms of fever, weight loss, night sweats, or fatigue in association with the sudden development of a neck mass may indicate a malignant process.

The physical examination of a child with a neck mass should begin with a comprehensive examination of the entire head and neck. Because the vascular, neural, and lymphatic patterns of the head drain into the neck, the source of neck disorders may be found in the head. Depending on the differential diagnosis, a physical examination of the entire body, including an assessment of lymph nodes in the groin and axillae and the presence of an enlarged spleen or liver, is essential. Palpable lymph nodes in the neck of children are a common finding, but lymph nodes larger than 2 cm fall outside the range of normal hyperplastic nodes and should be either monitored or investigated. The sudden appearance of large nodes in either the posterior cervical or supraclavicular regions may suggest a malignancy, especially if unilateral.[37] The consistency of a neck mass is also important in narrowing the differential diagnosis. Hard masses tend to be associated with either infection or malignancy. Fixation of a neck mass to skin or nearby structures is also suggestive of a malignancy. Cysts or abscesses tend to have a characteristic feel on palpation and are usually ballotable, and the overlying skin may be inflamed if infected. Depending on the differential diagnosis after a history and physical examination, radiologic studies may be useful. A lateral neck radiograph may demonstrate an abnormality of the nasopharynx, retropharynx, or cervical spine. Likewise, a chest radiograph may identify a malignancy, sarcoidosis, or tuberculosis. Infection or a neoplastic process in the sinuses may appear on a sinus series. CT and MRI are useful in the evaluation of a neck mass. Demonstration of hypodensity on CT suggests an inflammatory or necrotic process. Ring enhancement of a hypodense region on a contrast CT scan is indicative of an abscess. MRI is excellent for distinguishing fine detail within soft tissue and in the evaluation of vascular lesions of the neck. Finally, ultrasonography is helpful in distinguishing solid and cystic masses and may be the only imaging modality required in the assessment of neck masses. Use of ultrasonography preoperatively in patients with a thyroglossal duct cyst is also a simple and economic way to assess the presence of normal thyroid tissue when it is not easily felt. Ultrasonography should be used in the assessment of any thyroid mass, while thyroid scanning is now thought to be of limited value in the pediatric age group.

Selected laboratory studies may be helpful in the evaluation of a child with a neck disorder. A complete blood cell count with differential may identify patients with either a malignancy or systemic infection. Serologic testing for EBV or cytomegalovirus infection, toxoplasmosis, or cat-scratch disease may be diagnostic. Thyroid function testing is essential in any child with a suspected thyroid disorder. Finally, collection of urine for catecholamine metabolites (vanillylmandelic acid) may assist in the diagnosis of neuroblastoma.

If the diagnosis remains in doubt at this point, incisional or excisional biopsy may be indicated. Biopsy provides material for pathologic examination, culture, and other more sophisticated testing if necessary. Fine-needle aspiration of a neck mass in children for suspected malignancy is not as reliable as in adults.

## CONGENITAL TRACTS AND CYSTS

Congenital sinuses and cysts are discussed in Chapter 59.

## INFLAMMATORY AND INFECTIOUS MASSES

Viral adenitis is the most common infectious disorder to involve the neck in children. Enlarged or hyperplastic lymph nodes are frequently the result of viral upper respiratory tract illnesses. Common pathogens include rhinovirus, adenovirus, and enterovirus, but measles, mumps, rubella, varicella, EBV, and cytomegalovirus may also cause lymphadenopathy. The diagnosis is often suspected by other findings in the history or physical examination and can be confirmed by serologic testing. Acute human immunodeficiency virus infection may present, as do other viral syndromes, with fever, headache, malaise, gastrointestinal symptoms, and a neck mass.

The usual source of bacterial cervical adenitis is the pharynx. Causative organisms are often streptococcal or staphylococcal species. Patients present with systemic symptoms of fever and malaise in addition to a neck mass that is diffusely swollen, erythematous, and tender. In contrast to viral adenitis, which is frequently bilateral, bacterial infections of the neck are usually unilateral. CT with contrast medium enhancement may be helpful in the evaluation of large infectious neck masses that may contain an abscess cavity (Fig. 55-6, *B*), although ultrasound examination can provide similar information without radiation. Needle aspiration of suspected infectious masses may provide material for culture and decompress the mass.

Most children with bacterial cervical adenitis respond to oral antibiotics chosen to cover group A streptococci and *S. aureus,* but those who fail to improve require IV antibiotics. The initial choice of antibiotic is important. A recent study has shown a predominance of *S. aureus* (63%) compared with *Streptococcus* group A isolates (22%) obtained from those abscesses requiring surgical drainage. Of those with *S. aureus* infections, 27% were methicillin-resistant *Staphylococcus aureus* (MRSA), and all of these were sensitive to clindamycin and trimethoprim-sulfamethoxazole. Of the methicillin-sensitive *Staphylococcus aureus* (MSSA) isolates; 100%, 86%, and 82% were sensitive to trimethoprim-sulfamethoxazole, clindamycin, and ciprofloxacin, respectively.[38]

Cat-scratch disease is caused by *Bartonella henselae* infection. The clinical picture includes the sudden appearance of unilateral lymphadenopathy after a scratch from a cat. Fever and malaise may be accompanying symptoms in many cases. Serologic testing for antibodies to *Bartonella* is diagnostic. Cat-scratch disease is usually self-limited, although some

benefit has been described with the use of erythromycins and other antibiotics.[39]

In the past, most mycobacterial infections have been caused by atypical organisms, such as *Mycobacterium avium-intracellulare, M. scrofulaceum, M. bovis,* or *M. kansasii*. These organisms are commonly found in the environment in dirt, dust, water, and sometimes in food. In the past decade or so, mycobacterial tuberculosis has made a resurgence as the pathogen responsible for a neck infection. A chest radiograph should be obtained if *M. tuberculosis* is suspected. *M. tuberculosis* is usually associated with abnormal chest radiograph and the presence of a positive tuberculous skin test. Tuberculosis should be treated with appropriate antituberculous chemotherapy.

Children with nontubercular (NTM) or atypical mycobacterial infections have weakly positive or negative skin tests and present with a typical indolent course consisting of slowly growing, nontender nodes in the preauricular, intraparotid, submandibular, or posterior triangle regions that do not respond to antibiotics. Systemic symptoms are rare. After several days to weeks, the skin overlying the node typically assumes a violet color, and the area may become fluctuant and tender to palpation. The diagnosis is mainly clinical, because the organism will often take several weeks to grow in culture, and acid-fast bacilli are not always demonstrated. The treatment is surgical and consists of excision of the involved node(s). Combination therapy using clarithromycin and rifabutin may be effective but requires a prolonged course; it is generally reserved for recurrences or nodes that are not safely accessible by surgical approach.

Rarely, the neck may be involved with infections such as tularemia, brucellosis, actinomycosis, plague, histoplasmosis, or toxoplasmosis. Inflammatory disorders that may affect the neck include Kawasaki syndrome, sarcoidosis, sinus histiocytosis (Rosai-Dorfman disease), Kikuchi-Fujimoto disease, and PFAPA syndrome (periodic recurrent fever).

## MALIGNANT NEOPLASMS

Thyroid malignancies are discussed in Chapter 58, and malignant lymphadenopathies in Chapters 38 and 57.

Neurofibromatosis is a benign disorder that in some forms (plexiform) may infiltrate surrounding tissues. For this reason, CT and/or MRI are vital in the preoperative evaluation of these lesions. When the tumors are multiple and extensive, surgical resection is reserved for symptomatic lesions, because complete excision is usually impossible without compromising neurovascular structures. Neuroblastoma is a malignancy that develops from neural crest cells and may present as a solitary tumor or as lymphadenopathy. Clinical staging determines the mode of therapy that includes surgery, chemotherapy, and radiation therapy.

Rhabdomyosarcoma rarely presents as a primary tumor in the neck, more often being found as a primary tumor in the orbit, temporal bone, or nasopharynx. The diagnosis is made by biopsy, and patients are staged according to involvement. Treatment includes surgery, chemotherapy, and radiation therapy.

Malignancies of almost any type and location in the body can metastasize to the neck. The most common are thyroid malignancies. In adolescents, carcinomas, especially those arising in the nasopharynx, may spread to the neck lymphatics.

*The complete reference list is available online at www.expertconsult.com*.

CHAPTER 56

# Salivary Glands

Douglas Sidell and Nina L. Shapiro

Salivary gland disorders are rare in children. They often present as a painful or, less commonly, a painless swelling in the affected gland. Disease processes may be of infectious, inflammatory, systemic, autoimmune, congenital, neoplastic, or traumatic origin.[1] Treatment is guided by the medical or surgical nature of the specific disease process.

## Classification

Salivary glands may be divided into major and minor categories. The former category includes the parotid, submandibular, and sublingual glands, all of which are paired structures with their own well-defined anatomy, including blood supply and ductal drainage. Their function is augmented and facilitated by the minor salivary glands, which include the mucus-secreting tissues in the buccal mucosa, palate, mucosal surfaces of the lips, and floor of the mouth.

## Embryology

In the sixth week of gestation, solid epithelial buds of ectoderm from the developing mouth invaginate into the surrounding mesenchyme. A groove from this invagination develops into a tunnel, which subsequently forms branches of salivary ductal tissue. The mesenchymal tissue forms the capsule and connective tissue of the salivary glands. This process is similar for all of the major salivary gland embryogenesis.[2] During early gestation, the parotid ductules begin to grow around the facial nerve and its branches. This is of great clinical and surgical significance, because the facial nerve may be compressed or invaded by parotid gland lesions, or its branches may be injured during parotid gland surgery.[3]

## Anatomy and Physiology

The parotid gland is located in the space between the external auditory canal and the mandible. Its main duct (Stensen duct) crosses the masseter muscle and opens in the buccal mucosa at the level of the second maxillary molar. The deep lobe of the parotid gland lies medial to the facial nerve branches and the mandible. Deep lobe parotid gland masses may extend to the parapharyngeal space and present as intraoral growths. The parotid gland is the only salivary gland containing lymph nodes, which may become apparent during certain pathologic processes, such as atypical mycobacterial adenitis (see Chapter 57). Accessory parotid tissue is present in some children and in approximately 20% of adults. It can occur superficial to the masseter and is often mistaken for a neoplasm.[4] The submandibular gland is located in the submandibular triangle of the neck. The main submandibular duct (Wharton duct) exits the gland at a right angle and enters the mouth just lateral to the midline lingual frenulum. The sublingual gland is located at the lateral aspect of the floor of the mouth.[1]

The salivary glands serve to lubricate the mouth for hygiene, speech, and deglutition; to moisten food for taste and mastication; and to initiate early starch digestion with $\alpha$-amylase.[1] These processes may be initiated by various stimuli, including cerebral, visual, olfactory, or gustatory.

## Pathology

The majority of salivary masses in children are congenital vascular lesions, with hemangiomas seen in 50% to 60% of salivary gland masses and lymphatic malformations in approximately 25%.[5] Acquired lesions are of inflammatory, infectious, autoimmune, traumatic, or neoplastic origin. Salivary gland swelling is characteristic of nearly all glandular pathologic processes, and may be accompanied by pain, tenderness, or abnormal ductal discharge.[4] Advanced stages of disease may lead to cranial nerve involvement with resultant paresis or paralysis.

## Diagnosis

### HISTORY

A careful history should focus on the duration of the lesion, its bilateral or unilateral presentation, and whether there is any symptom fluctuation associated with eating. A complete medical history is essential, because the salivary glands may be involved in several systemic conditions.

### PHYSICAL EXAMINATION

The physical examination should include careful inspection of the overlying skin, both local and distant, to evaluate for any cutaneous hemangiomas, as well as of the intraoral mucosa to

evaluate for intraoral extension of the mass. Longitudinal duct massage will assess for duct obstruction or purulent material in the saliva. Benign salivary lesions tend to be mobile, soft, and spongy, whereas malignant and infectious lesions are more often fixed and firm on palpation.

## DIAGNOSTIC IMAGING

Plain radiographs of the salivary glands are helpful in detecting salivary duct calculi or diffuse glandular calcification.[1] Sialography is useful in identifying strictures, sialectasis, calculi, or saccular dilatation (Fig. 56-1).[6] High-resolution ultrasonography is a useful, noninvasive technique in the diagnosis of sialectasis and salivary gland calculi.[7] The addition of color-flow Doppler imaging can provide accurate information regarding the consistency of the lesion and its vascular pattern (Fig. 56-2).[8]

### Computed Tomography

Computed tomography (CT) is an excellent diagnostic modality for assessing both the pathology and anatomy of the salivary glands. It can aid in distinguishing intrinsic or extrinsic lesions. Use of an intravenous contrast agent can help detect an abscess or delineate the vascularity of congenital and acquired vascular lesions.[1] These features help in both medical and surgical planning.[9,10]

### Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) provides the best soft tissue detail of the salivary glands, and it is the only imaging technique that can delineate the facial nerve anatomy within the parotid glands. Signal intensity variations (T1- and T2-weighted images) provide additional valuable information regarding the nature of the mass.[11,12]

FIGURE 56-1 Sialogram shows saccular sialolithiasis of the parotid gland.

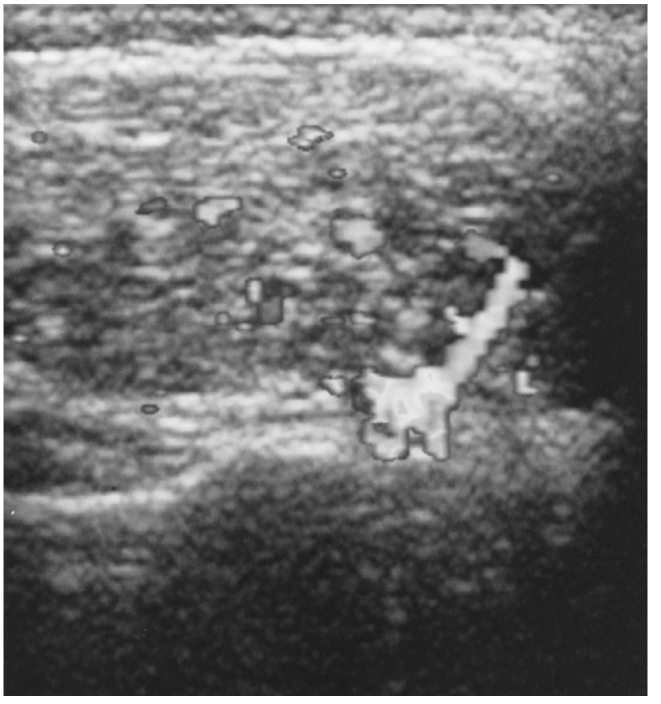

FIGURE 56-2 Doppler ultrasound study shows vascular pooling in a parotid hemangioma.

## BIOPSY

Fine-needle aspiration (FNA) biopsy is an excellent tool in the diagnostic evaluation of salivary gland masses.[13,14] The overall diagnostic accuracy is 84%, with a sensitivity and specificity approaching 92% for parotid lesions.[15–17] Obtaining an adequate needle biopsy specimen may preclude the necessity for surgical therapy or aid in surgical planning. Understandably, the accuracy and dependability of FNA rely heavily on the expertise of the cytopathologist and may vary based on institution or clinical setting.[13] For deeper salivary gland tumors, fine-needle aspiration may be performed under image guidance. Open excisional biopsy is the definitive tool for investigation and may be curative. If the size and location of the lesion are favorable, the entire tumor may be resected intact with a clear surrounding cuff of normal tissue. The diagnosis of Sjögren syndrome may be obtained by incisional biopsy of the minor salivary glands of the labial mucosa, or, alternatively, of the parotid gland.[18]

## SIALENDOSCOPY

Sialendoscopy involves semirigid endoscopy and microinstrumentation to evaluate and treat certain disorders of the parotid and submandibular glands. Although relatively new, this technique is increasing in popularity and has been demonstrated to effectively classify and treat ductal lesions, such as stricture and calculi. Sialendoscopy has been reported to produce a greater sensitivity in detecting salivary calculi than conventional radiography, MRI, or ultrasonography. Duct marsupialization and intraductal calculi retrieval have been demonstrated, allowing for the early treatment of some lesions without the requirement for open surgery.[19,20]

# Inflammatory Disease

## VIRAL SIALADENITIS

Acute inflammation of the salivary glands may be viral in up to 85% of cases, and the majority of viral sialadenitis involves the parotid glands. Viral infections are characterized by a benign self-limiting course over 2 to 3 weeks. Antipyretics, analgesics, and anti-inflammatory agents may be given for relief of symptoms. Causative organisms include coxsackievirus A and echovirus. Before the nearly universal implementation of the mumps vaccine in 1967, mumps virus (paramyxovirus) was the most common cause of acute parotid inflammation in children.[21–24] Other potential causes include cytomegalovirus (CMV), which is most commonly seen as a component of disseminated CMV infection in infants and young children,[25] and Epstein-Barr virus (EBV), which in healthy children is associated with infectious mononucleosis and in chronically ill children may be associated with human immunodeficiency virus (HIV) infection.[26,27]

## BACTERIAL SUPPURATIVE SIALADENITIS

Acute suppurative sialadenitis most often presents as rapidly developing pain, swelling, and occasional ductal discharge, with associated fever and poor oral intake. It is primarily seen in the parotid glands and less commonly in the submandibular or sublingual glands. The causative organisms are usually *Staphylococcus aureus* and *Streptococcus viridans*.[28] Acute sialadenitis often occurs in dehydrated patients because of decrease in salivary flow and dry oral mucosa.[29] Most cases will respond to antistaphylococcal antibiotics, with careful attention to hydration, oral hygiene with mouthwashes, warm local compresses, and sialogogues, such as sour lemon drop candies, to stimulate salivary flow. Rarely, despite treatment, the infected tissue will coalesce to form an abscess. Treatment of a salivary gland abscess includes intravenous antibiotics and surgical drainage.[30] If an abscess develops in the parotid gland, fascial incisions parallel to the course of the facial nerve are made to drain the abscess. If the facial nerve is paretic preoperatively, abscess drainage will usually facilitate resolution of nerve function.[1]

## CHRONIC SIALADENITIS

Chronic sialadenitis is the most common cause of inflammatory salivary gland disease in children and may lead to structural changes in the gland and acinar destruction (Fig. 56-3). There are obstructive and nonobstructive causes of this condition. Obstruction is caused by ductal stenosis, which may be congenital, caused by a stone, or result from chewing or biting the ductal opening. In such cases, the duct should be probed and stented for continuous drainage. Nonobstructive chronic sialadenitis may occur in conjunction with metabolic disorders, such as Sjögren syndrome, or chronic granulomatous disease, such as sarcoidosis, tuberculosis, or atypical mycobacterial disease.

The treatment of obstructive sialadenitis is initially conservative, with warm compresses and anti-inflammatory medications. Ductal dilatation or marsupialization may be necessary for recalcitrant disease. Gland excision is rarely required.

Sialolithiasis (salivary gland or duct calculi) is rare in children and occurs in the submandibular gland in 80% of cases. When the stone is located at the distal salivary duct, it may be excised by a simple incision at the ductal orifice. Temporary stent placement may be necessary. Rarely, a large calculus will be located in the proximal salivary duct or salivary gland parenchyma and may require complete gland excision with the stone-containing duct.

# Cystic Disease

Cystic disease may be acquired, congenital, or traumatic. Congenital cystic disease may occur in the salivary glands, but it is not of salivary gland origin. Work type I and type II first branchial cleft cysts may present as parotid gland masses, and depending on the orientation of the tract, may have accompanying otorrhea.[31,32] Congenital lymphatic malformations may also present in the parotid, submandibular, or sublingual glands. Large, bilateral intraparotid lymphoepithelial cysts are characteristic of HIV infection.[1] Small mucous retention cysts may present in the minor salivary glands of the labial or buccal mucosa; these cysts usually result from single or


**FIGURE 56-3** **A,** Sialogram of patient with history of recurrent parotid swelling. Note normal ductal system with early diffuse punctate sialectasis. **B,** Parotid gland swelling between acute attacks of inflammation.

**FIGURE 56-4** Floor of mouth ranula with posterosuperior lingual elevation.

repeated local trauma to the minor salivary glands and may lead to recurrent local mucosal swellings. If they do not resolve spontaneously, they will require complete excision. Local drainage or marsupialization will result in recurrence.

## RANULA

A ranula is a mucus extravasation cyst of the sublingual gland. Initial presentation is a bluish, cystic mass at the floor of mouth, which may lead to lingual elevation or difficulty with deglutition. They may extend to the neck through the mylohyoid (plunging ranula) (Fig. 56-4). Surgical management is controversial and ranges from simple transoral marsupialization to combination transoral-transcervical approaches.[33,34] Despite controversy, recurrence rates as high as 67% have been described with marsupialization alone. Recent evidence, derived from the largest review to date, suggests that the excision of the ipsilateral sublingual gland produces the lowest incidence of recurrence.[35] During sublingual gland excision, care must be taken to avoid Wharton duct injury, and it can be avoided by placing a lacrimal probe in the duct intraoperatively. The lingual nerve must also be meticulously dissected just deep to the sublingual gland.

# Neoplasms

Salivary gland neoplasms are extremely rare in children and comprise less than 1% of all pediatric neoplasms.[5,28,36,37] Less than 5% of salivary gland neoplasms occur in patients younger than 16 years of age.[38,39] However, when present, a pediatric salivary tumor must be assessed to rule out malignancy.[40–42] In the pediatric population, greater than 90% of salivary neoplasms occur in the parotid gland.[43] Caution should be exercised when evaluating adolescents, because imaging characteristics change over time as the gland is replaced with fat. Occasionally, this can cause benign disease to be mistaken for an infiltrative tumor on CT.[4]

## BENIGN NEOPLASMS AND MALFORMATIONS

Benign neoplasms account for 60% of salivary tumors in children and are most commonly vascular in origin.[5] Vascular lesions include hemangiomas and lymphatic malformations, which are both congenital in origin (Fig. 56-5).

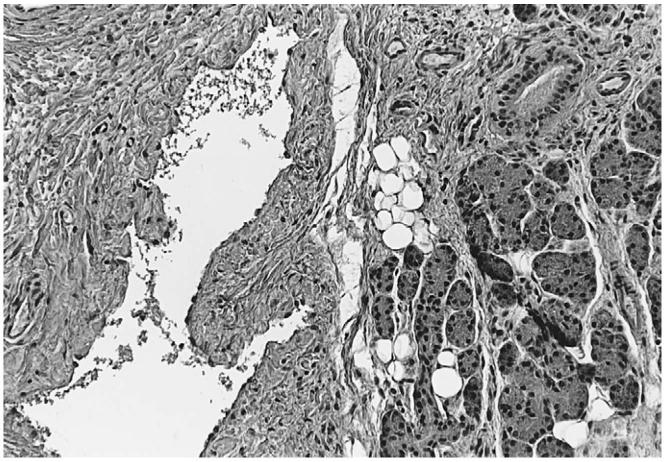

**FIGURE 56-5** Vascular malformation of the parotid gland, showing large, irregular vascular spaces. (Hematoxylin-eosin stain, ×50.)

### Hemangiomas

Hemangiomas are one of the most common salivary (primarily intraparotid) neoplasms in children, with infantile hemangiomas comprising greater than 90% of all salivary lesions in children less than 1 year of age.[4] Hemangiomas usually present in infancy as a soft, nontender parotid swelling, with or without associated pigmented cutaneous lesions.[44] Diagnosis is usually confirmed with ultrasonography, which demonstrates a lobulated, hypervascular mass, with arterial and venous signals visible on color-flow Doppler.[4,45] MRI may also be useful but is rarely required. Parotid hemangiomas often resolve spontaneously and do not require treatment. If they are rapidly growing or are causing functional impairments, such as facial nerve weakness, external auditory canal obstruction, or cutaneous breakdown, systemic therapy such as corticosteroids, propranolol, or interferon alfa-2a or alfa-2b are viable options to inhibit vascular growth and promote involution of the tumor.[46–49]

### Lymphatic Malformations

Lymphatic malformations are less common than hemangiomas. They do not undergo spontaneous involution, are usually present at or soon after birth, and grow with the growth of the child.[44] They are not true salivary lesions, but they are commonly seen in the submandibular and parotid region in infants and young children.[50] Lymphatic malformations are susceptible to infection, with potential for cellulitis, intralesional bleeding, abscess formation, or lymphangiomatous extension to the floor of mouth or trachea with airway compromise. Treatment modalities have been an area of much investigation. Surgical resection must be complete to obviate recurrence. This is often difficult, because of the fragility of the tumor lining, its infiltrative nature, and its proximity to major vessels and branches of the facial nerve.[51,52] In an effort to avoid surgical morbidity, success with intralesional sclerotherapy has been demonstrated, resulting in reduction in tumor size and minimal scarring or recurrence.[53]

### Pleomorphic Adenoma

Pleomorphic adenomas (benign mixed tumors) are the most common nonvascular benign salivary tumors in children (Fig. 56-6).[42,54] They present as firm, rubbery masses, most often in the parotid gland, with an average age at presentation of 9.5 years within the pediatric population.[54,55] The tumor

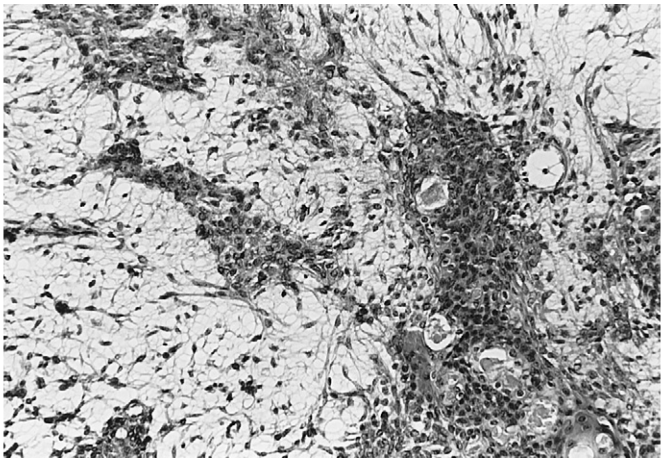

FIGURE 56-6 Pleomorphic adenoma (mixed tumor) of the parotid gland. Epithelial areas are mixed with myxomatoid and chondroid stroma. (Hematoxylin-eosin stain, ×50.)

presents as a painless, slowly growing mass and is rarely infiltrative.[56] They have variable echogenicity on imaging, with increased heterogenicity seen in larger lesions secondary to necrosis or cystic changes.[4] Treatment of superficial lobe tumors includes superficial parotidectomy with facial nerve dissection and preservation. Recurrence rates have been reported to be up to 40%; so, long-term follow-up is recommended.[57,58] Simple excisional biopsy should be avoided, because it is associated with a higher recurrence rate. Rarely, recurrent pleomorphic adenomas may undergo malignant degeneration.[59]

### Monomorphic Adenomas

Monomorphic adenomas are rare in children. Histologically, they may resemble adenoid cystic carcinoma, a highly aggressive malignant salivary tumor.[60] Treatment includes complete surgical resection and close long-term follow-up.

### Papillary Cystadenoma Lymphomatosum (Warthin Tumor)

These tumors are most commonly seen in men and are often bilateral parotid lesions. They may rarely present as benign parotid tumors in children.[1] Treatment is similar to that for pleomorphic adenomas.

## MALIGNANT NEOPLASMS

Malignant salivary neoplasms are rare in children. When present, they are often low-grade lesions, located most commonly in the parotid gland, and have a female preponderance.[54] Diagnostic evaluation should include CT or MRI and fine-needle aspiration biopsy. Treatment is surgical, with complete tumor excision with clear margins. Invasive malignancies may require sacrifice of the facial nerve branches. Postoperative radiation therapy is recommended for high-grade lesions.[61,62]

### Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common pediatric salivary malignancy and is most commonly low grade and located in the parotid gland. Surgery is usually curative.[39,63] For high-grade mucoepidermoid carcinomas, or those involving the submandibular or minor salivary glands, concomitant neck dissection and adjuvant radiation therapy is recommended by many institutions.[36,64,65]

### Acinic Cell Carcinoma

Acinic cell carcinomas present in a similar fashion as mucoepidermoid carcinomas. They tend to be low grade, and treatment is similar to that of mucoepidermoid carcinoma (Fig. 56-7).

### Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is a rare, high-grade salivary gland tumor. Perineural invasion may result in cranial nerve deficits. There is a high incidence of regional nodal metastases, as well as distant metastases to the lungs, liver, and bone. Treatment includes wide surgical resection, neck dissection, and adjuvant radiation therapy.[61]

### Rhabdomyosarcoma

Rhabdomyosarcoma may present as a parotid mass. Histologic variants include undifferentiated and embryonal types (Fig. 56-8). Treatment and outcomes depend on tumor stage and may include wide local surgical resection with radiation and chemotherapy.

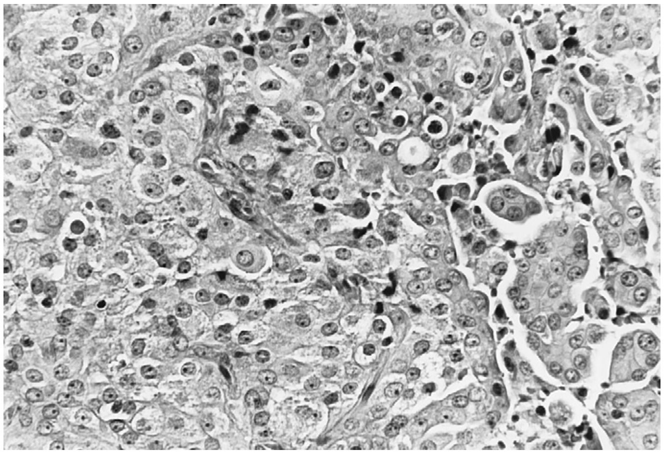

FIGURE 56-7 Acinic cell carcinoma of the parotid gland showing invasive proliferation. (Hematoxylin-eosin stain, ×100.)

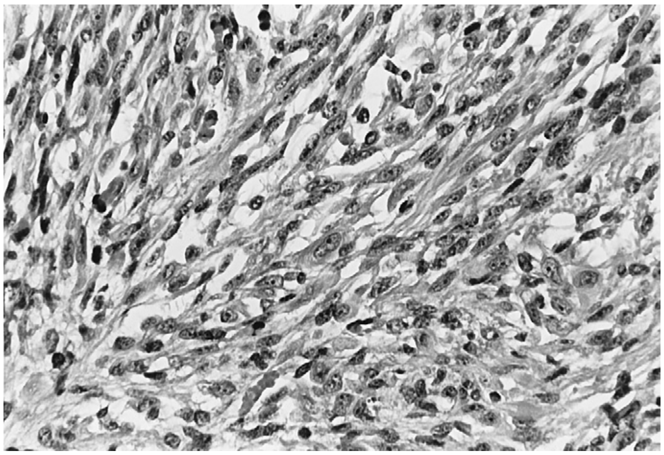

FIGURE 56-8 Rhabdomyosarcoma of the parotid gland showing spindle cell sarcoma with myogenous differentiation. (Hematoxylin-eosin stain, ×100.)

# Surgical Considerations

## PAROTID GLAND

An S-shaped incision is made, beginning in the preauricular crease and extending in a curvilinear fashion to the postauricular region, followed by an inferior extension to 2 fingerbreadths below the angle of the mandible (Fig. 56-9). Skin flaps are elevated, and the greater auricular nerve and posterior facial vein will be identified and may need to be sacrificed to expose the posterior border of the parotid gland. Blunt dissection along the tragal pointer and mastoid process, following the posterior belly of the digastric muscle, will allow visualization of the main trunk of the facial nerve as it emerges from the stylomastoid foramen. Meticulous dissection along the facial nerve branches in an anterior direction will elevate

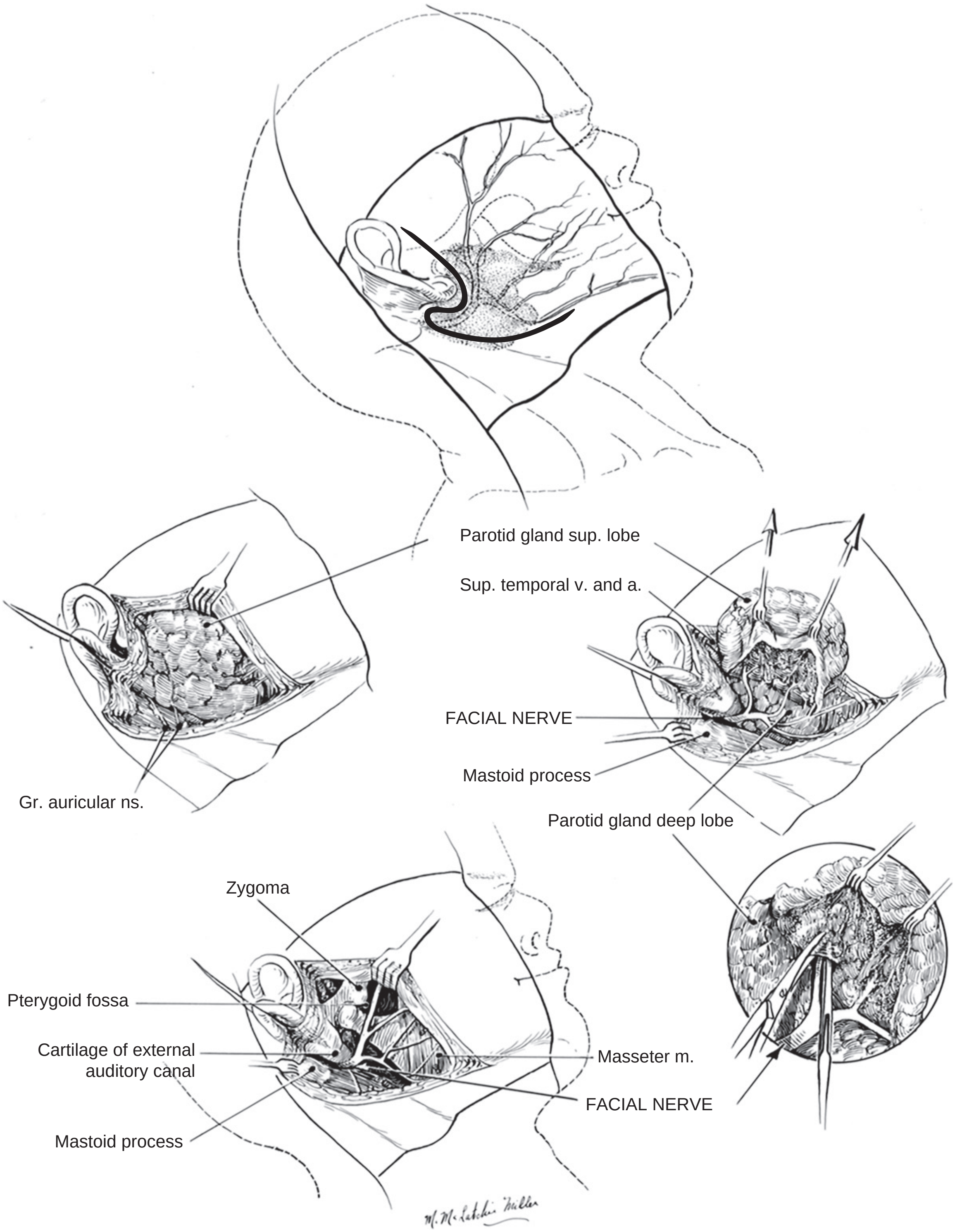


**FIGURE 56-9** Technique for parotidectomy.

the superficial lobe of the parotid gland. Careful blunt dissection, with use of the bipolar cautery and facial nerve monitor, will maximize excellent surgical results with minimal morbidity.[64,67]

### SUBMANDIBULAR GLAND

For submandibular gland resection, a horizontal skin incision is made in a natural skin crease approximately two fingerbreadths inferior to the body of the mandible. The dissection plane is carried to the investing fascia of the submandibular gland. Exposure should reveal the mylohyoid muscle anteriorly, the sternocleidomastoid muscle posteriorly, and the digastric muscle inferiorly. Identification and division of the anterior facial vein, just deep to this fascia, will facilitate protection of the facial nerve. Anterior retraction of the mylohyoid muscle and downward retraction on the submandibular gland will enable identification of the lingual nerve and Wharton duct. Division of the duct will free the lingual nerve from the gland and allow complete blunt dissection of the gland.[66]

## Conclusion

Although salivary gland disorders are rare in childhood, knowledge of the anatomy of the major salivary glands and understanding of both systemic and neoplastic physiology is critical. Neoplasms of the salivary glands are very rare in children and are commonly benign.[31,68] Evaluation and management should be tailored to the specific entity. A multitude of diagnostic tools are available and may include radiologic or pathologic studies.

Inflammatory and infectious disorders are often treated medically, whereas neoplastic disorders require surgical intervention. Patients and families must be counseled regarding potential short-term and long-term complications of facial nerve injury.

Despite the rigorous demands of parotid and submandibular gland surgery, in experienced hands, with adequate monitoring and meticulous dissection and hemostasis, surgical results are excellent.[67]

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 57

# Lymph Node Disorders

Faisal G. Qureshi and Kurt D. Newman

Lymphadenopathy is defined as an enlargement or a change in the character of a lymph node. Pathologic lymphadenopathy is usually a symptom of infectious, noninfectious conditions, or, in rare cases, malignant disease. Lymphadenopathy, especially cervical lymphadenopathy, is quite common in childhood, with a reported prevalence of 28% to 55% in otherwise normal infants and children.[1,2] In addition, children have palpable nodes in most of the superficial lymphatic basins, including cervical, axillary, and inguinal regions that are nonpathologic; there is progressive increase in lymphoid mass from birth until early adolescence. This lymphoid tissue then normally diminishes throughout puberty.[3]

Many lymph nodes are palpable in children, and generally, cervical nodes less than 2 cm, axillary nodes less than 1 cm, and inguinal nodes less than 1.5 cm are considered physiologic in young children. Palpable epitrochlear and supraclavicular nodes should, however, be viewed with suspicion and trigger investigations.

The primary goal of a consulting surgeon is to determine the need for a tissue diagnosis. A key consideration is to resolve the family's fears of malignancy in an efficient and cost-effective manner. This chapter focuses primarily on lymphadenopathy in the cervical region. Some comments are made about other regions.

## Anatomy

The regional lymph node groups of the head and neck are shown in Figure 57-1. The precise borders for these groups have been classified by the American Head and Neck Society and are shown in Figure 57-2.[4] Drainage to lymphatic basins usually follows predictable, anatomic routes, with the nomenclature reflecting the site of the lymph nodes. The face and oropharynx drain predominantly to the preauricular, submandibular, and submental nodes; the posterior scalp drains to the occipital nodal group; and the mouth, tongue, tonsils, oropharynx, and nasopharynx drain to superficial and deep chains of the anterior cervical nodes. Significant lymphatic collateralization exists.

## Differential Diagnosis

Most lymphadenopathy is benign in nature and is generally associated with a short duration of symptoms. Table 57-1 shows a list of differential diagnoses. Generalized lymphadenopathy is defined as enlargement of more than two noncontiguous lymph node groups.

### MALIGNANCY

Malignancy accounts for 11% to 24% of the diagnoses, depending on the nature of the group reporting their result. The higher rates are reported in series from oncology practices.[5,6] Malignant processes are more common in the age group of 2 to 12 years old and very rare in the age group of less than 2 years old. Malignancy as a cause is also more common in children with chronic generalized lymphadenopathy, nodes greater than 3 cm in diameter, and nodes in the supraclavicular region. Associated symptoms of night sweats, weight loss, and hepatosplenomegaly also increase the chance of malignancy. Finally abnormal laboratory and radiologic evaluation are associated with increased malignancy rates.[7] Soldes and colleagues reviewed predictors of malignancy in children with peripheral lymphadenopathy and determined that increasing node size, increasing number of sites of adenopathy, and age were associated with an increasing risk of malignancy ($P < 0.05$).[8] In addition, supraclavicular adenopathy, an abnormal chest radiograph, and fixed nodes were all significantly associated with malignancy.

The most common malignancies as a cause of lymphadenopathy are Hodgkin and non-Hodgkin lymphomas, leukemia, and metastatic disease.

## Evaluation

A careful history, physical examination, appropriate laboratory evaluation, and targeted imaging will usually help in deciding the need for tissue sampling. Persistent or progressive new-onset lymphadenopathy of greater than 4 to 6 weeks duration usually triggers a workup by the referring pediatrician. Indeed, most children with acute lymphadenopathy are rarely ever evaluated by pediatric surgeons. Most will improve with antibiotic therapy initiated by their pediatrician or the lymphadenopathy will resolve spontaneously when related to viral illnesses.

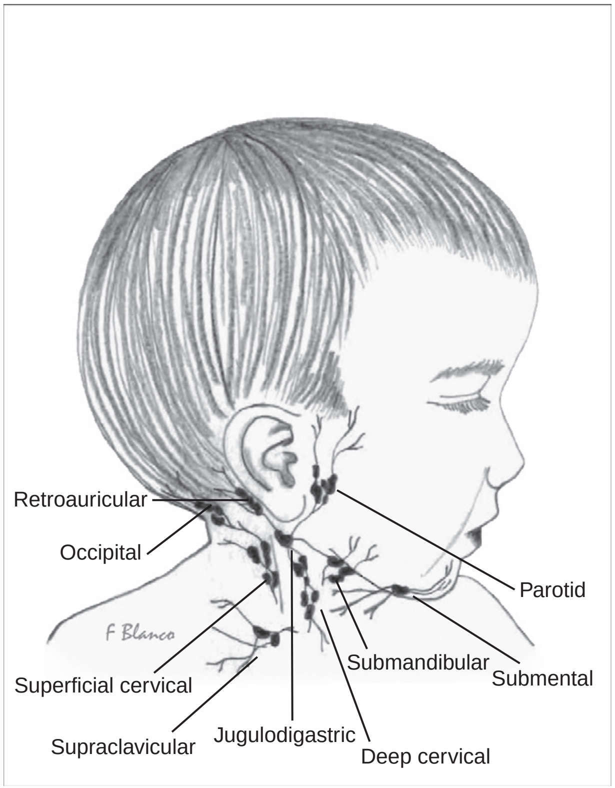


**FIGURE 57-1** Regional lymph node groups of the head and neck.

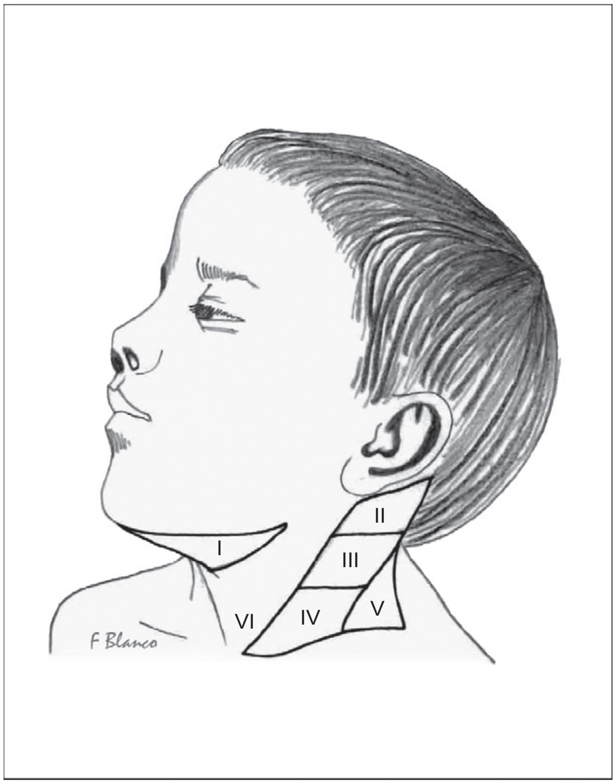


**FIGURE 57-2** Lymphatic node levels of the neck. Level I: submental and submandibular; level II: superior jugular; level III: middle jugular; level IV: inferior jugular; level V: supraclavicular or posterior; and level VI: central or anterior.

**TABLE 57-1**

**Differential Diagnosis of Lymphadenopathy in Children**

| | |
|---|---|
| Generalized lymphadenopathy: infectious | Viral: CMV, HIV, rubella, varicella, measles, EBV, herpes, hepatitis<br>Bacterial: typhoid, tuberculosis, mycobacterial, syphilis, LGV, leptospirosis, brucellosis<br>Protozoal: for instance, toxoplasmosis, leishmaniasis<br>Fungal: for instance, coccidioidomycosis, *Cryptococcus*, histoplasmosis<br>Other: syphilis, Lyme disease |
| Generalized lymphadenopathy: malignant | Lymphoma, leukemia, neuroblastoma, thyroid tumor, metastasis (e.g., osteosarcoma, glioblastoma) |
| Generalized lymphadenopathy: others | Autoimmune disorders: for instance, JRA, SLE, drug reactions, CGD, lymphohistiocytosis, LCH, dermatomyositis<br>Storage disorders: for instance, Gaucher disease, Niemann-Pick disease<br>Miscellaneous: Addison disease, Castleman disease, Churg-Strauss syndrome, Kawasaki disease, Kikuchi disease, lipid storage disease, sarcoidosis |
| Localized lymphadenopathy: infectious | *Staphylococcus aureus,* group A *Streptococcus* (e.g., pharyngitis), anaerobes (periodontal disease), acute bacterial lymphadenitis, cat-scratch disease, tularemia, bubonic plague, diphtheria, chancroid, viral URI, mononucleosis, tuberculosis/atypical mycobacterium |
| Localized lymphadenopathy: malignant | Lymphoma, leukemia, neuroblastoma, rhabdomyosarcoma, parotid tumor, nasopharyngeal tumor, solid tumor metastasis |
| Localized lymphadenopathy: site specific | Cervical: Kawasaki disease<br>Occipital: tinea capitis, pediculosis capitis<br>Preauricular: cat-scratch disease, chronic eye infections<br>Supraclavicular: histoplasmosis, coccidioidomycosis<br>Mediastinal: sarcoidosis, cystic fibrosis, histoplasmosis,<br>Axillary: local infection, brucellosis, immunization reactions, JRA<br>Inguinal: syphilis, LGV, diaper rash |
| Localized cervical masses: non-nodal masses | Mumps, thyroglossal duct, branchial cleft cyst, sternocleidomastoid tumor, cervical ribs, lymphatic malformation, hemangiomas, laryngocele, dermoid cyst |

CGD, chronic granulomatous disease; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; JRA, juvenile rheumatoid arthritis; LCH, Langerhans cell histiocytosis; LGV, lymphogranuloma venereum; SLE: systemic lupus erythematosus; URI, upper respiratory infection.

Once a child is referred to a surgeon, important historical questions include duration, progression, location, and associated symptoms, such as pain, fever, weight loss, and night sweats. Additional clinical information includes recent illnesses, especially upper respiratory tract symptoms, infections, trauma, bites, and dental problems. Drug use and sexual activity are important questions, especially in adolescents. Recent immunizations, especially bacillus Calmette-Guérin (BCG) should be evaluated. Social history, including recent travel, animal exposure, and exposure to tuberculosis and tropical diseases should be sought.

Once a general physical examination is completed, including a search for organomegaly, specific evaluation of the enlarged lymph nodes and other nodal basins should be performed. The skin and subcutaneous tissue that is drained by the affected lymph nodes should be evaluated; the characteristics of the lymph node should be noted. Normal nodes are usually soft, mobile, small, and nontender. Lymphadenopathy secondary to infections is also usually soft and can be mobile. However, on occasion, bacterial invasion of lymph nodes can result in erythema, tenderness, and fluctuance. With time, infected nodes can become adherent and have no inflammatory signs. Firm, fixed, nontender rubbery nodes can indicate a neoplastic process in older children.[8]

A thorough history and physical examination usually help separate local from generalized processes and help guide further evaluation, including laboratory and radiologic evaluation.

## INVESTIGATION

### Laboratory Studies

Most patients have had a laboratory evaluation prior to referral to surgery. These tests usually include a complete blood count (CBC) with manual differential, sedimentation rate, and C-reactive protein. However, these are not always helpful in determining the specific etiology of the disease process. Pancytopenia can be seen in leukemia; lymphocytosis is seen with mononucleosis, cytomegalovirus (CMV), and toxoplasmosis.

Based on the history and physical examination, more specific tests for Epstein-Barr virus (EBV), CMV, toxoplasmosis, brucellosis, histoplasmosis, syphilis, bartonellosis, and coccidioidomycosis should be considered. Tests for human immunodeficiency virus (HIV) should also be considered, based on the history as well as the tuberculin skin test.

Serum lactate dehydrogenase should be assayed when suspecting leukemia or lymphoma as a byproduct of high cell turnover.

### Radiologic Evaluation

Diagnostic imaging can be used to determine the characteristic of the lymphadenopathy, identify potential sources of infection, identify mediastinal and abdominal masses, and to help differentiate enlarged lymph nodes from other pathology. Chest radiographs, ultrasonography with Doppler, and computer tomography have all been used in the evaluation of adenopathy.

In children with long-term lymphadenopathy, a two-view chest radiograph is helpful to rule out mediastinal masses that may compress the airway with or without significant symptoms. A chest radiograph should be performed prior to any operative intervention, including biopsies done under general anesthesia. Patients with large mediastinal masses compressing the airway should not undergo general anesthesia, because this could result in airway collapse (see Chapter 38).[9]

Ultrasonography (US) is helpful when the nodes are difficult to palpate and to help differentiate nodes from other structures, such as thyroglossal duct cysts and dermoid cysts in the neck, and undescended testis and inguinal hernias in the groin, US may also be helpful in determining the characteristics of the node. Fluctuance and abscess formation will help guide therapies such as needle aspiration or incision and drainage.

Attempts have been made to use ultrasonography and Doppler characteristics to differentiate neoplastic from non-neoplastic etiologies. Reactive lymphadenopathy is associated with central necrosis, central hyperechogenicity, long to short–axis ratio (>2.0), hilar vascularity, and low pulsatility index.[10–14] However, these modalities are not sensitive or specific enough to primarily rule out neoplastic processes. The decision to delay biopsy diagnosis should not be dependent on US/Doppler findings.

Computed tomography (CT) is useful in patients with mediastinal masses and suspected intra-abdominal malignancies. Airway compromise may be best evaluated by chest CT. Interventional radiologists sometimes use CT scans to help guide biopsies from mediastinal masses.

### Diagnostic Procedures

The decision to proceed with obtaining tissue from the involved lymph node is made in conjunction with the referring physician and after appropriate physical, laboratory, and radiologic evaluation as required. Often, the child has been observed for several weeks prior to referral to a surgeon. Small, soft, mobile nodes should not undergo biopsy, because these are most likely benign unless they are in the supraclavicular region. Tissue diagnosis is helpful when lymph nodes persist or enlarge after adequate antibiotic therapy, when they are associated with signs or symptoms of malignancy, and, finally, if the diagnosis is questioned.

Most authors recommend waiting at least 4 to 6 weeks before obtaining tissue samples. Earlier biopsy should be considered for nodes in the supraclavicular or epitrochlear region, nodes greater than 3 cm in diameter, and for children with a history of malignancy, weight loss, night sweats, fever, or hepatosplenomegaly. Similarly, physical characteristics of the lymph node may also indicate earlier biopsy.[15,16]

***Fine-Needle Aspiration*** Fine-needle aspiration (FNA) has been used extensively in adults, with practical advantages, including its simplicity, speed in the outpatient setting without sedation, as well as its cost effectiveness. In addition, the sensitivity and specificity reaches more than 90%.

The use of FNA in children has increased, especially in countries where tuberculosis is prevalent.[17–20] Aspirates should be sent for Gram stain, acid-fast stain, and cultures for aerobic/anaerobic bacteria, mycobacteria, and fungi.

However, the use of FNA in children has not become universal, because the aspirate usually provides a small sample, which limits the ability to perform flow cytometry, chromosomal analysis, and electron microscopy. Most pediatric hematologists and pathologists prefer excisional biopsy, because it allows the assessment of nodal architecture and permits

the use of special stains. In addition, some children will not permit FNA without some sedation, which negates a primary benefit of FNA. Aspirates may also have a higher rate of false-negative rates in the diagnosis of Hodgkin disease, a common malignant condition in children. Finally, the risk of seeding the needle site tract with malignant cells, although small, is a legitimate concern of physicians and parents alike.[21]

***Excisional Biopsy*** Excisional biopsy provides enough tissue to perform flow cytometry, chromosomal analysis, electron microscopy, and the use of special stains. Indications for an excisional biopsy include

1. Lymph nodes that are hard/matted
2. Lymph nodes fixed to surrounding tissue
3. Progressively enlarging nodes without response to antibiotic therapy
4. Presence of abnormally enlarged nodes after 4 to 6 weeks
5. Supraclavicular, epitrochlear lymph nodes
6. Hepatosplenomegaly
7. Mediastinal or hilar masses
8. Laboratory anomalies, especially anemia, leukocytosis, leucopenia, and thrombocytopenia
9. Symptoms such as fever, weight loss, and night sweats
10. Suspicion of atypical mycobacterial adenitis
11. Diagnostic dilemma

Most excisional biopsies are done under general anesthesia or sedation and, very rarely, under local anesthesia. The biopsy should be coordinated with pathology so that the lymph node can be sent as a fresh specimen. The nodes should not be fixed in formalin. As discussed earlier, a chest radiograph should be obtained to rule out a mediastinal mass that may compromise the airway prior to exposing children to general anesthesia or sedation.

In a recent review, Oguz et al. reviewed their experience with 457 children (2 months to 19 years old) with lymphadenopathy who were referred to their oncology group; 346 (75.7%) had benign processes, and 111 (24.3%) had malignant disease. Of these, 134 patients underwent excisional biopsy for indications highlighted previously. Table 57-2 highlights the findings on excisional biopsy and compares them to findings by other authors.[7]

**TABLE 57-2**
**Excisional Biopsy Results**

| ***Excisional Biopsy Results*** | ***Oguz et al, 2006[7] (n = 134)*** | ***Moore et al, 2003[5] (n = 1332)*** | ***Yaris et al, 2006[21a] (n = 38)*** |
|---|---|---|---|
| Malignant | 79.8% | 11.8% | 50% |
| Hodgkin lymphoma | 40.2% | 6% | |
| Non-Hodgkin lymphoma | 29.1% | 2.1% | |
| Nasopharyngeal cancer | 3.7% | | |
| Thyroid cancer | 2.2% | | |
| Miscellaneous | 4.2% | 3.9% | |
| Benign | 20.1% | 88.2% | 50% |
| Chronic lymphadenitis | 5.9% | 11.3% | |
| Hyperplasia | 5.9% | 47.8% | 25% |
| Tuberculosis | 2.9% | 25% | 15.7% |
| Reactive | 2.2% | | |
| Miscellaneous | 3.2% | 4.1% | |

As can be seen, the pathologic diagnosis varied depending on the reporting group and the associated referral pattern, with higher malignant rates documented by oncology groups[7,21a] and higher infectious rates reported by authors in developing countries.[5]

# Management of Adenopathy

Darville and colleagues have suggested a helpful algorithm for the management of cervical lymphadenopathy (Fig. 57-3).[22] This algorithm is a useful tool to help surgeons determine their role in the management of enlarged lymph nodes. As suggested elsewhere in this chapter, most of the medical evaluation and management has usually been performed by the referring physician; however, it is the surgeon's responsibility to review each case prior to intervention.

## SURGICAL MANAGEMENT

Surgical management is usually limited to diagnostic FNA, excisional biopsy, incision and drainage, and total excision. Further details are provided under the specific conditions discussed later.

## ACUTE LYMPHADENITIS

The most common cause of self-limiting, acute, inflammatory lymph node is a viral infection.[23] Acute bilateral cervical adenopathy is most often caused by a viral respiratory tract infection (rhinovirus, parainfluenza virus, influenza virus, respiratory syncytial virus, coronavirus, adenovirus, reovirus) and is usually hyperplastic in nature.[24] Viral-associated adenopathy does not suppurate and usually resolves spontaneously.

Unilateral lymphadenitis is usually caused by streptococcal or staphylococcal infection in 40% to 80% of the cases.[25] These are usually large (>2 cm), solitary, and tender in the preschool child.[26] The submandibular, upper cervical, submental, occipital, and lower cervical nodes are affected in decreasing order of frequency.[27] Suppurative adenitis is associated with group A streptococcal or penicillin-resistant staphylococci. *Staphylococcus* infection leading to lymphadenitis seems to occur more commonly in infants.[28] Other less frequent causal organisms include *Hemophilus influenzae* type B, group B streptococci, and anaerobic bacteria. Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is now more commonly being isolated from superficial abscesses and suppurative lymphadenitis in children. Clindamycin is an appropriate agent to use under these circumstances.[25,29]

Suppurative lymphadenitis presents with local inflammatory signs, including unilateral tender adenopathy involving the submandibular or deep cervical nodes draining the oropharynx. Erythema, fever, malaise, and signs of systemic illness may occur. The primary infection in the head and neck regions should be looked for with careful attention to the oropharynx and middle ear. Appropriate treatment should be started, usually an empirical 5- to 10-day course of an oral β-lactamase–resistant antibiotic. Intravenous antibiotics should be started if systemic signs are present or in very young infants. A response should be observable within 72 hours, and failure of therapy usually necessitates additional diagnostic testing. This is usually fine-needle aspiration or ultrasonography.

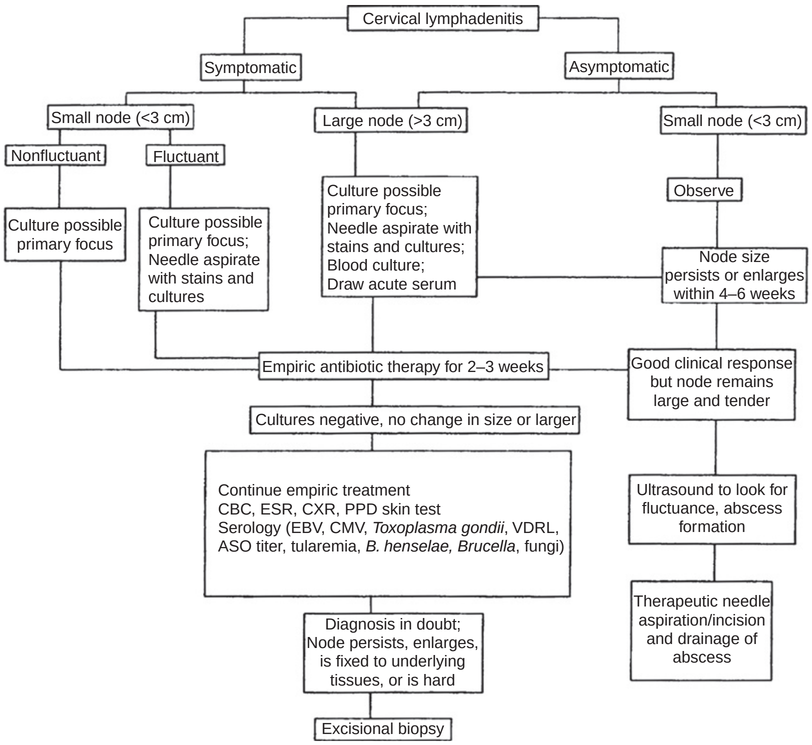


**FIGURE 57-3** Evaluation and treatment algorithm. ASO, antistreptolysin titer; CBC, complete blood count; CMV, cytomegalovirus; CXR, chest radiograph; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; PPD, purified protein derivative; VDRL, Venereal Disease Research Laboratory. (Reprinted with permission from Elsevier.[22])

Aspirate culture by FNA can guide further organism-specific antibiotic treatment, including clindamycin if MRSA is encountered. If no fluid is aspirated, sterile saline can be injected and then aspirated to obtain material for culture.[26] In addition, repeated aspiration together with antibiotics is an effective treatment for fluctuant lymphadenitis.[30] As stated previously, however, FNA may require sedation or anesthesia in young children.

Ultrasonography may help to differentiate between solid and cystic masses and can identify fluid that may require operative drainage. Incision and drainage is a more definitive surgical approach to suppurative fluctuant lymphadenitis. Gauze packing has been used to prevent early skin closure and achieve hemostasis; however, the use of minimal incisions, with vessel loops functioning as drains, has been gaining wider acceptance recently.[31]

## PERSISTENT LYMPHADENITIS

Persistent lymphadenitis that does not resolve despite 2 to 4 weeks of appropriate therapy warrants additional diagnostic workup. Some common causes of persistent lymphadenitis are discussed in this section.

### Atypical Mycobacterial Adenitis

The genus *Mycobacterium* is characterized on light microscopy to be bacilli distinguished by their dense lipid capsules. The lipid capsules resist decolorization by acid alcohol after staining and thus are termed *acid-fast bacilli*. In the United States, 70% to 95% of mycobacterial lymphadenitis cases are caused by atypical mycobacteria (nontuberculous strains). The most common agents include *M. avium-intracellulare, M. scrofulaceum, M. fortuitum,* and *M. chelonei*.[32] In contrast to tuberculous adenitis, atypical (or nontuberculous) mycobacterial adenitis is generally considered a local infectious process, without systemic involvement in immunocompetent hosts. Disseminated disease is more commonly observed in patients with underlying acquired or congenital immunodeficiency states. Atypical mycobacterial adenitis is not contagious, and the portal of entry in otherwise healthy children is the oropharynx.[33]

Atypical mycobacterial adenitis usually occurs in young children between 1 and 5 years of age. The common clinical presentation is focal, unilateral involvement of the jugulodigastric, preauricular, or submandibular nodal group. There is rapid onset of nodal enlargement, and the skin gradually develops a pink or red hue; with time, the overlying skin becomes thin.[26] In contrast to acute suppurative lymphadenitis, there is no response to first-line antibiotics, and the clinical course is described as indolent, with the involved nodal group being minimally tender, firm, and rubbery to palpation, well circumscribed, and sometimes adherent to underlying structures. Although remarkably nontender, these lesions develop a draining sinus tract in 10% of patients.[34,35] Signs of systemic illness or inflammation are usually minimal or nonexistent. Chest radiographs are usually normal.

Differentiating atypical mycobacterial and mycobacterial tuberculous cervical lymphadenitis can occasionally be challenging, based purely on epidemiologic and clinical features. Age (<5 years), race (white), place of residence (rural), bilaterality (rare) all point toward atypical mycobacterial infection. Purified protein derivative (PPD) skin testing in

children with atypical mycobacterial lymphadenitis can result in an intermediate reaction because of cross reactivity, usually less than 15 mm. Blood interferon-gamma release assay is emerging as the discriminating test of choice; it was originally described for pulmonary disease but is now being used for nodal disease as well.[36] Other criteria that point toward a diagnosis of tuberculous lymphadenitis are (1) a positive PPD, (2) abnormal chest radiograph, and (3) contact with a person with infectious tuberculosis. Spyridis and colleagues have shown that fulfilling two of three criteria results in diagnosis of tuberculous lymphadenitis with a 92% sensitivity.[37]

Unlike tuberculous adenitis, atypical mycobacterial adenitis generally does not respond to chemotherapy. The treatment of choice is complete surgical excision with primary wound closure. In a literature review of the surgical treatment of atypical mycobacterial cervicofacial adenitis in children, excision, incision and drainage, curettage, and needle aspiration were compared across 16 studies. The cure rates were 92%, 10%, 86%, and 41%, respectively.[38] Incision and drainage should be avoided, because it often results in a chronically draining sinus. There have been reports of adequate medical treatment of atypical mycobacterial lymphadenitis; however, in a recent multicenter randomized trial comparing surgical excision and antibiotics, surgical excision was superior, with a 96% cure rate compared with 66% with antibiotic therapy.[39] Multidrug antibiotic therapy, usually including clarithromycin and rifabutin, may be used as an adjunct for unresectable or recurrent disease.[40] Surgical treatment should include elliptic excision of the overlying skin when it is thinned out, debridement of subcutaneous granulation tissue, and complete excision of the involved node(s) with closure of the overlying skin; formal lymph node dissection is not required. Curettage is recommended only if surgical excision is not possible because of unacceptable cosmetic outcomes or risk of injuries to adjacent nerves. A nerve stimulator may be helpful for lesions at the angle of the mandible to avoid injury to branches of the facial nerve.

### Mycobacterial Adenitis

In developed countries, tuberculous adenitis or scrofula is almost exclusively caused by *M. tuberculosis*. Before control of bovine tuberculosis, the predominant cause of tuberculous adenitis was *M. bovis*. Occasional cases of *M. bovis* are observed from underdeveloped regions in which consumption of contaminated raw meat occurs. Patients proven to have human tuberculous adenitis often report previous exposure to a known carrier of tuberculosis, but most patients do not have active disease on a chest radiograph.[37] Differentiation between tuberculosis and atypical mycobacterial adenitis has been highlighted previously. Tuberculous adenitis is considered to be a local manifestation of a systemic disease and not an initial primary focus of tuberculous infection.[41]

Clinically, children with tuberculous adenitis are usually older and present with nonsuppurative lymphadenitis, which may be bilateral.[42] A retrospective review of 24 immunocompetent children with tuberculous lymphadenitis showed that no patient had bilateral disease, and the submandibular (29%) and the anterior cervical (71%) sites were the only areas of involvement.[37] However, posterior triangle nodal involvement does occur.

The diagnosis of tuberculous adenitis can be made on the criteria established by Spyridis and colleagues[37] and positive acid-fast bacteria on stain or culture of nodal tissue. Diagnostic confirmation may be aided by FNA with aspirate culture and cytologic examination.[43] Rapid diagnosis of tuberculous adenitis by DNA amplification of nodal material using polymerase chain reaction (PCR) has been reported.[44] Blood testing and PPD are also used. A negative tuberculin PPD test essentially excludes the diagnosis of tuberculous adenitis. If a diagnostic dilemma persists, surgical excisional biopsy is warranted. Incisional biopsy or incision and drainage should be avoided to prevent development of chronic, draining sinus tracts.[23,45] Fistula and cheloid formation can be seen in up to 100% of patients who undergo incision and drainage of tuberculous infected lymph nodes.[37]

Tuberculous adenitis generally responds to medical management that consists of multiple-agent chemotherapy. The World Health Organization recommends directly observed short-course therapy, including isoniazid, rifampin, ethambutol, and pyrazinamide for the first 2 months, followed by isoniazid and rifampin for an additional 4 months.[46] Nodal regression usually occurs within 3 months. Although antituberculous chemotherapy remains essential, the role of complete surgical excision of involved nodes is more controversial.[47] Complete excision of involved nodes is prudent when biopsy is required for diagnosis, when a chronically draining sinus tract evolves during medical treatment, or when optimal medical management fails.

## CAT-SCRATCH DISEASE

Cat-scratch disease is a common cause of lymphadenitis in children, with an estimated incidence in the United States of 9.3 per 100,000 ambulatory pediatric and adult patients per year.[48] The highest age-specific incidence is among children younger than 10 years of age.[2] Current microbiologic and PCR-directed DNA analysis demonstrates that the pleomorphic, gram-negative bacillus *Bartonella henselae* (formerly *Rochalimaea)* is the causative organism of cat-scratch disease.[49] Most cases can be directly related to contact with a cat, and the usual site of inoculation is an extremity. Subsequent adenitis occurs at regional lymphatic drainage basins (inguinal, axillary, epitrochlear nodes) 5 days to 2 months later.[50] Similarly, cervical lymphadenopathy is observed with scratches in the head and neck region. Although the primary manifestation of *Bartonella henselae* infection is lymphadenopathy, some series report up to 25% of cases resulting in severe systemic illnesses.[51]

Initial infection occurs at the portal of entry in the skin, such as a scratch or bite. Papule formation may be observed at the site of inoculation in 3 to 5 days, with development of subacute lymphadenopathy at regional nodal drainage beginning within 1 to 2 weeks. Early systemic symptoms of fever, malaise, myalgia, and anorexia are commonly reported.

Although most cases involve the lymph nodes of limbs, approximately 25% of cases involve the cervical nodes.[50] Diagnosis is based on a history of exposure to cats, presence at a site of inoculation, and regional lymphadenopathy. Identification of *Bartonella henselae* from involved lymph nodes using Warthin-Starry silver impregnation stain has

traditionally been used for diagnosis, but the stain has been found to be unreliable and lacking specificity. PCR for *Bartonella henselae* using paraffin sections from lymph nodes or other tissue is more reliable and specific.[52] To confirm diagnosis without obtaining tissue, many centers use serologic testing, which has been available for several years; it has a low sensitivity but is highly specific.[53]

Lymphadenitis associated with cat-scratch disease is usually benign, self-limiting, and resolves within 6 to 8 weeks without specific treatment.[54] Antibiotic treatment has thus been controversial, although azithromycin has been associated with rapid resolution of the adenitis.[55] Suppuration is unusual; however, if it occurs, needle aspiration may provide symptomatic relief. Excisional biopsy is generally unnecessary but may be warranted if a draining sinus tract develops or if the diagnosis is uncertain and the potential for malignancy cannot be excluded.

## MISCELLANEOUS LESIONS

Various other infectious and inflammatory conditions can produce lymphadenopathy in infants and children. Most patients with these disorders do not require surgical management or, in particular, excisional biopsy of the lesions. A systematic approach to evaluation of these patients, as outlined previously, generally leads to the correct diagnosis. Surgical management of these lesions should be directed to patients who present diagnostic dilemmas and have nodal disease in suspicious areas, or have persistent adenopathy despite adequate medical therapy.

### Infectious Lymphadenopathy

Lymphadenopathy caused by infectious agents include toxoplasmosis (caused by *Toxoplasma gondii*), tularemia (caused by *Francisella tularensis),* and mononucleosis (caused by Epstein-Barr virus). Infection with *Actinomyces israelii* in the head and neck may lead to cervicofacial actinomycosis that is characterized by a woody indurated cervical mass and development of chronic, draining fistulas. Direct involvement of the lymph nodes is uncommon, but the induration can make the clinical differentiation difficult.[56] Infection with HIV can produce general lymphadenopathy in infants and children.[57]

### Inflammatory Disorders

Inflammatory disorders include Kawasaki disease, Kikuchi disease, Castleman disease, and Rosai-Dorfman disease.

*Kawasaki disease,* or mucocutaneous lymph node syndrome, is a febrile disorder of childhood that is characterized in part by the abrupt onset of erythematous changes in the oropharyngeal mucosa, acute vasculitis, and extensive nonsuppurative, nontender cervical adenopathy.[58] Diagnosis is made on clinical grounds, and the resolution of the nodal disease occurs relatively quickly in the course of the disease.

*Kikuchi disease*, or histiocytic necrotizing lymphadenitis, may present as cervical lymphadenopathy that resolves spontaneously. It typically presents in the older child with bilateral, painful cervical nodes. There are associated fevers, night sweats, splenomegaly, leucopenia with atypical lymphocytosis, and elevated erythrocyte sedimentation rate (ESR). This disease can be clinically confused with malignant disease, and the patients often appropriately undergo excisional biopsy for definitive diagnosis.[59]

*Castleman disease,* also called angiofollicular or giant lymph node hyperplasia may also occasionally present as a solitary, enlarged cervical lymph node. The enlarged node appears hypervascular on US/Doppler or CT scan. Surgical excision is curative in the localized form.[60] The multicentric form of the disease, often accompanied by visceral involvement, is considered a type of lymphoproliferative disorder and requires systemic therapy.

*Rosai-Dorfman disease,* or sinus histiocytosis with massive lymphadenopathy, is a rare disorder affecting predominantly African-American children in the first decade of life. Disease progresses from unilateral cervical adenopathy to massive bilateral cervical involvement and extension to other nodal groups or extra nodal sites. The disorder is benign but has a slow rate of resolution spanning 6 to 9 months. Excisional biopsy may aid diagnosis.[61]

## MALIGNANT DISORDERS

Although lymphoma is the most common malignant disorder manifested by cervical adenopathy, neuroblastoma and thyroid carcinoma are other childhood cancers that can present as enlarged cervical lymph nodes.

*Lymphomas* are one of the more common malignant conditions in children. They may present as primary neck adenopathy that does not resolve with antibiotics or is enlarging. Patients with congenital or acquired immunodeficiency states, including HIV infection, are at greater risk for developing malignant lymphoproliferative conditions. Excisional biopsy is often used to help diagnose lymphomas.

In *neuroblastoma,* adenopathy is usually bilateral. These patients often have stage 4 disease, and if the primary is not evident on examination and radiologic evaluation, excisional biopsy is performed for initial diagnosis of neuroblastoma.

*Metastatic thyroid carcinoma* may present with unilateral cervical lymph node enlargement that should not be mistaken for ectopic thyroid gland. If a thorough neck examination does not reveal a thyroid nodule, and a history of neck irradiation or other high-risk factors is obtained, thyroid ultrasonography should be performed as part of the evaluation of neck lymphadenopathy.

# Summary

Most adenopathy in children is nonpathologic and spontaneously resolves. Pathologic lymphadenopathy has a large differential diagnosis, with viral lymphadenitis being the most common. Surgical consultation is often obtained when the lymph nodes do not spontaneously resolve, if there is concern for malignancy, or if there is a diagnostic dilemma. Most of the investigation is usually performed prior to surgical consult, but the surgeon must be aware of an adequate workup prior to intervention. The surgeon's role is usually limited to excisional biopsy, incision and drainage, and, rarely, aspiration in children, depending on the pathology suspected. FNA for diagnosis has a more limited role in children but may be useful in selected cases.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 58

# Childhood Diseases of the Thyroid and Parathyroid Glands

Hannah G. Piper and Michael A. Skinner

Diseases of the thyroid and parathyroid glands are relatively uncommon in the pediatric population. The incidence of thyroid nodules is estimated to be 20 per 1000 children, and the incidence of hyperparathyroidism is approximately 4 per 100,000 children.[1,2] However, although rare, there is a wide range of pathology, both benign and malignant, with which pediatric surgeons must remain familiar. Surgery plays a central role in the management of many of these disorders, including thyroid nodules, parathyroid adenomas, and, occasionally, goiter and hyperthyroidism.

## Thyroid Embryology and Physiology

The thyroid begins to form 24 days after fertilization and is both the first and the largest of the endocrine glands in the developing embryo. The thyroid commences as an endodermal outpouching on the floor of the primordial pharynx and becomes the thyroid diverticulum. This diverticulum then descends from the pharynx, passing anterior to the hyoid bone and maintains a connection to the base of the tongue, known as the thyroglossal duct. The migration is usually complete by 7 weeks of gestation, at which point the thyroglossal duct is obliterated. Initially, the thyroid diverticulum is hollow but then becomes solid cellular parenchyma with both a right and left lobe. The cells are arranged in spherical units called follicles, which are filled centrally with proteinaceous colloid. Parafollicular cells, or C cells, derived from neural crest cells, are found between the follicles and are the source of calcitonin. In approximately 50% of people, a pyramidal lobe extends superiorly from the isthmus. Infrequently, there will be an ectopic thyroid gland found along the normal route of descent. A lingual thyroid is the most common ectopic location, representing 90% of cases.[3] When present, a lingual thyroid is usually the only thyroid tissue and can sometimes be mistaken for accessory thyroid tissue or a thyroglossal duct cyst. Ectopic tissue will often produce insufficient amounts of hormones and can become secondarily enlarged; therefore care must be taken to avoid inadvertent removal of the only viable thyroid tissue.[4,5] Accessory thyroid tissue can also be found anywhere along the normal pathway of thyroid descent, as seen in Figure 58-1, but these remnants are usually insufficient in size to have any normal function.

Thyroid follicular cells are responsible for the synthesis of thyroid hormones. This begins when tyrosine molecules within thyroglobulin are iodinated to form monoiodotyrosine (MIT) and diiodotyrosine (DIT), neither of which is biologically active. Active hormone synthesis occurs when either two DIT molecules couple to form thyroxine ($T_4$), accounting for 90% of excreted hormone, or one DIT and one MIT molecule combine to form triiodothyronine ($T_3$), accounting for about 9% of excreted hormone. Thyroid-stimulating hormone (TSH) is the main stimulus for hormone production and release and is produced by the anterior pituitary gland. TSH release, in turn, is controlled by thyrotropin-releasing hormone (TRH) produced in the hypothalamus. Circulating thyroid hormone is reversibly bound to carrier proteins, most commonly thyroxine binding globulin (TBG) and has a wide range of physiologic effects. Children with congenital hypothyroidism are at risk for significant neurologic impairment, delayed bone development, and decreased metabolism. In contrast, infants and children with hyperthyroidism may have tachycardia with increased cardiac output, excessive sweating, weight loss, and tremors.

The parafollicular cells produce calcitonin, a 32–amino acid polypeptide. Calcitonin lowers serum calcium and phosphate by inhibiting bone resorption and likely plays a role in calcium deposition after a postprandial serum rise. Interestingly, there are no known definitive complications in humans from either excess or deficient calcitonin.

## Evaluation of the Thyroid Gland

Proper evaluation of a child with potential thyroid disease begins with a focused history inquiring about symptoms of hyperthyroidism or hypothyroidism as well as any family history of thyroid disease or multiple endocrine neoplasia. This is followed by a detailed examination of the neck. The thyroid should be palpated to evaluate size, consistency, symmetry, and whether there are any nodules or associated enlarged

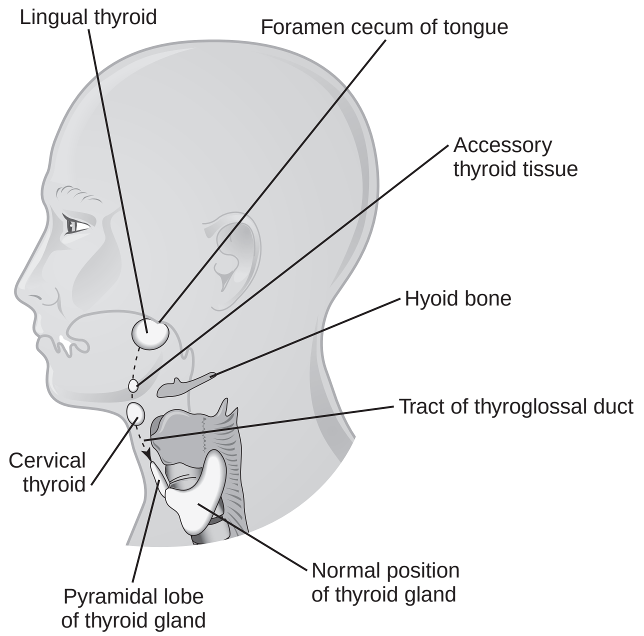


**FIGURE 58-1** Usual sites of ectopic thyroid tissue. The broken line demonstrates the path of normal thyroid descent. (Reprinted from The Pharyngeal (Branchial) Apparatus: In Moore K, Persaud TVN: The Developing Human: Clinically Oriented Embryology, ed 6. Philadelphia, WB Saunders, 1998, p 233; with permission from WB Saunders.)

lymph nodes. Certain features on physical exam are suggestive of specific disease processes. For example, diffuse enlargement can be seen in Graves' disease and Hashimoto and endemic goiter. A tender gland can be found with an acute inflammatory process, multiple nodules are more common in a metabolic or inflammatory process, and a single nodule is more likely to be neoplastic. Other worrisome signs suggestive of a neoplasm are rapid growth, hardness, fixation to surrounding structures, and enlarged cervical nodes.

Useful laboratory tests include measurement of TSH, which when elevated, suggests hypofunction and when suppressed suggests elevated hormone circulation. To estimate circulating thyroid hormone, a plasma free $T_4$ level can be measured. Plasma total $T_4$ and $T_3$ can be measured along with thyroglobulin to properly calculate unbound, active hormone.

Finally, thyroid imaging may be necessary. Ultrasonography (US) can be used to evaluate cysts and nodules and can be helpful in following these lesions over time. In addition, US can be used to help guide FNA for diagnostic purposes. Features on US suggestive of malignancy include hypoechogenicity, microcalcifications, irregular margins, and hypervascularity.[6] Radionuclide scintigraphy is also occasionally useful for thyroid imaging. In patients with suppressed TSH iodine-131 ($^{131}$I) or technetium-99m ($^{99m}$Tc) can be used to identify hyperfunctioning areas of the thyroid gland. Scintigraphy can also be used to assess for recurrent disease or metastatic disease in the setting of malignancy. An emerging imaging technique is single-photon emission computed tomography (SPECT), which gives a more three-dimensional view of increased uptake. This can also be combined with traditional CT (SPECT/CT) to add anatomic detail, increasing both the sensitivity and specificity over conventional scintigraphy,[7] as seen in Figure 58-2.

# Non-neoplastic Thyroid Conditions

## GOITER

A goiter is an enlargement of the thyroid gland that can be diffuse or nodular in nature, and patients can be euthyroid, hypothyroid, or hyperthyroid. The most common cause worldwide is iodine deficiency, resulting in hypertrophy secondary to substrate deficiency. However, in locations with

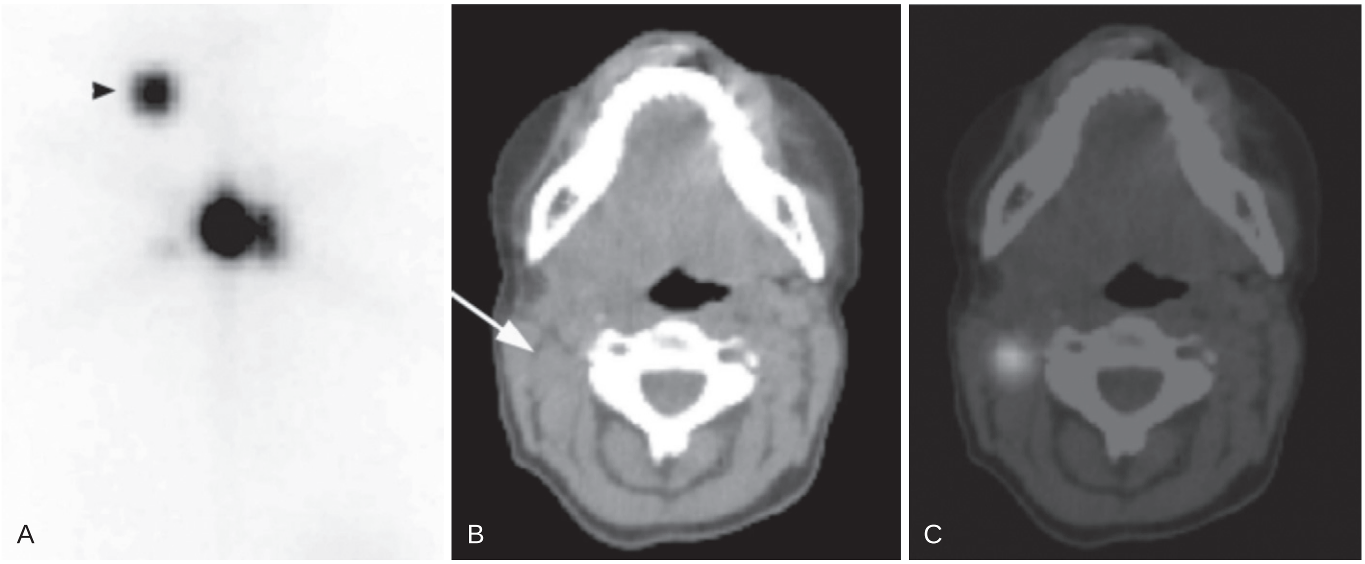


**FIGURE 58-2** SPECT/CT for nodal localization: cervical nodal metastasis in a 12-year-old girl. **A,** Planar image shows a single focus in the right upper neck *(arrowhead)* and two foci of activity in the central neck. **B** and **C,** Computed tomography (CT) and fused single-photon emission computed tomography (SPECT)/CT localizes the right upper neck focus to an enlarged lymph node *(arrow)*. (Reprinted from Wong KK, Zarzhevsky N, Cahill JM, et al: Hybrid SPECT-CT and PET-CT imaging of differentiated thyroid cancer. Br J Radiol 2009;82:860-876, 2009; with permission from the British Journal of Radiology.)

adequate dietary iodine intake, most patients will have simple colloid goiter and maintain normal thyroid function. For the most part, this type of goiter requires no specific therapy, because the rate of regression is no different whether or not the patient is treated with hormone suppression.[8] Surgery is indicated if the goiter grows so large that there is significant airway compression or if there is a nodule that is concerning for possible malignancy.

## THYROIDITIS

Inflammation of the thyroid gland can have several different etiologies, including autoimmune, viral, bacterial, or an infiltrative fibrous process. The most common type of thyroiditis in children is chronic lymphocytic or Hashimoto thyroiditis. Hashimoto thyroiditis is an autoimmune process in which antibodies against thyroid antigen are produced, resulting in a lymphocytic infiltrate within the gland. It often occurs in association with other autoimmune disorders, such as type I diabetes, Addison disease, systemic lupus and juvenile arthritis, as well as in children with Down and Turner syndromes. Initially, patients may be euthyroid or hyperthyroid, but this can be transient, and eventually hypothyroidism may ensue. Usually, the management is expectant with about 30% of patients, demonstrating resolution over time. Exogenous thyroid hormone should be provided to patients who are hypothyroid but does not seem to have any meaningful effect on reducing the size of the goiter or decreasing progression of disease in euthyroid patients.[9]

Other forms of thyroiditis, although rare, can also be seen in children, as listed in Table 58-1. Subacute thyroiditis is thought to be viral in nature, and patients often present with fever and gland tenderness in the setting of a recent upper respiratory infection. Initially, there may be excessive hormone release, followed by transient hypothyroidism. About 10% of patients develop permanent hypothyroidism. In most cases, nonsteroidal anti-inflammatory medication or low-dose corticosteroids is the only treatment required. Acute suppurative thyroiditis is bacterial in origin, can present with hard nodules, and be diagnosed on ultrasonography or with fine-needle aspiration (FNA). Treatment is with antibiotics, drainage if necessary, and, very rarely, thyroid lobectomy. Many cases formerly called acute suppurative thyroiditis are the result of a third or fourth branchial pouch remnant, also called pyriform sinus fistula. This should be suspected, especially when the infection presents in the left superior pole (see Chapter 59). Ideally, treatment is with antibiotics, followed by excision of the fistula tract to the pyriform sinus.[10]

## HYPOTHYROIDISM

The primary cause of congenital hypothyroidism is abnormal thyroid gland development rather than from a problem with the hypothalamic-pituitary-thyroid axis. Most commonly, it is secondary to either thyroid dysgenesis or agenesis and, less commonly, from defects in thyroid hormone synthesis or from the transfer of maternal thyroid blocking antibodies. Dietary iodine deficiency in utero can also lead to hypothyroidism, and in those cases, a palpable goiter may be appreciated. $T_4$ is essential for myelinization of the central nervous system during the first 3 years of life. Deficiencies in $T_4$ can lead to intellectual disability, which is completely preventable if recognized.[11] Newborn screening for hypothyroidism is essential and involves measuring TSH. Some states also require measuring $T_4$, which will allow for rare cases of central hypothyroidism to be detected. However, if these tests are normal but symptoms persist, it is important to maintain a high index of suspicion, because up to 50% of cases of central hypothyroidism will have a normal newborn screen.[12] In older children with acquired hypothyroidism, presenting signs and symptoms include a decline in linear growth, fatigue, constipation, and poor school performance. Preteens or teenagers may complain of dry skin, thin hair, weight gain, and menstrual irregularities. The most common causes of pediatric hypothyroidism can be seen in Table 58-2.

## HYPERTHYROIDISM

Graves' disease, or diffuse toxic goiter, is the most common cause of hyperthyroidism in children, with an incidence of 0.02%,[13] and it is approximately 5 times more common in girls than in boys. Thyroid gland hypertrophy occurs because antibodies against the TSH receptor bind and mimic the effect of TSH. Patients usually present with a firm, smooth goiter and symptoms of hyperthyroidism. Occasionally, there can be fibroblast deposition in the eyes, leading to exophthalmos, or in the skin, leading to pretibial myxedema, although these findings are less common in children. Severe hyperthyroidism is sometimes seen with associated hyperthermia and tachycardia, referred to as thyroid storm, and initial treatment includes active cooling and propanolol.

Usually, first-line therapy for Graves' disease is antithyroid medication (methimazole or propylthiouracil), and improvement in symptoms can occur within 1 month of treatment. Treatment is maintained for 12 to 18 months, during which time thyroid function is monitored routinely.[14] Remission is achieved in 30% of children after the first course of medication, and risk factors for relapse include young age and severe

**TABLE 58-1**
**Types of Thyroiditis**

| *Histopathology* | *Eponym* | *Etiology* | *Goiter* | *TSH* | *$T_4$* | *Thyroid Function* |
|---|---|---|---|---|---|---|
| Chronic lymphocytic | Hashimoto | Autoimmune | Yes | Variable | Variable | Hyper or hypo |
| Subacute granulomatous | De Quervain | Viral (mumps, Coxsackie virus, EBV) | Variable | Low | High | Hyper then hypo |
| Subacute lymphocytic | Silent | Autoimmune | Yes | Low | High | Hyper then hypo |
| Acute suppurative | Bacterial | Bacterial, fungal, parasitic | Variable | Normal | Normal | Variable |
| Invasive fibrous | Reidel | Unknown | No | Normal or low | Normal or low | Hypothyroid |

EBV, Epstein-Barr virus; $T_4$, thyroxine; TSH, thyroid-stimulating hormone.
Data from Arici C, Clark OH: Thyroiditis: Cameron J (ed): Current Surgical Therapy, ed 7. Philadelphia, Elsevier, 2001, p 597, with permission from Elsevier.

**TABLE 58-2**
**Pediatric Causes of Hypothyroidism**

| | | |
|---|---|---|
| No Goiter | Newborn to childhood<br>Adolescence | Gland dysgenesis<br>Deficiency of the hypothalamic/ pituitary axis<br>Postsurgical |
| Goiter | Newborn<br>Childhood to adolescence | Inborn error in hormone synthesis<br>Maternal ingestion (propylthiouracil, methimazole, iodides)<br>Severe endemic iodine deficiency<br>Ingestion of goiter-inducing drugs<br>Inborn error in hormone synthesis<br>Hashimoto thyroiditis<br>Infiltrative disease (lymphoma) |

biochemical hyperthyroidism at the time of diagnosis.[15,16] Because of the relatively low remission rate, some advocate the use of radioactive iodine ($I^{131}$). The radioactive iodine is ingested and then incorporated into the thyroid. The radiation to thyroid cells leads to gland ablation over the following 6 to 18 weeks. However, this is not recommended for children less than 5 years of age, and most patients will be made hypothyroid after treatment requiring hormone replacement therapy.

Surgery is also an option for some children with Graves' disease, usually for those who have very large goiters, are unable to take antithyroid medication, or cannot tolerate radioactive iodine. Surgery is also the treatment of choice if there is any concern of underlying malignancy in the gland. The preferred operation continues to be debated. In a large meta-analysis looking at more than 7000 adult patients, there were no cases of recurrent disease after total thyroidectomy versus an 8% recurrence rate after subtotal thyroidectomy. The incidence of other complications, including injury to the recurrent laryngeal nerve or hypoparathyroidism, did not differ between the two groups.[17]

# Neoplastic Thyroid Conditions

## MANAGEMENT OF THYROID NODULES

Thyroid nodules are less common in children than in adults, with an incidence of 1% to 2%.[2] However, when found, there is a 16% to 27% chance that the nodule will be malignant, which is far greater than the estimated 5% in the adult population.[18,19] In general, discrete lesions that are distinct from the surrounding thyroid tissue and are equal to 1 cm should be investigated. This begins with a history and physical exam, as well as measuring serum $T_4$ and TSH levels. The utility of imaging is less clear, especially in children. Some advocate that if a nodule is functional on scintigraphy, no further workup is required; however, this must be practiced with caution because, although rare, functional nodules can still harbor malignancy. Ultrasonography can be useful for measuring the size of a nodule, determining if it is solid or cystic, and locating it within the gland. Certain features on ultrasonography can raise or lower the suspicion of malignancy; for example, an entirely cystic lesion has a very low probability of being malignant. However, ultrasonography cannot definitively make the diagnosis of a malignancy.[6] The use of FNA for cytologic evaluation is now the most accurate diagnostic intervention in adult patients[20] and is standard in the workup of a thyroid nodule. FNA is also commonly used in children and adolescents, with the goal of trying to reduce diagnostic thyroid surgery for benign lesions. The question that is raised is whether this test has a low enough false-negative rate to justify its use in the pediatric population. Most would agree that for adolescents FNA can be used reliably, because it has an accuracy of at least 90%, and any potential delay in diagnosis will not likely result in decreased survival. Because younger children have a higher incidence of malignancy in any thyroid nodule, there has been some reservation in relying on FNA.[21] However, FNA results are useful for planning a resection (thyroidectomy versus hemithyroidectomy) in this population. A recent meta-analysis supporting the use of FNA included 12 studies collectively reviewing 183 patients with malignant nodules and 347 patients with benign nodules, the age range being 1 to 21 years. The analysis found that FNA has a sensitivity of 94% and specificity of 81% for detecting malignancy.[22] A selection of individual studies included in the analysis can be seen in Table 58-3.[18,23–27] In part, FNA is not very specific because when the cytology reveals follicular cells, malignancy cannot be determined because the diagnosis hinges on the presence of capsular invasion, which can only be seen on histology.[28,29] Overall, FNA is a useful tool in the workup of pediatric patients with thyroid nodules but should not overshadow other important clinical information, such as a history of radiation or prior malignancy; the family history; enlarging, fixed nodules; or associated cervical lymphadenopathy.

If FNA is performed, the results are reported as benign, malignant, or indeterminate. Resection is indicated for malignant or indeterminate nodules, or for benign nodules that continue to grow or have other worrisome features on follow-up.

## WELL-DIFFERENTIATED THYROID CARCINOMA

Well-differentiated thyroid cancer (WDTC) includes papillary and follicular cell tumors, accounting for approximately 1% of malignancies in prepubertal children and up to 7% in

**TABLE 58-3**
**Sensitivity and Specificity of FNA in Children and Adolescents**

| *Study* | *Type of Study* | *Age Range (Years)* | *No. of Patients* | *Minimum Follow-up* | *Sensitivity* | *Specificity* |
|---|---|---|---|---|---|---|
| Chang and Joo, 2006 | Retrospective | 2-21 | 37 | 23 months | 100% | 85.7% |
| Amrikachi et al, 2005 | Retrospective | 10-21 | 31 | 24 months | 100% | 64.7% |
| Arda et al, 2001 | Prospective | Children | 44 | 24 months | 100% | 95% |
| Khurana et al, 1999 | Retrospective | 9-20 | 57 | 24 months | 92.9% | 81.4% |
| Raab et al, 1995 | Retrospective | 1-18 | 63 | 24 months | 88.9% | 92.6% |
| Gharib and Goellner, 1993 | Retrospective | $<17$ | 41 | 24 months | 90% | 96.8% |

Data from Stevens C, Lee JK, Sadatsafavi M, Blair GK: Pediatric thyroid fine-needle aspiration cytology: A meta-analysis. J Pediatr Surg 2009;44:2184-2191; with permission from Elsevier.

adolescents, making it the most common endocrine cancer in the pediatric population.[13] Thyroid cancer occurs at least 4 times as often in females as males and is most common in white patients.[30] The overall incidence does appear to be increasing in children at a rate of approximately 1.1% per year. This is potentially because of a rise in the use of radiotherapy for other malignancies.[31] Head and neck radiation has been widely recognized as a significant risk factor for the development of WDTC. Patients exposed to as little as 50 cGy prior to the age of 4 years have presented 10 to 30 years later with thyroid cancer.[32] Malignancies with the strongest correlation with a secondary thyroid cancer include Hodgkin and non-Hodgkin lymphoma, neuroblastoma, and Wilms' tumor.[33] It is therefore important to provide careful follow-up for children who have been successfully treated for cancer.

On a molecular level, there is increasing evidence that the *RET* (rearranged during transfection) proto-oncogene plays a role in WDTC. The *RET* proto-oncogene is a tyrosine kinase receptor that, when exposed to radiation, can fuse to another gene to form a hybrid oncogene (*RET/PTC*), resulting in increased tyrosine kinase activity.[34] Even more common is for WDTC to be caused by an activating mutation in the B isoform of the Raf kinase (BRAF). These cancers tend to be larger at the time of presentation and may have a poorer prognosis.[35]

Papillary cancer is the most common type of thyroid cancer seen in children but also has the best survival, with estimates of 98% at 5 years. Follicular cancer is about 6 times less common, with approximately 96% survival at 5 years.[30,36]

In general, the treatment of WDTC in children is similar to that of adults. However, it must be taken into consideration that children often present with larger tumors, are more likely to have metastatic spread to cervical nodes, have a higher recurrence rate, and have a longer overall survival.[37] The primary therapy is surgical resection of the gland with or without lymph node dissection, depending on whether there is clinical evidence of nodal disease.[38] There continues to be some debate regarding how much of the gland should be resected. The surgical options include total thyroidectomy, near-total thyroidectomy (leaving less than 1 g of tissue near the ligament of Berry), subtotal thyroidectomy, and hemithyroidectomy. The argument for more aggressive resection revolves around decreased recurrence rates, the ability to treat residual disease with radioiodine ablation therapy, and the ability to assess for recurrence by following thyroglobulin levels. In addition, some surgeons prefer total or near-total thyroidectomy in the setting of malignancy, because at least 50% of children will have bilateral or multifocal disease.[39] In a retrospective review of 68 children who were less than 19 years of age and undergoing thyroid surgery for malignancy, 75% had a total thyroidectomy, 9% had a lobectomy, and 6% had a subtotal thyroidectomy. Forty-four percent of patients who had less than a total thyroidectomy needed further surgery for recurrence compared with only 12% of patients who had a total thyroidectomy, which was a significant difference.[36] Similarly, a larger, recent review of 215 children with papillary thyroid cancer also found that recurrence rates were significantly higher in children having undergone lobectomy compared with total or near-total thyroidectomy (35% vs. 6%).[40] However, mortality from thyroid cancer in children is very low, with 98.8% overall survival at 10 years, and therefore it is unclear whether the increased recurrence rate affects mortality.

Support for less-than-total thyroidectomy is based upon minimizing potential morbidity from the operation. Estimates of complications after total thyroidectomy vary widely, depending on the series and the time frame of the study, ranging anywhere from 12% to 20%.[36,41,42] Two of the most significant complications are injury to the recurrent laryngeal nerves and permanent hypoparathyroidism. For an experienced surgeon, the incidence of recurrent laryngeal nerve injury is less than 1%, and it is less than 2% for permanent hypoparathyroidism.[43] However, a recent study found that incidental removal of parathyroid glands occurs in up to 21% of thyroid surgeries and is not clearly dependent on the extent of resection.[44] A retrospective review of 1200 children undergoing thyroid and parathyroid surgery found that hypocalcemia accounted for 68% of the complications, and voice disturbances accounted for another 6%. Interestingly, they also found that the complication rates were age dependent: 22% in children less than 6 years, 15% in children aged 7 to 12 years, and 11% in children aged 13 to 17 years, and these differences were statistically significant.[45] It does appear that surgeons with more experience and a higher case volume of thyroid surgery have fewer complications. In a study by Tuggle and colleagues,[46] surgeons were classified as high volume (>30 cases per year), pediatric (>90% of cases were children), or other. A total of 607 patients were included in the study, and the authors found that high-volume surgeons, on average, performed 72 thyroid procedures per year, pediatric surgeons performed 2 thyroid procedures per year, and other surgeons performed 7 thyroid procedures per year. The complication rates were 8.7%, 13.4%, and 13.2%, respectively.

One strategy to reduce the incidence of hypoparathyroidism is to autotransplant one or two of the glands into the sternocleidomastoid, which can be done immediately during the dissection if the blood supply is thought to be compromised.[47] To minimize injury to the recurrent laryngeal nerve, intraoperative nerve stimulation can be used, which can help identify its course during dissection.[48,49]

Unfortunately, the recurrence rate for thyroid cancer in children after surgical resection is up to 32% when followed for 40 years.[40] For this reason, long-term follow-up for these children is required. Current recommendations for children who have had a total or near-total thyroidectomy include a $^{131}$I whole-body scan 6 weeks after thyroid resection to assess for any residual disease, and treatment with the radionuclide can be administered as needed, at this time, for remnant ablation.[50] These children can then be monitored for recurrence by checking annual plasma thyroglobulin and antithyroglobulin antibody levels, as well as obtaining an annual neck ultrasound scan. Further whole-body radionuclide scanning is unnecessary for children with low-risk tumors, undetectable thyroglobulin levels, and negative neck US. Annual scans can be considered for patients with intermediate- or high-risk tumors but should be done with a low-activity radionuclide.[51]

There is now evidence that radiation exposure from radioiodine remnant ablation (RRA) may predispose children to other malignancies. This potential risk must be carefully considered given the low mortality (<2%) associated with thyroid cancer. In a recent review of 215 patients less than 21 years of age with papillary thyroid cancer, there were no disease-associated deaths within the first 20 years following surgery. In addition, none of the patients with distant metastases died of their disease. It was found that recurrence rates of local and

**TABLE 58-4**
**ATA Risk Category Guidelines for Prophylactic Thyroidectomy and Screening for Medullary Thyroid Cancer**

| *ATA Risk Level* | *Age at RET Testing* | *Age at First US* | *Age at First Serum Calcitonin* | *Age of Prophylactic Surgery* |
|---|---|---|---|---|
| D | Within first year | Within first year | 6 months unless already postoperative | Within first year |
| C | <3-5 years | >3-5 years | >3-5 years | Before age 5 years |
| B | <3-5 years | >3-5 years | >3-5 years | Consider before age 5 years; may delay* |
| A | <3-5 years | >3-5 years | >3-5 years | May delay after age 5 years* |

*Criteria for delay must be met: normal basal and stimulated calcitonin, normal annual neck US, less aggressive MTC family history.
ATA, American Thyroid Association; MTC, medullary thyroid cancer; RET, rearranged during transfection (proto-oncogene); US, ultrasonography.
Adapted from Kloos RT, Eng C, Evans DB, et al: Medullary thyroid cancer: Management guidelines of the American Thyroid Association. Thyroid. 2009;19:565-612; with permission from Mary Ann Liebert, Inc.

distant disease were lower in patients treated with RRA, but this did not reach statistical significance. Interestingly, they did report a statistically higher mortality rate from secondary malignancy compared with an aged-matched control group. Of the patients in the study who died of a secondary malignancy, 73% had received RRA. This does not prove the association, but it does raise some concern.[40]

### MEDULLARY THYROID CANCER

Medullary thyroid cancer (MTC) arises from the parafollicular cells of neuroectodermal origin and accounts for approximately 5% of thyroid cancers. MTC that arises sporadically usually involves only one lobe, whereas cases of familial inheritance usually involve both lobes. Inherited MTC includes the multiple endocrine neoplasia type 2 syndromes (MEN2A and MEN2B) as well as familial medullary thyroid cancer. In general, hereditary medullary thyroid cancer begins with parafollicular cell hyperplasia and then progresses to invasive microcarcinoma, followed by macroscopic disease if left untreated. The *RET* proto-oncogene also plays an important role in medullary thyroid cancer, including not only familial but also 40% of sporadic cases,[52–55] and *RET* testing is used to make the diagnosis of MEN2. When there is a germline *RET* mutation, the aberrant protein is expressed in all of the tissues in which it is produced, leading to MEN2 or familial medullary thyroid cancer. Sporadic MTC occurs when there is a somatic mutation with aberrant protein expression only in the thyroid.[56] Although essentially all patients with MEN2A will eventually develop medullary thyroid cancer, MTC in MEN2B tends to develop earlier and is in general more aggressive.[35] Because of this, when families are known to carry the *RET* mutation, genetic testing should be performed before 5 years of age in families with MEN2A and even earlier for MEN2B. Less clear is the age at which to perform prophylactic thyroidectomy. On the one hand, the goal is to perform thyroidectomy well before the onset of metastatic disease, after which point cure can be difficult,[56] but on the other hand it is also important to minimize the risks to the recurrent laryngeal nerve and parathyroid glands, which are at higher risk in smaller children. Determining the ideal age for thyroidectomy has been based upon numerous criteria, including the age of the youngest family member to develop cancer, the mean age of onset for a particular genotype, and yearly neck ultrasound findings.[57–59] It is known that for MEN2A, microinvasive carcinoma can be seen in children as young as 5 years of age.[60] The most current recommendations have been established by the American Thyroid Association (ATA) and are guided by the fact that the risk of developing MTC correlates with specific *RET* mutations where different codons are known to have different clinical behavior.[61] There are four risk categories—ATA-A having the lowest risk and ATA-B through ATA-D almost always resulting in MTC.[62] Specific recommendations based on these risk categories are seen in Table 58-4. In general, a central neck node dissection is not necessary during prophylactic thyroidectomy for children, unless there is evidence of nodal disease.[63] For patients with a suspicion of sporadic medullary thyroid cancer, serum calcitonin levels are useful for screening.[62] Treatment after the diagnosis of established medullary cancer includes total thyroidectomy with central node dissection of all nodal tissue from the hyoid bone to the sternal notch and to the carotid sheaths laterally. Preoperative neck ultrasonography is recommended for all children with medullary thyroid cancer to assess for nodal disease.[64] Children can then be followed with serum calcitonin and carcinoembryonic antigen (CEA) levels, which reliably correlate with disease recurrence. Survival in patients with established medullary thyroid cancer has been most recently reported as 96% at 5 years and 86% at 15 years.[30] Novel therapy in adults with metastatic medullary thyroid cancer includes the use of an oral RET inhibitor that blocks kinase signaling. There is evidence that the inhibitor may halt disease progression in the adult population.[65] To date, similar studies have not been done in children.

## Parathyroid Embryology and Physiology

The parathyroid glands arise from the third and fourth pharyngeal pouches, which are paired endoderm-lined structures between the branchial arches. By the sixth week of gestation, the dorsal aspects of the third and fourth pouches differentiate into the inferior and superior parathyroids, respectively. The ventral aspects of the third pouches form the thymus and the ventral aspects of the fourth pouches develop into the ultimobranchial body, which eventually fuses with the thyroid to supply the parafollicular cells that produce calcitonin. The thymus and parathyroid glands then lose their connection to the pharynx and descend into the neck. Typically the parathyroid glands migrate to the posterior aspect of the thyroid gland, where they obtain their blood supply from the thyroid capsule. However, there is significant variability in the eventual location of the parathyroid glands, as seen in Figure 58-3. They are variable in both location and number and can be found anywhere in the vicinity of the thyroid or thymus. The superior glands tend to be more consistent in their location than the inferior glands.

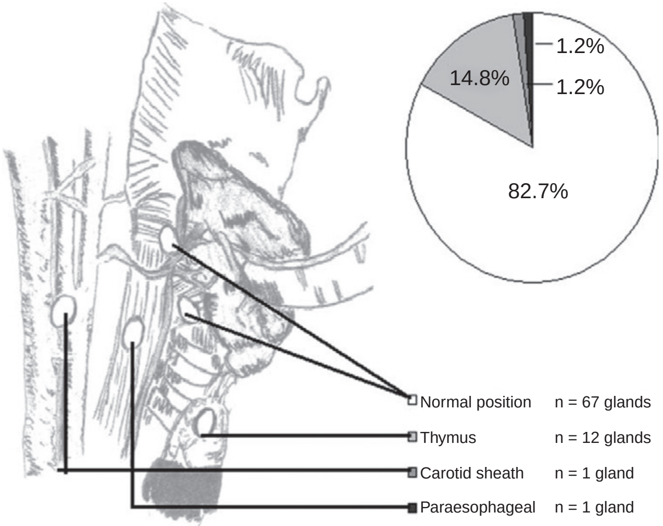


**FIGURE 58-3** Location of parathyroid glands found and removed during primary parathyroidectomy. (Reprinted from Schlosser K, Schmitt CP, Bartholomaeus JE, et al: Parathyroidectomy for renal hyperparathyroidism in children and adolescents. World J Surg 2008;32:801-806; with permission from Springer.)

The parathyroid glands regulate calcium and phosphorous by secreting parathyroid hormone (PTH). PTH is an 84–amino acid protein with a very short half-life that is primarily metabolized by the liver and kidney. PTH secretion is normally stimulated by a drop in circulating calcium and is then inhibited by a negative feedback loop. An increase in serum phosphorus also indirectly stimulates PTH secretion by lowering serum calcium. PTH also acts directly on bones by increasing osteoclast activity, on the kidneys by increasing renal calcium absorption, and on the gastrointestinal (GI) tract by increasing vitamin D activation.

# Disorders of the Parathyroid Glands

## DiGEORGE SYNDROME

DiGeorge syndrome is a congenital disorder characterized by athymia or thymic hypoplasia and absence of the parathyroid glands due to failure of the third and fourth pharyngeal pouches to differentiate. Infants are hypocalcemic and also have increased susceptibility to infection. Additional associated characteristics can include shortened philtrum, low set ears, nasal clefts, thyroid hypoplasia, and cardiac anomalies, especially truncus arteriosum. Treatment is largely symptomatic and includes supplementation with calcium and vitamin D. Emerging therapies include replacement with synthetic PTH[66] and thymus transplantation for children with severe immunodeficiency.[67]

## HYPERPARATHYROIDISM

There are several forms of hyperparathyroidism, all of which lead to excessive PTH secretion. In the case of primary hyperparathyroidism, this results from one or more abnormal parathyroid glands. In secondary hyperparathyroidism, elevated PTH is in response to hypocalcemia, and in tertiary hyperparathyroidism, PTH remains elevated despite correction of the hypocalcemia. Both secondary and tertiary types are seen in the setting of renal disease. Neonatal severe hyperparathyroidism (NSHPT) is a rare disorder that presents with severe hypercalcemia resulting from a homozygous loss-of-function mutation with four-gland hyperplasia. Treatment has traditionally been with a three and one half–gland parathyroidectomy or total parathyroidectomy with autotransplantation. More recently, there has also been some success with medical management with bisphosphonates.[68]

In general, hyperparathyroidism presents clinically with symptoms related to elevated calcium or is suspected when hypercalcemia is found incidentally. However, the differential diagnosis of hypercalcemia in children is quite broad, and this must be kept in mind during the initial evaluation, as outlined in Table 58-5. For example, familial hypocalciuric hypercalcemia is an autosomal dominant condition resulting from a mutation in the calcium sensing receptor. Children have elevated serum calcium but can be distinguished from having hyperparathyroidism by detecting decreased 24-hour urinary calcium levels. PTH levels are often within the normal range. Usually these children are completely asymptomatic, and no specific treatment is required. This condition should be excluded prior to considering parathyroid resection for hypercalcemia.

The incidence of primary hyperparathyroidism in children is estimated to be 2 to 5 per 100,000.[69] In contrast to adults, children may present with more serious effects of hypercalcemia, including renal failure, cardiac arrhythmias, and osteopenia.[2] When suspected, the diagnosis can be confirmed by measuring serum calcium and PTH. Most commonly, there will be a solitary parathyroid adenoma, and there are several localization studies that can be used to identify the abnormal gland. The imaging options include ultrasonography,

**TABLE 58-5**

| Causes of Hypercalcemia in Children |
|---|
| Endocrine |
| Primary hyperparathyroidism |
| Secondary hyperparathyroidism |
| Tertiary hyperparathyroidism |
| Thyrotoxicosis |
| Familial hypocalciuric hypercalcemia |
| Neonatal severe hyperparathyroidism |
| Ectopic parathyroid hormone production |
| Granulomatous disease |
| Sarcoidosis |
| Tuberculosis |
| Fungal infection |
| Pharmacologic |
| Vitamin D |
| Vitamin A |
| Thiazide diuretics |
| Theophylline |
| Milk alkali |
| Lithium |
| Immobilization |
| Subcutaneous fat necrosis |

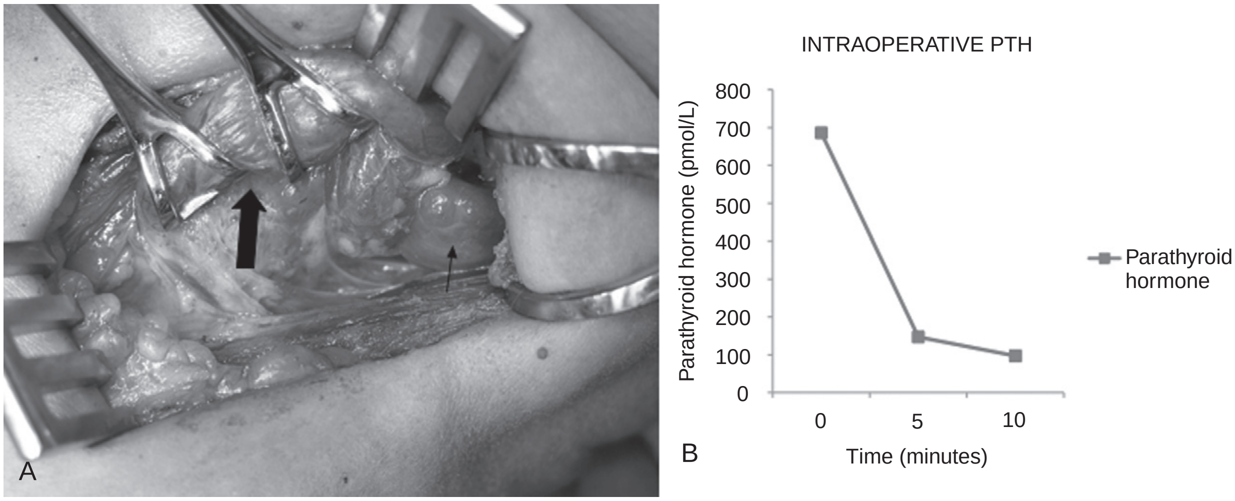


**FIGURE 58-4** **A**, Parathyroid adenoma in the setting of hypercalcemia. The small arrow demonstrates the parathyroid adenoma, and the large arrow demonstrates the retracted thyroid gland. **B**, Intraoperative PTH monitoring for the patient seen in **A** demonstrating the fall in PTH over 10 minutes after removal of the parathyroid gland.

$^{99m}$Tc-sestamibi planar scintigraphy, SPECT, SPECT/CT, and/or magnetic resonance imaging (MRI). Because of the rarity of parathyroid adenomas in children, most of the studies used to compare techniques have been done in adults. In one study by Munk and colleagues,[70] ultrasonography and $^{99m}$Tc-sestamibi scans were in agreement 70% of the time and, when in agreement, identified the correct gland in 97% of cases. When these tests were not in agreement, MRI was used, and if consistent with either an ultrasound or $^{99m}$Tc-sestamibi scan, the correct gland was identified 100% of the time. There were six patients (11%) in whom there was no definitive agreement among the three tests. More advanced scintigraphy is now being used (SPECT), which allows for a three-dimensional reconstruction, and this can also be combined with traditional CT (SPECT/CT), allowing for more anatomic detail.[71] However, whether the added detail improves accurate localization is still debated.[72] If localization is successful, a directed resection can then be used instead of the traditional four-gland exploration. However, in the hands of an experienced surgeon, this remains a very reliable approach. To confirm resection of the adenoma, intraoperative PTH measurement can be used. The half-life of PTH is approximately 3 to 4 minutes, and at least a 50% decrease from baseline should be observed to confirm removal of the abnormal parathyroid.[73] An example of a typical decline can be seen in Figure 58-4. It is important to follow the PTH level far enough out to ensure the decline is not temporary, which can be seen with multiple-gland disease.[74] If the PTH remains elevated, a complete cervical exploration should be pursued. If a normal parathyroid is resected or devascularized during thyroid surgery, the gland should be autotransplanted into the forearm or sternocleidomastoid.[75] Hyperparathyroidism is also seen in the setting of multiple endocrine neoplasia and is usually the result of four-gland hyperplasia. The surgical options include resection of only visibly enlarged glands, three and one half–gland parathyroidectomy, or total parathyroidectomy with autografting.[76,77]

Secondary and tertiary hyperparathyroidism are most commonly seen with end-stage renal disease and affect all four glands. Usually, this can be managed with dietary modifications, dialysis, phosphate binders, and vitamin D. However, vitamin D analogs and calcimimetics have not been approved for long-term use in children because of concern for interference with longitudinal growth and the possible impact on timing of puberty.[78] There is some debate as to whether the optimal surgical management is total parathyroidectomy with autotransplantation or subtotal parathyroidectomy, but the preferred management in the United States tends to be the former.[75,79]

# Parathyroid Carcinoma

Parathyroid carcinoma is exceedingly rare in children, with only seven case reports in the literature to date. In all cases, the patients presented with a neck mass and severe hypercalcemia with extremely elevated PTH (3 to 10 times normal). The first step in management is to control the hypercalcemia, followed by surgical excision if appropriate. The recommended resection includes en-bloc hemithyroidectomy, parathyroidectomy, and lymph node dissection. If completely resected, 90% long-term survival can be achieved. However, with incomplete resection, the recurrence rate is up to 50%.[80]

*The complete reference list is available online at www.expertconsult.com.*

# CHAPTER 59

# Neck Cysts and Sinuses

Craig Lillehei

Cysts and sinuses of the neck represent a wide variety of anomalies, both congenital and acquired. The focus of this chapter is on those of congenital origin. It is a fascinating opportunity to apply our understanding of embryologic development to the spectrum of malformations seen and to guide appropriate management. The most common lesions arise from thyroglossal duct or branchial anomalies (particularly from the second cleft). Nonetheless, one must be cognizant of the range of usual variants as well as the broad differential diagnosis. Lymphatic and vascular malformations will be addressed elsewhere (see Chapter 125). Although present at birth, congenital lesions may not become evident for weeks, months, or even years. However, there are recognizable patterns. Accurate diagnosis guides appropriate intervention. Proper identification is aided by careful history and physical examination. Age at presentation, evolution, anatomic location, and associated drainage are often important diagnostic clues. Radiographic studies, such as ultrasonography or cross-sectional imaging (computed tomography [CT], magnetic resonance imaging [MRI]), may be helpful in selected cases. Although the exact identity is not always evident preoperatively, an awareness of differential diagnostic possibilities will guide the prepared mind and improve prospects for optimal outcomes. The emphasis is total excision of the lesions to minimize the risks of recurrence, infection, or malignancy. Knowledge of the relevant local anatomy and adjacent structures is crucial to safe surgical dissection.

## Embryology

During the fourth week of gestation, neural crest cells migrate into the future head and neck region. A series of six paired branchial or pharyngeal arches begin to develop (Fig. 59-1). In humans the fifth arch, if present, is only very short lived. Their mesoderm is covered externally by ectoderm and lined internally by endoderm. Each arch contains a distinct artery, nerve, cartilage rod, and muscle. These arches are separated by depressions that are referred to as clefts on their external ectodermal surface, and pouches on their internal endodermal surface. These swellings may give rise to normal cervical structures, leave pathologic remnants, or involute entirely. In fish and amphibians, the closing membranes that separate the branchial pouches and clefts regress with the resultant connections forming gills.[1]

Each branchial arch and its components can be traced to the formation of future anatomic structures as outlined in Table 59-1. The first branchial arch forms the mandible and a portion of the maxilla. It is also involved in structures of the inner ear. The first cleft and pouch connect to form the eustachian tube/middle ear, tympanic membrane, and external auditory canal. The other branchial cleft components usually regress. However, it is important to note that during development the second, third, and fourth branchial clefts share a common external opening, the cervical sinus of His (Fig. 59-2, *A*). For this reason the location of the external opening of a persistent sinus or fistula from these clefts cannot be used to distinguish between them.

The remaining pouches give rise to normal glandular structures (Fig. 59-2, *B*). The palatine tonsil and supratonsillar fossa originate from the second pouch. The tonsils are the only structures to remain at their pouch of origin. The third pouch gives rise to the thymus and inferior parathyroid glands, while the fourth pouch is responsible for the superior parathyroid glands. It is believed that the calcitonin-producing cells of the thyroid gland arise from the ultimobranchial body, probably a remnant of the ventral portion of the caudal pharyngeal complex formed by the fourth and vestigial fifth pouch (see Fig. 59-2).

The thyroid gland arises from an endodermal thickening in the floor of the primitive pharynx called the tuberculum impar (see Fig. 59-1). A bilobate diverticulum develops between the anterior and posterior muscle complex of the tongue. As the embryo elongates this anlage descends anterior to or through the eventual location of the hyoid bone and fuses with elements of the fourth and fifth branchial pouches to form the thyroid gland. This descending median thyroid anlage gives rise to the thyroglossal duct, which usually obliterates by the fifth week of gestation.[2] The proximal remnant of this pathway is the foramen cecum at the base of the tongue, whereas the distal remnant is represented by the pyramidal lobe of the thyroid gland (Fig. 59-3). Cystic remnants or accessory thyroid tissue can remain anywhere along this tract (Fig. 59-4).

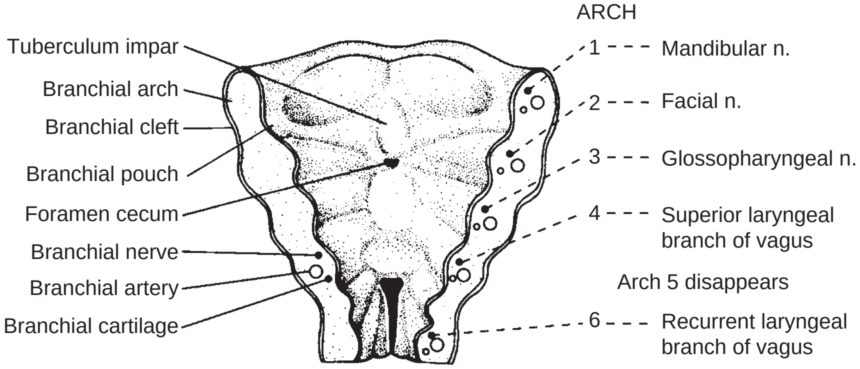


**FIGURE 59-1** Early development of branchial apparatus. (From Donegan JO: Congenital neck masses. In Cummings CW, Fredrickson JM, Harker LA, et al [eds]: Otolaryngology—Head and Neck Surgery, ed 2. St Louis, Mosby-Year Book, 1993.)

**TABLE 59-1**
**Derivatives of Branchial Arches, Clefts, and Pouches**

| | *Dorsal* | *Ventral* | *Midline Floor of Pharynx* |
|---|---|---|---|
| **I** | | | |
| Arch | Incus body | Meckel cartilage | Body of tongue |
| External maxillary artery | Malleus head | Malleus | |
| Nerve V | Pinna | | |
| Cleft | External auditory canal | | |
| Pouch | Eustachian tube | | |
| | Middle ear cavity | | |
| | Mastoid air cells | | |
| **II** | | | |
| Arch | Stapes | Styloid process | Root of tongue |
| Stapedial artery | | Hyoid (lesser horn and part of body) | Foramen cecum |
| Nerves VII and VIII | | | Thyroid gland's median anlage |
| Pouch | Palatine tonsil | | |
| | Supratonsillar fossa | | |
| **III** | | | |
| Arch | | Hyoid (greater horn and part of body) | |
| Internal carotid artery | | Part of epiglottis | |
| Nerve IX | | Thymus | |
| Pouch | Inferior parathyroid | | |
| | Piriform fossa | | |
| **IV** | | | |
| Arch | | Thyroid cartilage | |
| Arch of aorta (L) | | Cuneiform cartilage | |
| Part of subclavian artery (R) | | Part of epiglottis | |
| Nerve X | | | |
| Pouch | Superior parathyroid (lateral anlage of thyroid gland) | Thymus (inconstant) | |
| **V** | | | |
| Arch | | | |
| Pouch | Ultimobranchial body (lateral anlage of thyroid gland) | | |
| **VI** | | | |
| Arch | | Cricoid | |
| Pulmonary artery | | Arytenoid | |
| Ductus arteriosus (L) | | Corniculate cartilage | |
| Nerve X (recurrent laryngeal) | | | |

From Skandalakis JE, Gray SW, Todd NW: The pharynx and its derivatives. In Skandalakis JE, Gray SW (eds): Embryology for Surgeons, ed 2. Baltimore, Williams & Wilkins, 1994.

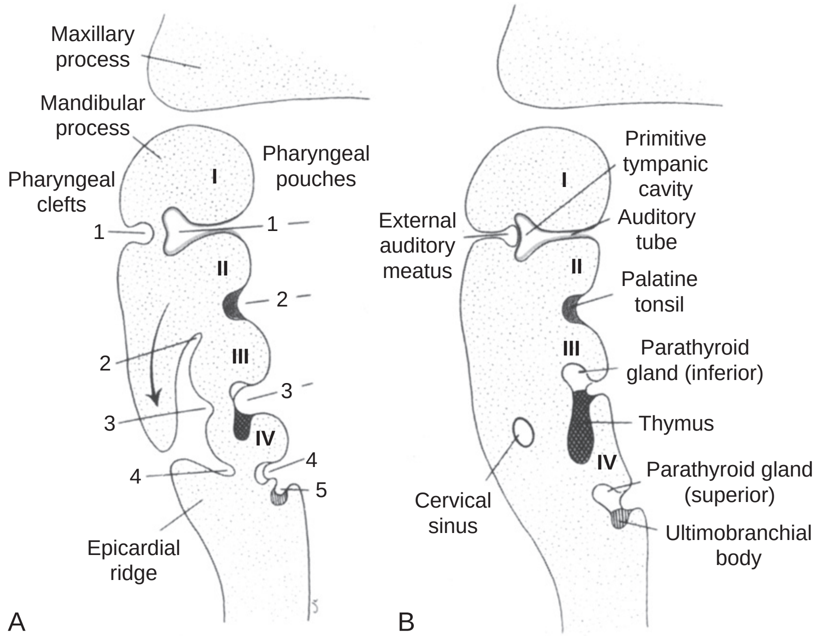


**FIGURE 59-2** **A,** Schematic representation of the development of the pharyngeal (or branchial) clefts and pouches. Note that the second arch grows over the third and fourth arches, thereby burying the second, third, and fourth pharyngeal clefts. **B,** Remnants of the second, third, and fourth pharyngeal clefts form the cervical sinus, which is normally obliterated. Note the structures formed by the various pharyngeal pouches. (From Sadler TW: Head and neck. In Langman J, Sadler TW (eds): Langman's Medical Embryology, ed 7. Baltimore, Williams & Wilkins, 1995.)

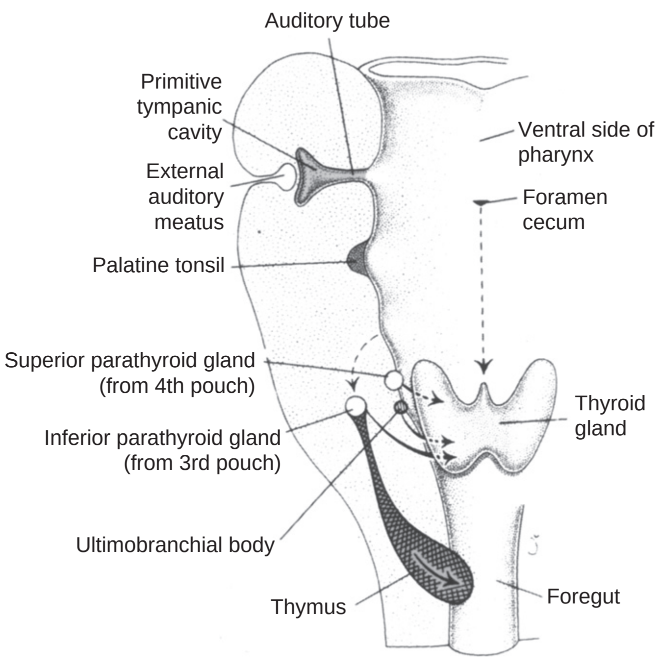


**FIGURE 59-3** Schematic representation of migration of the thymus, parathyroid glands, and ultimobranchial body. The thyroid gland originates in the midline at the level of the foramen cecum and descends to the level of the first tracheal ring. (From Sadler TW: Head and neck. In Langman's Medical Embryology, ed 7. Baltimore, Williams & Wilkins, 1995.)

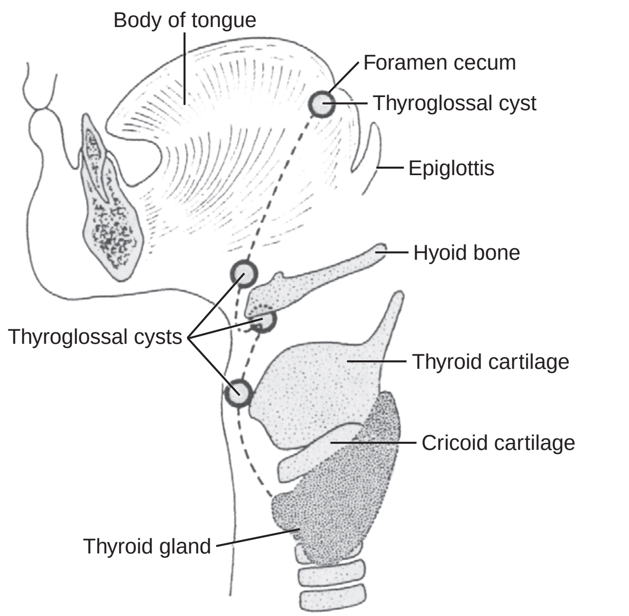


**FIGURE 59-4** Various locations of thyroglossal duct cysts. (From Sadler TW: Head and neck. In Sadler TW (ed): Langman's Medical Embryology, ed 11. Baltimore, Lippincott Williams & Wilkins, 2010.)

Although the exact incidence varies between different pediatric series, thyroglossal duct remnants are typically the more common etiology of congenital neck cysts or sinuses, followed closely by branchial cleft remnants.[3–5] In general, thyroglossal duct lesions lie close to the midline, whereas branchial remnants present more laterally in the neck, although atypical locations have been described.[6]

## Thyroglossal Duct Cysts

Thyroglossal duct remnants are clearly the most common midline congenital cervical anomalies. As described, they occur along the path of thyroid descent from the foramen cecum at the base of the tongue to the lower neck. The remnants usually lie in close proximity to the hyoid bone. Given this relationship one can appreciate why the cysts often move cephalad with swallowing or tongue protrusion. Although classically described as midline, up to 40% may lie just lateral to the midline. Most lesions present as cystic masses, but up to 25% have a draining sinus.[7] Because the thyroglossal duct

does not communicate with ectoderm during development, the sinus is either the result of spontaneous rupture, infection, or a prior drainage procedure. Approximately 60% of thyroglossal duct cysts are adjacent to the hyoid bone, 24% lie above the hyoid, and 13% lie below.[8] The remaining 8% of cysts are intralingual and may pose a risk for acute airway obstruction, particularly in the neonate.[9] Most thyroglossal duct cysts present during the first 5 years of life.[2]

In view of the potential communication with the oral cavity, it is not surprising that the cysts may fluctuate in size or that approximately one third of patients present with an active infection of the cyst or history of prior infection.[2] Some patients may actually report noticing a foul taste. The most common pathogens are *Haemophilus influenzae, Staphylococcus aureus,* and *Staphylococcus epidermidis*.[7,10]

The thyroglossal duct remnants are lined by ductal epithelium and may contain solid thyroid tissue. In fact, in roughly 1% to 2% of patients with presumed thyroglossal duct cysts, the actual lesion is a median ectopic thyroid.[8] It may represent their only functional thyroid tissue in which case excision would be problematic. Further evaluation may be obtained with a screening thyroid-stimulating hormone (TSH) level and neck ultrasonography. If there is evidence of hypothyroidism or the mass appears solid without a visible normal thyroid gland, one might wish to obtain a thyroid scan to determine whether there is any additional thyroid tissue. Such patients are often hypothyroid with an elevated TSH, which is responsible for the hypertrophy of the ectopic tissue. In the setting of hypothyroidism, hormonal supplementation would be appropriate and might promote shrinkage of the hypertrophic thyroid tissue, thereby obviating the need for surgery.

## SURGICAL MANAGEMENT

The primary indication for excision of thyroglossal duct remnants is to avoid problems with recurrent infection. However, malignancy within thyroglossal duct remnants is also well described.[11] Such tumors usually present as papillary carcinoma in adults, but pediatric cases are reported, and multiple cell types have been encountered.[12–14]

Appropriate surgical management of uncomplicated thyroglossal duct disease involves complete resection of the cyst and its tract in continuity with the central hyoid bone, as described by Sistrunk.[15] One should be aware that in young children the hyoid bone may override the thyroid notch, potentially placing the larynx at risk. The patient is positioned supine with the head elevated and neck extended. A transverse cervical incision is used to carefully mobilize the cyst along with its tract. The underlying hyoid bone is divided about 1 cm from the midline on either side after dividing the attachments of the mylohyoid and hyoglossus muscles from its superior border. En-bloc resection is completed with suture ligation of the proximal tract, prior to removal of the specimen (Fig. 59-5). Elegant studies of resected surgical specimens by Horisawa and colleagues, as depicted in Figure 59-6, demonstrate the importance of this strategy to achieve complete excision, thereby reducing the likelihood of recurrence.[16]

In the setting of acute infection, initial efforts are aimed to control the infection. If antibiotics alone are insufficient, aspiration or incision and drainage of the cyst/abscess may be required. Once the infection is well-controlled, the described Sistrunk procedure can be performed using an elliptic skin incision around the cutaneous opening to permit excision of this tract in continuity with the remainder of the specimen.

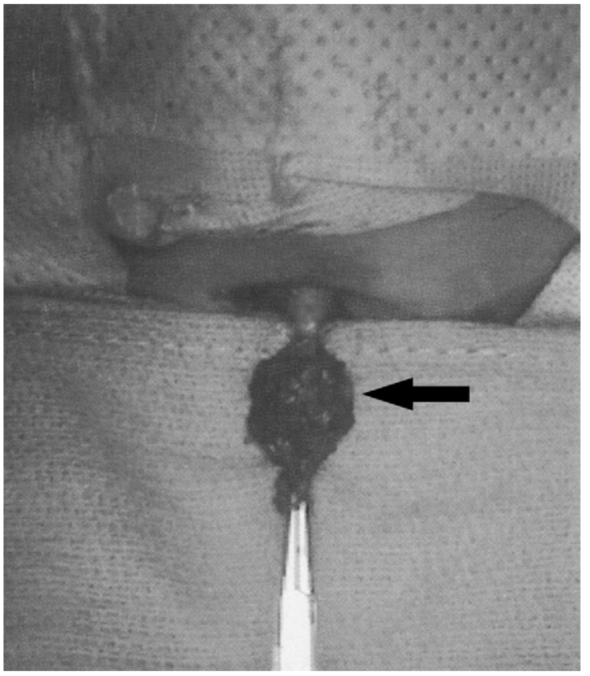

**FIGURE 59-5** Sistrunk procedure: intraoperative photograph of resection of thyroglossal duct cyst in continuity with central hyoid bone *(arrow)*.

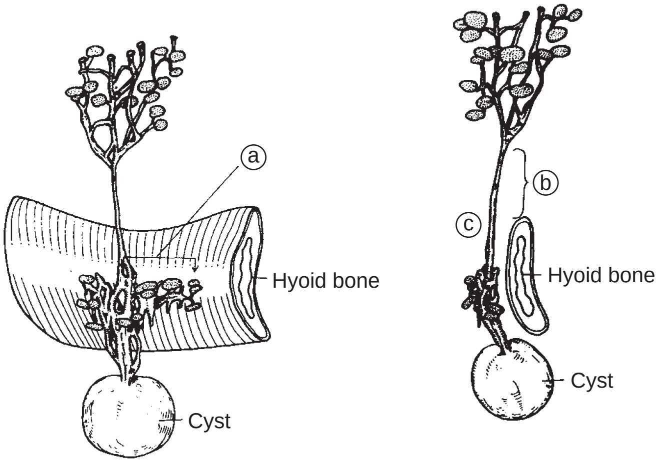


**FIGURE 59-6** Diagram of the common running pattern of the thyroglossal duct based on anatomic reconstruction. *a,* Horizontal distance from midline to the most distant thyroglossal duct; *b,* length of the single duct above the hyoid bone; *c,* point where the diameter of the duct is measured. (From Horisawa M, Niinomi N, Ito T: What is the optimal depth for core-out toward the foramen cecum in a thyroglossal duct cyst operation? J Pediatr Surg 1992;27:710-713.)

Recurrences after thyroglossal duct excisions may occur in up to 10% of cases.[17,18] The most likely cause is incomplete excision of the tract or intraoperative rupture. An association with preoperative infection has been suggested,[19,20] but not confirmed in more recent analyses. Postoperative infection is clearly associated with recurrence, but it is uncertain whether this development represents cause or effect.[18] Excision of a recurrent thyroglossal duct remnant has a 20% to 35% risk of failure.[10,21] Wider resection is recommended, including the pyramidal lobe if present, central strap muscles, additional hyoid bone, and residual tissue up to the foramen cecum.[17,22]

## Branchial Anomalies

Most branchial cleft anomalies arise from the second cleft/pouch, with a much smaller proportion from the first. Remnants of the third or fourth pouches are rare. It is the internal opening of branchial sinuses that best defines their embryologic origin. The anomalies may present as fistulae, cysts, sinus tracts, or cartilaginous remnants and are thought to arise from incomplete obliteration during embryogenesis. To clarify, cysts have mucosal or epithelial lining, but no external openings. Sinuses may communicate either externally with the skin or internally with the pharynx, whereas fistulae connect to both. When an external tract is present, branchial anomalies are usually diagnosed within the first decade of life. However, when there is no external opening the diagnosis may be delayed into adulthood. Up to 10% of these lesions are bilateral as depicted in Figure 59-7.[23,24] The presence of preauricular pits in patients with branchial anomalies should raise the suspicion for the branchio-oto-renal (BOR) and branchio-oculo-facial (BOF) syndromes. Both are autosomal dominant conditions with associated hearing loss, ear malformations, and renal anomalies in the BOR syndrome, while BOF includes eye anomalies, such as microphthalmia and obstructed lacrimal ducts, and facial anomalies consisting of cleft or pseudocleft lip/palate.[24,25]

It is worth mentioning that short sinus tracts, pedunculated skin appendages or subcutaneous cartilaginous remnants are often encountered in the anterior neck and upper chest. These structures are probably branchial remnants, but cannot usually be ascribed to a specific arch. Lesions presenting below the clavicles are more likely epidermoid or dermoid cysts rather than branchial remnants. Most often elective excision is used.

### SECOND BRANCHIAL ANOMALIES

Second branchial cleft anomalies typically lie somewhere between the lower anterior border of the sternocleidomastoid (SCM) muscle and tonsillar fossa of the pharynx. They may be in close proximity to the glossopharyngeal and hypoglossal nerves as well as carotid vessels as the tract travels through the carotid bifurcation and over the nerves to enter the lateral pharyngeal wall as depicted in Figure 59-8.

**FIGURE 59-7** Child with bilateral second branchial cleft sinuses *(arrows)*.

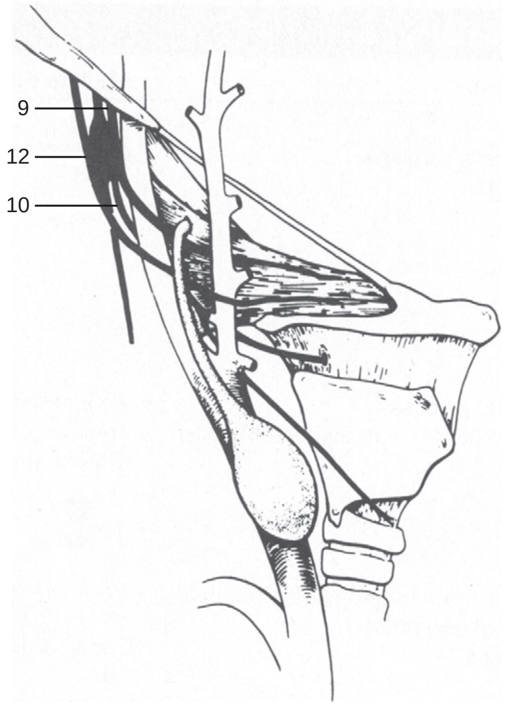


**FIGURE 59-8** Second branchial cleft cyst and sinus tract. (From Donegan JO: Congenital neck masses. In Cummings CW, Fredrickson JM, Harker LA, et al [eds]: Otolaryngology—Head and Neck Surgery, ed 2. St Louis, Mosby-Year Book, 1993.)

The branchial anomalies are lined by epithelium. Overall cystic lesions are more common than fistulae, but usually present later (e.g., second decade).[7] Cysts most often present as nontender soft tissue masses beneath the SCM muscle. However, they may present with acute infection. Change in size during upper respiratory infections is noted in up to 25%.[26] The anomalies have been classified into four types.[5] Type 1 are superficial, but located deep to the platysma and cervical fascia, along the anterior border of the SCM muscle. Type 2 anomalies are the most common. They course deep to the SCM muscle and either anterior or posterior to the carotid artery. Type 3 lesions pass between the carotid bifurcation and lie adjacent to the pharynx. Type 4 lesions are medial to the carotid sheath and in close approximation to the pharynx, usually at the level of the tonsillar fossa.

The most common presentation in infants and young children is a second branchial cleft sinus with drainage from a small cutaneous pit along the anterior border of the lower sternocleidomastoid muscle. On occasion, a subcutaneous tract is palpable more cephalad. Less common symptoms include stridor, dysphagia, odynophagia, or cranial nerve palsies. Branchiogenic carcinoma has been diagnosed in adults.[27]

Given the risks of infection, further enlargement or malignancy, elective excision is recommended once the diagnosis has been made. There is typically no urgency; so, one can defer excision beyond 3 to 6 months of age or to allow treatment of an acute infection. Systemic antibiotics and aspiration are generally preferable to incision and drainage, which might produce more distortion of the surgical planes; however, when diagnosis is unclear, the latter allows biopsy of the cyst wall, which can help to distinguish between an infected branchial cleft cyst and simple bacterial lymphadenitis.

**FIGURE 59-9** Intraoperative photo showing excision of second branchial cleft sinus/fistula using second parallel ("step-ladder") cervical incision.

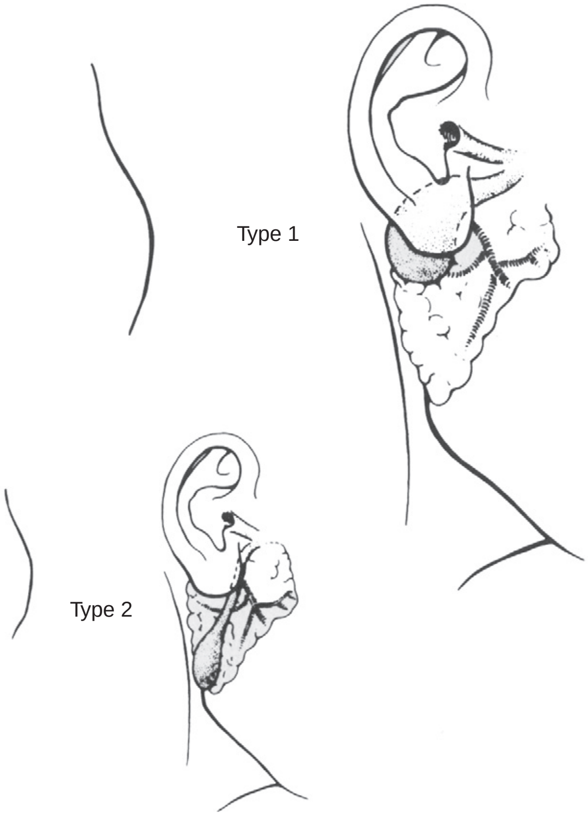


**FIGURE 59-10** Type I and type II first branchial cleft abnormalities. (From Donegan JO: Congenital neck masses. In Cummings CW, Fredrickson JM, Harker LA, et al [eds]: Otolaryngology—Head and Neck Surgery, ed 2. St Louis, Mosby-Year Book, 1993.)

The goal is complete excision of the tract without injury to surrounding nerves or vascular structures. A transverse cervical incision in a skin crease directly over the cyst will aid to optimize the future cosmetic result. In the case of a sinus or fistula, precise identification may be facilitated by gently inserting a probe, catheter, or monofilament suture into the tract. A lacrimal probe dipped in methylene blue has also been used to stain the tract and make it easier to identify should it break during dissection. Excision is best accomplished by dissection directly on the surface of the lesion. The tract may be very thin-walled; so, one must be careful to avoid avulsion with possible loss of the proximal lumen. If the tract is long, exposure may be improved by a second (so-called "stepladder") incision along a skin crease more cephalad (Fig. 59-9). Second branchial anomalies presenting as pharyngeal cysts can be excised by an intraoral approach.[28,29]

## FIRST BRANCHIAL ANOMALIES

First branchial cleft anomalies are rare, but more common in females. Accurate diagnosis is difficult and may be quite delayed.[30] Remnants may persist anywhere between the external auditory canal and submandibular area. They should be distinguished from preauricular pits and sinuses, which arise from failure of the auricular hillocks to fuse. The first cleft anomalies often lie in close association to the parotid gland and facial nerve. In 1972, Work classified first branchial anomalies into types 1 and 2 (Fig. 59-10).[31] Type 1 lesions are rarer and considered duplications of the membranous external auditory canal. They are of ectodermal origin and generally course lateral to the facial nerve. Type 2 lesions contain both ectodermal and mesodermal elements, which may include cartilage. These anomalies pass medial to the facial nerve but may present in preauricular, infraauricular, or postauricular locations. Sinuses may present with external drainage below the angle of the mandible or otorrhea, which may become infected. Cysts present as soft tissue masses in this region which may also become secondarily infected. A communication with the external auditory canal may be present. A careful otologic examination is important to define the pathology.

Complete surgical excision is once again recommended, but great care must be taken given the proximity of the facial nerve. In infants and children, the nerve is probably even more susceptible given that it is smaller and more superficial without well-developed landmarks.[32] Many authors recommend initial exposure of the main trunk of the facial nerve and its peripheral branches with superficial parotidectomy to reduce the risk of facial nerve injury.[33,34] Prior infection may distort accurate tissue dissection planes. It is necessary to excise the involved skin and cartilage of the external auditory canal. Furthermore, if the tract extends medially to the tympanic membrane a second operation may be required to remove this segment.[35,36]

## THIRD AND FOURTH BRANCHIAL ANOMALIES

Third and fourth branchial anomalies are very rare and almost always occur on the left side of the neck. Most present as sinuses or infected cysts rather than congenital fistulae and drain into the piriform sinus. Although sometimes combined

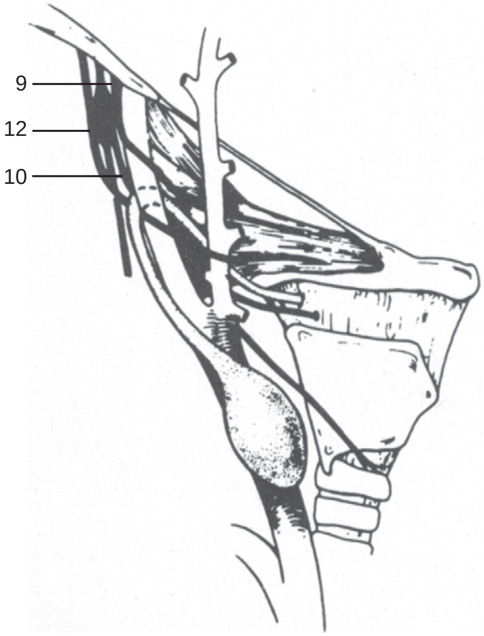


FIGURE 59-11 Third branchial cleft cyst and sinus tract. Note that these occur much more frequently on the left side (approximately 90%); also, during surgery the tract is often seen to go straight up from the left upper thyroid lobe area toward the thyroid cartilage, without passing behind the carotid artery as the embryologic development would suggest. (From Donegan JO: Congenital neck masses. In Cummings CW, Fredrickson JM, Harker LA, et al [eds]: Otolaryngology—Head and Neck Surgery, ed 2. St Louis, Mosby-Year Book, 1993.)

generically as piriform sinus tracts, distinction is possible. As noted in Figure 59-1 the superior laryngeal nerve represents the nerve to the fourth branchial arch. Third pouch anomalies enter the piriform sinus above the superior laryngeal nerve, whereas fourth pouch anomalies enter below this nerve. A third branchial cleft fistula theoretically would extend from the anterior border of the SCM, traversing deep to the internal carotid artery and glossopharyngeal nerve, piercing the thyroid membrane above the internal branch of the superior laryngeal nerve and entering the pharynx at the piriform sinus as depicted in Figure 59-11. A fourth branchial fistula would course around the subclavian artery on the right or aortic arch on the left to ascend back up over the hypoglossal nerve and enter the piriform apex or cervical esophagus (Fig. 59-12). A complete fourth branchial fistula has yet to be identified in humans,[5] and most third branchial fistulae described appear to have been secondary to infection or repeated surgery.[37]

Presentation of piriform sinus tracts may be quite subtle and their diagnosis very challenging. Noncommunicating or noninfected communicating cysts may present as cold thyroid nodules, which may be partly or totally intrathyroid.[37] A history of repeated upper respiratory tract infections and sore throats, hoarseness or pain, and tenderness of the thyroid gland should raise suspicion. Infection may result in suppurative thyroiditis[38]; any thyroid abscess in a child should raise the suspicion of a branchial remnant, particularly if closely related to the left upper pole of the thyroid gland. Acute respiratory compromise in neonates has been described.[39] Needle aspiration may be required to temporarily relieve respiratory symptoms. A contrast esophagogram after resolution of the acute infection may demonstrate the tract from the piriform

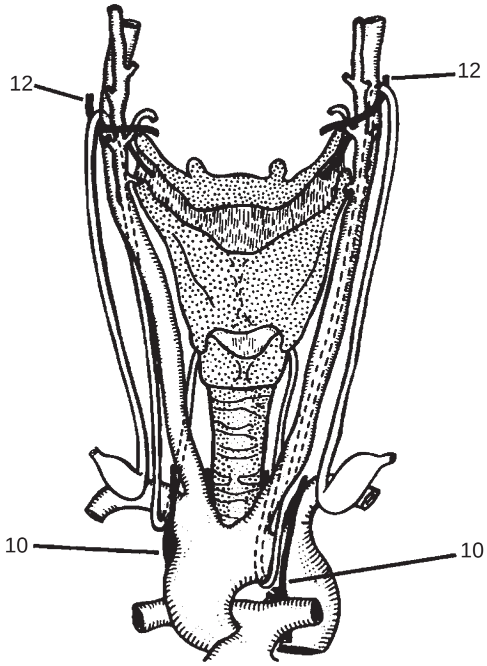


FIGURE 59-12 Anatomic relationships of theoretical course of fourth branchial fistula. Such a complete fistula has never been described in humans. (From Liston SL: Fourth branchial fistula. Otolaryngol Head Neck Surg 1981;89:520-522.)

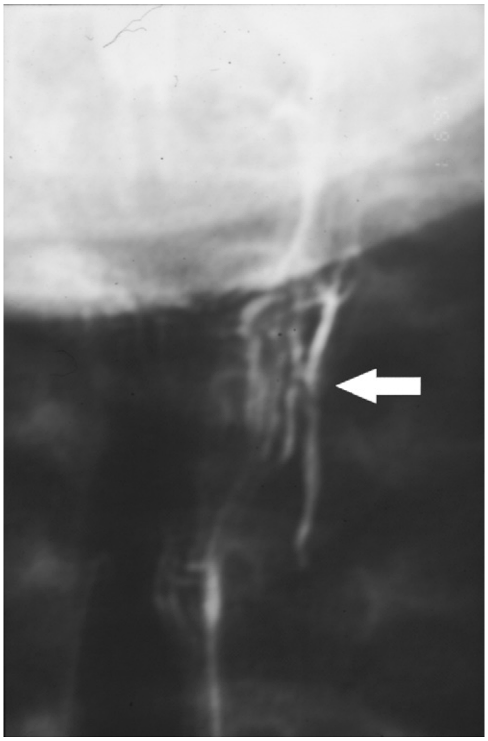

FIGURE 59-13 Contrast esophagogram demonstrating contrast within piriform sinus tract *(arrow)*.

sinus as depicted in Figure 59-13. Other imaging has been successful if air is visualized within the cyst or tract originating from the piriform fossa opening.[40] Combinations of ultrasonography, CT, MRI, and thyroid scan may help in establishing a diagnosis.[37]

Once again, complete excision is necessary to avoid continued difficulties. Often several previous operations have been performed before the correct pathology is recognized.[41,42] Direct laryngoscopy or rigid pharyngoscopy, using a Hopkins rod-lens telescope, is recommended for accurate diagnosis as well as endoscopic cannulation of the opening into the piriform sinus, if possible, to facilitate accurate dissection.[37,43] A standard collar incision is used with identification of the recurrent laryngeal nerve. Partial or total ipsilateral thyroid lobectomy with excision of the tract to the piriform sinus is usually required. Partial resection of the thyroid cartilage may also be necessary to remove the entire tract.[44] Cauterization of the internal opening has been described.[45,46]

## Dermoid Cysts

Cervical dermoid cysts are thought to arise from elements trapped during fusion of the anterior branchial arches. They are composed of ectodermal and mesodermal elements, but in contrast to teratomas, do not contain any endodermal derivatives.[35] These lesions are typically midline and well-circumscribed. They are lined by squamous epithelium and usually contain sebaceous debris, which can become secondarily infected. Although they appear echogenic rather than cystic on ultrasound examination, imaging is useful to differentiate submental dermoids from benign reactive lymph nodes. The overlying skin is often adherent, and a small cutaneous pit may be visible. If the cyst is adherent to the underlying fascia or lies within the strap muscles, it may move with swallowing or tongue protrusion, making the distinction from a thyroglossal duct cyst impossible. Complete excision is appropriate. A yellowish appearance at surgery and the sebaceous cyst content allow distinction from a thyroglossal duct cyst, which more often contains a clear viscous fluid. If the cyst lies adjacent to the hyoid bone and a diagnostic doubt exists, a formal Sistrunk procedure with in continuity excision of the central hyoid bone is recommended to ensure complete removal of the pathology.

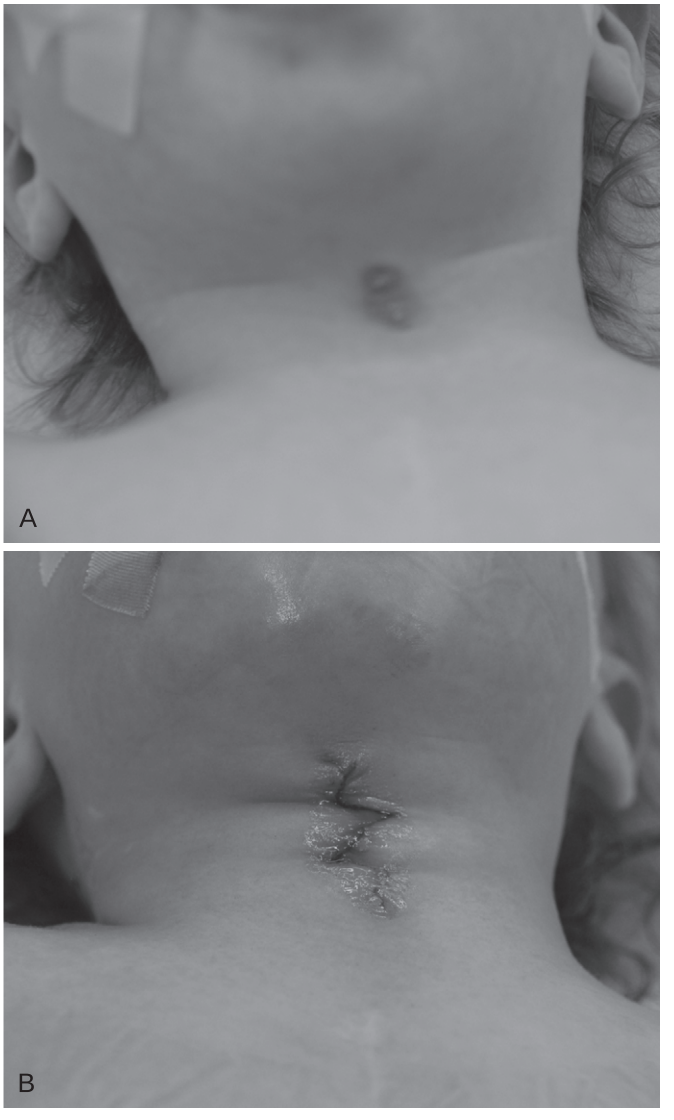


FIGURE 59-14 Photographs of infant with midline cervical cleft (**A**) and Z-plasty reconstruction after excision (**B**).

## Congenital Midline Cervical Clefts

Congenital midline cervical clefts are very rare anomalies thought to arise from failure of anterior fusion of the first two branchial arches.[47,48] They typically present as a longitudinal area of thinned or atrophic skin along the anterior midline of the neck. Characteristically, there are skin tags at the upper end and small sinus tracts at the inferior aspect. Secretions may be noted from accessory salivary glands draining into the cleft.[49,50] Early complete excision is recommended, both for cosmesis as well as to avoid limitations to neck extension and mandibular growth. Wound closure is accomplished using a series of Z-plasties, to avoid a contracting linear scar (Fig. 59-14).[51,52]

## Cervical Thymic Cysts

Thymic cysts are usually seen within the chest and mediastinum. However, given that the thymus arises from the third, and sometimes fourth, branchial pouches, one can appreciate the possibility for a cervical location. Cervical thymic cysts typically present in the anterior triangle, more commonly on the left than the right. They occur more frequently in males, with peak onset at age 5 to 7 years.[53] They may be difficult to distinguish preoperatively from more common cystic lesions, such as branchial cleft cysts or lymphatic malformations. They can be unilocular or multilocular. Extension into the mediastinum is common and accounts for the often-described physical finding of enlargement with a Valsalva maneuver. The precise diagnosis is usually made postoperatively when elements of

thymus are identified within the cyst wall. The fluid within these cysts is typically brownish in color. The lesions are almost always benign. Surgical excision is generally quite straightforward, although one needs to be cognizant of potentially adherent vessels (e.g., carotid artery, jugular vein) or nerves (e.g., phrenic, recurrent laryngeal). Although the aim is to completely remove the cyst, one should be careful in very young children, to avoid removing the entire thymus, which might have untoward immunologic consequences.

Although the focus of this chapter has been congenital lesions, the differential diagnosis for neck cysts and sinuses must be much broader. A wide variety of acquired conditions, including infections and tumors, should also be considered. The distinction between infection of a congenital cervical remnant and a primary cervical infection with the development of an abscess or draining sinus may not always be straightforward. Nonetheless, an awareness of the congenital possibilities and their likely anatomic locations will assist the astute clinician.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 60

# Torticollis

Spencer W. Beasley

There are many causes of torticollis in childhood (Table 60-1), but most are rare. The most common cause of torticollis is tightness and shortening of one sternomastoid muscle, a condition that occurs in about 0.4% of all births. Typically, at about 3 weeks of age, a visible or palpable swelling develops in part or all of the muscle; this swelling is called a sternomastoid tumor. It affects the right side in about 60%,[1] is bilateral in 2% to 8%,[2,3] and often persists for up to 1 year. Older children may present with a fibrotic, shortened sternomastoid muscle, which is presumed in many to be the legacy of a previously unrecognized sternomastoid tumor.

## History

Alexander the Great may have had torticollis, according to Plutarch.[4] Antyllus is said to have performed tenotomies in 350 AD, but the first authenticated division of the sternocleidomastoid was by Minnus in Amsterdam in 1641.[5] A sternocleidomastoid tumor was described by Heusinger in 1826.[6] Torticollis was also a subject of interest to Dupuytren.[7]

## Etiology

Although often referred to as "congenital torticollis," the sternomastoid mass and the torticollis are rarely noticeable at birth. Little is known about the etiology of sternomastoid fibrosis, although several theories have been put forward to explain the condition. It may be due to an idiopathic intrauterine embryopathy[8] or could be the manifestation of an intrauterine positional disorder producing sternocleidomastoid compartment syndrome.[9] The high incidence of obstetric difficulties, such as breech presentation and the need for assisted delivery,[10,11] may be the result rather than the cause of the shortened sternomastoid muscle, as was initially thought. There is no report of a sternomastoid tumor detected by antenatal ultrasonography.[12] Concomitant hip dysplasia is common.[10]

## Pathology

The basic abnormality on histology is fibrous replacement of muscle bundles.[13] The lesion, called fibromatosis colli, is often classified with other types of fibromatoses, such as the Dupuytren contracture and plantar fibromatosis. Jones[8] has described endomysial fibrosis involving the deposition of collagen and fibroblasts around individual muscle fibers that undergo atrophy. The sarcoplasmic nuclei are compacted to form giant cells that appear to be multinucleated. The maturity of the fibrous tissue in neonates suggests that the disease may begin before birth[8,14,15] and may therefore contribute to the frequency of obstetric difficulties during delivery. The reported incidence of breech deliveries is about 20% to 30%[16]—much higher than the normal incidence. About 60% of affected infants are involved in a complicated birth,[16] which suggests that the fibrosis may affect the position of the fetus in utero and perhaps even prevent normal engagement of the head in the maternal pelvis.

The natural history of untreated sternomastoid fibrosis is complete resolution in 50% to 70% of patients at 6 months of age. In about 10%, the tumor and sternomastoid shortening persist beyond 12 months of age.[2,17] The severity and distribution of the fibrosis within the sternomastoid muscle is variable and has led to a variety of classifications based either on a palpable localized sternomastoid tumor or thickening and shortening of the whole muscle or on the basis of ultrasonographic findings.[18,19] The systems of classification have some prognostic significance in that localized lesions within the sternomastoid (clinically or ultrasonographically) are more likely to resolve spontaneously than those involving the whole muscle. In older children with torticollis, the appearance of degenerating fibers is more consistent with disuse atrophy produced by limitation of movement caused by the fibrosis.

## Clinical Features

### STERNOMASTOID TORTICOLLIS

The tumor is a hard, spindle-shaped, painless, discrete swelling usually about 1 to 3 cm in diameter within the substance of one sternomastoid muscle. Almost always, it first becomes evident at about 3 weeks after birth. Obvious head tilt or torticollis tends to develop later.[12] In infants, the head is rotated to the side opposite the tumor, with only slight flexion of the head to the affected side (Fig. 60-1).

In other patients, the sternomastoid tumor is less discrete, and the sternomastoid appears to be thickened and tightened along its whole length. The shortening of the muscle restricts rotation and lateral flexion of the head (Fig. 60-2).

**TABLE 60-1**
**Causes of Torticollis in Infants and Children**

| *Cause* | *Comment* |
|---|---|
| Sternomastoid "tumor" | Common; appears at 3 weeks of age |
| Abnormal position in utero | Tends to improve with age |
| Cervical hemivertebrae | Structural; confirmed on plain radiograph |
| Cervical lymphadenitis/abscess | Acute; usually occurs in first 2 years of life |
| Retropharyngeal abscess[31,58] and pyogenic cervical spondylitis[59] | Acute; signs of toxicity, cervical pain |
| Posterior fossa tumors[61] | A rare cause; headaches, vomiting, and other neurologic signs present[61] |
| Acute atlantoaxial subluxation | May occur after tonsillectomy[30] |
| Atlantoaxial rotatory subluxation | Significance disputed[58,59]; diagnosed on dynamic CT |
| Spasmodic with Sandifer syndrome[59] | Due to gastroesophageal reflux |
| Congenital absence of sternomastoid | Unilateral, extremely rare[60] |
| Postural | Familial |

CT, computed tomography.

**FIGURE 60-1** Appearance of a right sternomastoid tumor in infancy; the head is turned to the contralateral side.

The rotational component of the action of the sternomastoid is easy to measure. It is assessed by standing behind the child's head and passively rotating the head while it is held between both hands. The sternomastoid muscle is stretched to its maximum length by rotation to the side of the affected muscle. Where the muscle is fibrotic, it cannot be stretched to its full length, and rotation to the ipsilateral side is restricted.

Older children with torticollis compensate for the more pronounced tilt by elevating one shoulder to enable the eyes to keep as level as possible (Fig. 60-3). Such compensation is not seen in infants, because there is no need for them to maintain their eyes in a horizontal plane until they stand up.[20] Moreover, older children do not turn their heads to the contralateral side as much, because they tend to compensate by twisting the neck and back to keep their eyes pointing forward.

## DIFFERENTIAL DIAGNOSIS

Initial clinical assessment must establish whether the wry neck is caused by shortness of one sternomastoid muscle or by some other condition. In sternomastoid fibrosis, the anterior border of the muscle stands out as a tight band, although in some small infants in whom the neck is relatively short, the muscle may be difficult to see readily. For this reason, the full length of the muscle must be palpated to determine whether there is an area of thickening or fibrosis along part or all of its length. In about two thirds, there is a definite localized swelling (tumor) in the muscle; in the remainder, the whole muscle appears to be affected. There is no role for plain radiography where the sternomastoid is tight or shortened.[21] Although not required for diagnosis, appearance on ultrasonography may help predict (to a degree) the likelihood of spontaneous resolution.[1,19,22] Inexperienced ultrasonographers, worried by the infiltrative and ill-defined appearance, may recommend

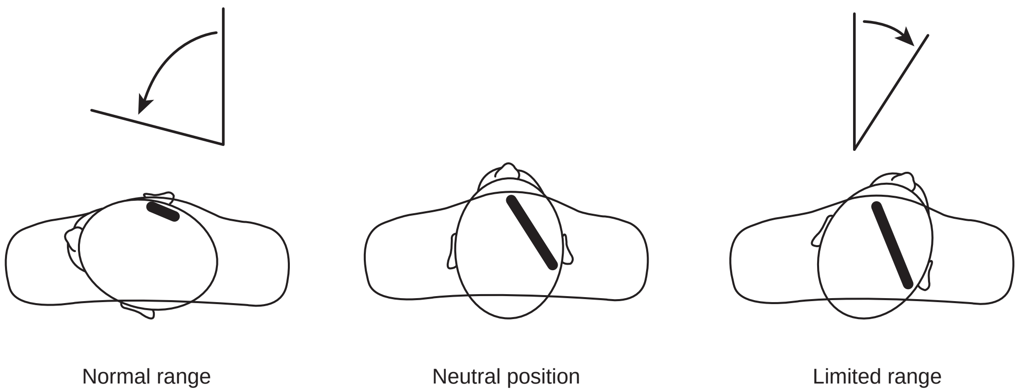


**FIGURE 60-2** Restriction of rotation of the head secondary to shortening of the sternomastoid muscle as viewed from above the head. The black bars represent the right sternomastoid muscle and show that its inability to lengthen limits rotation to that side.

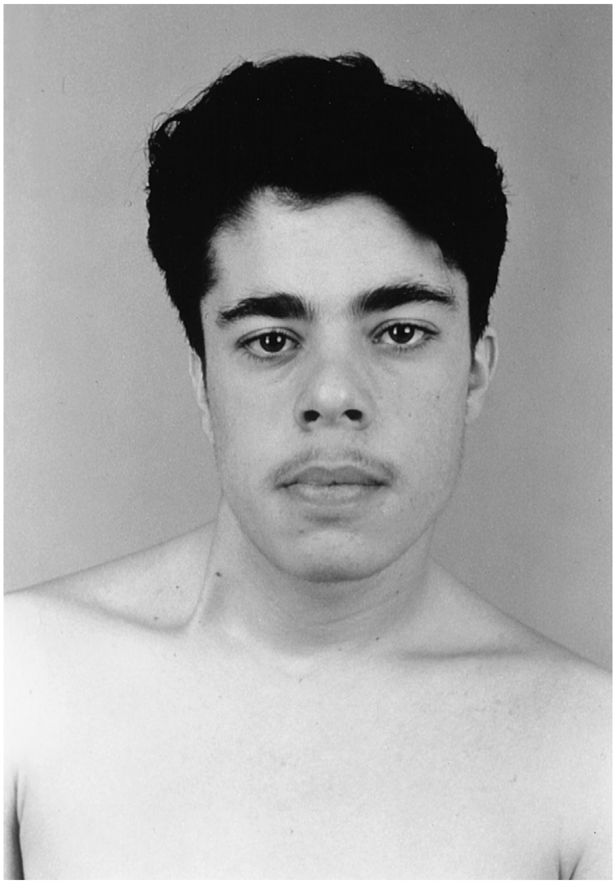

**FIGURE 60-3** Appearance of torticollis as a result of sternomastoid fibrosis in an older child. The eyes are kept horizontal, but the shortened sternomastoid muscle causes compensatory elevation of the shoulder. (From Beasley SW, et al: Pediatric Diagnosis. London, Chapman & Hall, 1994, with permission.)

**FIGURE 60-4** Torticollis caused by atlanto-occipital subluxation after tonsillectomy. Notice that there is no tightness of the sternomastoid muscle on either side. (From Beasley SW, et al: Pediatric Diagnosis. Chapman & Hall, London, 1994, with permission.)

further imaging or biopsy of the "tumor"; this is not indicated in the presence of the typical palpable mass within the sternomastoid and torticollis. It is possible to diagnose a sternomastoid torticollis on magnetic resonance imaging (MRI)[22,23] and computed tomography (CT),[24] but neither alters management and should not be performed routinely.[23,25]

An obvious mass or fibrosis of the muscle may not always be noticeable in idiopathic torticollis, but in such instances, alternative diagnoses must be sought (see Table 60-1 and Fig. 60-4).[20,26]

A squint may cause head tilt from imbalance in rotation of the eyes. The squint may not be obvious at first because the tilt compensates for the abnormal position of the eyes. When the head is straightened passively, the squint becomes apparent. Occasionally, sternomastoid fibrosis may occur coincidentally with ocular torticollis.

Posterior fossa tumors may compress the brainstem at the foramen magnum and produce acute stiffness of the neck that causes it to be held to one side. The neck is frozen in this position and is difficult to move actively or passively. The presence of a central nervous system tumor may be known already, but occasionally, acute torticollis is the first manifestation. Careful neurologic examination may show abnormalities of the lower cranial nerves and cerebellar function, and the causative lesion is demonstrated on CT or MRI.

Hemivertebrae involving the cervical spine may produce a tilt of the head that is evident from birth and does not progress. Vertebral lesions can be identified clinically by inspection and palpation of the dorsal cervical spines and confirmed on plain radiographs of the neck.

Acute torticollis has been attributed to atlantoaxial rotatory subluxation as determined on dynamic CT,[27,28] but others doubt the existence or significance of these findings and suggest that CT scans are not necessary at the initial examination.[29] Atlantoaxial subluxation has been reported after tonsillectomy.[30] Acute torticollis can also result from inflammatory conditions of the neck, including retropharyngeal abscess,[31] and can be a symptom of acute lymphoblastic leukemia.[32]

## Secondary Effects of Torticollis

Table 60-2 lists the secondary effects of torticollis.

**TABLE 60-2**
**Secondary Effects of Torticollis**

| | |
|---|---|
| Infants | Plagiocephaly |
| | Hemifacial hypoplasia |
| Older children | Compensatory scoliosis |

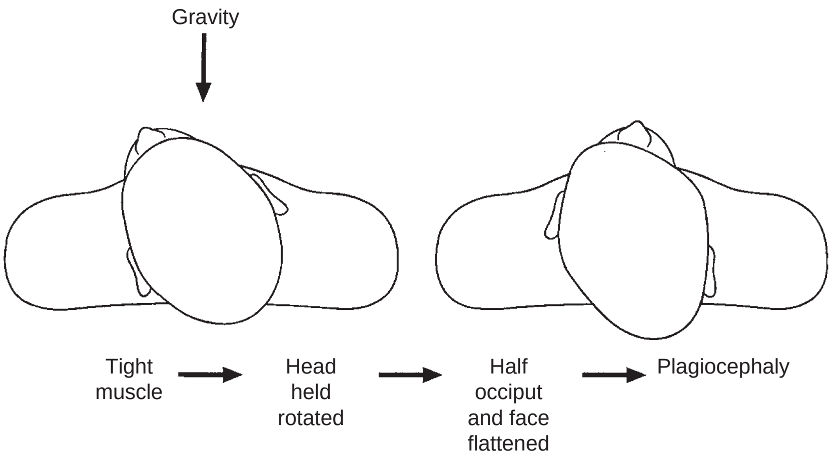


**FIGURE 60-5** Plagiocephaly.

## PLAGIOCEPHALY

In small infants with torticollis and fixed rotation of the head, gravity deforms the relatively soft head as it lies in the same position for a prolonged period. Flattening of one occiput leads to secondary flattening of the contralateral forehead (Fig. 60-5). This asymmetric skull deformity is called plagiocephaly and develops in the first few months of life.[33] It is best observed from above the head. Once the child begins to sit up or the torticollis resolves, the plagiocephaly tends to resolve as well.[34] It may take several years to disappear, and a few children have a slight permanent deformity. It is possible that many children with plagiocephaly have had unrecognized torticollis during infancy.[35]

## HEMIFACIAL HYPOPLASIA

Progressive facial deformity is seen when one sternomastoid muscle immobilizes the face for a long time. The malar eminence on the side of the face limited by the fibrotic muscle grows more slowly than the normal side does[9] and causes progressive asymmetry (Fig. 60-6). This inhibition of growth of the mandible and maxilla embodies an important principle of pediatrics: Normal growth of bones depends on normal muscular movement.

**FIGURE 60-6** Hemifacial hypoplasia on the right side.

The degree of hypoplasia of one side of the face can be determined by the angle between the plane of the eyes and the plane of the mouth. Normally these lines are parallel, but they form an angle to each other when the face is asymmetric. The development of hemifacial hypoplasia is one indication for surgery; division of the tight sternomastoid muscle allows resolution of the skeletal abnormality and subsequent normal growth.[9]

Significant hemifacial hypoplasia takes about 8 months to develop[8] but is more often recognized at about 3 to 4 years of age.[17] It becomes less obvious with ongoing growth once the torticollis has resolved.

## POSTURAL COMPENSATION

When children are old enough to walk, the eyes are kept horizontal to facilitate balance and horizontal eye movement. The child compensates for the short fibrous sternomastoid by elevating the ipsilateral shoulder (see Fig. 60-3). In addition, there may be compensatory cervical and thoracic scoliosis. Adjacent muscles, such as the trapezius, may be wasted because of relative inactivity.[8]

# Conservative Management

Sternomastoid fibrosis resolves spontaneously in the vast majority of infants. Therefore surgery is required only rarely, in those in whom the torticollis has not resolved. The value of manipulation of the head and neck has not been proven,[12] although it is widely used and may have some benefit in the first year of life.[36] Physiotherapy and regular neck exercises appear to be safe[36] and may make the parents feel that "something is being done" for their infant. Unintentional snapping during manipulation has been reported with no apparent deleterious effect on outcome.[37] Some clinicians advocate early institution of intensive passive neck range-of-motion stretching exercises and have reported high rates of resolution,[9,38–40] while others believe that there is no convincing evidence that these measures alter the natural history of the condition.

Others consider it important to encourage parents to place toys and other desirable objects on the ipsilateral side to encourage the infant to turn toward the affected side.[8] Again, this

strategy probably helps the parent more than the infant, but is unlikely to do any harm. Attempts to put the infant to sleep with the head facing toward the affected side tend to fail, particularly if the muscle is tight. Botulinum toxin injection appears to be ineffective in patients presenting in late childhood or adulthood,[41] but results are more encouraging in younger children.[42]

In most cases, reassurance is all that is required. The passage of time is probably as effective as the various manipulations when torticollis is due to sternomastoid fibrosis.

# Operative Treatment

## INDICATIONS FOR SURGERY

Indications for surgery include

1. Persistent sternomastoid tightness limiting head rotation in children more than 12 to 15 months of age[43]
2. Persistent sternomastoid tightness with progressive hemifacial hypoplasia
3. Diagnosis in children older than 1 year[44]

## OPERATIVE TECHNIQUE

The procedure is performed under general anesthesia with laryngeal or endotracheal intubation, according to the expertise and preference of the pediatric anesthetist. The child is placed supine with the shoulders elevated and the neck rotated to the contralateral side. The muscle is best divided at its lower end,[4,9] although division at its upper end,[45] at both ends,[46–48] or in its midportion[8,49] have all been described. Endoscopic tenotomy of the muscle is also feasible[50–53] including through a transaxillary approach.[54,55]

A 3- to 4-cm transverse incision is made in a skin crease about 1 cm above the sternal and clavicular heads of the affected sternomastoid (Fig. 60-7). The platysma is divided with diathermy so that no bleeding occurs in the line of the incision. The external jugular vein can be retracted if it is within the field of view. The tight fibrosis of the two heads of sternocleidomastoid are divided with diathermy near their lower end. Tightness of the cervical fascia between the sternomastoid and trapezius is usually palpable once the sternomastoid has been divided, and this fascia also should be divided (Fig. 60-8). This is done under direct vision to avoid damage to other structures, particularly the spinal accessory nerve and brachial plexus.

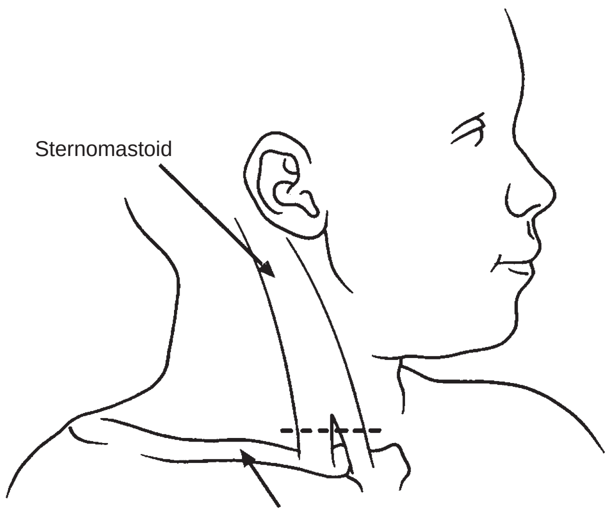


FIGURE 60-7 Skin incision for low division of the sternomastoid muscle.

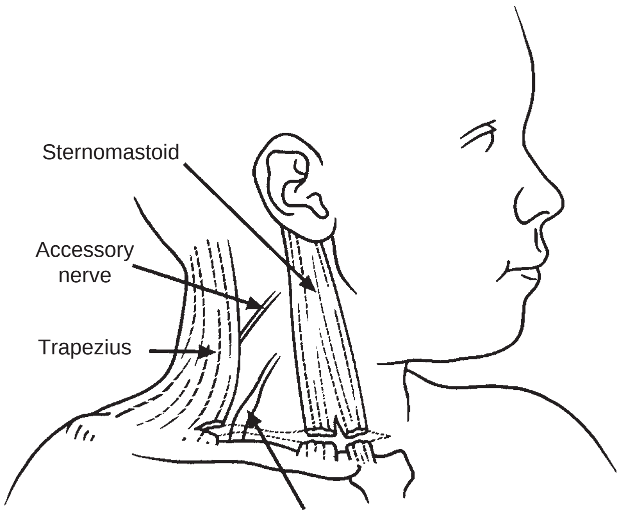


FIGURE 60-8 Division of the sternomastoid and investing cervical fascia to the anterior border of the trapezius.

The wound is infiltrated with bupivacaine or other local anesthetic agent. The platysma is closed with continuous 4-0 absorbable suture and the skin with subcuticular 5-0 Monocryl absorbable suture. No drains are required.

The procedure can be performed as a day case, and no postoperative restriction of movement is necessary. Full range of the neck is normally achieved within 1 week of surgery. Physiotherapy is usually unnecessary, although some advocate an extended period of physiotherapy postoperatively.[46] In older children, restoration of a full range of movement may take longer, and the final cosmetic appearance is less certain.[56]

## COMPLICATIONS

A hematoma may develop if hemostasis was inadequate at the time of surgery. Diathermy dissection keeps blood loss to a minimum. Larger superficial veins may require ligation and division if they cannot be retracted.

Incomplete division of both heads of the sternocleidomastoid muscle or failure to divide the cervical fascia over the posterior triangle of the neck may produce persistent torticollis. Careful inspection and palpation of the neck for residual tightness and bands at the time of surgery should prevent this complication from occurring. Recurrent torticollis is rare after surgical treatment and is seen in less than 3% of patients.[57]

## FOLLOW-UP

Patients should be monitored until (1) the torticollis has resolved completely, (2) there is full range of movement of the head and neck, and (3) the sternomastoid muscle feels normal. In an older child with secondary scoliosis, follow-up, including radiologic studies, if required, should continue until the scoliosis has resolved.

*The complete reference list is available online at www.expertconsult.com.*

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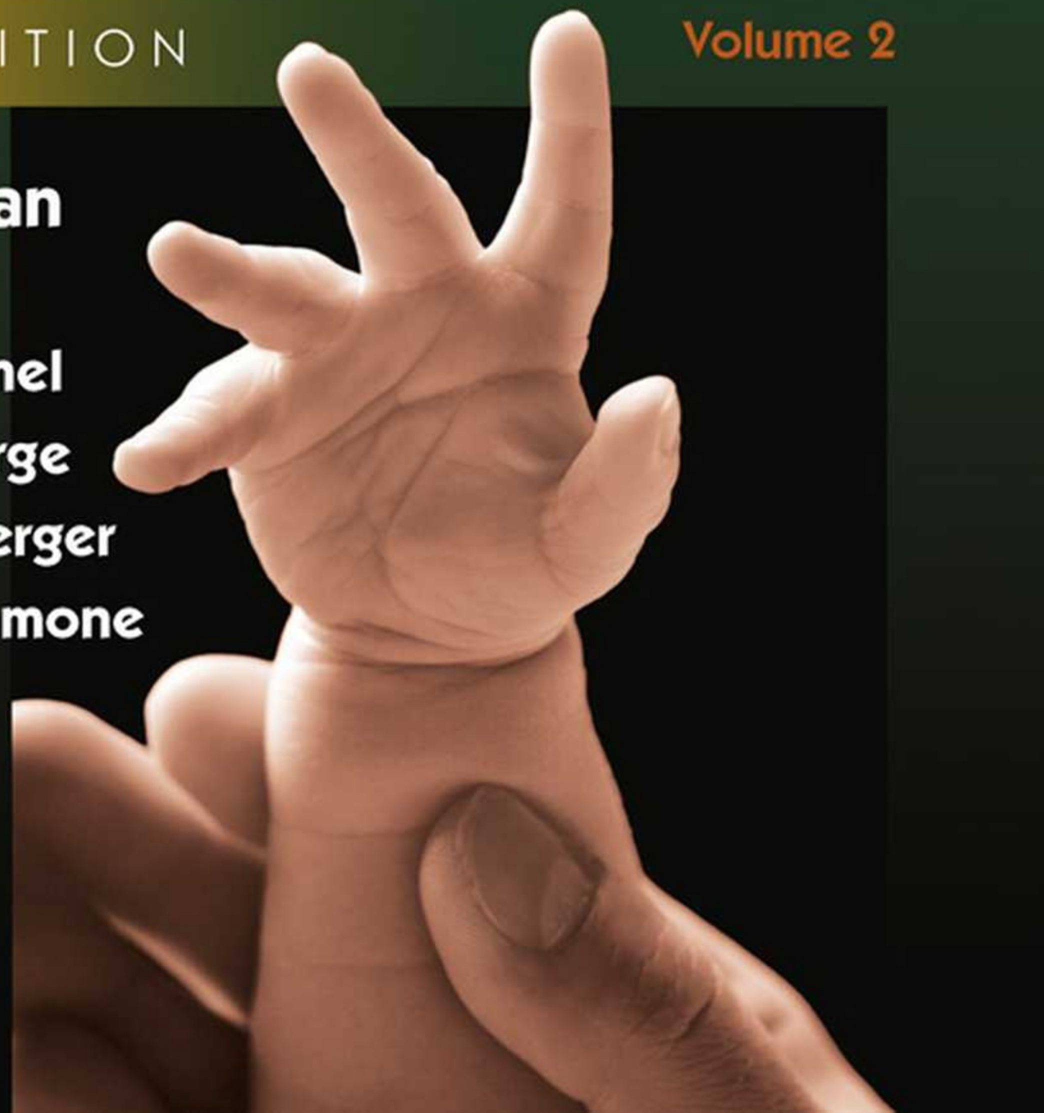


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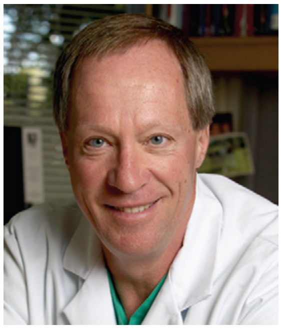

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# Preface

In June 1959, a group of five distinguished pediatric surgeons from the United States and Canada formed an editorial board to investigate the possibility of writing an authoritative, comprehensive textbook of pediatric surgery. The five individuals assembled were Kenneth Welch, who served as chairman of the board from Boston Children's Hospital (the original name); Mark Ravitch from The Johns Hopkins Hospital; Clifford Benson from Detroit Children's Hospital (the original name); William Snyder from Los Angeles Children's Hospital; and William Mustard from The Hospital for Sick Children in Toronto, Canada. From 1953 to 1962, the most comprehensive textbook of pediatric surgery was *The Surgery of Infancy and Childhood* by Robert E. Gross. At that time, Dr. Gross had no plans to write a second edition of his book. He was the sole author of the first edition of his book and did not wish to carry out such a monumental task with a second edition. The five editors thought that an updated textbook of pediatric surgery was needed. The first edition was published in 1962 and quickly became recognized as the most definitive and comprehensive textbook in the field. Between 1962 and 2006, six editions of the book were published. During this period, this textbook has been considered the bible of pediatric surgery. The editors and authors have changed during the 44 years that elapsed from the first to the sixth editions. In most cases, the editorial board changed gradually with the deletion and addition of two to three pediatric surgeons with each edition. The editors of the fifth edition also continued as the editors of the sixth edition. In the current seventh edition, the editorial board has been replaced except for Arnold Coran, who has functioned as the Chief Editor of this edition, and Anthony Caldamone, who continues to be the editor for the urology section. A new generation of pediatric surgical leaders has emerged since the last edition, and the editorial board reflects that change. Robert Shamberger from Children's Hospital Boston, Scott Adzick from The Children's Hospital of Philadelphia, Thomas Krummel from the Lucile Packard Children's Hospital and Stanford University Medical Center, and Jean-Martin Laberge from the Montreal Children's Hospital of the McGill University Health Centre represent the new members of the editorial board.

The seventh edition continues its international representation, with authors from several countries contributing chapters. Most of the previous chapters have been retained, but, in several cases, new authors have been assigned to these chapters. Of special interest is the addition of a new chapter (Chapter 16) on patient- and family-centered pediatric surgical care, a relatively new concept in the management of the pediatric surgical patient. Two chapters from the sixth edition, “Bone and Joint Infections” and “Congenital Defects of Skin, Connective Tissues, Muscles, Tendons, and Joints,” have been deleted because currently, most pediatric surgeons do not deal with these problems. A few of the urology chapters have been merged, but all the material from the previous edition is included in these chapters. The chapter “Congenital Heart Disease and Anomalies of the Great Vessels” (Chapter 127) was kept comprehensive because so many of these patients have co-existent pediatric surgical problems or have surgical problems after cardiac surgery. Overall, there are 131 chapters in this edition, all of which are written by experts in the field and represent a comprehensive treatise of the subject with an exhaustive bibliography. In addition, each chapter provides a complete discussion of both open and closed techniques, when appropriate, for the management of the surgical problem.

One of the remarkable things about this edition is that not a single sheet of paper was used by the authors or editors in the creation of the book. Everything from the writing of the chapter to its editing was done electronically. This entire process was overseen by Lisa Barnes, the developmental editor at Elsevier. All the editors wish to thank her for her patience, availability, and efficiency in completing this textbook. Finally, we want to thank all the authors for their outstanding chapters, which will provide definitive and comprehensive information on the various pediatric surgical problems to pediatric surgeons throughout the world and thus improve the surgical care of infants and children worldwide.

THE EDITORS

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CHAPTER 61

# Disorders of the Breast

Mary L. Brandt

Development of the breast begins at around 35 days' gestation, when the ectoderm on the anterior body wall thickens into a ridge known as the milk line, milk ridge, or Hughes line.[1] This ridge of tissue extends from the area of the developing axilla to the area of the developing inguinal canal. The ridge above and below the area of the pectoral muscle recedes around the tenth week of gestation, leaving the mammary primordium, which is the origin of the lactiferous ducts.[2,3] The initial ducts form in the remaining pectoral ridge between weeks 10 and 20 and become interspersed through the developing mesenchyme, which becomes the fibrous and fatty portions of the breast.[2] The breast bud becomes palpable at 34 weeks' gestation.[2] The nipple appears much later at 8 months' gestation. It is initially a depression and later becomes elevated.[3]

Thelarche, or the onset of pubertal breast development, occurs between the ages of 8 and 13 years, at an average 11 to 11.5 years.[4] Lack of development by age 13 is considered delayed thelarche and warrants endocrinologic evaluation.[5] Normal breast development is hormonally mediated.[6] Adipose tissue and the lactiferous ducts grow in response to estrogen. Progesterone stimulation results in lobular growth and alveolar budding.[4,6] The normal development of the breast, which occurs over a period of 2 to 4 years after thelarche, is classified by the Tanner system into five stages (Table 61-1). Menarche usually occurs approximately 2 years after Tanner stage 2.

## Premature Thelarche

Although normal thelarche occurs between 8 and 13 years of age, breast buds can appear in girls as young as 1 to 3 years.[7] Although the vast majority of patients with premature thelarche have no associated medical problems, there are rare cases caused by hypothyroidism.[6] Premature thelarche is often an isolated condition but may be the first symptom of precocious puberty, particularly in girls older than 2 years.[7] Precocious puberty has been reported to occur in up to 18% of girls with premature thelarche who are followed over time.[8] Serial examinations, with particular emphasis on growth velocity and secondary sexual characteristics such as pubic hair and pigmentation of the labia or areola, are usually sufficient to identify precocious puberty in girls with premature thelarche.[2,7] Radiographs to estimate bone age may be indicated in some patients if precocious puberty is suspected.[8] Unless a patient with thelarche has associated signs of precocious puberty, the parents should be reassured and the child followed.[4] Ninety percent of patients with isolated premature thelarche have resolution of the breast enlargement 6 months to 6 years after diagnosis.[9] In asymmetrical premature thelarche, the resolution may also be asymmetric.[7] Long-term follow-up has shown that patients with isolated premature thelarche develop normal breasts at puberty and are at no increased risk for disorders or tumors of the breast.[9]

## Congenital Anomalies of the Breast

### AMASTIA AND HYPOMASTIA

Complete absence of the breast, or amastia, is rare.[3] Amastia, particularly if it is bilateral, can be associated with syndromes of more diffuse ectodermal anomalies such as congenital ectodermal dysplasia.[3,10] It can also be associated with anomalies of the underlying mesoderm, such as the abnormal pectoral muscle seen in Poland syndrome.[3,11,12] Athelia is defined as presence of breast tissue with absence of the nipple and usually occurs in ectopic locations along the milk line.[3] Amastia or hypomastia can also result from injuries sustained during thoracotomy, chest tube placement, inappropriate biopsy of the breast bud, radiotherapy, or severe burns.[2] Because the nipple complex does not normally develop until the eighth month of gestation, it can be difficult to identify in premature infants. As a result, placement of chest tubes or central lines can inadvertently injure the developing breast (Fig. 61-1).

### POLYMASTIA AND POLYTHELIA

Supernumerary breast tissue occurs in approximately 1% to 2% of the population.[1,3,6] Although the most common abnormality is accessory nipples (polythelia), polymastia may also occur (Fig. 61-2) The ectopic tissue is almost universally

**TABLE 61-1**
**Tanner Stages of Breast Development**

| *Tanner Stage* | *Description* |
|---|---|
| 1 (preadolescent) | Elevation of breast papilla only |
| 2 | Elevation of breast bud and papilla as small mound<br>Enlargement of the diameter of the areola<br>Areola becomes more pink |
| 3 | Further enlargement of breast and areola, with no separation of their contours<br>Montgomery tubercles appear |
| 4 | Further enlargement, with projection of areola and papilla to form a secondary mound above the level of the breast |
| 5 (mature stage) | Projection of papilla only, resulting from recession of areola to general contour of breast<br>Erectile areolar tissue |

From Duflos D, Plu-Bureau G, Thibaud E, Kuttenn F: Breast diseases in adolescents. In Sultan C (ed): Pediatric and Adolescent Gynecology. Basel, Karger, 2004; and Templeman C, Hertweck SP: Breast disorders in the pediatric and adolescent patient. Obstet Gynecol Clin North Am 2000;27:19-34.

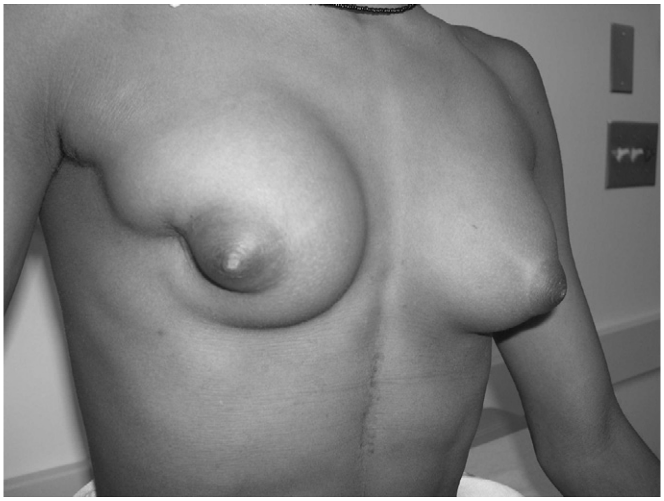

**FIGURE 61-1** Breast deformity from placement of a neonatal chest tube.

located in the axilla or just inferior to the normally positioned breast along the embryonic milk line.[3] The normal axillary extension of breast tissue (the tail of Spence) should not be confused with supernumerary breast tissue. Sixty-five percent of children with supernumerary breast tissue have a single accessory nipple or breast, and 30% to 35% have two.[3] The largest number of reported supernumerary structures is 10.[3] Many studies have suggested an association between polythelia and abnormalities of the urinary tract and congenital heart disease, although this is debated by others.[1,2,10,11,13] True ectopic breast tissue, or breast tissue found outside the normal milk line, is exceedingly rare but has been reported on the face, back, and perineum, and in the midline of the anterior torso.[3,14,15] Polymastia warrants surgical excision in girls to prevent painful swelling during pregnancy. Resection of accessory nipples is usually warranted for cosmetic reasons.

**FIGURE 61-2** Polymastia. This complete breast, with nipple complex, is located in the most common position, just below the normal breast.

## Congenital Anomalies of the Nipple

Inverted nipples may predispose patients to infection, which can usually be prevented by careful attention to hygiene of the recessed area.[6] Surgical correction is possible, but elevation of the nipple inevitably divides the lactiferous ducts and makes future breast-feeding problematic if not impossible.[6] Other anomalies of the nipple that have been described include bifid nipples and intra-areolar polythelia, which is also called dysplastic divided nipples (Fig. 61-3).[6,10]

**FIGURE 61-3** Intra-areolar polythelia, which is also called a dysplastic divided nipple.

# Breast Asymmetry and Hypomastia

Some degree of asymmetry is normal in women and may be more pronounced during puberty while the breasts are developing.[6,8] Significant asymmetry is called hypomastia and may be associated with connective tissue disorders or mitral valve prolapse.[6] Hypomastia is frequently familial.[2] Unilateral hypomastia has been reported in association with a Becker nevus of the breast, which on examination appears as a clear brown stain on the chest wall.[2] Hypomastia can also occur after radiation therapy to the chest wall. Girls with bilateral breast hypoplasia should be evaluated for ovarian dysfunction, hypothyroidism, or androgen-producing tumors.[6] Hypoplastic breast tissue is also associated with a tuberous breast anomaly. In this condition, the base of the breast is limited and the hypoplastic breast tissue "herniates" into the areolar complex.[6,8] Plastic surgery to correct the areolar complex and augment the hypoplastic breast may be indicated.[16]

# Breast Enlargement

## MACROMASTIA

Excessively large breasts are referred to as macromastia. The differential diagnosis of macromastia in adolescents includes juvenile hypertrophy, pregnancy, tumors of the breast, and excessive endogenous or exogenous levels of estrogen or progesterone, or both (Table 61-2).[17] d-Penicillamine and marijuana have also been reported as exogenous causes of macromastia.[17]

## JUVENILE OR VIRGINAL HYPERTROPHY

Spontaneous massive growth of the breast in an adolescent, which may be unilateral or bilateral, is thought to be the result of excessive end-organ sensitivity to gonadal hormones.[2,17] An autoimmune cause has been suggested by some authors because of the occasional association with autoimmune disorders such as Hashimoto's thyroiditis, rheumatoid arthritis, and myasthenia.[2] The breast growth in patients with juvenile hypertrophy is rapid, begins shortly after thelarche, and can be dramatic, resulting in breasts that weigh up to 50 pounds each.[6,8] Spontaneous resolution is very rare.[17] Skin changes, such as peau d'orange and even necrosis, may occur during phases of rapid growth.[17] Treatment depends on whether breast growth is complete. If the patient is still growing, progesterone or antiestrogen medications can be used to control breast growth.[8] If this is unsuccessful, or if breast growth is complete, breast reduction surgery is necessary.[17] Patients should be counseled that lactation may be affected by juvenile hypertrophy, particularly after breast reduction surgery, but there is no increased risk of breast cancer.[17]

**TABLE 61-2**

| Differential Diagnosis of Macromastia |
|---|
| Juvenile hypertrophy |
| Tumors of the breast |
| Giant fibroadenoma |
| Hamartoma[49] |
| Cystosarcoma phyllodes |
| Carcinoma |
| Hormonally active tumors |
| Ovarian granulosa cell tumor |
| Ovarian follicular cyst |
| Adrenal cortical tumor |
| Exogenous hormones |
| Estrogen |
| Testosterone |
| Gonadotropins |
| Corticosterone |
| Medications |
| D-Penicillamine |
| Marijuana |

# Infections of the Breast

Neonatal mastitis is an uncommon infection that usually occurs in term or near-term infants.[18] It affects female infants twice as often as male infants.[18] A breast abscess develops in approximately 50% of infants with neonatal mastitis.[18] Adolescents may experience nonpuerperal mastitis or a breast abscess as a result of irritation of the skin, a foreign body, or infection of an epidermal cyst.[8] The initial therapy of all breast infections is administration of antibiotics and analgesics.[18] Adolescent girls with mastitis may have symptomatic relief with breast support.[8] Although *Staphylococcus aureus* (often methicillin resistant) is the offending organism in almost all cases, in infants, infections with *Shigella, Escherichia coli,* and *Klebsiella* species have been reported.[18] Gram-negative coverage may be indicated until culture results are obtained, particularly in neonates. Small abscesses are treated by aspiration, using ultrasonographic guidance if necessary, and antibiotic therapy.[8] Larger abscesses may require incision and drainage, although some authors recommend needle aspiration initially, with surgery reserved for failure of aspiration.[8] If incision and drainage are performed, a small periareolar incision is indicated. Probing and disrupting the tissue should be kept to a minimum to avoid injury to the underlying breast bud in a prepubertal child.

# Nipple Discharge

## BLOODY DISCHARGE

The differential diagnosis of bloody discharge in children and adolescents includes mammary duct ectasia, chronic cystic mastitis, intraductal cysts, and intraductal papillomas. Mammary duct ectasia is an anomaly of duct development that results from "pleats" of obstructing epithelium in the lumen of the duct.[2,19] This obstruction can lead to bacterial overgrowth and formation of an abscess, most commonly with *S. aureus.*[4] Infants with mammary duct ectasia typically present with a bloody discharge.[19] Adolescents typically present with a retroareolar, often bluish, mass. There may be a bloody or brownish discharge. All children with bloody discharge should have the discharge cultured and be given appropriate antibiotics.[4] Ductal ectasia often resolves spontaneously.[2,4,20] There may be recurrences but they usually respond to conservative therapy. Surgical excision may be indicated for

persistent or recurrent symptoms or for an associated persistent cyst.[4] In girls the excision should be limited to any identified cyst, with great care taken not to injure the underlying breast bud. In boys with this condition, a simple mastectomy is curative.[4]

Intraductal papillomas are rare subareolar lesions that are often difficult to palpate.[6] They are bilateral in 25% of patients.[6] Cytologic examination of the bloody discharge shows ductal cells.[6] Local excision through a circumareolar incision is curative.[6] Adenoma of the nipple, which is very rare, may also present with erosion of or discharge from the nipple.[21] In adolescent athletes, bloody discharge may be due to chronic nipple irritation (jogger's nipple) or cold trauma (cyclist's nipple).[22]

### GALACTORRHEA

Milky discharge from the neonatal breast is a normal response to fetal prolactin levels, which peak at birth (Fig. 61-4).[23] In an adolescent, nonpuerperal lactation can be classified as neurogenic, hypothalamic, pituitary, endocrine, drug-induced, or idiopathic in origin.[23] Neurogenic lactation occurs as a result of disorders of the chest wall, thorax, or breast. It has been reported after thoracotomy, burns or injuries of the chest wall, herpes zoster, or chronic stimulation of the nipple.[23] Pituitary tumors, especially prolactinomas, are the most common hypothalamic or pituitary cause of galactorrhea.[23] The most common cause of galactorrhea in adolescents is hypothyroidism.[23] A wide variety of drugs has been implicated in causing galactorrhea, including dopamine-receptor blockers and catecholamine-depleting agents.[8,23] Patients with galactorrhea require a careful history and physical examination directed at the possible causes of galactorrhea. Laboratory studies should include serum prolactin, follicle-stimulating hormone, luteinizing hormone, and thyroid function studies.[23]

## Breast Masses

### PREPUBERTAL BREAST MASSES

Neonatal breast hypertrophy is a normal response to maternal estrogen and occurs in both boys and girls in the first weeks of life.[6] Stimulation, such as attempting to squeeze the breast to promote discharge, may result in persistence of the hypertrophied tissue. Neonatal breast hypertrophy resolves spontaneously and no treatment is necessary. There are some data that suggest soy formulas may delay regression of neonatal breast tissue.[24]

Breast development at the onset of thelarche starts with a firm, disklike area of tissue under the areolar complex that can be mistaken for a mass. It is often initially unilateral.[4] Biopsy is contraindicated because of the high risk of injury to the developing breast bud.[5]

Hemangiomas and lymphatic malformations can involve the developing breast (Fig. 61-5). Although hemangiomas may involute after an initial growth spurt, compression of the breast bud during rapid growth may lead to injury and subsequent breast deformity. The diagnosis is usually made on physical examination but can be confirmed with ultrasonography or magnetic resonance imaging (MRI). If there is doubt about the diagnosis, a fine-needle biopsy may be indicated. Rapid growth of hemangiomas may require resection (if technically possible) or treatment with steroids.[4,25] In girls, the risk of injuring the breast bud by resection must be weighed against injury to the breast bud from the enlarging hemangioma or lymphatic malformation. MRI may aid in determining the resectability of the lesion and hence the risk/benefit ratio of surgical resection. Surgical resection of the lesion, with protection of the normal breast tissue, is indicated for complications such as ulceration or hemorrhage.[4]

Other primary or metastatic tumors of the breast are rare but can present in prepubertal children (Table 61-3). The majority of lesions are benign, but if the diagnosis is uncertain, fine-needle or open biopsy may be indicated.[4]

### MASSES IN ADOLESCENT GIRLS

#### Fibroadenomas

Fibroadenomas are the most common breast masses in adolescent girls. They usually occur in late adolescence, but can occur as early as 1 to 2 years before menarche.[6] Fibroadenomas are most often located in the upper outer quadrant of the breast and are more common in African American patients.[4] The average size is 2 to 3 cm, but they can become massive

FIGURE 61-4 Normal breast bud and milky discharge in a neonate.

FIGURE 61-5 Hemangioma of the breast in a newborn infant.

**TABLE 61-3**

**Differential Diagnosis of Prepubertal Breast Masses**

| |
|---|
| Unilateral breast bud development (premature thelarche) |
| Hemorrhagic cyst[50] |
| Abscess[50] |
| Lymphangioma[50] |
| Hemangioma[50] |
| Lipoma[50] |
| Metastatic tumor |
| Galactocele[4] |

(Fig. 61-6).[8] Ten percent of patients have bilateral lesions.[8] Up to 25% of patients have multiple fibroadenomas, a condition called fibroadenomatosis.[2,6] The lesions may enlarge slightly during the menstrual cycle.[4] The physical examination is usually diagnostic, as fibroadenomas are well circumscribed, "rubbery," mobile, and nontender. In equivocal cases, ultrasonography may be helpful in making the diagnosis.[26] Mammography is not indicated in adolescent patients because the large amount of fibroglandular tissue makes interpretation difficult and exposes the breast to avoidable radiation.[4]

Fibroadenomas are thought to develop because of a local exaggerated response to estrogen stimulation.[4] The natural history is usually an initial period of 6 to 12 months of growth, during which the mass doubles in size, and then stabilization. Only 5% of fibroadenomas grow more rapidly.[27] Fibroadenomas have been reported to resolve spontaneously.[4,28] This is supported by findings of sclerotic vestiges of fibroadenomas in women older than age 40 years.[29] In 99 women aged 14 to 55 years (median age, 20 years) followed over 7 to 9 years, 38% of 107 clinically diagnosed fibroadenomas resolved spontaneously.[28] One group reported that up to 40% of presumed fibroadenomas in adults decreased in size over a 2-year period.[30] Although these adult data suggest a high rate of spontaneous resolution, there are no data to suggest this is true in adolescents. However, these findings support observation of presumed fibroadenomas as an alternative to early resection. All presumed fibroadenomas smaller than 5 cm can be safely observed for at least one or two menstrual cycles.

**FIGURE 61-6** Giant fibroadenoma, mimicking juvenile hypertrophy, in an adolescent girl.

If there is growth of the lesion or symptomatic tenderness, excisional biopsy is warranted.[30] If the lesion remains stable, there are two options that should be discussed with the patient and family:

1. Observation with or without fine-needle aspiration. Approximately 200 cases of carcinoma of the breast have been reported in adults with fibroadenomas.[31] There are no reports of malignant fibroadenomas in adolescents. The risk of malignancy in an adolescent girl with a typical fibroadenoma on examination is exceedingly low. In the setting of a classic examination and no tumor growth, there is essentially no risk in observation.
2. Excisional biopsy. Many authors recommend excision of all lesions that persist to adulthood, so a case could be made to excise all fibroadenomas that persist during adolescence.[4] Patients should be counseled that the biopsy may result in cosmetic changes to the breast. Persistent local pain after removal of a fibroadenoma has also been reported.[32]

## Giant Fibroadenomas

Fibroadenomas greater than 5 cm are termed giant fibroadenomas. On examination, these may be softer than typical fibroadenomas and may even resemble the normal surrounding breast tissue.[8] There may also be dilated veins over the surface, and the skin overlying the mass may be warm to the touch (see Fig. 61-6).[8] Giant fibroadenomas should be excised because they cannot be distinguished from cystosarcoma phyllodes by physical examination, mammography, or ultrasonography.[33] In addition, giant fibroadenomas have been reported rarely to double in size in as little as 3 months.[6] Fine-needle aspiration and core-needle biopsy should be performed. If the histologic features lead to a definitive diagnosis of cystosarcoma phyllodes, a more radical procedure would be indicated . However, it is very difficult to distinguish between fibroadenoma and cystosarcoma phyllodes by aspiration or needle biopsy, so a negative result should not affect the decision to operate.[33]

The incision for removal of a giant fibroadenoma can be problematic. Whenever possible, a periareolar incision should be used. Large lesions can be removed through a periareolar incision by placing them in a bag and morcellating them before removal.[34] If the mass is close to the inframammary crease, this offers a second, cosmetically appropriate approach. It is best to mark out the inframammary crease with the patient sitting before induction of anesthesia. In either case, plans for a future wide excision should be taken into account when planning the initial excisional biopsy. Excision of large fibroadenomas can result in significant deformity of the breast. Placing a drain is not recommended because this results in adherence of skin to the chest wall. However, leaving the space to fill with serum or blood is also suboptimal, as this may result in contraction of the space and skin adherence. An alternative approach is to distend the space with a mixture of saline and local anesthetic by inserting an intravenous catheter using a "Z" puncture. In theory, this should prevent the rapid influx of serum and decrease the risk of skin adherence.

## Phyllodes Tumors

Phyllodes tumors were first described by Muller in 1838, who coined the term cystosarcoma phyllodes. This term is misleading, however, because these tumors are rarely cystic and do

not have the malignant potential of most sarcomas.[30] For that reason, they are better termed phyllodes tumors.

Phyllodes tumors are stromal tumors that are histologically classified as benign, intermediate, or malignant.[4] The distinction is largely semantic because benign phyllodes lesions can metastasize and may recur locally. The median age of presentation of phyllodes tumors is 45 years; however, they have been reported to occur in girls as young as 10 years.[30,35] These tumors may occur more frequently in African American adolescents.[6]

The diagnosis is difficult to make without a biopsy. On examination, the tumor may resemble a giant fibroadenoma. Large tumors may cause skin stretching, ulceration, and venous distention.[6] If the nipple complex is involved, there may be a bloody discharge.[6] Ultrasonographic findings that are suggestive but not diagnostic of phyllodes tumors include lobulations, a heterogeneous echo pattern, and the absence of microcalcifications.[33]

The treatment of benign phyllodes tumors is total surgical excision with a 1-cm margin of normal tissue.[36] Patients with histologically malignant phyllodes tumors should undergo mastectomy.[33] Some authors have reported that adolescents with malignant phyllodes tumors have a more "benign" course than adults and suggest that the breast can be preserved in these patients.[30] Only clinically palpable nodes, which are present in approximately 20% of patients, should be resected.[37] The role of sentinel node biopsy has not been clarified for this tumor. The majority of nodes are enlarged in response to tumor necrosis and inflammation; metastases occur by hematogenous not lymphatic dissemination.[6] Reexcision is indicated if adequate margins were not obtained at the first surgery.[37] If an adequate margin cannot be achieved on the chest wall, local radiation therapy should be considered.[37]

Local recurrence occurs in up to 20% of patients with phyllodes tumors and is treated with reexcision or mastectomy.[30] Metastatic disease has been reported in 14% to 15% of patients.[37] Metastases can occur in the lung, pleura, soft tissue, bone, pancreas, and central nervous system and usually occur without lymph node involvement.[30,37] There have been isolated reports of palliation from single or multiple chemotherapeutic agents, but in general, adjuvant therapy plays a limited role in the treatment of phyllodes tumors.[30]

The 5-year survival rate in adults with benign, borderline, and malignant phyllodes tumors is 96%, 74%, and 66%, respectively.[30] Overall, the 5-year survival rate for malignant phyllodes tumors in adults is approximately 80%.[30] Because adolescents with phyllodes tumors may have biologically less aggressive tumors than adults, their prognosis may be better.[30]

## Cysts of Montgomery

Montgomery tubercles are the small papular projections on the edge of the areola and are related to the glands of Montgomery, which may play a role during lactation.[8] In adolescents, these glands can obstruct and present with either acute inflammation (62%) or an asymptomatic mass (38%).[38] The diagnosis of these retroareolar cysts is primarily clinical but can be confirmed with ultrasonography, which most commonly demonstrates a cystic lesion, usually unilocular, located in the expected retroareolar location. The most common presentation of patients with retroareolar cysts is acute inflammation with localized tenderness, erythema, and swelling under the areola and extending into the breast tissue.[38] Treatment with oral antibiotics directed at staphylococci and nonsteroidal antiinflammatory agents usually results in resolution of the acute inflammation within 7 days.[38] Only rarely is drainage of a persistent abscess necessary. After this nonoperative treatment, an asymptomatic mass is usually present. Patients with retroareolar cysts may describe a brownish discharge from a Montgomery tubercles, particularly with compression of the mass. In the absence of persistent infection or other complications, retroareolar cysts should be observed with serial physical examinations and, if needed, repeated ultrasonography. More than 80% of these cysts resolve spontaneously, although this can take up to 2 years.[38] Patients should be instructed not to compress the area, as this may delay resolution of the mass. Resection may be indicated if the mass persists or if the diagnosis is in question.[8]

## Fibrocystic Changes

Fibrocystic changes in the breast can result in both localized masses and pain in the breast (mastalgia). Patients should be reassured that fibrocystic changes are normal variants of female physiology, with these changes reported in 50% of women of reproductive age and 90% of women on autopsy.[8] Physical examination alone usually suffices to make this diagnosis because there is usually significant change with serial examinations performed at different points in the menstrual cycle. Ultrasonography may be helpful if the diagnosis is equivocal, but mammography is not indicated. The treatment of mastalgia is a firm brassiere and nonsteroidal anti-inflammatory drugs.[6] Oral contraceptives have been reported to improve symptoms in 70% to 90% of women.[8] Treatment with vitamin E and evening primrose oil and avoidance of caffeine are unproved but popular treatments.[6,8]

## Other Benign Breast Masses

A variety of benign tumors of the breast have been described in adolescents and young adults (Table 61-4). Hamartomas of the breast are rare tumors composed of normal breast components that can present as unilateral macromastia.[39,40] (They have also been called lipofibromas, adenolipomas, and fibroadenolipomas.[39] Only eight cases have been reported in women younger than 20 years.[39] The treatment of hamartomas is total excision.

**TABLE 61-4**

| Differential Diagnosis in Girls of Postpubertal Breast Masses |
|---|
| Fibroadenoma |
| Cyst of Montgomery |
| Mammary duct ectasia |
| Fat necrosis |
| Vascular lipoma[50] |
| Subareolar neuroma[50] |
| Hamartoma[49] |
| Abscess[50] |
| Lymphangioma[50] |
| Hemangioma[50] |
| Lipoma[50] |
| Juvenile secretory carcinoma |
| Ductal carcinoma |
| Metastatic disease |

Adenomas of the nipple are very rare but have been reported to occur in children and adolescents.[41] They are treated by local excision.[21] Tubular adenomas cannot be distinguished from fibroadenomas by history or examination, and the diagnosis is usually made by pathologic evaluation.[29] No further treatment is necessary after local excision.

Erosive adenomatosis is a rare benign tumor that presents with erythema, erosion, and crusting of the nipple.[42] Serosanguineous discharge may occur and a nodule may or may not be palpable.[42] Treatment is local excision of the lesion, which may be delayed until breast growth is complete; successful treatment with cryosurgery has also been reported.[42]

Juvenile papillomatosis is a benign, localized, proliferative lesion usually seen in girls older than 10 years, although it has been reported in prepubertal boys as well.[43] Juvenile papillomatosis usually presents with a mass, similar on examination to a fibroadenoma, in one breast. When resected, this is a well-demarcated mass with multiple cysts separated by fibrous stroma, giving it a “Swiss cheese” appearance.[29] Juvenile papillomatosis is considered a marker for increased breast cancer risk in family members but not necessarily in the patient unless it is recurrent.[43] However, other authors suggest that it does confer an increased risk for the patient as in situ and invasive carcinoma (usually juvenile secretory carcinoma) has been reported in up to 15% of patients with juvenile papillomatosis.[29] The treatment of juvenile papillomatosis is total resection, with preservation of the normal breast.[43]

Trauma can result in lesions that resemble either an infection or a mass in adolescents. In particular, fat necrosis that occurs after trauma can resemble a solid mass in the breast.[6] This has been reported after seat-belt injury and other direct blows to the breast.[44]

### Malignant Tumors of the Breast

Primary carcinoma of the breast has been reported in fewer than 50 pediatric patients.[4,45,46] More than 80% of these patients were diagnosed with juvenile secretory carcinoma, with the remainder having intraductal carcinoma. Juvenile secretory carcinoma has been associated with juvenile papillomatosis.[4] Juvenile secretory carcinoma often has a thick-walled capsule, which may cause the lesion to appear cystic on ultrasonography.[45] The treatment of primary breast cancer in children is complete surgical excision, usually by mastectomy.[4] The role of sentinel node mapping has not been determined in children. Estrogen and progesterone receptors should be assessed. Local recurrence is treated by reexcision or completion mastectomy. Adjuvant therapy for juvenile secretory carcinoma is rarely used, and the prognosis is excellent after local excision. Adjuvant therapy for intraductal carcinoma is based on the node status and hormone receptors, with most oncologists using modified adult protocols for the treatment of children.

Chest wall irradiation, used to treat malignancies such as Hodgkin lymphoma, increases the lifetime risk for breast cancer. This is particularly true for girls who are 10 to 16 years old when they receive radiation therapy, because this is a period of rapid breast growth.[47,48] Girls with Hodgkin disease who require radiotherapy of the chest have a markedly increased risk of breast cancer (estimated at 37 to 82 times normal), with almost 40% of patients ultimately experiencing breast cancer.[47,48] The median time from radiation therapy to diagnosis of breast cancer is 20 years. The risk of breast cancer is also increased if there is a significant family history of breast cancer or known mutations in the *BRCA1* and *BRCA2* genes.[8] Girls who have mutations in one of these genes have a 3.2% risk of breast cancer at age 30 years and an 85% risk by age 70 years.[8] Testing of adolescents for adult-onset disease is controversial, and referral to appropriate specialists for counseling is recommended.[49,50] Sarcoma of the breast is rare in all age groups and exceedingly rare in children. Rhabdomyosarcoma can occur as a primary tumor of the breast, usually in adolescent girls.[51] These tumors are typically rapidly growing mobile masses with no skin involvement; histologically, they are usually alveolar rhabdomyosarcomas.[51] Angiosarcoma of the breast has been reported in adult women after external beam radiation for breast conservation.[35] This rare tumor has also been reported in adolescents.[36] The treatment is mastectomy without routine axillary dissection.[36] Liposarcoma has been reported within a phyllodes tumor of the breast in an adolescent patient.[52] These tumors may appear encapsulated but should be treated by wide local excision.[35] Fibrosarcoma and malignant fibrous histiocytoma are among the most common soft tissue sarcomas of the breast; other rare primary sarcomas of the breast include leiomyosarcoma and osteogenic sarcoma.[35] Primary non-Hodgkin lymphoma of the breast has been reported in children.[53] Treatment of these rare primary malignancies of the breast is based on established protocols for more common tumors of childhood.

Cancer metastatic to the breast has been reported in children with primary hepatocellular carcinoma, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, and rhabdomyosarcoma, particularly the alveolar variant.[4,53,54] Other less common tumors that have been reported to metastasize to the breast in children include histiocytosis, medulloblastoma, renal cell carcinoma, and neuroblastoma.[54] Bilateral breast disease occurs in 30% of children with rhabdomyosarcoma metastatic to the breast.[54] Ultrasonography is the diagnostic tool of choice because it may differentiate metastatic lesions from more common benign lesions.[54]

## Gynecomastia

Gynecomastia occurs in up to 70% of boys at the time of puberty.[6,55] The majority of boys have bilateral gynecomastia, with only 10% having unilateral breast enlargement.[56] A history of drug ingestion should be obtained because gynecomastia has been reported to occur secondary to anabolic steroids, digitalis, isoniazid, tricyclic antidepressants, spironolactone, and marijuana.[4] Gynecomastia can be classified using a scale defined by Nydick, which is similar to the Tanner stages of breast development in girls. Stage 1 is limited to the subareolar area but does not reach the edge of the areola; stage 2 extends to the edge of the areola (B2) or beyond the edge (B3). In stages 4 and 5 gynecomastia, the breast assumes the characteristics of a female breast.[56] Examination of the testes is important in boys with gynecomastia to rule out disorders such as Klinefelter syndrome, primary hypogonadism, and androgen resistance (Reifenstein syndrome).[57,58] The combination of gynecomastia with hypogonadism suggests the diagnosis of Klinefelter syndrome. In the vast majority of boys, physiologic gynecomastia resolves spontaneously as puberty progresses, although it may take several years.

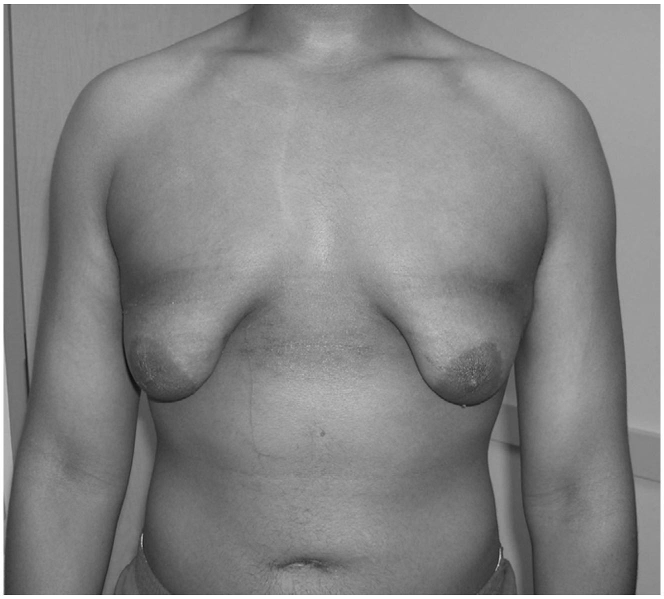

FIGURE 61-7 Stage 5 gynecomastia in an adolescent boy.

The risk of low self-esteem and decreased physical activity is significant in many boys with gynecomastia (Fig. 61-7). Surgery is indicated to allow normal psychological growth and development. In addition, surgery eliminates the small but present risk of carcinoma. [59–61] Liposuction may be adequate treatment for limited gynecomastia, but most patients require a simple mastectomy,[16,62,63] which is performed through a periareolar incision. Nipple reconstruction may be indicated if the areolar complex is large.[64] Drains are often necessary when significant breast tissue has been resected to prevent postoperative seromas, and compression vests are helpful as well. A "pad" of breast tissue should be left underneath the nipple to avoid retraction and adherence of the nipple to the chest wall, as well as subcutaneous tissue with the skin to avoid dermal adherence to the underlying pectoral muscles.[4]

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 62

# Congenital Chest Wall Deformities

Robert E. Kelly, Jr. and Robert C. Shamberger

Congenital chest wall deformities are usually divided into five categories: pectus excavatum, pectus carinatum, Poland syndrome, sternal defects, and the miscellaneous dysplasias or the thoracic deformities seen in diffuse skeletal disorders. Most are not life-threatening lesions and produce limited functional abnormalities. Rare lesions, such as thoracic ectopia cordis and Jeune asphyxiating thoracic dystrophy, are, however, almost uniformly fatal.

## Depression Deformities: Pectus Excavatum

Pectus excavatum (funnel chest, trichterbrust, or thorax en entonnoir) is the most common anterior chest wall deformity, involving posterior depression of the sternum and the lower costal cartilages. It occurs more frequently in boys than in girls by a greater than 3:1 ratio. In many cases, it is noted within the first year of life.[1] Although cases of spontaneous resolution occur, they are infrequent, and the advice that a child will "grow out" of the pectus depression should be offered cautiously. Some patients do not develop the depression of the chest wall until the rapid growth of puberty. Children with pectus excavatum, in addition to the central chest depression, are often noted to be tall and lanky, with poor posture, and to have an overall decrease in anteroposterior (AP) chest depth.[2,3] The incidence of the condition was reported to vary from 38 per 10,000 births among white infants to 7 per 10,000 births among black infants, to 20 per 10,000 infants categorized as other than black or white in a 1975 Collaborative Perinatal Project in the United States. In South America, the prevalence of pectus excavatum was 1.275% in a sample of 1,332 11- to 14-year-old students in Brazil.[4] In 1936, Nowak examined 30,000 Austrian school children and found 0.4% affected.[5] A recent report of congenital chest wall malformations in Nigerians, surveying 2,195 autopsied patients, reported one patient with Poland syndrome, one with Cantrell syndrome, and none with pectus excavatum, suggesting that the condition occurs infrequently in that region of Africa. Large numbers of surgically treated patients have been reported in the Far East.[6]

### CAUSE

The cause of pectus excavatum has not been established. Pectus excavatum does occur in animals, and reports of successful surgical treatment in cats and dogs have been published.[7,8] Otters are thought to develop the condition by cracking open shellfish on their chests while floating in the sea.[9] Purported theories in humans include intrauterine pressure, rickets, and abnormalities of the diaphragm resulting in posterior traction on the sternum.[10–12] Some support for this last theory has been provided by reports of pectus excavatum occurring after repair of agenesis of the diaphragm or congenital diaphragmatic hernia.[13] A study of 60 adult congenital diaphragmatic hernia survivors (mean age, 29 years) documented chest asymmetry in 48 and pectus excavatum in 18.[14] The association between pectus excavatum and other musculoskeletal abnormalities, particularly scoliosis (15% incidence) and Marfan syndrome (Table 62-1), suggests that abnormal connective tissue plays a role. Studies have demonstrated abnormalities in the costal cartilage, including decreased levels of zinc and increased levels of magnesium and calcium.[15] Biomechanical analysis has suggested increased flexibility of costal cartilages in individuals with pectus excavatum, but abnormalities in the proteoglycan or collagen distribution between affected individuals and controls were not demonstrated.[16] Fokin and colleagues found that cartilage samples from surgical cases had significantly dysregulated collagen genes, but no clear causative gene was identified.[17] Recent computed tomography (CT) scan studies have thrown considerable doubt on a theory that there is differential growth, with the cartilages growing in length faster than the ribs.[18] A family history of chest wall deformity, identified in 37% to 47% of cases, supports a genetic predisposition.[19] Family studies have shown inheritance by autosomal dominant, autosomal recessive, X-linked, and multifactorial inheritance in different kindreds.[20] An autopsy series study covering 112 years at a major center did not conclusively demonstrate an adverse effect on survival; patients who died before age 56 had shorter survival ($P = 0.0001$), but those who survived past the age of 56 tended to survive

**TABLE 62-1**
**Musculoskeletal Abnormalities Identified in 704 Patients with Pectus Excavatum**

| *Abnormality* | *No. of Patients* |
|---|---|
| Scoliosis | 107 |
| Kyphosis | 4 |
| Myopathy | 3 |
| Poland syndrome | 3 |
| Marfan syndrome | 2 |
| Pierre Robin syndrome | 2 |
| Prune-belly syndrome | 2 |
| Neurofibromatosis | 3 |
| Cerebral palsy | 4 |
| Tuberous sclerosis | 1 |
| Congenital diaphragmatic hernia | 2 |

From Shamberger RC, Welch KJ: Surgical repair of pectus excavatum. J Pediatr Surg 1988;23:615-622.

longer than their matched controls.[21] The autopsy reports did not include information to judge the severity of the pectus depression.

## CLINICAL PRESENTATION

Children present with a wide spectrum of depression deformities (Fig. 62-1), from a mildly depressed sternum to a severe case in which the sternum almost abuts the vertebral bodies. The depression is created by two components: (1) posterior angulation of the body of the sternum, generally beginning just below the insertion of the second costal cartilage, and (2) posterior angulation of the costal cartilages to meet the sternum. In older teenagers and adults, posterior angulation of the most anterior portion of the osseous ribs occurs. The depression may be deeper on one side than the other, more frequently on the right than the left, and the sternum may be rotated as well producing an asymmetric depression.[22] The AP depth of the ribs may be different between the two sides as well, and in many children, the AP depth of the chest is narrower than normal.[2] Children may have a broad, shallow defect or a narrow central pocket. A long trench may extend from the area just below the clavicles to the costal margin. Mixed protrusion of the costal cartilages on one side of the sternum (pectus carinatum) and depression on the other side (excavatum) occurs with significant frequency. Currarino-Silverman deformity, a variant of pectus *carinatum*, produces protrusion of the sternomanubrial joint and depression of the lower sternum; patients with this problem are often referred for evaluation of pectus excavatum. An asthenic build and slumped posture are frequently associated with pectus excavatum. Congenital heart disease was identified in 1.5% of children undergoing chest wall correction in one series, and the frequency of chest wall deformities among children with congenital heart disease was 0.17%.[23]

Many methods of assessing the severity of the depression have been developed. Most include the distance between the sternum and the spine as a primary factor. Willital[24] and Klinke and colleagues[25] used a ratio between the depth of the depression and the AP diameter of the chest. Welch used a ratio of the sternovertebral distance divided by the AP depth of the chest at the angle of Louis and added additional increments of severity if the cardiothoracic ratio was greater than 50% or the rib angles were greater than 25 degrees

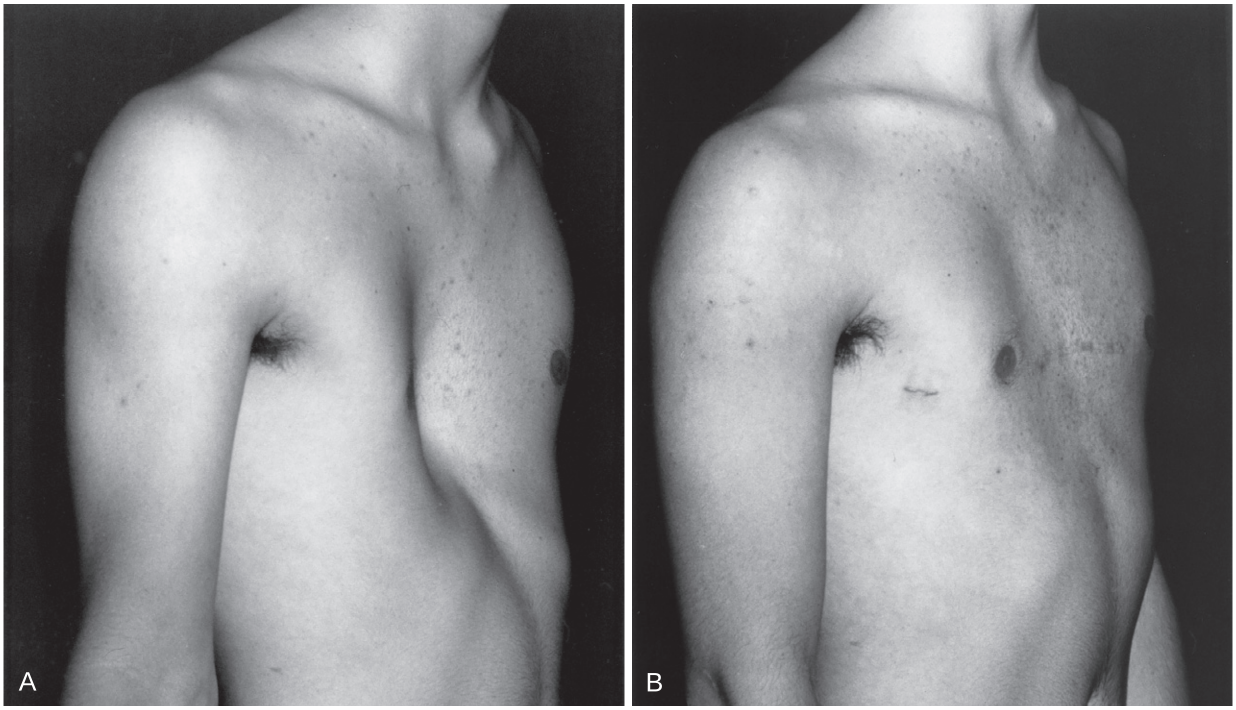


**FIGURE 62-1** **A,** Preoperative clinical photograph of a 14½-year-old boy with a symmetric pectus excavatum deformity. **B,** Postoperative clinical photograph a year after open repair using retrosternal struts shows full correction of the deformity. (From Shamberger RC: Chest wall deformities. In Shields TW [ed]: General Thoracic Surgery, ed 5. Philadelphia, Lippincott Williams & Wilkins, 2000.)

from horizontal.[26] Backer and colleagues used a ratio between the vertebral body diameter and the distance between the xiphisternal junction and the posterior border of the vertebral body to express the severity of the depression.[27] Haller and colleagues proposed a method of grading that uses transverse and AP measurements obtained from computed tomographic scanning of the chest, but similar measurements can be obtained from standard chest radiographs.[28] Recently, magnetic resonance imaging (MRI) scans have been used to assess both the anatomy of the chest wall and the performance of the heart.

Pectus excavatum is well tolerated in infancy and childhood. Chronic upper airway obstruction because of tonsillar and adenoidal hypertrophy may accentuate the depression in an infant with a flexible chest but is not causative. Older children may complain of pain in the area of the deformed cartilages or of precordial pain at rest or after sustained exercise. Occasionally, palpitations occur, which presumably are the result of transient atrial arrhythmias and may be associated with mitral valve prolapse. A systolic ejection murmur is frequently identified in individuals with pectus excavatum. It is attributed to the close proximity between the posterior aspect of the sternum and the pulmonary artery, which results in transmission of a flow murmur.[29] The physiologic impact of pectus excavatum has been the topic of many reports and much debate. Some authors contend that no cardiovascular or pulmonary impairment results from pectus excavatum. This position contrasts with the clinical impression that many patients have increased stamina and exercise tolerance after surgical repair. The cardiopulmonary impact of pectus excavatum has been extensively studied, with variable results. Despite 6 decades of work in the field, no consensus has been achieved on what degree of cardiopulmonary impairment, if any, this common chest wall deformity produces. Early pathologic studies of patients with pectus excavatum demonstrated compression of the heart between the vertebral column and the depressed sternum. The left lung was also compressed more than the right because of the frequent asymmetry of the deformity. Translation of these anatomic findings into their physiologic components has been the goal of many subsequent studies. Reviews in 1988 and 2008 tabulated this long series of studies.[30,31]

## PULMONARY FUNCTION EVALUATION

Deformity of the chest wall led many early authors to attribute the symptomatic improvement after pectus surgery to an improvement in pulmonary function. In an early work, Brown performed respiratory studies on patients before and after surgical repair. Vital capacity was normal in these patients, but maximal breathing capacity was markedly diminished (50% or more) in 9 of 11 cases.[32] Maximal breathing capacity increased an average of 31% after surgical repair.

Orzalesi and Cook performed studies in 12 children with severe pectus excavatum deformities.[33] The data for individual patients were within two standard deviations of normal values based on height, except for three patients with low vital capacity and one with low maximal breathing capacity. In the aggregate, however, the group showed a significant ($P < 0.001$) decrease in vital capacity, total lung capacity, and maximal breathing capacity compared with height-matched normal children. Weg and colleagues evaluated 25 Air Force recruits referred for respiratory symptoms and pectus excavatum and compared them with 50 unselected basic trainees.[34] Although the lung compartments of both groups were equal, as were mean vital capacity and maximal voluntary ventilation, which best reflects chest wall function, muscular ability and patient effort showed a significant deviation from predicted normal values ($P = 0.005$).

Liese and Bühlmann determined preoperative and postoperative lung volume and physical work capacity in an upright position on a bicycle ergometer in 12 adults with severe funnel chest.[35] Postoperative studies were performed 3 to 11 years (mean, 8 years) after surgical correction. Absolute lung volume increased only in patients who had grown in height after surgery. Work capacity increased in 9 of 10 patients but was difficult to assess, given the interval between testing. Godfrey reported on a select group of five patients with pectus excavatum and segmental bronchomalacia involving the left mainstem bronchus.[36] Radionuclide pulmonary scans demonstrated severe gas trapping in the left lung in two patients and underventilation and underperfusion of the left lung in a third patient. This appeared to be a clinically distinct group of patients with bronchomalacia demonstrated at bronchoscopy in all cases. It is not clear that the bronchomalacia was caused by the pectus deformity.

Castile and colleagues extensively evaluated eight patients, seven with pectus excavatum and one with pectus carinatum deformity.[37] Five patients were symptomatic with exercise but were asymptomatic at rest. Complete pulmonary mechanics studies were performed, including standard lung volume, forced vital capacity (FVC), static pressure-volume curve, and progressive steady-state exercise testing on a bicycle ergometer. Flow and volume for the one patient with pectus carinatum were normal. The mean total lung capacity as a percentage of predicted in the pectus excavatum patients was 79%, a mild restrictive deficit. Flow volume configurations were normal and did not suggest airway obstruction. Workload tests revealed a normal dead-space response to exercise; tidal volume ratio and alveolar-arterial oxygen difference did not suggest a significant ventilation-perfusion abnormality in the symptomatic patients. However, the measured oxygen uptake increasingly exceeded predicted values as the workload approached maximum; this was a strikingly different pattern when compared with normal subjects, who exhibit a linear response. The mean oxygen uptake at maximal effort exceeded the predicted values by 25.4% in the symptomatic patients. The three asymptomatic patients demonstrated normal linear oxygen uptake during exercise. Increased oxygen uptake suggests increased work of breathing in these symptomatic individuals, despite normal or mildly reduced vital capacity. Increases in tidal volume with exercise were uniformly depressed in those with pectus excavatum. No postoperative studies were performed in these subjects.

Cahill and colleagues performed preoperative and postoperative studies (3 to 9 months postoperatively) in 19 children and adolescents with pectus carinatum (5) and excavatum (14), ranging from 6 to 17 years of age.[38] No preoperative abnormalities or postoperative changes were demonstrated in the pectus carinatum patients. The pectus excavatum patients demonstrated low-normal vital capacity that was unchanged by operation.

Surgical correction did, however, result in a small improvement in their total lung capacity ($3.21 \pm 1.12$ to $3.49 \pm 1.07$;

$P < 0.02$) and a significant improvement in maximal voluntary ventilation ($65.1 \pm 31.5$ to $78.9 \pm 31.5$ L/minute; $P < 0.001$). Exercise tolerance was also improved after surgery, as determined by both total exercise time and maximal oxygen consumption ($1.26 \pm 0.44$ to $1.46 \pm 0.42$ mL/kg/minute; $P < 0.01$), although both these factors are clearly effort related. The heart rates at three identical work rates were assessed for each patient in the preoperative and postoperative workload study. There was a consistent decrease in heart rate at a given power output in the postoperative study ($P < 0.02$ by paired $t$-test) of the excavatum patients, but no decrease was observed in the carinatum patients. No difference in oxygen consumption at each work rate after surgery could be defined to support an improved efficiency of work. The observed decrease in heart rate at each workload level supported the hypothesis that some of the improvement in exercise capacity was a result of increased cardiac stroke volume. Mead and colleagues studied rib cage mobility by assessing intra-abdominal pressure. The finding of normal abdominal pressure tracings in subjects with pectus excavatum suggested normal rib cage mobility.[39]

Derveaux and colleagues used pulmonary function tests to evaluate 88 subjects with pectus excavatum and pectus carinatum before and 1 to 20 years (mean, 8 years) after repair involving a fairly extensive chest wall dissection.[40] Preoperative studies were within the normal range (i.e., >80% predicted values), except in those subjects with both scoliosis and pectus excavatum. The postoperative values for forced expiratory volume in 1 second ($FEV_1$) and vital capacity were decreased in all groups when expressed as a percentage of predicted values, although the absolute values at follow-up may have been greater than at the preoperative evaluation. Radiologic evaluation of these individuals confirmed improved chest wall configuration; so, the deterioration in pulmonary function was not the result of recurrence of the pectus deformity. An inverse relationship was found between preoperative and postoperative function. Those with less than 75% of predicted function preoperatively had improved function after surgery, whereas postoperative results were worse if the preoperative values were greater than 75%. Almost identical results were found in a study by Morshuis and colleagues who evaluated 152 subjects before and a mean of 8 years after surgery for pectus excavatum.[41] These physiologic results were in contrast to the subjective improvement in symptoms reported by the subjects and their improved chest wall configurations. The decline in pulmonary function in the postoperative studies was attributed to the surgery, because the preoperative defect appeared to be stable on sequential studies, regardless of the age at initial repair. Both these studies were marred by the obvious lack of an age-matched and severity-matched control group without surgery.

Derveaux and colleagues evaluated transpulmonary and transdiaphragmatic pressures at total lung capacity in 17 individuals with pectus excavatum. Preoperative and long-term follow-up evaluations were performed at a mean of 12 years apart.[42] Reduced transpulmonary and transdiaphragmatic pressures showed that the increased restrictive defect was produced by extrapulmonary rather than pulmonary factors, suggesting that surgery produced increased rigidity of the chest wall.

Wynn and colleagues assessed 12 children with pectus excavatum by pulmonary function tests and exercise testing.[43] Eight had repair and were evaluated preoperatively and postoperatively. Four had two sets of evaluations but no surgery. A decline in total lung capacity was identified in the repaired children, whereas values were stable in the control group. Cardiac output and stroke volume increased appropriately with exercise before and after operation in both groups, and operation was thought to have no physiologically significant effect on the response to exercise.

Kaguraoka and colleagues evaluated pulmonary function in 138 individuals before and after repair of pectus excavatum.[44] A decrease in vital capacity occurred during the initial 2 months after surgery, with recovery to preoperative levels by 1 year after surgery. At 42 months, the values were maintained at baseline, despite a significant improvement in chest wall configuration. Tanaka and colleagues had similar results and demonstrated that individuals with a more extensive sternal turnover procedure had more significant and long-term decreases in vital capacity.[45]

Morshuis and colleagues evaluated 35 subjects with pectus excavatum repaired as teenagers or young adults (age $17.9 \pm 5.6$ years).[46] Preoperative evaluations were performed and repeated 1 year after surgery. Preoperative total lung capacity ($86.0 \pm 14.4\%$ of predicted) and vital capacity ($79.7 \pm 16.2\%$) were significantly lower than predicted values and decreased further after surgery ($-9.2 \pm 9.27\%$ and $-6.6 \pm 10.7\%$, respectively). The efficiency of breathing at maximal exercise improved significantly after operation. Ventilatory limitation of exercise occurred in 43% of the subjects after surgery, and there was a tendency toward improvement after operation. The group with no ventilatory limitation, however, initially demonstrated a limitation after operation, with a significant increase in oxygen consumption.

Haller and colleagues evaluated 36 patients with pectus excavatum and 10 normal controls. Six months after surgery, the studies were repeated on 15 patients and 6 controls.[47] Before surgical correction, a decrease in FVC was seen in the excavatum cohort, and no change occurred after repair. Although 58% of patients had subjective complaints of exercise limitation that improved after surgery in 66%, they exercised at similar workloads as controls. The respiratory parameters during exercise were similar between the two groups, suggesting that exercise was not limited by restrictive disease. After surgery, the subjects could exercise longer and had higher pulse oxygen levels than before surgery, with no change in the controls. The enhanced exercise tolerance was attributed to improved cardiac function, as demonstrated by increased pulse oxygen levels and no change in pulmonary function parameters.

Borowitz and colleagues performed an early evaluation of patients undergoing the minimally invasive repair of pectus excavatum (MIRPE) technique.[48] In that study of 10 patients, normal pulmonary function was demonstrated both before and after surgical repair. Sigalet and colleagues also reported on the early effects of MIRPE in 11 patients, based on an evaluation of pulmonary function, exercise tolerance, and cardiac function as assessed by echocardiography.[49] Although patients reported a subjective improvement in their exercise tolerance, pulmonary function (FVC and vital capacity) was significantly reduced at 3 months; similarly, maximal oxygen uptake was reduced. In contrast, cardiac function was enhanced, with an increase in stroke volume.

Malek and colleagues evaluated 21 physically active patients with pectus excavatum.[50] The observed values for FVC, $FEV_1$, maximal voluntary ventilation, and diffusing capacity of the lung for carbon monoxide were significantly lower than normal values, but those for total lung capacity and residual volume

were not. Exercise testing revealed that the maximal oxygen uptake and oxygen tension were significantly lower than in normal controls. It was thought that the subjects' limitation in maximal exercise had a cardiovascular rather than a pulmonary cause, as demonstrated by an abnormally low metabolic threshold for lactate accumulation. This impairment was greatest in those with the most severe pectus deformities.

Lawson and colleagues reported pulmonary function tests on 408 patients with pectus excavatum before operation and a subset of 45 who had pulmonary function studies after Nuss operation and bar removal. Observed preoperative values for FVC, $FEV_1$, and forced expiratory flow between 25% and 75% (FEF25-75) were lower than average values by 13% to 20%. The postoperative group had statistically significant improvement after surgery for all parameters. Patients older than 11 years at the time of surgery had lower preoperative values and larger mean postbar removal improvement than younger patients.[51]

A multicenter study of 327 patients with pectus excavatum showed that prior to surgical repair, in patients with a mean CT index of 4.4, FVC was 90% of predicted (that is, average) values for the population; FEV1, 89%; and FEF25-75 85%. Each of these was statistically decreased with the *P* value of difference from 100% being less than 0.0001. Postoperative values are not yet reported in this study.[19]

Until recently, most studies of pulmonary function were carried out on small numbers of patients and failed to document consistent improvement in pulmonary function resulting from surgical repair. In fact, many studies demonstrated deterioration in pulmonary function at long-term evaluation, attributable to increased chest wall rigidity after open surgery. Despite this finding, several workload studies have shown improvement in exercise tolerance after repair.

In the last decade, increased interest in the condition has allowed studies of hundreds of patients with pectus excavatum to be performed in collaboration with pediatric pulmonologists. These demonstrate that pectus excavatum is associated with diminution in pulmonary function. The usual distribution of values around the mean is "shifted to the left." The amount of the decrement is, on average, to about 85% of "predicted" values; 80% predicted is two standard deviations less than the mean or "predicted" number for controls. The improvements in measured function occur in patients with normal pulmonary parenchyma and airways (asthma occurs at the same rate as in the general population).

## CARDIOVASCULAR FUNCTION

Posterior displacement of the sternum can produce deformity of the heart, particularly anterior indentation of the right ventricle. Garusi, using angiography, showed displacement of the heart to the left side, with a sternal imprint on the anterior wall of the right ventricle.[52] Bevegard, in 1962, studied 16 patients with pectus excavatum using right heart catheterization and workload studies.[53] The physical work capacity at a given heart rate was significantly lower in the sitting than in the supine position. Those with a 20% or greater decrease in physical work capacity from the supine to the sitting position had a shorter sternovertebral distance than did those with a less than 20% decrease. Measured stroke volume at rest decreased from the supine to the sitting position a mean of 40.3%, similar to normal subjects. In the supine position, stroke volume increased 13.2% with exercise. In the sitting position, the increase in stroke volume from rest to exercise was 18.5%, significantly lower ($P < 0.001$) than the 51% increase measured in normal subjects. Thus increased cardiac output can be achieved primarily by increased heart rate, despite a limited stroke volume. This explains the lower work capacity achieved at any given heart rate in the sitting position. Intracardiac pressures were normal in all subjects measured at rest and with exercise, despite the apparent limitation of ventricular volume.

Beiser and colleagues provided further evidence that cardiac function is impaired during upright exercise yet is relatively normal in the supine position.[54] Cardiac catheterization was performed in six subjects with moderate pectus excavatum. Normal right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures were obtained at rest in the supine position. The cardiac index during moderate exercise was normal, although the response to upright exercise was below that predicted in two subjects and at the lower limit of normal in three. The difference in cardiac performance in an upright position was produced primarily by a smaller stroke volume in subjects with pectus excavatum. Stroke volume was 31% lower and cardiac output was 28% lower during upright exercise compared with supine exercise. Postoperative studies were performed in three subjects; two achieved a higher level of exercise after repair. The cardiac index increased an average of 38%. An enhanced stroke volume response produced this increase, because heart rate at maximal exercise was not higher after repair.

Radionuclide angiography was used by Peterson and colleagues to assess cardiac volume and output in 13 subjects with pectus excavatum.[55] Eleven subjects were symptomatic before surgical repair, but the degree of symptoms could not be correlated with the severity of the anatomic deformity. Upright exercise was performed with a bicycle ergometer at progressive workloads, until 85% of the age-predicted maximal heart rate was achieved or the patient could not continue because of fatigue or shortness of breath. Ten of the 13 subjects were able to reach the target heart rate before surgical repair, yet only 4 did so without symptoms. After operation, all but 1 subject reached the target heart rate during the exercise protocol, and 9 of 13 subjects did so without becoming symptomatic. This documentation of a marked decrease in symptoms after surgical correction of pectus excavatum in a regulated exercise protocol substantiated many anecdotal reports in the early literature regarding symptomatic improvement. The role of conditioning and subjective response to surgery is difficult to assess. Radionuclide injections were performed on subjects at rest and then at the target heart rate or exercise end point. This study failed to demonstrate any significant change after pectus repair in the left ventricular ejection fraction either at rest or during exercise. The left ventricular end-diastolic volume was consistently increased after repair at rest, and the mean stroke volume increased 19% after repair but did not consistently increase with exercise. The cardiac index did not increase significantly after operation at rest or during exercise. Kowalewski and colleagues performed a similar study with echocardiographic evaluation of cardiac function in 42 patients both before and 6 months after repair of pectus excavatum.[56] Statistically significant changes were seen in the right ventricular volume indices (systolic, diastolic, and stroke volume) after surgery. No correlation could be

defined between the changes in the pectus index and the cardiac changes. These results support those cited earlier by Haller and colleagues,[47] Sigalet and colleagues,[49] and Malek and colleagues,[50] which all suggest that limitations in the stroke volume result from right ventricular compression. Dramatic demonstration of the effect of mechanical compression by the sternum on the heart was published by Heiter and colleagues, describing a patient with a very severe deformity who had ischemic changes correlated by catheterization, CT scan, and electrocardiogram (ECG).[57]

Additional studies are needed to further define the relationship between pectus excavatum and cardiopulmonary function. Dynamic or exercise studies have been most promising in this area.

Methods to better evaluate preoperative cardiopulmonary function are needed to identify which children may achieve symptomatic and physiologic improvement after surgical repair.

### ECHOCARDIOGRAPHIC STUDIES

Prospective echocardiographic studies in adults with pectus excavatum demonstrated mitral valve prolapse in 6 of 33 subjects (18%) studied by Udoshi and colleagues,[58] in 11 of 17 subjects (65%) studied by Saint-Mezard and colleagues,[59] and 216 of 1215 patients (18%) at Children's Hospital of The King's Daughters (CHKD), Norfolk, Virginia. Anterior compression of the heart by the depressed sternum may deform the mitral valve annulus or the ventricular chamber and produce mitral valve prolapse in these subjects. Resolution of mitral valve prolapse was seen in 10 of 23 children and adolescents after repair in one report, and in 20 of 44 (44%) in another.[60]

### BODY IMAGE

Concerns about the appearance of the chest prompt many, if not most, patients to undergo surgical correction. A large percentage of pectus excavatum patients are self-conscious about their chests. Children and adolescents with physical differences may be at risk for body image and interpersonal difficulties.[61] We have been referred to children who have attempted suicide in response to depression precipitated in part by concern about their chest. Nevertheless, patients with pectus excavatum are often dismissed by pediatricians as having an inconsequential problem.[62] Pediatricians frequently tell children and parents that the chest wall deformity is "only cosmetic."

Validated psychometric assessments administered to more than 300 children less than 21 years old, before and after operation, demonstrated marked improvement in psychosocial functioning.[19] An enormously important finding was that severity of the depression by CT scan did not correlate with the patients' or parents' perception of body image concerns. In other words, even a depression which is "mild" to the physician can be very concerning to the patient and family. Physicians generally support surgical treatment of cleft lip, syndactyly, revision of burn scars, and other conditions in which the only justification for operative risk is anatomic abnormality. Pectus excavatum is reasonably viewed as a correctible anatomic deformity that worsens during the decade of life during which body image is crucial.

## Evaluation Before Operation

In recent years, efforts to develop objective criteria for surgery have been advocated by some centers and rejected by others, where they are thought to not be helpful. Most surgeons agree that patients with mild or moderate depression of the chest are best managed by exercise and posture brace treatment only, with intermittent (e.g., annual) follow-up. At our centers, a minority of patients who present are treated surgically, despite prior screening. Centers with a formal selection process may include three-dimensional imaging (CT or MRI scan of the chest), static and/or exercise pulmonary function testing, and echocardiography to look for mitral valve prolapse. Many agree that surgical correction is warranted if the patient has two or more of the following criteria: (1) progressive or symptomatic pectus excavatum; (2) restrictive disease, decreased work production, or decreased oxygen uptake, as determined by pulmonary function studies; (3) CT scan showing cardiac compression or displacement, pulmonary atelectasis, and a Haller CT index greater than 3.25; (4) cardiac abnormalities, including mitral valve prolapse or bundle branch block; and (5) recurrent pectus excavatum after a failed repair.

Although surgical correction can be performed in very young children with good results, at this time we believe that repair is best deferred until around the time of the pubertal growth spurt (10 to 15 years of age). In younger children (e.g., 4 to 8 years old) with severe exercise intolerance, operation at a younger age may be required. Although in prior years correction in infancy was often advised, at this time it is the exceptional infant who requires operation. The condition may be successfully treated in adult patients, though an upper age for correction remains controversial.

Prior to operation, patients should be asked about metal allergies whenever a metal implant is planned. Patients with a personal or family history of metal allergy should undergo patch testing before having a stainless steel bar implanted. If an allergy to nickel or another component of stainless steel is detected, a titanium bar should be used. Titanium is less malleable than stainless steel, and it is thought that scratches in the bar will cause tissue ingrowth, making it difficult to extract. For these reasons, titanium bars are bent using computer-assisted design/computer-assisted manufacturing (CAD/CAM) techniques at the factory, using the patient's CT scan (Biomet Microfixation, Jacksonville, Fla.). Titanium is much more expensive than stainless steel. Patients with Currarino-Silverman deformity do not respond to the Nuss procedure and should undergo an open operation.

## History of Surgical Treatment

Meyer,[63,39] in 1911, and Sauerbruch,[64] in 1913, first achieved surgical repair of pectus excavatum. Significant changes in the method of repair have evolved as experience has increased, and the primary components of the deformity have been identified. In 1939, Ochsner and DeBakey[65] summarized the early, sometimes fatal experience with a variety of repairs. Ravitch,[66] in 1949, reported a technique that involved excision of all deformed costal cartilages with the perichondrium, division of the xiphoid from the sternum, division of the intercostal bundles from the sternum, and transverse sternal

osteotomy displacing the sternum anteriorly with Kirschner wires in the first two patients and silk sutures in later patients. His technique was later modified to preserve the perichondrial sheaths, but he continued to separate the intercostal bundles and the sheaths from the sternum.[67] In his 1953 textbook, Gross reported correction in eight patients using cartilage incisions bilaterally, median sternotomy, and external splint fixation.[68] In 1957 and 1958, Baronofsky[69] and Welch,[70] respectively, reported similar techniques that emphasized total preservation of the perichondrial sheaths of the costal cartilage, preservation of the upper intercostal bundles, sternal osteotomy, and anterior fixation of the sternum with silk sutures. Haller and colleagues[71] subsequently developed a technique called tripod fixation in which subperichondrial resection of the abnormal cartilages is followed by a posterior sternal osteotomy. The most cephalad normal cartilages are then divided obliquely in a posterolateral direction. When the sternum is elevated, the sternal ends of the cartilage rest on the costal ends, providing further anterior support of the sternum.

Several authors used rib or cartilage placed posterior to the sternum for support, but this technique was never widely accepted.[67,72] A variation on this technique uses a vascularized rib.[73] Support of the sternum by an external brace secured to the mobilized sternum with sutures or wire has also been used by numerous authors, but the duration of its use must be limited to avoid infection of the surgical wound.[11,65,74–76] Support of the sternum by metal struts has also been promoted by multiple authors.[77,78] Rehbein[79] developed struts that could be placed into the marrow cavity of the ribs at the costochondral junction. The struts were secured anterior to the sternum to create an arch, and the sternum was attached to this arch. Paltia[80] placed a transverse strut through the caudal end of the sternum with the two ends of the strut supported laterally by the ribs, firmly fixing its location. Adkins and Blades[81] and later Jensen and colleagues[82] used retrosternal elevation by a metal strut. Willital[24] used a similar retrosternal strut after creating multiple chondrotomies in the costal cartilages to provide flexibility to the sternum and the chest wall. Innovations in these methods include the use of bioabsorbable struts, Marlex mesh or a Dacron vascular graft as a strut, or miniature metallic plates. There is no evidence, however, that any of these are preferable to traditional methods.[39,83–88]

In 1954 and 1956, Judet[89] and Jung,[90] respectively, proposed the sternal turnover in the French literature. This method has been used primarily in Japan, where a large series was reported by Wada and colleagues.[91] This technique uses a free graft of sternum that is rotated 180 degrees and then secured back to the costal cartilages from which it was divided. This method has a significant incidence of severe complications, including wound infection, dehiscence, and necrosis of the sternum. Taguchi modified this method by preserving the internal mammary artery in an effort to prevent osteonecrosis and wound infection.[92] Others have described microvascular anastomosis of one set of internal mammary vessels to preserve perfusion of the sternum.[93] Sternal turnover is a radical approach for children with pectus excavatum deformity, given the acceptable alternatives for repair.

A method of repair favored by some plastic surgeons is implantation of a Silastic mold into the subcutaneous space to fill the deformity.[94–96] Although this approach may improve the contour of the chest, it achieves no increase in intrathoracic volume and is often complicated by early seroma or hematoma formation.

In 1998, Nuss reported correction accomplished by inserting a convex steel bar under the sternum with the convexity facing posteriorly. When the bar is in position, it is turned over 180 degrees, thereby correcting the deformity (see Figs. 62-4 to 62-9). The technique is possible because of the malleability and flexibility of the anterior chest wall; it requires no cartilage incision or resection and no sternal osteotomy.

## SURGICAL TECHNIQUE (OPEN PROCEDURE)

The surgical technique is depicted in Figure 62-2. In females, particular care is taken to place the incision within the projected inframammary crease to avoid injury to the breast bud or the creation of a scar extending onto the breast.[97] Most surgeons performing the open procedure use a retrosternal strut to secure the sternum firmly in an anterior position. Preservation of the connections between the intercostal bundles, the perichondrium, and the rectus muscles provides a more normal chest contour than results when the sternum is skeletonized.

Perioperative antibiotics are used, giving one dose immediately before surgery and three doses postoperatively. All patients are warned not to take aspirin or ibuprofen-containing compounds for 2 weeks before surgery to avoid abnormalities of platelet function. The Hemovac drain (Snyder Laboratories, New Philadelphia, Ohio) is removed when the drainage is less than 15 mL for an 8-hour shift. Rehbein or retrosternal struts are removed 6 months after repair, to allow solid fixation of the sternum. The retrosternal struts are removed through a small incision over one end of the strut.

## COMPLICATIONS

Complications of surgical repair should be limited, including wound infection and pneumothorax. A multicenter study of repair of pectus excavatum reported low and equivalent frequency of complications after either open or minimally invasive (Nuss) repair.[19] Use of electrocautery can avoid the need for blood transfusion in most cases. Most pneumothoraces can be simply observed, unless they are large enough to produce pulmonary impairment. Recurrence is the bane of this procedure and can occur regardless of the technique used. Use of strut fixation of the sternum to optimize early results, and delay of repair until the child is well into his or her pubertal growth spurt are both seen as methods to decrease the risk of recurrence. Growth of the chest may produce the opportunity for remodeling of the chest wall and subsequent recurrence. No randomized study of strut fixation versus no strut fixation has been performed, and it is doubtful that such a study could ever be completed. In large series with adequate follow-up, recurrence is reported to occur in 5% to 15% of cases.[24,98–101] Progressive deterioration of the repair over time is well described, particularly during the interval of rapid growth at puberty.[102–104] Rigid fixation is fairly uniformly applied to patients with Marfan syndrome because of their well-recognized high risk of recurrence.[105]

One serious complication has been noted in children who undergo repair at an early age, generally younger than 4 years—impaired growth of the ribs after resection of the costal cartilages, which produces a bandlike narrowing of the midchest (Fig. 62-3). In some cases, the first and second ribs have relative overgrowth, producing anterior protrusion of

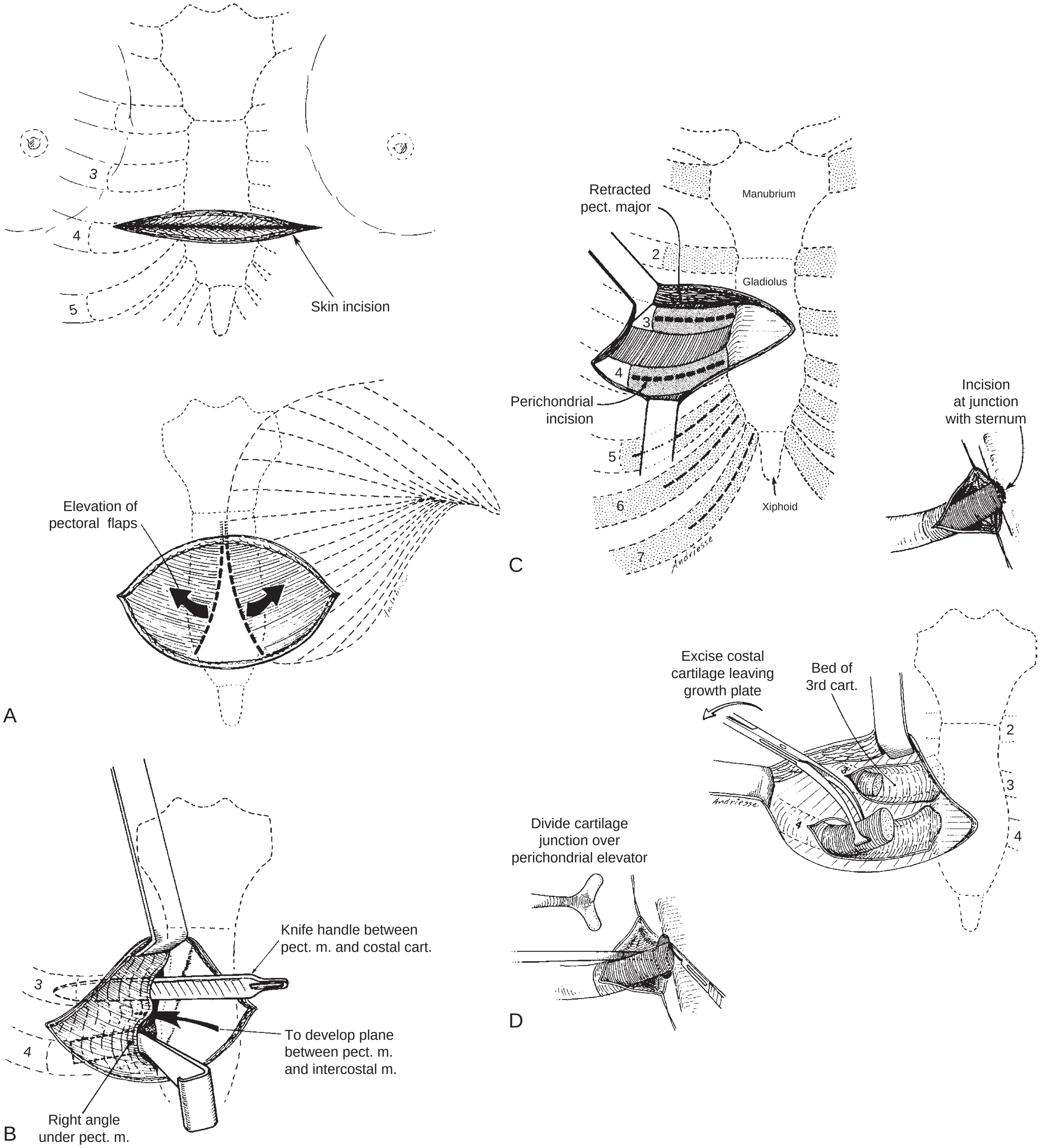


**FIGURE 62-2** Surgical technique for pectus excavatum repair. **A,** A transverse incision is placed below and well within the nipple lines at the site of the future inframammary crease. Skin flaps are mobilized using electrocautery, primarily in the midline to the angle of Louis superiorly and to the xiphoid inferiorly. The pectoralis major muscle is elevated from the sternum, along with portions of the pectoralis minor and serratus anterior muscles. **B,** The correct plane of dissection of the pectoral muscle flap is defined by passing an empty knife handle directly anterior to a costal cartilage after the medial aspect of the muscle is elevated with electrocautery. The knife handle is then replaced with a right-angle retractor, which is pulled anteriorly. The process is then repeated anterior to an adjoining costal cartilage. The lateral extent of muscle dissection and elevation is to the costochondral junctions of the third to fifth ribs. Anterior distraction of the muscles during the dissection facilitates identification of the avascular areolar plane and avoids entry into the intercostal muscle bundles. **C,** Subperichondrial resection of the costal cartilages is achieved by incising the perichondrium anteriorly. It is then dissected away from the costal cartilages in the bloodless plane between the perichondrium and the costal cartilage. Cutting back the perichondrium 90 degrees in each direction at its junction with the sternum (*inset*) facilitates visualization of the back wall of the costal cartilage. **D,** The cartilages are divided at the junction of the sternum with a knife. A Welch perichondrial elevator is held posterior to the cartilage to protect the mediastinum (*inset*). The divided cartilage can then be held with an Allis clamp and elevated, and the costal cartilage is excised, preserving a 5- to 10-mm margin on the rib to protect the costochondral junction and the longitudinal growth plate. Segments of the sixth and seventh costal cartilages are resected to the point where they flatten to join the costal arch. Familiarity with the cross-sectional shape of the medial ends of the costal cartilages facilitates their removal. The second and third cartilages are broad and flat, the fourth and fifth are circular, and the sixth and seventh are narrow and deep.

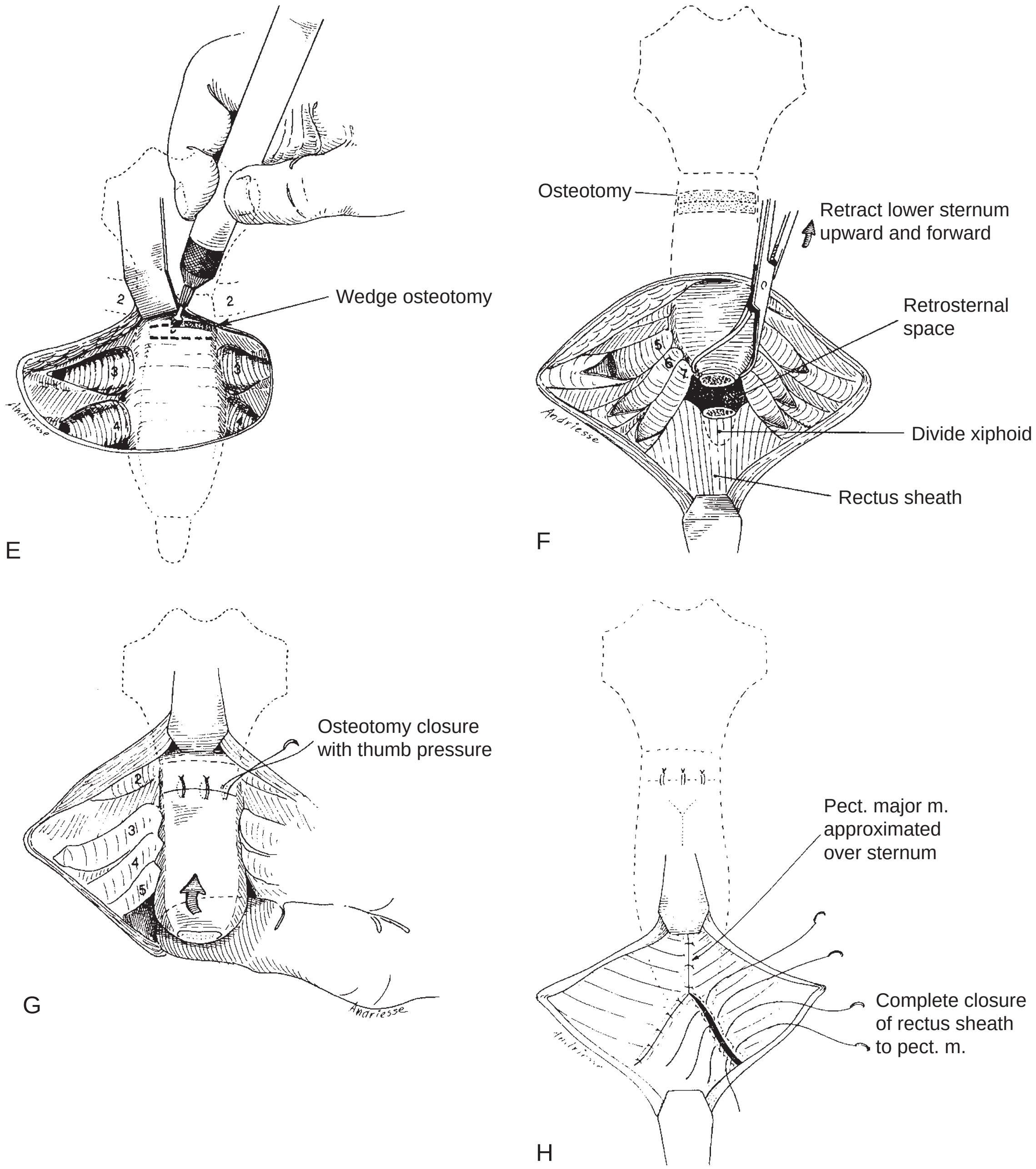


**FIGURE 62-2—CONT'D** **E,** The sternal osteotomy is created above the last deformed cartilage at the point of posterior angulation of the sternum. This is generally above the insertion of the third cartilage, or occasionally the second. Two transverse sternal osteotomies are created through the anterior cortex with a Hall air drill (Zimmer USA, Warsaw, Ind.) 2 to 4 mm apart. The short intervening segment of anterior cortex is then removed, along with the underlying cancellous bone. **F,** The base of the sternum and the rectus muscle flap are elevated with two towel clips, and the posterior plate of the sternum is fractured. The xiphoid can be divided from the sternum with electrocautery, allowing entry into the retrosternal space. This step is not necessary with the use of a retrosternal strut. Preservation of the attachment of the sheaths and xiphoid avoids an unsightly depression, which can occur below the sternum. **G,** When a strut is not used, the osteotomy is closed with several heavy silk sutures as the sternum is elevated to an overcorrected position with the assistant's thumb. **H,** A single-limb medium Hemovac drain (Snyder Laboratories, New Philadelphia, Ohio) is brought through the inferior skin flap to the left of the sternum and placed in a right parasternal position to the level of the highest costal cartilage resection. The pectoral muscle flaps are secured to the midline of the sternum, advancing the flaps to achieve coverage of the entire sternum. The rectus muscle flap, if divided, is joined to the pectoral muscle flaps.

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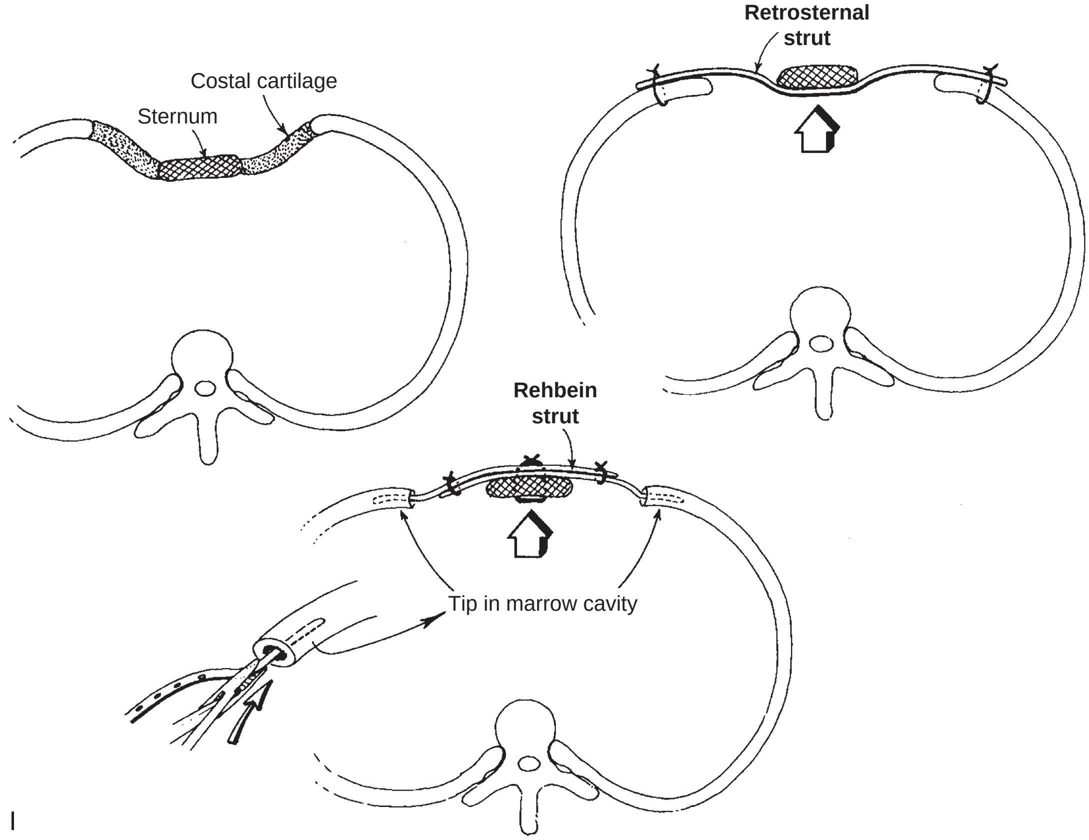


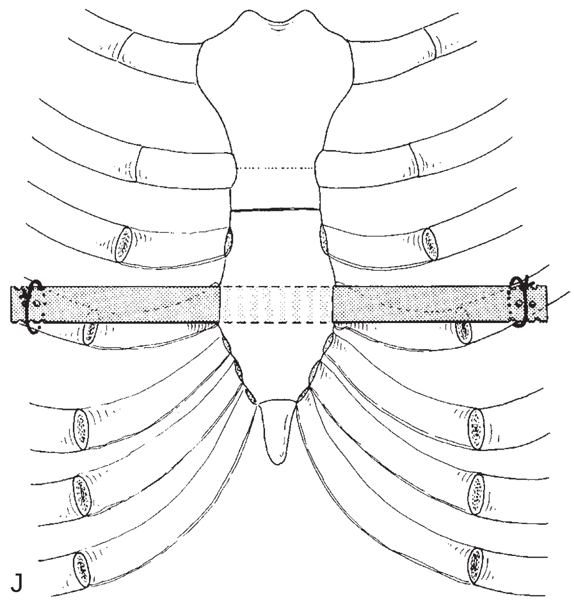




FIGURE 62-2—CONT'D **I,** Use of both retrosternal struts and Rehbein struts is demonstrated. The Rehbein struts are inserted into the marrow cavity (*inset*) of the third or fourth ribs and are then joined to each other medially to create a metal arch anterior to the sternum. The sternum is sewn to the arch to secure it in a forward position. The retrosternal strut is placed behind the sternum and is secured to the rib ends laterally to prevent migration. **J,** Anterior depiction of the retrosternal strut. The perichondrial sheath, to either the third or fourth rib, is divided at its junction with the sternum, and the retrosternal space is bluntly dissected to allow passage of the strut behind the sternum. An adequate space must be created to avoid injury to the pericardium. The strut is secured with two pericostal sutures laterally to prevent migration. (**A** to **H,** From Shamberger RC, Welch KJ: Surgical repair of pectus excavatum. J Pediatr Surg 1988;23:615-622. **I** and **J,** From Shamberger RC: Chest wall deformities. In Shields TW [ed]: General Thoracic Surgery, ed 5. Philadelphia, Lippincott Williams & Wilkins, 2000.)

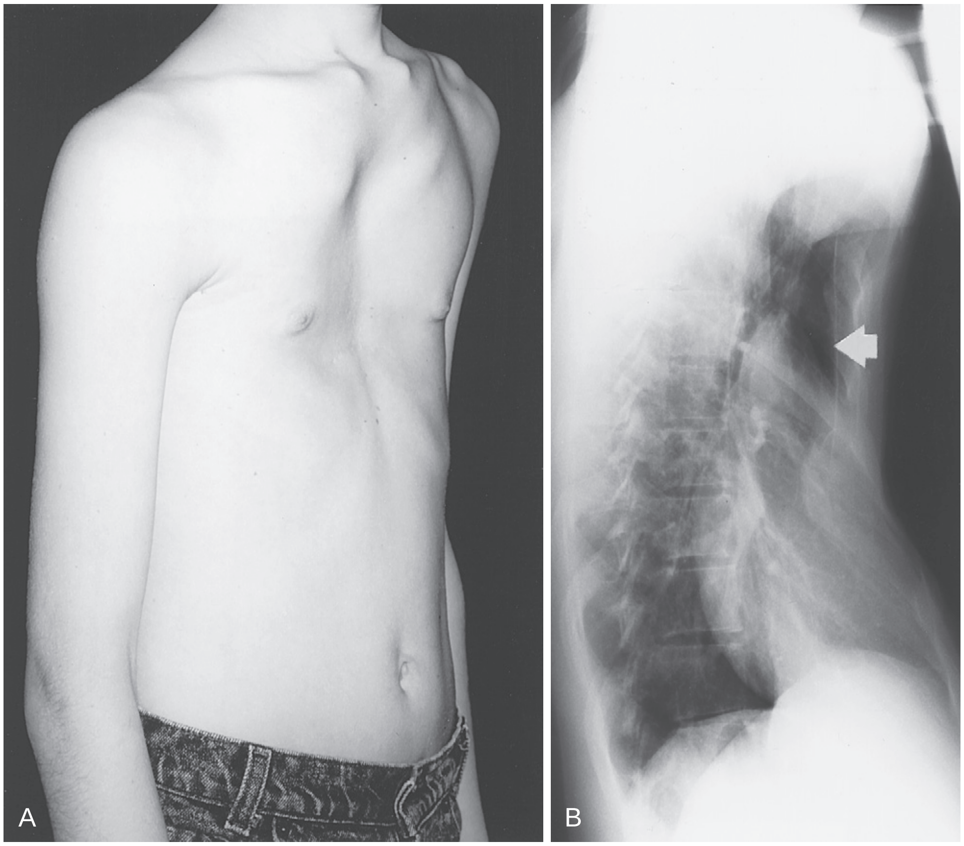



**FIGURE 62-3** **A,** Eighteen-year-old man 15 years after open pectus excavatum repair with a central broad recurrence and relative overgrowth of the upper unresected costal cartilages and ribs. **B,** Lateral radiograph demonstrates the sternum (*arrow*) lying parallel to the spine and the relative protrusion of the upper ribs.

the upper sternum. In 1990, Martinez first described this deficiency in thoracic growth after repair of pectus excavatum during the preschool years.[106] In 1995, Haller reported this occurrence in three boys who presented in their teens after resection of the costal cartilages at an early age, labeling this complication acquired Jeune disease.[107] Haller and colleagues[107] attributed this complication to injury during surgical repair of the costochondral junctions, the longitudinal growth centers for the ribs.

Martinez[106] demonstrated experimentally in 6-week-old normal rabbits that resection of the costal cartilage produced a marked impairment in chest growth, particularly the AP diameter, during a 5.5-month period of observation. Less severe impairment occurred if only the medial three fourths of the costal cartilage was resected, preserving the growth centers at the costochondral junction. This impairment was attributed to fibrosis and scarring within the perichondrial sheaths. Perichondrial sheaths, bone, or other prosthetic tissues that cannot grow should not be joined posterior to the sternum, because they will form a bandlike stricture across the chest. This complication can be avoided by delaying surgery until the children are older.

Preservation of the costochondral junction by leaving a segment of the cartilage on the osseous portion of the rib may partially minimize growth impairment. Weber and Kurkchubasche[108] described a method of improving the severe pulmonary impairment encountered in one patient with acquired Jeune syndrome. A sternotomy was performed and wedged open permanently with rib struts. The pleura was opened bilaterally, along with subperichondrial resection of six ribs. Pulmonary function was improved after the procedure. A subsequent report involving 10 patients further substantiates the efficacy of this technique to improve pulmonary function in 8 of the 10 patients.[109]

Fracture of struts left in place for extended periods has been reported, with erosion of the strut into the myocardium.[110] For this reason, most struts should be removed after an adequate interval to allow complete healing of the chest wall (e.g., 3 to 6 months).

# Surgical Technique (Nuss Procedure)

## PREOPERATIVE CONSIDERATIONS

Using a bar to correct pectus excavatum requires that attention be given to the bar. First, the patient should not be allergic to the components of the stainless steel bar. If there is a history of allergy to metal, patch testing should be done. If allergy is identified, a titanium bar can be used. The titanium bar is not as malleable as steel, and must be bent at the factory with CAD/CAM (computer-assisted design/computer-assisted manufacturing) technology using a copy of the patient's CT scan or

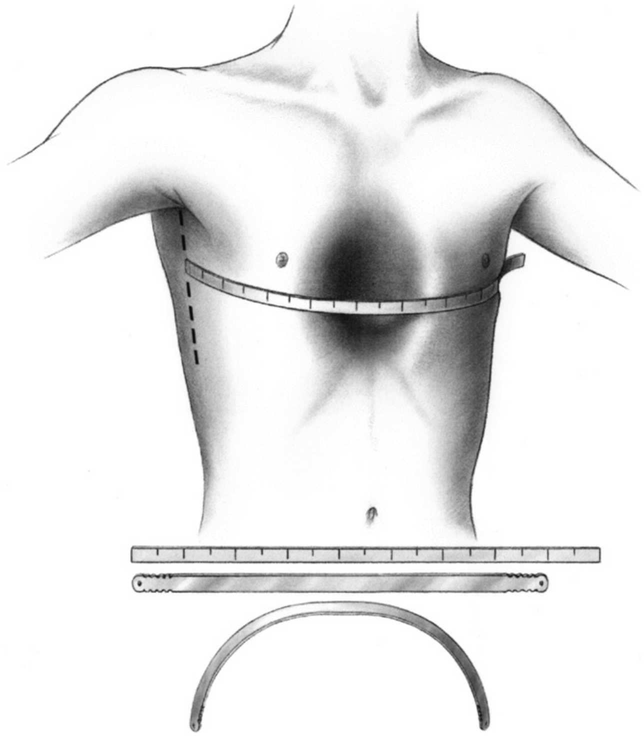


FIGURE 62-4 The bar should be 2 cm (1 inch) shorter than the distance from right to left midaxillary lines. The bar should be bent as shown, with a 2- to 4-cm flat section in the middle. The correct bar length should be decided in advance. Positioning is important. Both arms are abducted at the shoulder to make an angle of 75 degrees with the torso. Elbows are slightly flexed.

MRI. Titanium is also 4 times as expensive as steel and so is not used in every instance. The correct size bar should be determined well in advance. The bar should be 2.5 cm (1 inch) shorter than the distance from the right to left midaxillary line. The correct size and shape of the bar are crucial to success of the operation. The stainless steel pectus support bar is bent to conform to the patient's chest configuration, leaving a 2-cm section flat to support the sternum (Fig. 62-4). Bending the bar into an arch allows sustained load bearing of the bar. If the central flat section of the bar is too long, there will be undercorrection.

### OPERATION OVERVIEW

Operation is performed under general anesthesia. In Norfolk, we no longer use epidural analgesia supplementation, following two episodes of lower extremity paralysis that could not be explained despite exhaustive evaluation; these occurred after more than 1,000 uncomplicated epidural placements. Antibiotics are administered perioperatively, just as for open operation.

Careful attention to positioning and thoracoscope placement inferior to the proposed position of the bar facilitate good visualization (Fig. 62-5 illustrates the surgical technique). Some surgeons prefer to approach the mediastinal tunneling from the left rather than the right side. Other surgeons make a third incision over the xiphoid and then apply a towel clip or bone hook to elevate the sternum (Fig. 62-6); others do a finger dissection under the sternum before inserting the introducer (Fig. 62-7).

In younger and smaller patients, a single bar is adequate to correct the deformity. But in older or larger patients, especially if they have a severe deformity, a second bar should be added without hesitation. Sternal elevation using the introducer device improves the result by moving the sternum and cartilages and allowing easier rotation of the bar. Great care should be taken to prevent the bar from moving after operation by securing it to the underlying ribs with heavy absorbable suture. Using the thoracoscope, a wound closure device such as the Endoclose autosuture (Covidien, Mansfield, Mass.) can feed a double thickness of heavy suture safely, avoiding vascular and intercostal nervous structures (Fig. 62-8).

### POSTOPERATIVE MANAGEMENT

In the recovery room, smooth emergence from anesthesia, avoiding thrashing or wriggling movements, is ensured. Patients are usually discharged home on the fourth or fifth postoperative day. Patients may return to school after 2 weeks but may not participate in sports for 6 weeks after surgery. After 6 weeks, patients are encouraged to resume their pectus breathing and posture exercises and to participate in aerobic sports activities (e.g., soccer, basketball, swimming). Heavy contact sports (e.g., boxing, football, ice hockey) are prohibited until the bar is removed.

### TIMING OF REMOVAL OF THE BAR

The pectus bar should be left in place for at least 2 years. Patients are evaluated on an annual basis, and their growth and activity level are monitored. Patients between the ages of 6 and 10 years often do not grow rapidly, and they tolerate the bar well for 3 or even 4 years. In contrast, teenagers who undergo a massive growth spurt may require removal of the bar after 2 years.

We consider the exercise programs to be just as important as the surgery. Deep breathing with breath-holding for 10 to 15 seconds and aerobic activities, such as running (e.g., soccer, basketball) and swimming, are vigorously encouraged (Fig. 62-9).

## Complications

### EARLY COMPLICATIONS[15,69,111]

There were no deaths and no cardiac perforations during the 1,215 repairs performed at our institution over the last 21 years. Chest tube drainage was necessary in 4% of cases. Hemothorax requiring drainage occurred after 7 repairs (0.6%). Three were in the perioperative period, and 4 occurred months later; two of these late cases were explained by external trauma, and two were not. Three pleural effusions required treatment by either chest tube or aspiration (0.3%).

Pericarditis requiring treatment with indomethacin occurred after four repairs (0.4%), with one requiring pericardiocentesis. Pneumonia occurred after 6 repairs (0.5%). Fifteen percent of patients had transient Horner syndrome at varying times during thoracic epidural administration. Early superficial wound infection was noted in 11 patients (1%).

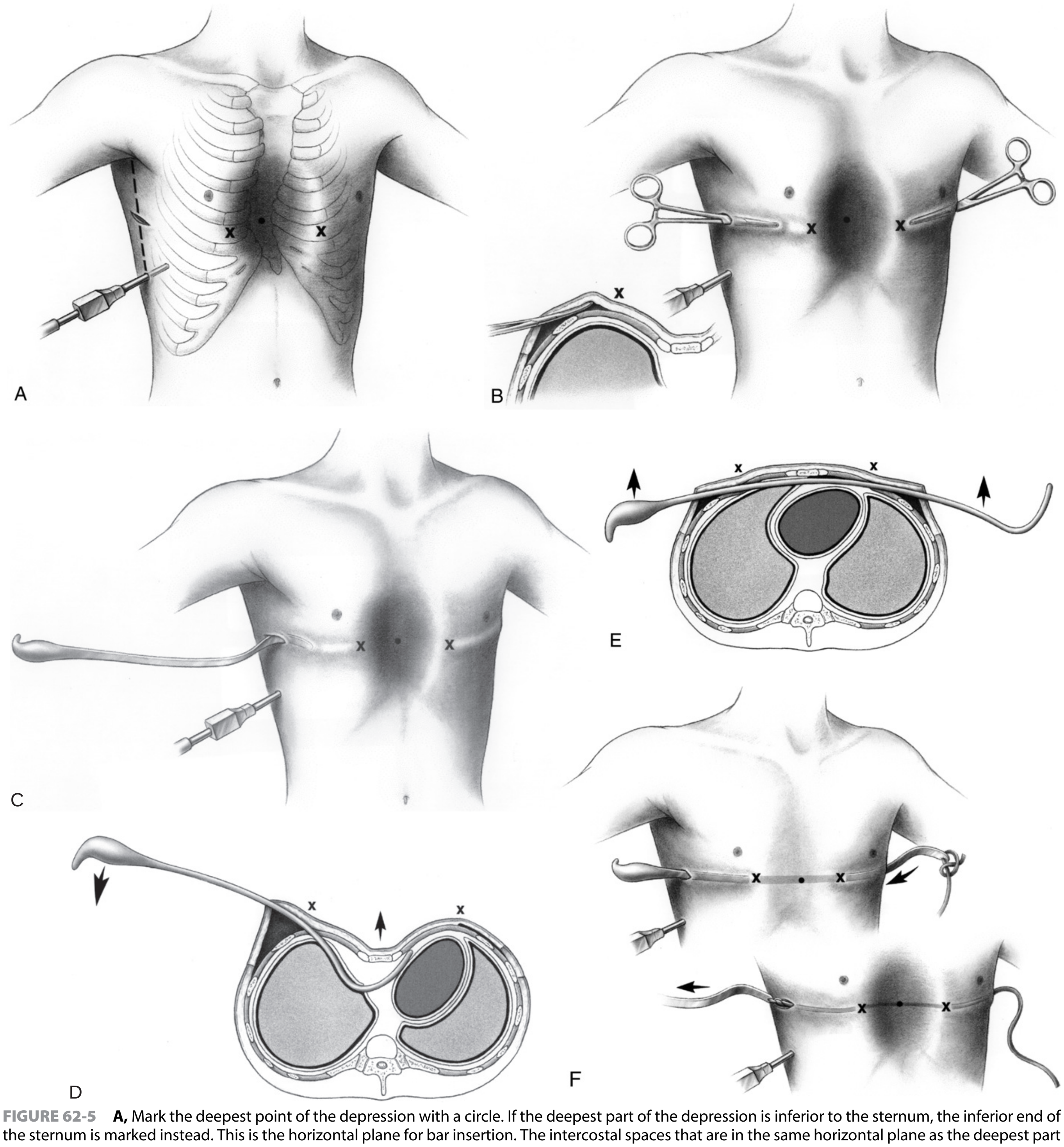



**FIGURE 62-5** **A,** Mark the deepest point of the depression with a circle. If the deepest part of the depression is inferior to the sternum, the inferior end of the sternum is marked instead. This is the horizontal plane for bar insertion. The intercostal spaces that are in the same horizontal plane as the deepest part of the depression are marked with an X. These entry and exit points on each side of the sternum should be medial to the top of the pectus ridge. These marks should all be in the same horizontal plane. The thoracoscope is inserted two intercostal spaces below the incision site. A thorough inspection of the right hemithorax and mediastinum is performed, ensuring that there is no contraindication for repair. The pressure is applied with a finger to the intercostal spaces marked for bar insertion to ensure that the external markings line up well with the internal anatomy. **B,** After confirming by thoracoscopy that the internal and external anatomy match up well, bilateral thoracic skin incisions are made, and a deep subcutaneous tunnel is raised anteriorly toward the intercostal space (marked with an X) medial to the top of the pectus ridge. If the site chosen is beneath the pectoralis major muscle, a subpectoral plane is developed. **C,** A Lorenz introducer is inserted into the subcutaneous tunnel on the right. Under thoracoscopic guidance, it is pushed through the right intercostal space marked with an X. **D,** Under thoracoscopic guidance, a transthoracic substernal tunnel is created by dissecting the pleura and pericardium off the undersurface of the sternum with the introducer. The scope position must be advanced and adjusted as the dissection proceeds from right to left, but there should be excellent visualization. A 30-degree angled scope may facilitate this process. The introducer is pushed through the left intercostal space (marked with an X) and advanced out of the left lateral thoracic incision. **E,** The sternum is elevated out of its depressed position by lifting the introducer on each side while applying pressure to the lower costal margin. The lifting is repeated until the pectus excavatum is corrected. **F,** After correcting the pectus excavatum, umbilical tape is attached to the end of the introducer, which is then slowly withdrawn from the chest, thereby pulling the umbilical tape through the transthoracic tunnel.

*Continued*

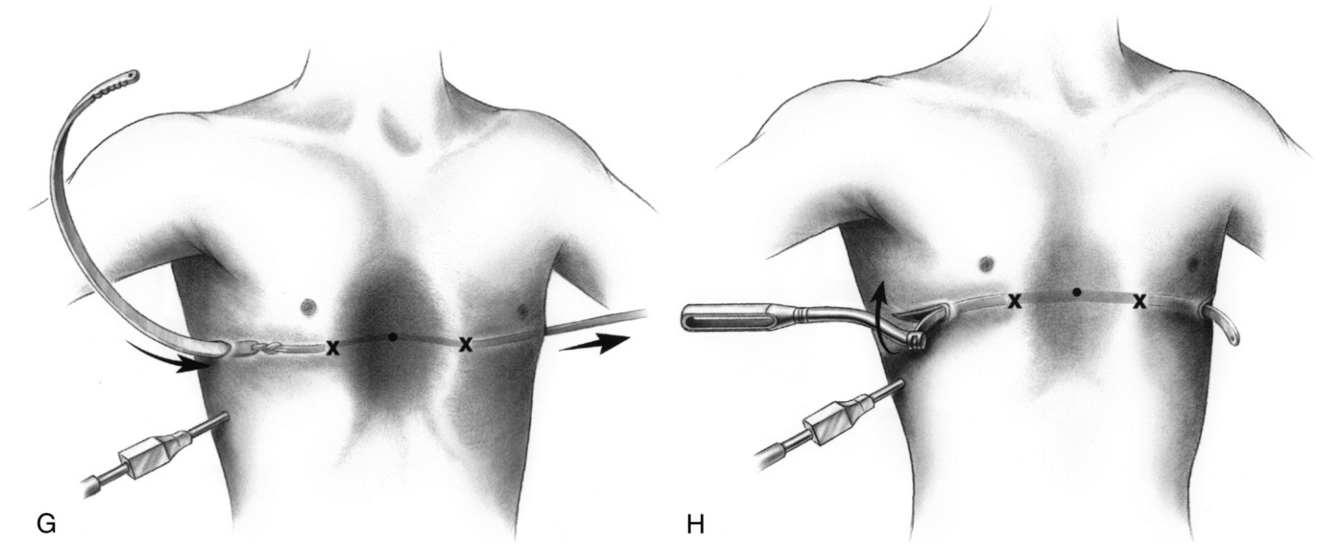



**FIGURE 62-5—CONT'D** **G,** The previously prepared pectus support bar is tied to the umbilical tape and, under thoracoscopic guidance, is pulled through the substernal tunnel, with the convexity facing posteriorly. **H,** When the bar is in position, it is rotated 180 degrees using the bar flipper.

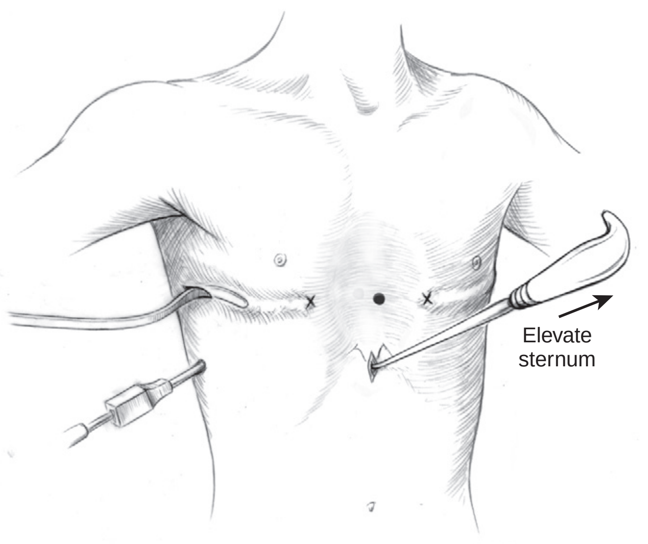



**FIGURE 62-6** Lifting the sternum with a bone hook improves the view of dissection between the sternum and pericardium.

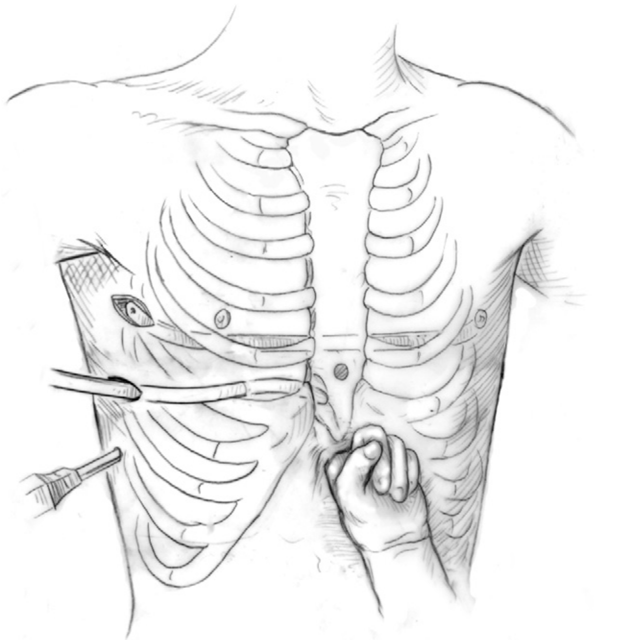


**FIGURE 62-7** Inserting a finger posterior to the sternum can allow dissection between the sternum and pericardium. The finger can guide the introducer across from right to left. Pneumothorax (which facilities thoracoscopy) is difficult to maintain after this opening is created, until the wound is closed.

### LATE COMPLICATIONS

Sixty-four patients (5.7%) experienced bar displacement. The incidence of bar displacement has fallen dramatically as we have gained experience with the procedure, and the incidence of bar displacement is now less than 1%. Deep infection, involving the bar (not superficial wound infection) occurred in six patients (0.5%), requiring early bar removal in three (0.2%).

Allergy to the bars has occurred in about 3% of patients overall but has been almost entirely prevented by patch testing after our group recognized and reported the problem.[112] These presented as rashes in the area of the bar or the stabilizer, sterile abscesses at the incision site, and pleural and/or pericardial effusions. Of all our primary surgery patients, 22 (2.0%) developed a moderate overcorrection of their deformity, and 4 (0.4%) developed a true carinatum deformity. We believe that the incidence of this problem has diminished with increased experience in bending the bar.

## Results

Of 1215 patients, 1123 had primary surgery (not re-do) operations. Of those, 790 have had the bar removed. A good or excellent result was obtained in 96%, fair in 1.4%, and

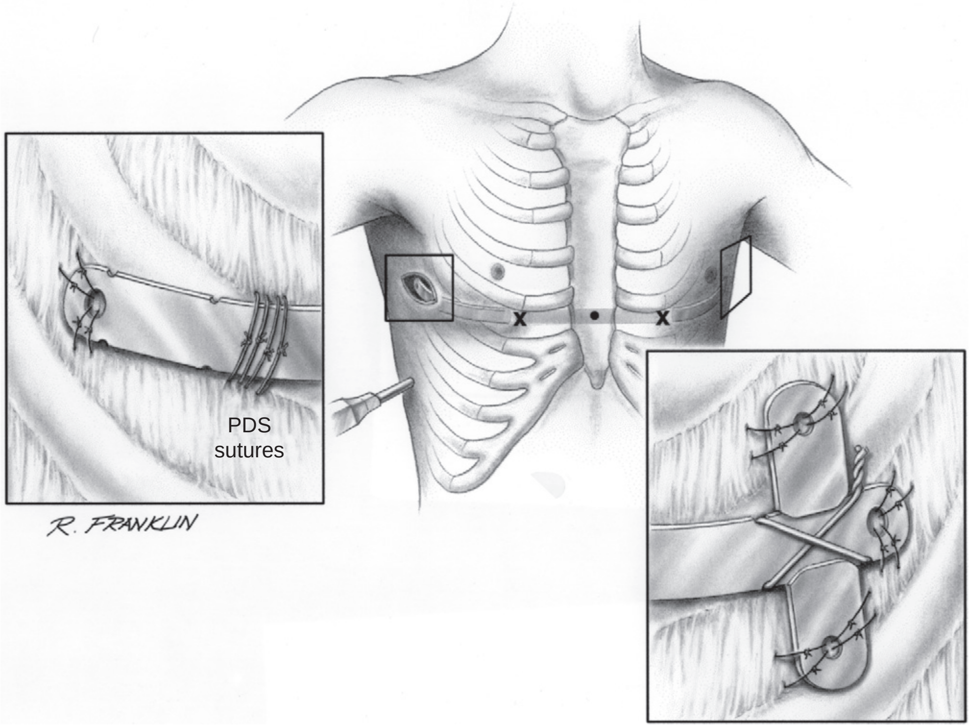



FIGURE 62-8 Stabilization of the bar is essential. A stabilizer is inserted on the left (the right may also be used) end of the bar and secured to the bar with No. 3 surgical steel wire. If the bar does not seem stable, usually a second bar rather than a second stabilizer is called for. On the right side, heavy absorbable sutures (0 or 1 polydioxanone sutures [PDS]) are placed around the bar and underlying rib. These are placed with an EndoCatch needle (Covidien, Mansfield, Mass.) with thoracoscopic guidance. In addition, heavy (0) absorbable (Vicryl) sutures are placed through the holes in the bar and stabilizer and in the underlying fascia. Hebra and colleagues advocate placing a suture adjacent to the sternum.[110a]

poor in 0.8%. Recurrence requiring re-do operation occurred in 11 patients (1.4%).

## Protrusion Deformities: Pectus Carinatum

Pectus carinatum consists of a spectrum of deformities that are less frequent than pectus excavatum by a ratio of 1:5 in North America.[60] In a recent report of 7,878 children from Buenos Aires, Argentina, it comprised 55% of chest wall deformities.[30] A recent report from Manaus, Brazil found the frequency to be half that of pectus excavatum (prevalance of pectus carinatum was 0.675% in 1332 11- to 14-year-old students).[4] It occurs more frequently in boys than in girls (4:1), as does pectus excavatum. In many of the children, the deformity is not appreciated until after the 11th birthday. A mild deformity noted at birth or in early childhood often worsens as the child grows, particularly at puberty. As a result, most children present for treatment as teenagers.

### CAUSE

The origin of pectus carinatum is no better established than that of pectus excavatum. Early investigators implicated abnormal development of the diaphragm, but this has never been confirmed.[10,12] Others proposed that excessive growth of the ribs or costal cartilages produces either pectus carinatum or pectus excavatum.[100] Two associations provide

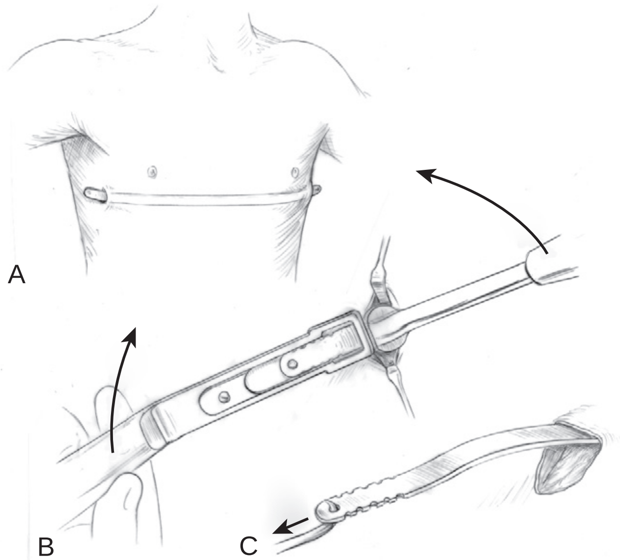



FIGURE 62-9 The bar and stabilizer are removed 2 or 3 years after insertion under general anesthesia. Position the patient supine, with both arms abducted at the shoulder. **A,** Bar removal is performed by opening both lateral incisions. The fibrous scar encasing the bar is freed from the serrations and holes in the bar and stabilizer. Rongeurs are used to remove any reactive bony overgrowth holding the bar. When this is done, the bar should move easily in the fibrous tunnel, with finger pressure at the end of the bar. **B,** Finger pressure is used to push the bar inside its sheath so that more protrudes from one side. The Malti bender is used to flatten the bar. The bar is then pushed with finger pressure on the end of the bar so that the other side protrudes from the skin. Then the other side is flattened. **C,** A bone hook is used to pull the bar out. It should come out with minimal resistance.

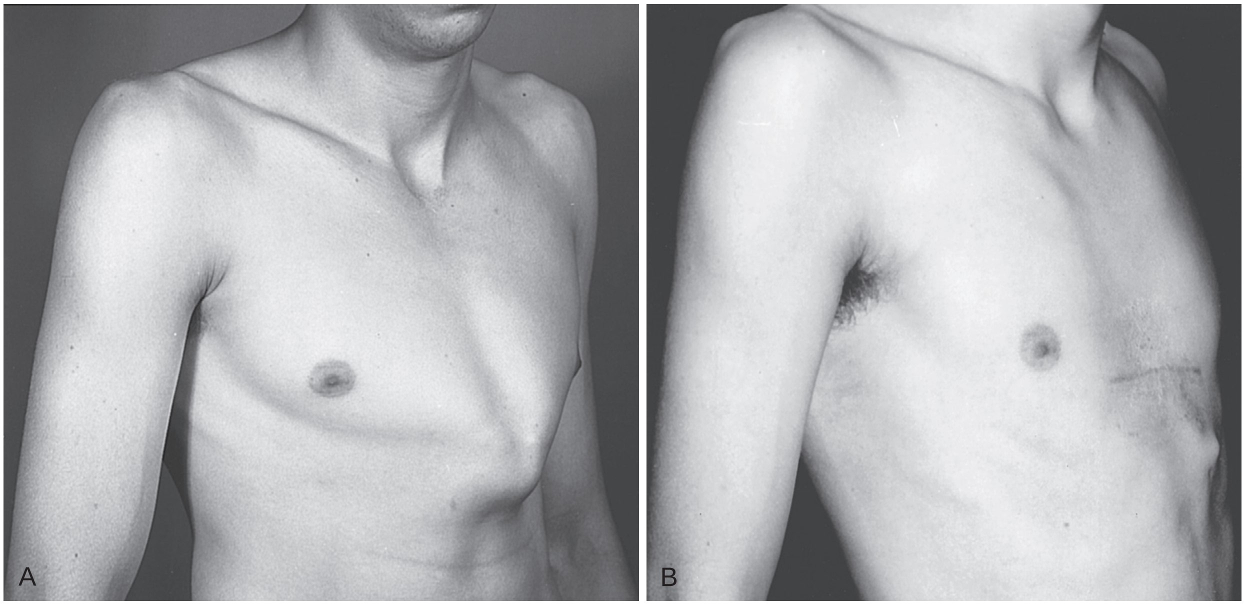



FIGURE 62-10 **A,** Nineteen-year-old man with symmetric chondrogladiolar pectus carinatum. **B,** Postoperative photograph shows correction of the protruding sternum and costal cartilages. (From Shamberger RC: Chest wall deformities. In Shields TW [ed]: General Thoracic Surgery, ed 5. Philadelphia, Lippincott Williams & Wilkins, 2000.)

some clues to its origin: (1) a family history of chest wall deformity has been identified in 26% of patients, suggesting some genetic predisposition,[60] and (2) scoliosis in 15% of patients implies a diffuse abnormality in connective tissue development.

## CLINICAL PRESENTATION

The most frequent form of pectus carinatum is symmetric protrusion of the body of the sternum (gladiolus) and costal cartilages, termed chondrogladiolar protrusion (Fig. 62-10). An associated lateral depression of the ribs (runnels or Harrison grooves) is often present. It has been likened to a giant hand crushing the chest from each side.[113] Protrusion can also be asymmetric, limited to one side of the sternum, with the costal cartilages producing a keel-like protrusion (Fig. 62-11). Tenderness at the area of sternal prominence when lying prone is commonly described. Though some patients are asymptomatic, a minority of patients clearly report pain in the area of the protrusion and/or exercise limitation. A mixed deformity also occurs with components of both protrusion and depression. The sternum is often rotated posteriorly toward the depressed side. This variant is most frequently seen in conjunction with Poland syndrome.

The rarest form of pectus carinatum, chondromanubrial protrusion, is produced by protrusion of the manubrium and the superior costal cartilages, with a relative depression of the body of the sternum (Fig. 62-12). It is frequently associated with premature fusion of the sternal sutures and a broad comma-shaped or Z-shaped sternum. An increased incidence of congenital heart disease has been identified in these children.[114] Lees and Caldicott[115] identified anomalies of sternal fusion in 135 of 1915 children. Twenty percent of those with sternal fusion had congenital heart disease.

FIGURE 62-11 Twelve-year-old boy with asymmetric pectus carinatum has protrusion of the costal cartilages on only the right side, producing a keel-like deformity. (From Shamberger RC: Chest wall deformities. In Shields TW [ed]: General Thoracic Surgery, ed 5. Philadelphia, Lippincott Williams & Wilkins, 2000.)

## TREATMENT

Surgical repair of pectus carinatum has a colorful past that has been reviewed elsewhere.[60] In 1973, Welch and Vos[116] reported their approach to these deformities in 26 children. They stressed the need to preserve the perichondrial sheaths and to tailor the osteotomies to achieve the appropriate position of the sternum. A similar method was used by Pickard and colleagues.[117]

Fonkalsrud reported excellent results and minimal complications in a series of 260 patients over 37 years. All were

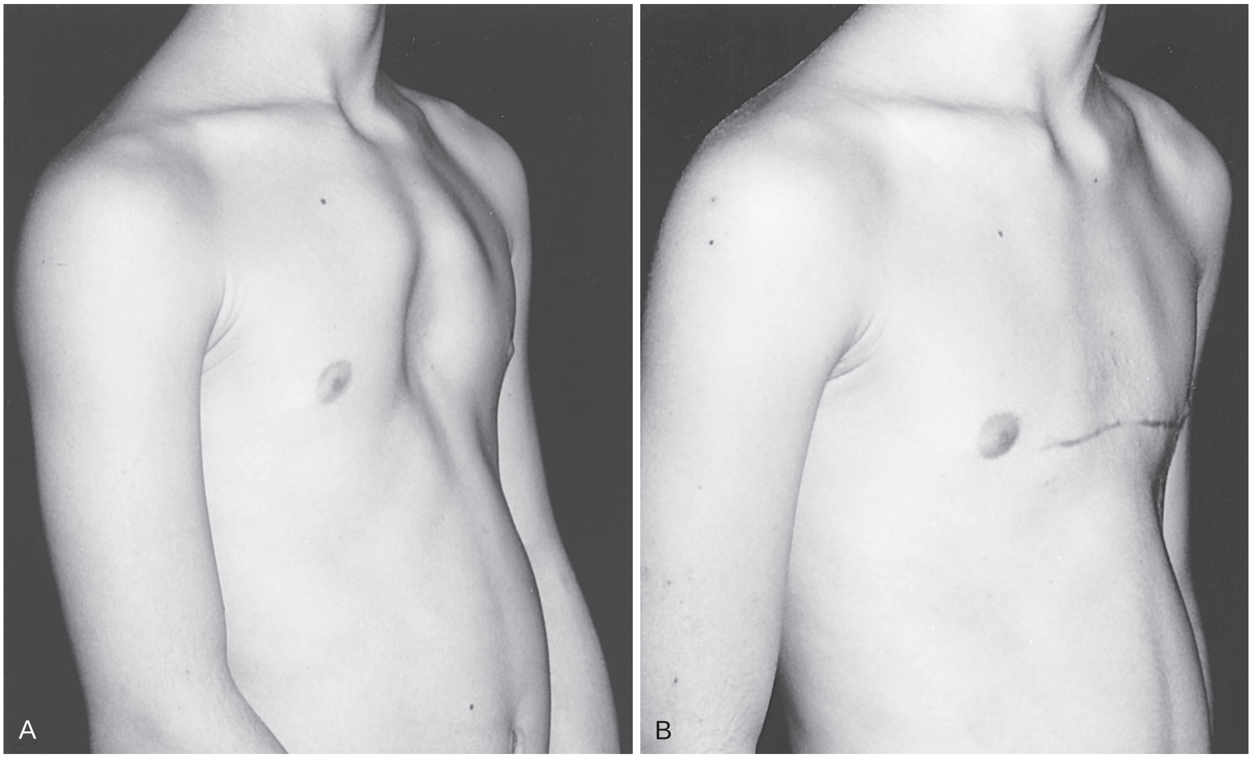



**FIGURE 62-12** **A,** Fifteen-year-old boy with chondromanubrial deformity. Note the posterior depression of the lower sternum accentuated by the anterior bowing of the second and third costal cartilages. **B,** After repair, the sternal contour is improved, and costal cartilages re-form in a more appropriate position.

symptomatic preoperative and had a cardiothoracic index by chest radiograph or CT scan of less than 2.[118]

Attempts to treat pectus carinatum by orthotic bracing have been reported, beginning in 1992 in Brazil. Evolution of bracing devices has led to increased success, and presently, several reports suggest that 65% to 80% of children will have resolution with brace treatment alone. Recently, efforts have focused on making the brace easy to conceal and comfortable to wear. Bracing strategies that work toward incremental correction over several months have met with better success than previous efforts. Brace treatment is best carried out in conjunction with physical therapists and/or physical medicine and rehabilitation physicians, who do most brace treatment in pediatric hospitals.[119–121] In teenagers, poor compliance with bracing programs can be addressed by peer pressure at a bracing clinic, along the lines of a spina bifida clinic.

## SURGICAL TECHNIQUE (OPEN PROCEDURE)

Initial exposure for repair of pectus carinatum is through a transverse incision identical to that for pectus excavatum repair, followed by mobilization of skin and pectoral muscle flaps. Many authors stress the need to remove all deformed or partially deformed cartilages, because with continued growth, mild deformities worsen and become apparent.[122,123] In the chondrogladiolar deformity, a single or, occasionally, a double osteotomy allows the posterior plate of the sternum to be fractured, returning the sternum to a normal position (Fig. 62-13, *A*). The wound is drained and closed in a fashion identical to that for pectus excavatum repair.

In the mixed deformity, the oblique position of the sternum must be corrected, as well as the position of the depressed and protruding costal cartilages. After subperichondrial resection of the abnormal costal cartilages is completed, a wedge-shaped osteotomy is created in the anterior sternal plate, with the broad portion of the wedge on the depressed side of the sternum (Fig. 62-13, *B*). Closure of the osteotomy both elevates and rotates the sternum into a corrected position. It is secured with sutures to close the osteotomy or with a strut.

With chondromanubrial and mixed deformities, management of the sternum requires special consideration. In the chondromanubrial form, the upper position of the sternum protrudes, and the lower body is angled toward the spine. In Ravitch's[66] first description of the repair of this deformity, he removed a wedge of the anterior plate of the sternum at its point of maximal protrusion and created a second osteotomy at the site of the second angle of the Z-shaped sternum. In our experience, the sternum has been comma shaped and truncated; so, a second osteotomy was not required (Fig. 62-13, *C*).[124] When the osteotomy is closed, both the posterior depression of the lower portion of the sternum and the anterior angulation of the manubrium are corrected as the manubrium rotates posteriorly on its attachment to the first costal cartilage.

## COMPLICATIONS

Complications of repair should be infrequent, including infection, pneumothorax, pneumonia, or wound separation. Blood transfusions are rarely required with the use of electrocautery. Results from correction are overwhelmingly

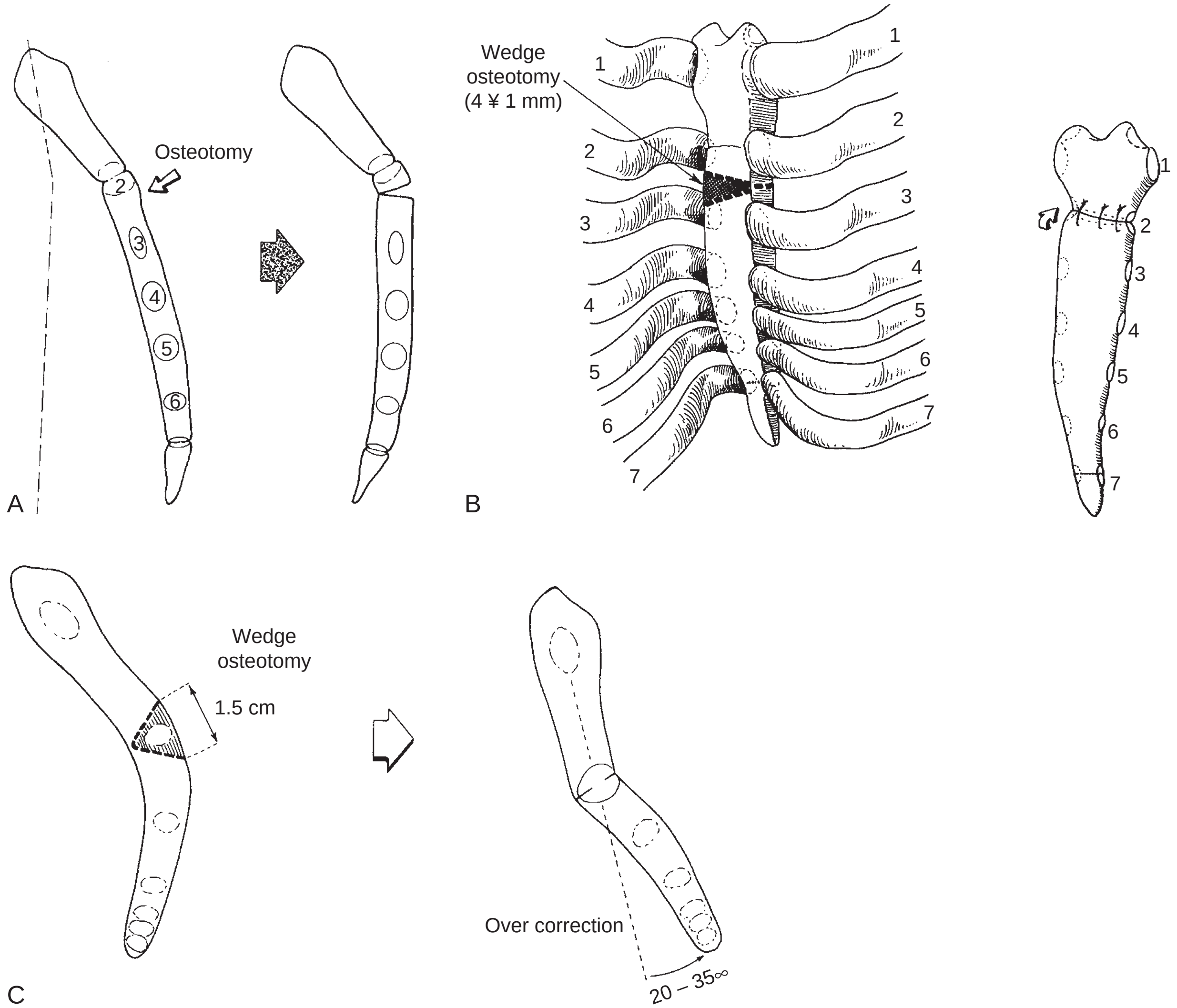



**FIGURE 62-13** **A,** Single or double osteotomy after resection of the costal cartilages allows posterior displacement of the sternum to an orthotopic position. **B,** Mixed pectus deformity is corrected by full and symmetric resection of the third to seventh costal cartilages, followed by transverse offset wedge-shaped sternal osteotomy. Closure of this defect permits both anterior displacement and rotation of the sternum. **C,** Chondromanubrial deformity is corrected with a broad, wedge-shaped sternal osteotomy placed through the anterior cortex at the obliterated sternomanubrial junction. Closure of the osteotomy after fracture of the posterior cortex achieves posterior displacement of the superior portion of the sternum, which is secured only by its attachment to the first rib. The lower portion of the sternum is overcorrected 20 to 35 degrees. (**B,** From Shamberger RC, Welch KJ: Surgical correction of pectus carinatum. J Pediatr Surg 1987;22:48-53. **C,** From Shamberger RC, Welch KJ: Surgical correction of chondromanubrial deformity [Currarino-Silverman syndrome]. J Pediatr Surg 1988;34:319-322.)

successful, and recurrence is rare. Incomplete correction of the deformity and repair at an early age before complete development of the deformity are the primary reasons for reoperation.[122,123]

## Surgical Technique, Minimally Invasive Procedures

Recently, Horacio Abramson of Buenos Aires, where there is a high incidence of pectus carinatum, has modified Nuss's operation for pectus excavatum to treat pectus carinatum.[125] In 2008, he described a series of 40 patients treated by passing a stainless steel bar anterior to the sternum subcutaneously/submuscularly and securing the bar to the ribs to hold the sternum in position.[126] Though still in evolution, this procedure appears likely to become a standard operative approach to treatment of pectus carinatum. In 2009, Kim and Odowu reported from Oakland the repair of the deformity by thoracoscopic cartilage resection, and the combination of these two approaches has met with early success at CHKD. Confirmation of broad applicability and long-term results are pending.[127]

## Poland Syndrome

The initial description of Poland syndrome appeared in the English literature in 1841,[128] although German and French cases had been described earlier.[100,129] Poland reported a case in which he performed an anatomic dissection while still a medical student. He described a constellation of anomalies,

including absence of the pectoralis major and minor muscles and syndactyly. Subsequent reports added other components of the syndrome, including absence of ribs, chest wall depression, athelia or amastia, absence of axillary hair, and limited subcutaneous fat. Thompson first summarized the full spectrum of anomalies in 1895.[100] Although described previously by others, this syndrome has been labeled Poland syndrome since 1962, when Clarkson[130] first applied this eponym to a group of patients.

## EMBRYOLOGY

Poland syndrome has a sporadic occurrence estimated at 1 in 30,000 to 32,000 live births; it is rarely familial.[131,132] Various causes have been suggested, including abnormal migration of the embryonic tissues forming the pectoral muscles, hypoplasia of the subclavian artery, and in utero injuries from attempted abortion, but none of these theories has been uniformly accepted.[133,134] Although some forms of syndactyly have been described as autosomal dominant traits, a similar pattern has not been demonstrated in patients with Poland syndrome, which is generally sporadic. Poland syndrome is associated with a second rare syndrome, Möbius syndrome, involving bilateral or unilateral facial palsy and abducens oculi palsy. Fontaine and Ovlaque[135] identified 19 such cases with these combined syndromes, but a unifying cause was lacking. Boaz and colleagues[136] reported an unusual association between Poland syndrome and childhood leukemia.

## CLINICAL PRESENTATION

Children demonstrate remarkable diversity in this syndrome (Fig. 62-14). The predominant defect varies, depending on the extent of involvement of the different components. By definition, all children with Poland syndrome have aplasia or hypoplasia of the sternocostal portion of the pectoralis major muscle and at least one other associated lesion. The degree of abnormality of the hand, breast, or chest wall can be quite variable. Thompson, in his early summary of this syndrome, found the pectoralis major muscle entirely absent in 20 cases and partially defective in 63; generally, the sternocostal component is the missing portion.[100] The pectoralis minor was described as absent in 53 cases and defective in many others. In no case was it described as normal. Children do not present with functional deficiency of the ipsilateral arm, however, because they compensate well for the missing pectoral muscles. Hand anomalies vary widely. In the report by Ireland and colleagues,[137] all their patients had syndactyly and a variable degree of brachydactyly, an obvious result of the authors' patient selection and referral patterns.[138] Al-Qattan has reported a recent classification of the hand anomalies occurring in Poland syndrome, recognizing the broad spectrum seen ranging from a perfectly normal hand or one with mild brachysyndactyly to those with severe loss of the central digits to the rarest and most severe cases with phocomelia-like deficiency.[138] In another series of 75 children with Poland syndrome, 50 had anomalies of the hand, and 37 had absence or hypoplasia of the breast or nipple.[139] In many, the nipple was lightly pigmented and higher on the chest than the normal contralateral nipple. There was no correlation between the severity of chest wall and hand anomalies. A broad range of thoracic deformities was seen in these children, ranging from a normal configuration of the ribs to aplasia of two to three ribs (Table 62-2; Fig. 62-15). Few children have a chest wall deformity so severe that it requires surgery.

CT scans have proved helpful in assessing the configuration of the chest wall and its need for reconstruction (Fig. 62-16).[15] CT scans can also evaluate the extent of muscular involvement. In one case, failure of a latissimus dorsi myocutaneous flap was attributed to unrecognized hypoplasia of the latissimus dorsi muscle.[140] All patients with absent ribs should be considered candidates for repair. The aplastic ribs are generally some combination of the second to the fifth, with the second being least frequently involved.[100] Only two cases have been published in which there was involvement of all the ribs inserting into the sternum below the first. Patients with a severe ipsilateral concave deformity of the chest wall should also be considered for repair.

## TREATMENT

Ravitch[67] and others have described reconstruction of aplastic ribs with autologous rib grafts. Use of the latissimus dorsi muscle to provide coverage for the ribs produces an improved appearance, but involves the possibility of functional loss when the pectoralis major muscle is also hypoplastic.[141–143] Use of the latissimus dorsi flap may be justified in females to optimize breast reconstruction, but its use in males—in whom arm strength is more important—is subject to debate, although it has been combined with implants in males to correct hypoplasia of the chest wall.[144] Haller and colleagues[145] and Urschel and colleagues,[146] in separate reports published in 1984, combined simultaneous latissimus dorsi muscle flaps with placement of rib grafts or Marlex mesh. The vital components of chest wall repair include correction of the abnormal position and rotation of the sternum, as well as replacement of the aplastic ribs. Haller and colleagues[147] described the frequent carinate deformity of the contralateral ribs, which require resection to optimize results. Resection also allows correction of the depression and rotation of the sternum. Hypoplasia of the ribs without localized depression is not surgically correctable (see Fig. 62-15, *A* to *C*).

## SURGICAL TECHNIQUE

Initial exposure of the chest wall is obtained through a transverse incision, as for pectus excavatum repair (Fig. 62-17, *A*). In patients requiring surgical correction, there is invariably severe depression of the involved side (occasionally with absent ribs) and rotation of the sternum, often producing a carinate protrusion on the contralateral side (Fig. 62-17, *B*). Caution must be used during this dissection when ribs are absent, because there is only a thin layer of attenuated pectoral fascia between the skin flaps and the endothoracic fascia (Fig. 62-17, *C*). Violation of this layer should be avoided to prevent entry into the thoracic cavity.

Subperichondrial resection of the costal cartilages is performed on both sides, removing the entire third, fourth, and fifth cartilages up to the costochondral junctions, which are preserved. Segments of the sixth and seventh costal cartilages are resected to the point where they flatten to join the costal arch. To correct the rotational deformity of the sternum and the depression of the involved ribs, a transverse wedge-shaped osteotomy is placed, as for the mixed pectus carinatum

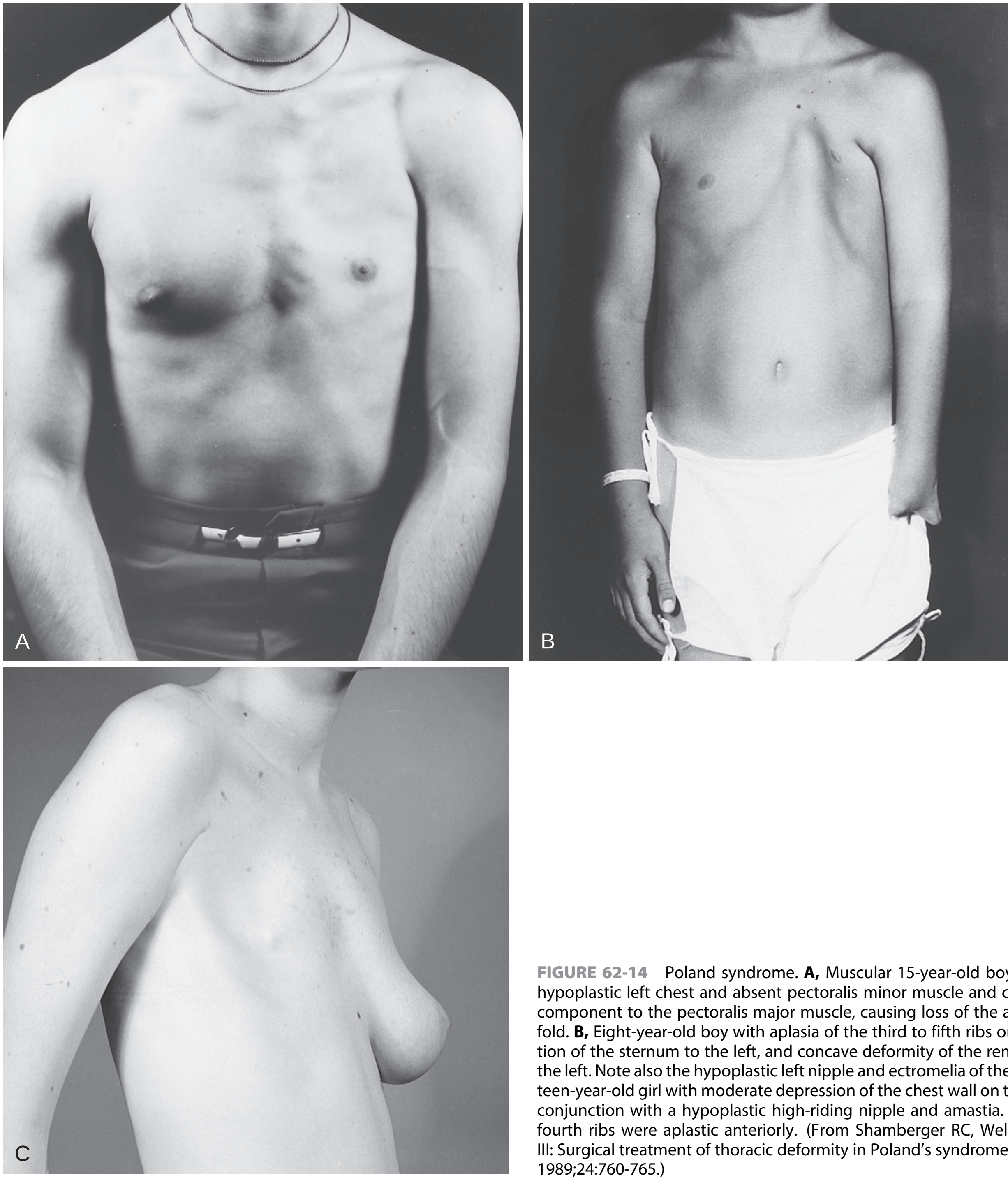



**FIGURE 62-14** Poland syndrome. **A,** Muscular 15-year-old boy with a mildly hypoplastic left chest and absent pectoralis minor muscle and costomanubrial component to the pectoralis major muscle, causing loss of the anterior axillary fold. **B,** Eight-year-old boy with aplasia of the third to fifth ribs on the left, rotation of the sternum to the left, and concave deformity of the remaining ribs on the left. Note also the hypoplastic left nipple and ectromelia of the hand. **C,** Fourteen-year-old girl with moderate depression of the chest wall on the right side in conjunction with a hypoplastic high-riding nipple and amastia. The second to fourth ribs were aplastic anteriorly. (From Shamberger RC, Welch KJ, Upton J III: Surgical treatment of thoracic deformity in Poland's syndrome. J Pediatr Surg 1989;24:760-765.)

deformity (Fig. 62-17, *D*). Closure of this osteotomy corrects both components of the abnormal sternal position. In patients with absence of the second, third, and fourth ribs, a rib graft is harvested from the contralateral fifth or sixth rib through the anterior incision used for the repair; the periosteum is left in situ to allow regeneration of the rib. A split rib graft is generally used to facilitate revascularization of the graft through the marrow cavity. This often achieves correction of the defect with only one harvested rib (Fig. 62-17, *E*). The graft is secured to notches created in the sternum before bringing the sternum anteriorly and to the involved ribs laterally with wire sutures placed through drill holes in the native rib and the graft. The rib grafts can be covered with a prosthetic mesh if further support is needed.

Breast reconstruction is required in most girls, but is best delayed until late puberty to optimize the match between the contralateral and reconstructed breasts. Implants are generally required, often in conjunction with a latissimus dorsi

**TABLE 62-2**

**Chest Wall Deformities in 75 Patients with Poland Syndrome**

| *Deformity* | *No. of Patients* |
|---|---|
| None | 41 |
| Hypoplasia of ribs without depression | 10 |
| Depression deformity of ribs | |
| Major | 11 |
| Minor | 5 |
| Aplasia of ribs | 8 |

From Shamberger RC, Welch KJ, Upton J III: Surgical treatment of thoracic deformity in Poland's syndrome. J Pediatr Surg 1989;24:760-765.

flap. Customized implants have been used that correct both the hypoplasia of the chest wall and the absent breast tissue, but they have not been uniformly successful.[148–151]

### COMPLICATIONS AND OUTCOME

The patient, his or her parents, and the surgeon must enter into correction of this deformity with appropriate expectations. The components of the chest wall deformity must be well defined to identify the correctable factors. Diffuse hypoplasia of the ribs without depression is not correctable. Ipsilateral depression and contralateral protrusion with rotation of the sternum can generally be improved, as can aplasia of the ribs. The concavity below the clavicle created by the hypoplastic pectoralis major muscle is frequently bothersome in girls, because this area is apparent when wearing a bathing suit or gown. It can be partially corrected with rotation of the latissimus dorsi muscle flap at the time of breast reconstruction, but these flaps have been noted to atrophy with time.[144]

## Sternal Defects

Sternal defects are rare compared with pectus excavatum and pectus carinatum, yet they have received a great deal of attention in the medical literature. Indeed, documentation of their occurrence dates to the ancient cuneiform tablets that made up the Royal Library of Nineveh.[1]

Translations of those tablets reveal that the ancients believed that births with "the heart open, and that has no skin" predicted calamity. Dramatic presentations of such defects since that time, particularly involving the naked heart, have led to many isolated case reports in the modern medical literature, as well as several excellent reviews.

Weese provided the first anatomic classification of sternal defects in 1818, dividing them into ectopia cordis cum sterni fissura, ectopia suprathoracica, and ectopia subthoracica.[100] Breschet, in 1826, provided three comparable

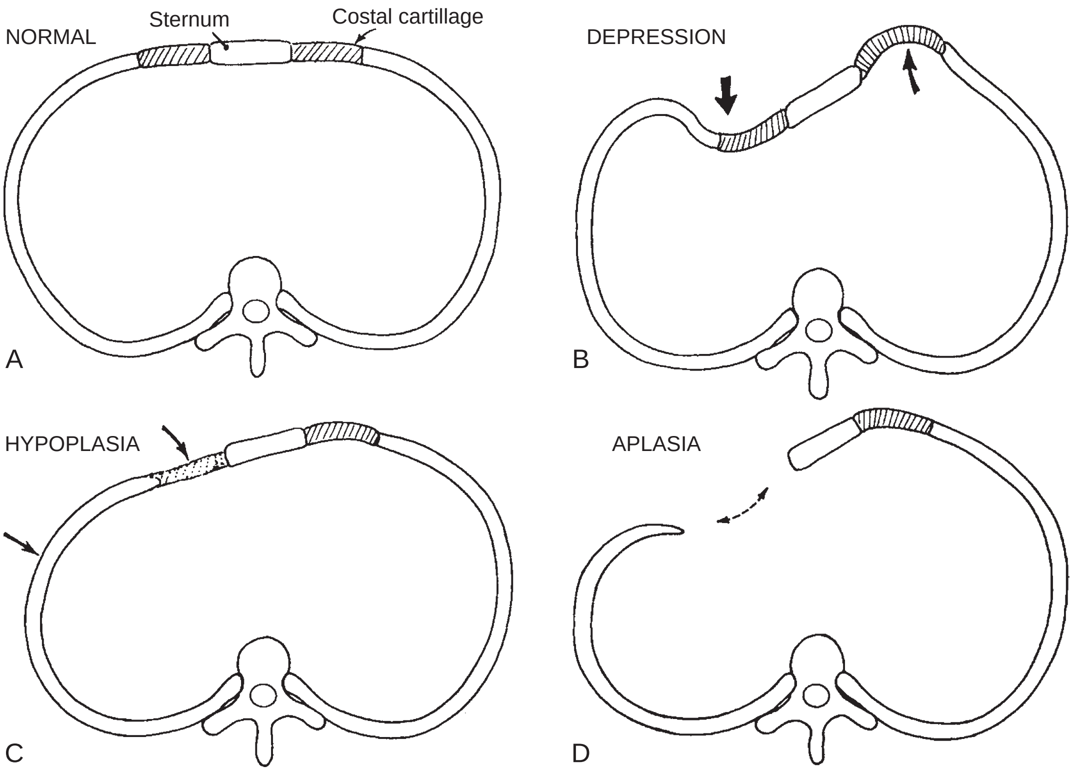



**FIGURE 62-15** Spectrum of rib cage abnormalities seen in Poland syndrome. **A,** Most frequently, the rib cage is normal, with only absent pectoral muscles. **B,** Depression of the involved side of the chest wall, with rotation and often depression of the sternum. A carinate protrusion of the contralateral side is frequently present. **C,** Hypoplasia of ribs on the involved side but without significant depression. This usually does not require surgical correction. **D,** Aplasia of one or more ribs is usually associated with depression of adjacent ribs on the involved side and rotation of the sternum. (From Shamberger RC, Welch KJ, Upton J III: Surgical treatment of thoracic deformity in Poland's syndrome. J Pediatr Surg 1989;24:760-765.)

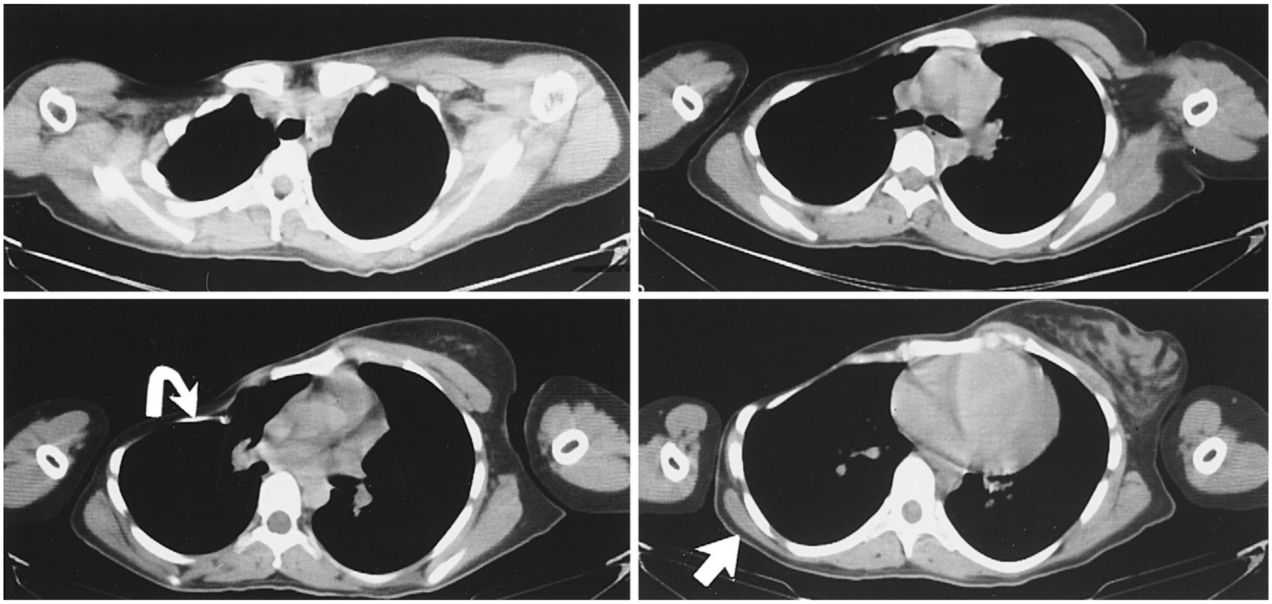


FIGURE 62-16 Computed tomography scan of the patient shown in Figure 62-14, *C*. Marked depression of the ribs is apparent (*curved arrow*), as well as aplasia of the ribs in the lower two frames. Hypoplasia of the latissimus dorsi muscle is also noted on the lower right frame (*straight arrow*). (From Shamberger RC, Welch KJ, Upton J III: Surgical treatment of thoracic deformity in Poland's syndrome. J Pediatr Surg 1989;24:760-765.)

divisions: ectopie thoracique du coeur, ectopie abdominale, and ectopie céphalique.[100] Roth, in 1939, divided these lesions into ectopia cordis thoracalis extrathoracica, ectopia cordis ventralis, and ectopia cordis suprathoracica (cervicalis); the first division was further subdivided into defects in the manubrium, defects in the body of the sternum, and ectopia cordis pectoralis sternoepigastrica.[100] Similarly, Shao-tsu[100] divided sternal defects into ectopia cordis cervicalis, with the heart in the neck; ectopia cordis thoracalis, with the heart outside the thorax and a sternal fissure; ectopia cordis thoracoabdominalis; and ectopia cordis abdominalis.

Despite these classifications, subsequent case reports often blurred the divisions and confused the field that had been so well defined by early authors. One sternal defect that was not accounted for in these classifications was the bifid or cleft sternum. In this deformity, the heart is in an orthotopic position in the thoracic cavity, but the sternum is cleft or only partially fused overlying the heart. Skin coverage is normal or with only a small superficial ulceration.

More than a century after these descriptions and classifications, Cantrell and Ravitch[152] summarized a group of patients with ectopia subthoracica or ectopia abdominale deformity, along with its associated defects of the diaphragm, pericardium, abdominal wall, and heart.

Subsequently, these patients were often referred to as having the Cantrell pentalogy, only adding to the confusion. A more recent report summarized the world literature and tabulated the associated anomalies that occur in these infants and children.[153] Review of this topic provides four basic types of sternal defects based on tissue coverage of the heart, with limited overlap between categories. Further divisions seem artificial and do not clarify the anatomy or have prognostic significance.

## THORACIC ECTOPIA CORDIS

Thoracic ectopia cordis consists of the ectopia cordis cum sterni fissura of Weese and the ectopie thoracique du coeur of Breschet. These lesions constitute the classical naked heart with no overlying somatic structures. The orientation of the apex of the heart is anterior and often superior (Fig. 62-18). Intrinsic cardiac anomalies are frequent, and associated lesions have been summarized.[153] Many case reports do not provide information on the intrinsic cardiac anatomy because of the striking external appearance of the heart. The sternum may be intact superiorly at the manubrium or entirely split; in rare cases, the heart may protrude through a defect in the central portion of the sternum. There is a severe lack of midline somatic tissues, and many attempts at primary closure have failed. Evaluation by CT has confirmed that the intrathoracic cavity is small in these infants.[154] Most successful repairs have not been achieved in true thoracic ectopia cordis but rather in thoracoabdominal ectopia cordis. Cutler and Wilens[155] first attempted repair in 1925 by skin flap coverage, but this failed because of cessation of cardiac function, presumably from pressure on the heart. In more than 29 attempts, only six survivors have been recorded.[156–162] The first successful repair of ectopia cordis was achieved by Koop in 1975, as reported by Saxena.[159] An infant with a normal heart had skin flap coverage at 5 hours of age, with inferior mobilization of the anterior attachments of the diaphragm. The sternal bands were 2 inches apart and could not be approximated primarily without cardiac compression and compromise. At 7 months of age, an acrylic resin of Dacron and Marlex mesh was inserted to widen the sternal cleft, with primary skin closure. Necrosis of the skin flaps complicated the postoperative course, and infection of the prosthetic material necessitated its removal. This child has survived to age 18 years and is reported to be entirely

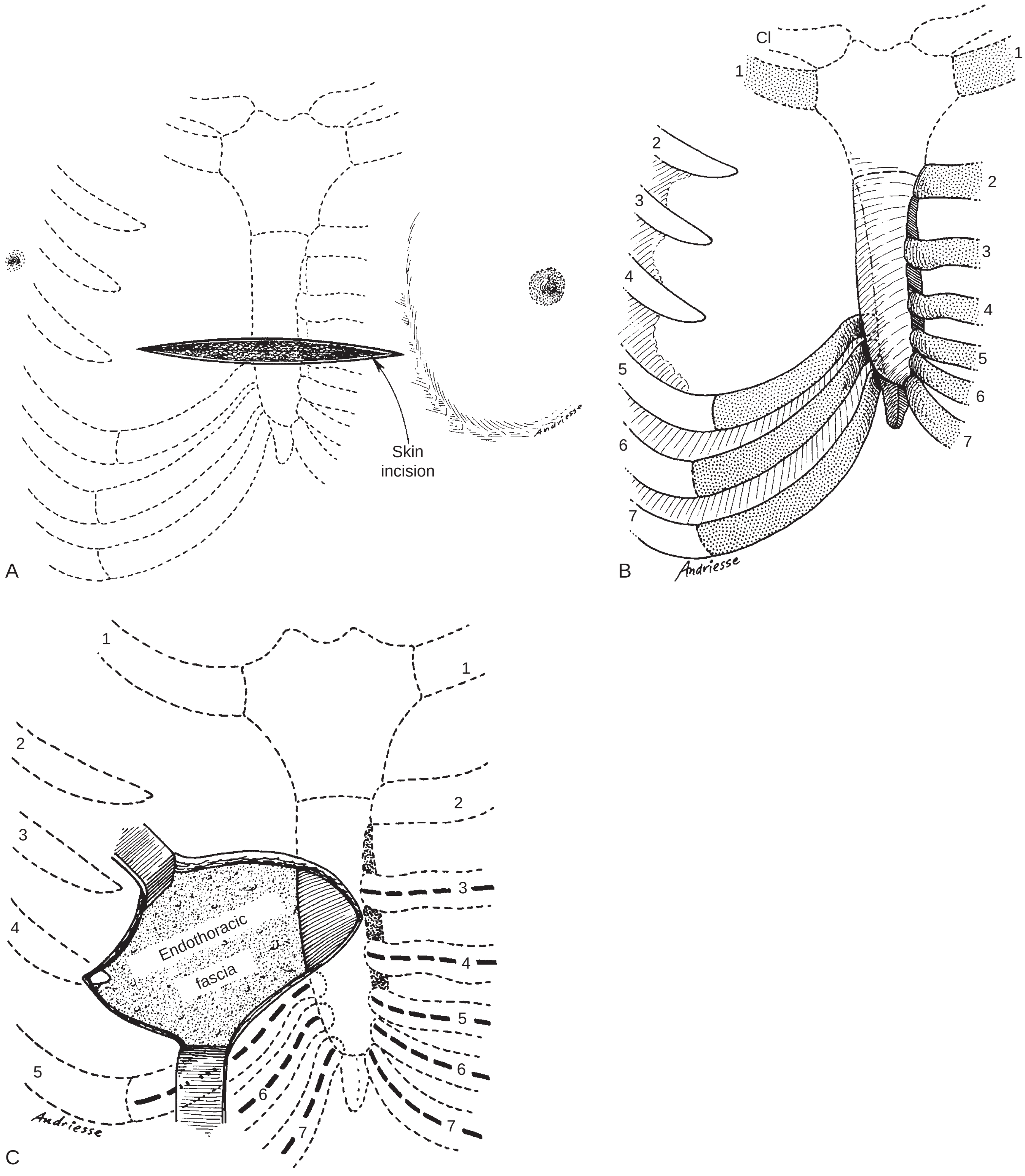
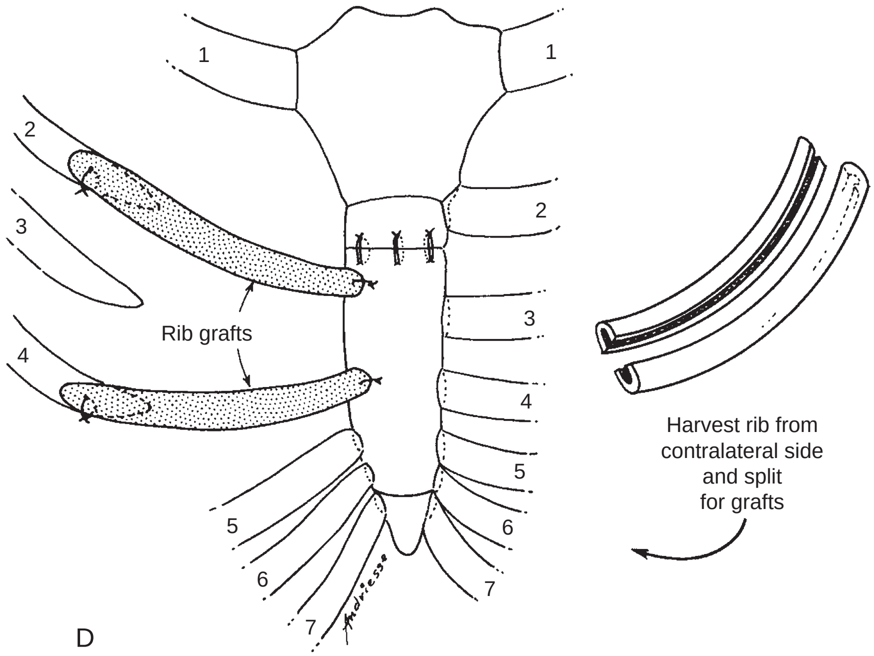



FIGURE 62-17 **A,** A transverse incision is placed below the nipple lines and, in females, in the inframammary crease. **B,** Schematic depiction of the deformity, with rotation of the sternum, depression of the cartilages on the involved side, and carinate protrusion on the contralateral side. **C,** In cases with aplasia of the ribs, the endothoracic fascia is encountered directly below the attenuated subcutaneous tissue and pectoral fascia. The pectoral muscle flap is elevated on the contralateral side and the pectoral fascia, if present, is elevated on the involved side. Subperichondrial resection of the costal cartilages is then carried out, as shown by the *dashed lines*. Rarely, this must be carried to the level of the second costal cartilage.

*Continued*



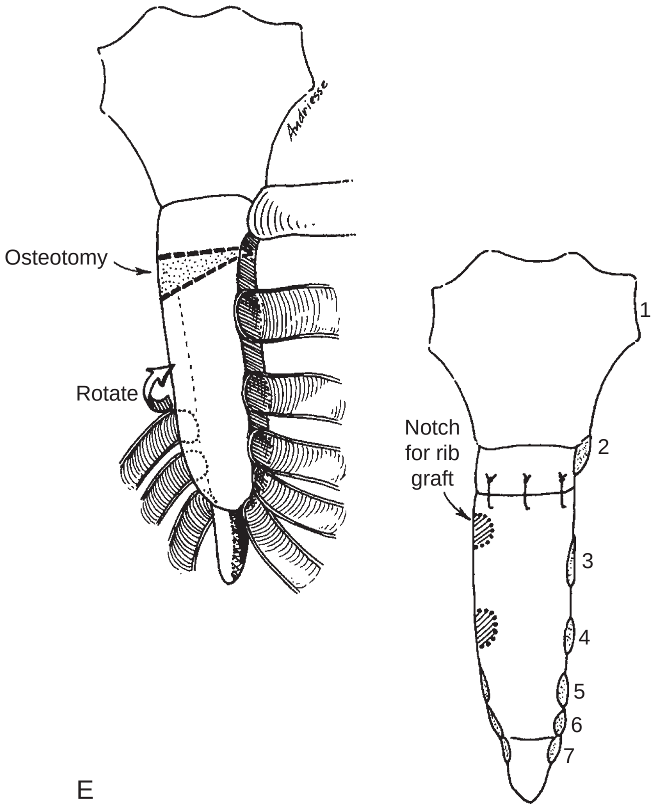




**FIGURE 62-17—CONT'D** **D,** A transverse offset wedge-shaped sternal osteotomy is created below the second costal cartilage. Closure of this defect with heavy silk sutures or by strut support corrects both the posterior displacement and the rotation of the sternum. **E,** In cases with rib aplasia, split rib grafts are harvested and secured medially with wire sutures into previously created sternal notches and with wire to the hypoplastic ribs laterally. Ribs are split as shown along their short axis to maintain maximal mechanical strength. (From Shamberger RC, Welch KJ, Upton J III: Surgical treatment of thoracic deformity in Poland's syndrome. J Pediatr Surg 1989;24:760-765.)

well. The case of Dobell and colleagues[156] is notable, because surgical correction was performed in two stages: skin flap coverage was provided as a newborn, and at 19 months of age, rib strut grafts were placed over the sternal defect and covered with pectoral muscle flaps. The pericardium was divided from its anterior attachments to the chest wall, allowing the heart to fall back partially into the thoracic cavity. The case of Williams, subsequently reported by Amato, was treated by moving

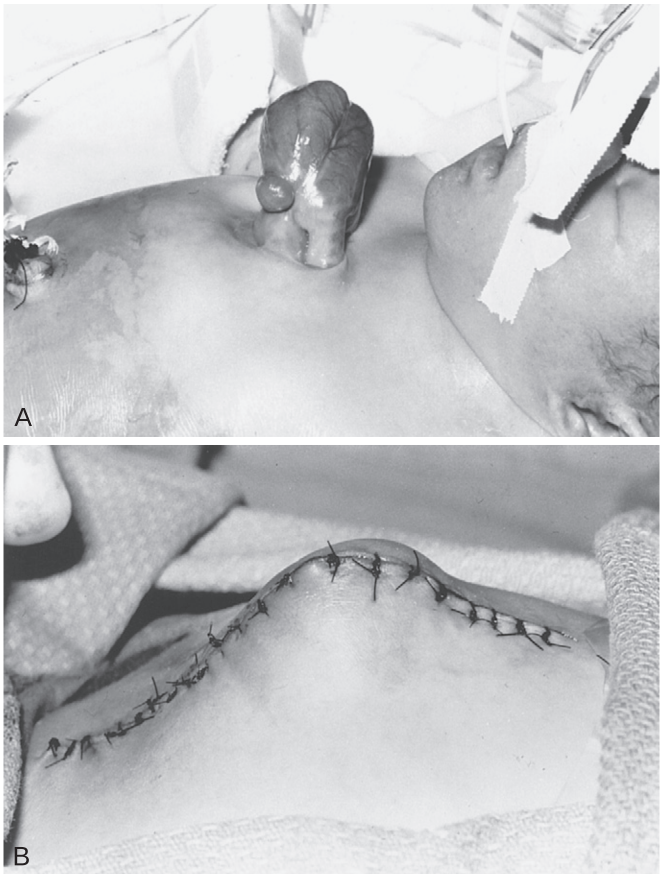



**FIGURE 62-18** **A,** Infant with thoracic ectopia cordis with no significant abdominal wall defect. **B,** Repair by skin flap coverage was achieved by extensive mobilization of the skin flaps laterally on the day of birth. Repair of the intracardiac defect—tetralogy of Fallot with long-gap pulmonary atresia—was achieved later through the skin flaps. (Courtesy Craig W. Lillehei, MD.)

the diaphragm inferiorly in three separate stages while the heart was covered with Silastic.[160] It was then ultimately covered by skin flaps. The child was lost to follow-up at 2½ years of age. Only Amato and colleagues[161] and Morales and colleagues[158] achieved complete soft tissue coverage in one stage. The unifying theme of successful management is the construction of a partial anterior chest cavity surrounding the heart and the avoidance of attempts to return the heart to an orthotopic location (see Fig. 62-12, *B*). Only one case, that of Lillehei and Mayer reported by Hornberger, survived with a significant intrinsic cardiac anomaly, tetralogy of Fallot with pulmonary atresia.[162] At 4 days of age, a left Blalock-Tausig shunt was performed, and the heart was covered with skin flaps. This was followed by a right Blalock-Tausig shunt and pulmonary arterioplasty at 20 months of age, and ultimately, at 2 years of age, a complete repair with an aortic homograft placed between the right ventricle and the pulmonary artery. The ventricular septal defect (VSD) was also closed at that time and the shunts removed. Of note, in the successful cases, intrinsic cardiac lesions and associated abdominal defects were absent, except for the final case and a muscular ventricular septal defect and a ventricular diverticulum in the case of Morales.[158] This characteristic, the absence of significant intrinsic cardiac anomalies, was what distinguished the successful cases from the failures in most cases, rather than any differences in surgical technique. In cases repaired with autologous tissue grafts (bone or cartilage) or synthetic materials, infection and extrusion of the graft invariably occur. Ultimate success can be achieved only with tissue coverage over the displaced heart that avoids posterior compression of the heart into an already limited thoracic space. This type of coverage may require the use of tissues from sites distant from the anterior chest wall or extensive mobilization of local tissues. The severe intracardiac defects associated with thoracic ectopia cordis also make achieving ultimate survival difficult. Regrettably, the only advancement in management of this lesion has been prenatal ultrasonographic identification, including definition of the intracardiac lesions and termination of the pregnancy if desired by the parents.[163]

Upper abdominal wall defects are also frequent in these patients, including upper abdominal omphalocele, diastasis recti, and rarely, eventration of the abdominal viscera. The presence of abdominal wall defects in conjunction with thoracic ectopia cordis should not, however, lead to the classification of these lesions as thoracoabdominal ectopia cordis; this term should be reserved for cases in which the heart is covered at birth.

## CERVICAL ECTOPIA CORDIS

Cervical ectopia cordis (ectopia suprathoracica of Weese and ectopie céphalique of Breschet) has historically been defined as a separate entity from thoracic ectopia cordis, based on the extent of superior displacement of the heart. Fusion between the apex of the heart and the mouth is often present, as are severe craniofacial anomalies. This lesion is relatively rare compared with thoracic ectopia cordis, but patients share the same dismal prognosis. In the summary of Shao-tsu, only five infants were classified with cervical ectopia cordis, whereas 121 infants had the thoracic variety.[100] No survivors or attempts at closure in this group of severely deformed infants have been reported.

## THORACOABDOMINAL ECTOPIA CORDIS

Thoracoabdominal ectopia cordis includes those lesions classified as ectopia subthoracica by Weese and ectopie abdominale by Breschet. It combines the rather artificial divisions of ectopia cordis thoracalis extrathoracica sternoepigastrica and ectopia cordis ventralis of Roth and the ectopia cordis thoracoabdominalis and ectopia cordis abdominalis of Shao-tsu. In this group, the heart is covered by a membrane of thin, often pigmented skin with an overlying, inferiorly cleft sternum (Fig. 62-19). The heart lacks the severe anterior rotation present in thoracic ectopia cordis. A 1798 report of this lesion by Wilson[157] clearly defined the associated somatic defects of the abdominal wall, diaphragm, and pericardium, as well as the intrinsic cardiac anomalies, more than 150 years before the reviews by Major[164] and Cantrell and Ravitch.[153] These patients almost invariably have associated abdominal wall defects (omphalocele, diastasis recti, or ventral hernia), along with anterior semilunar defects in the diaphragm and pericardium. Intrinsic cardiac lesions are frequently present in

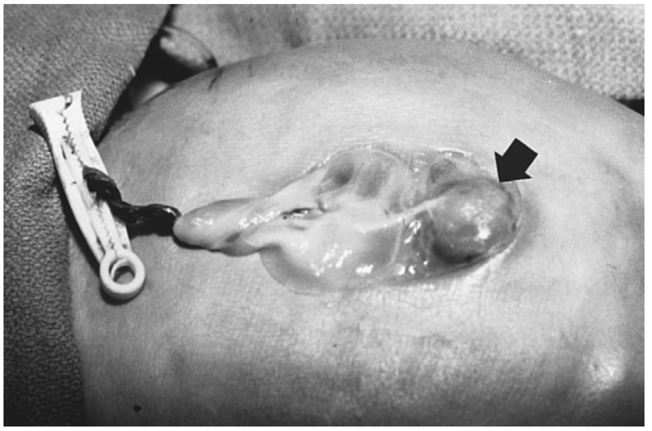


FIGURE 62-19 Infant with thoracoabdominal ectopia cordis, demonstrating a small abdominal wall defect covered by an omphalocele below the costal arch. The infant's head is to the right, and the heart (*arrow*) is visible just below the superior margin of the defect, covered by a thin membrane. Primary skin closure was achieved during the initial operation, with subsequent repair of the cardiac defect.

these patients and have been summarized.[153] The position of the heart varies; it may lie within the thoracic cavity, with only the diaphragmatic and pericardial defect below it, or it may reside entirely within the abdominal cavity, with the major vessels extending through the defect in the diaphragm. Diverticula of the left ventricle occur with surprising frequency in this anomaly. In many cases, the diverticulum protrudes through the diaphragmatic and pericardial defect into the abdominal cavity. Successful repair and long-term survival are more frequent in thoracoabdominal ectopia cordis than in thoracic ectopia cordis. Arndt[165] attempted the first repair in 1896, but return of the heart to the thoracic cavity resulted in death.

Wieting[166] performed the first successful surgical repair with primary closure of the diaphragm and abdominal wall fascia in 1912. Initial surgical intervention must address the skin defects overlying the heart and abdominal cavity. Primary excision of the omphalocele with skin closure is preferred to avoid infection and mediastinitis, although several cases have been managed successfully by local application of topical astringents, allowing secondary epithelialization to occur. Several early cases document the viability of individuals with thoracoabdominal ectopia cordis when there is intact skin coverage over an intra-abdominal heart.

Advances in pediatric cardiac surgery now allow correction of the intrinsic cardiac lesions that were often fatal in the past. An aggressive approach in these infants is appropriate. Closure of the abdominal wall defect or diastasis can be managed by either primary closure of the defect or prosthetic mesh closure. Primary closure is often difficult to achieve because of the wide distance between the two rectus muscles, which are attached superiorly to the splayed costal arches, limiting midline mobility.[167] The costal cartilages are divided laterally in one modification of closure, allowing them to rotate medially.[165] Complete repair of the intracardiac defect is best performed before placement of any prosthetic material over the heart. Once skin coverage is achieved, closure of this defect is important, primarily for mechanical protection of the heart. Fatal pulmonary hypoplasia has occurred in some infants with this anomaly.[153]

## CLEFT OR BIFID STERNUM

Cleft or bifid sternum is the fourth and least severe anomaly of the sternum. Infants in this group have an orthotopic heart, normal skin coverage, an intact pericardium, and a partially or completely cleft sternum (Fig. 62-20). Omphalocele is not associated with cleft sternum. The sternal defect, if partial, involves the upper sternum and manubrium, in contrast with the sternal defect in thoracic or thoracoabdominal ectopia cordis, in which partial defects involve primarily the lower sternum. Most cases are partially split (Table 62-3), with an intact xiphoid or lower third of the body of the sternum.

The bifid or cleft sternum is distinct from the other three categories of sternal defects, in that intrinsic cardiac defects are rare. Several distinct somatic associations are seen, including bandlike scars extending from the umbilicus to the inferior aspect of the sternal defect. Other children have superior scarlike extensions to the neck or mandible; rarely, a split mandible occurs (gnathoschisis). Fischer[77] reported an unexplained association with cervicofacial hemangiomas in 1879, and Ingelrans and Debeugny[166,168] later reported the occurrence of fatal postoperative hemorrhage from presumed hemangioma of the trachea after repair of a sternal defect.

In most cases, these infants' sternal defects are asymptomatic. Repair is performed to provide protective coverage for the heart. It may also improve respiratory mechanics, which are compromised by the paradoxical motion of the defect. Lannelongue,[157] in 1888, was allegedly the first to repair a cleft sternum, but his intervention was limited to excision of a small circular ulcer overlying the sternal defect. He created two relaxing incisions laterally, allowing primary closure of the skin, but ignored the underlying sternal separation. The first complete repair of a cleft sternum was accomplished by placing a cartilage graft from the costal arch over the defect.[169]

Maier and Bortone[170] achieved the first primary closure in 1949 in a 6-week-old infant. Subsequent methods have included bilateral oblique incisions through the costal cartilages to produce greater length and allow midline approximation of the sternal halves (sliding chondrotomies of Sabiston[171]; division of the cartilages laterally, swinging them medially to cover the defect (door-wing plasty of Meissner)[172]; rotation of the posterior sternal perichondrium to close the medial defect, followed by chondral grafts[173]; coverage with various autologous grafts (costal cartilage, rib, parietal skull); and coverage with prosthetic materials. Maier and Bortone[170] first stressed the importance of early repair in infancy, when the chest is most flexible, to achieve primary closure (Fig. 62-21). In most reported cases of primary repair, correction took place within the first 3 months of life (18 of 22 cases) and rarely after 1 year of age (2 cases).[153] In contrast, some form of chondrotomy was required in 22 patients, 8 of whom were older than 1 year. Often a wedge of cartilage must be excised from the point where the two sternal halves unite to allow approximation without tension.


FIGURE 62-20 Six-week-old infant with bifid sternum. Note the marked protrusion from the defect when crying (**A**) and depression of the defect with inhalation (**B**). Capillary hemangiomas are also visible on the lips.

**TABLE 62-3**
**Sternal Defects in 109 Patients with Cleft Sternum**

| *Defect* | *No. of Patients* |
|---|---|
| Upper cleft | 46 |
| Upper cleft to xiphoid | 33 |
| Complete cleft | 23 |
| Lower defect with manubrium or midsegment intact | 5 |
| Central defect with manubrium and xiphoid intact | 2 |
| Skin ulceration noted in only 3 cases | |

From Shamberger R, Welch KJ: Sternal defects. Pediatr Surg Int 1990;5:156-164.

# Thoracic Deformities in Diffuse Skeletal Disorders

## ASPHYXIATING THORACIC DYSTROPHY: JEUNE SYNDROME

In 1954, Jeune and colleagues[174] described a newborn with a narrow, rigid chest and multiple cartilage anomalies. The patient died early in the perinatal period because of respiratory insufficiency.

Subsequent authors further characterized this form of osteochondrodystrophy, which has variable skeletal involvement. It is inherited in an autosomal recessive pattern and has now been associated with several genetic alterations.[175,176] Its most prominent feature is a narrow, bell-shaped thorax and protuberant abdomen. The thorax is narrow in both the transverse and the sagittal axes and has little respiratory motion because of the horizontal direction of the ribs (Fig. 62-22). The ribs are short and wide, and the splayed costochondral junctions barely reach the anterior axillary line. The costal cartilage is abundant and irregular, similar to a rachitic rosary. Microscopic examination of the costochondral junction reveals disordered, poorly progressing endochondral ossification resulting in decreased rib length.

Associated skeletal abnormalities that occur with this syndrome include short, stubby extremities with relatively short and wide bones. The clavicles are in a fixed and elevated position, and the pelvis is small and hypoplastic with square iliac bones.

This syndrome has variable expression and extent of pulmonary impairment. Although the initial cases reported resulted in neonatal deaths, subsequent reports document a wide range of survival in patients with this syndrome.[177,178] The pathologic findings at autopsy are variable, showing a spectrum of abnormal pulmonary development, which may

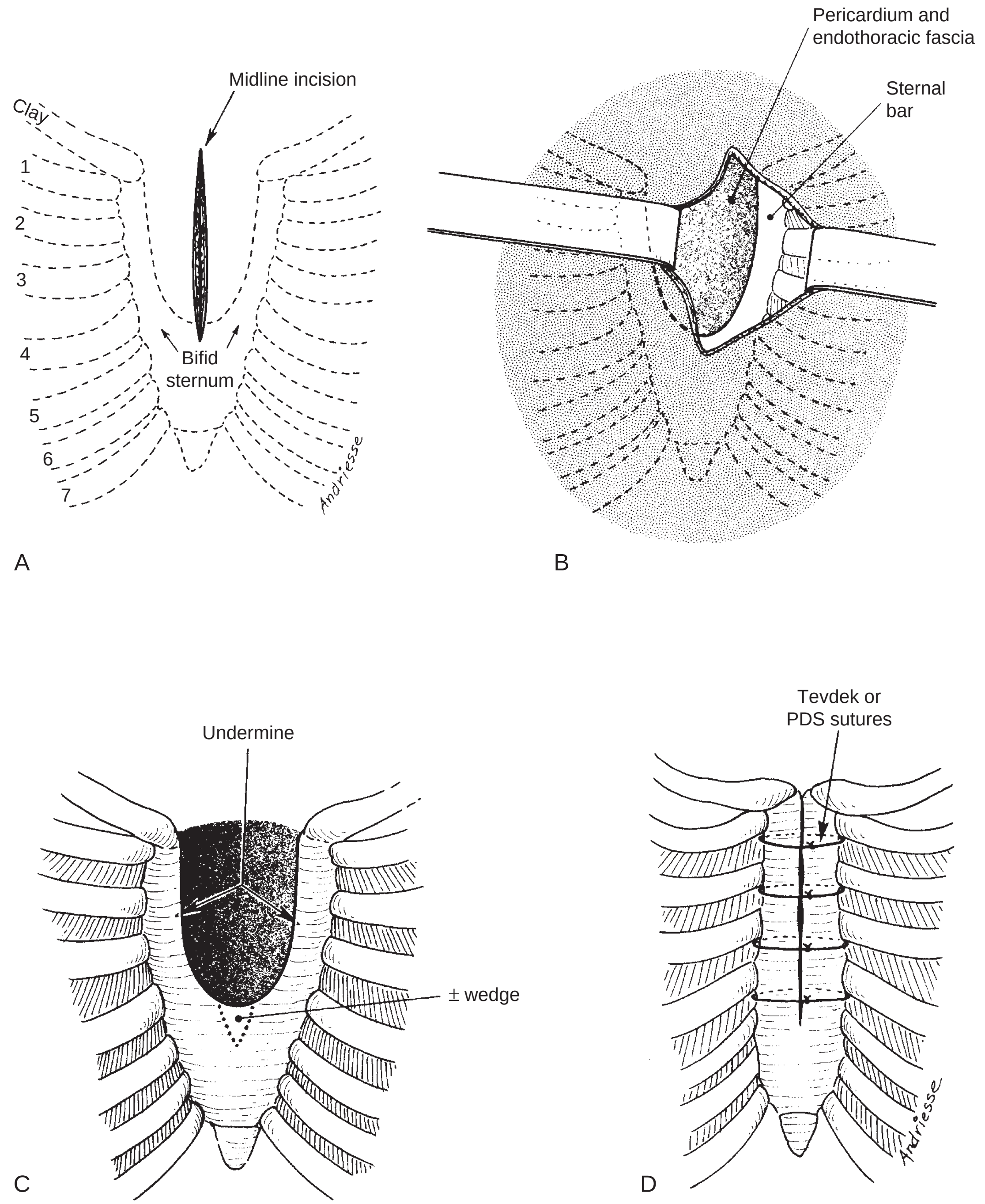



**FIGURE 62-21** **A,** Repair of bifid sternum is best performed through a longitudinal incision extending the length of the defect. **B,** Directly beneath the subcutaneous tissues, the sternal bars are encountered, with pectoral muscles present lateral to the bars. The endothoracic fascia and pericardium are just below these structures. **C,** The endothoracic fascia is mobilized off the sternal bars posteriorly with blunt dissection, to allow safe placement of the sutures. Approximation of the sternal bars may be facilitated by excising a wedge of cartilage inferiorly. Repair is best accomplished in the neonatal period, when there is greatest flexibility of the chest wall. **D,** Closure of the defect is achieved with nonabsorbable sutures. (From Shamberger RC, Welch KJ: Sternal defects. Pediatr Surg Int 1990;5:156-164.)

account for the variable survival. In most cases, however, bronchial development is normal, with fewer alveolar divisions, as described by Williams and colleagues[179] Surgical attempts to enlarge the thoracic cavity are generally unsuccessful and result in prolonged hospitalization and ultimate respiratory failure and death.

Initial attempts were made to divide the sternum with insertion of graft material to increase the diameter of the thoracic cavity. Subsequent reports describe an “expander” placed between the sternal halves.[180] Later, division of the costal cartilages laterally with overlapping of them to broaden the chest wall (lateral thoracic expansion) has been used as

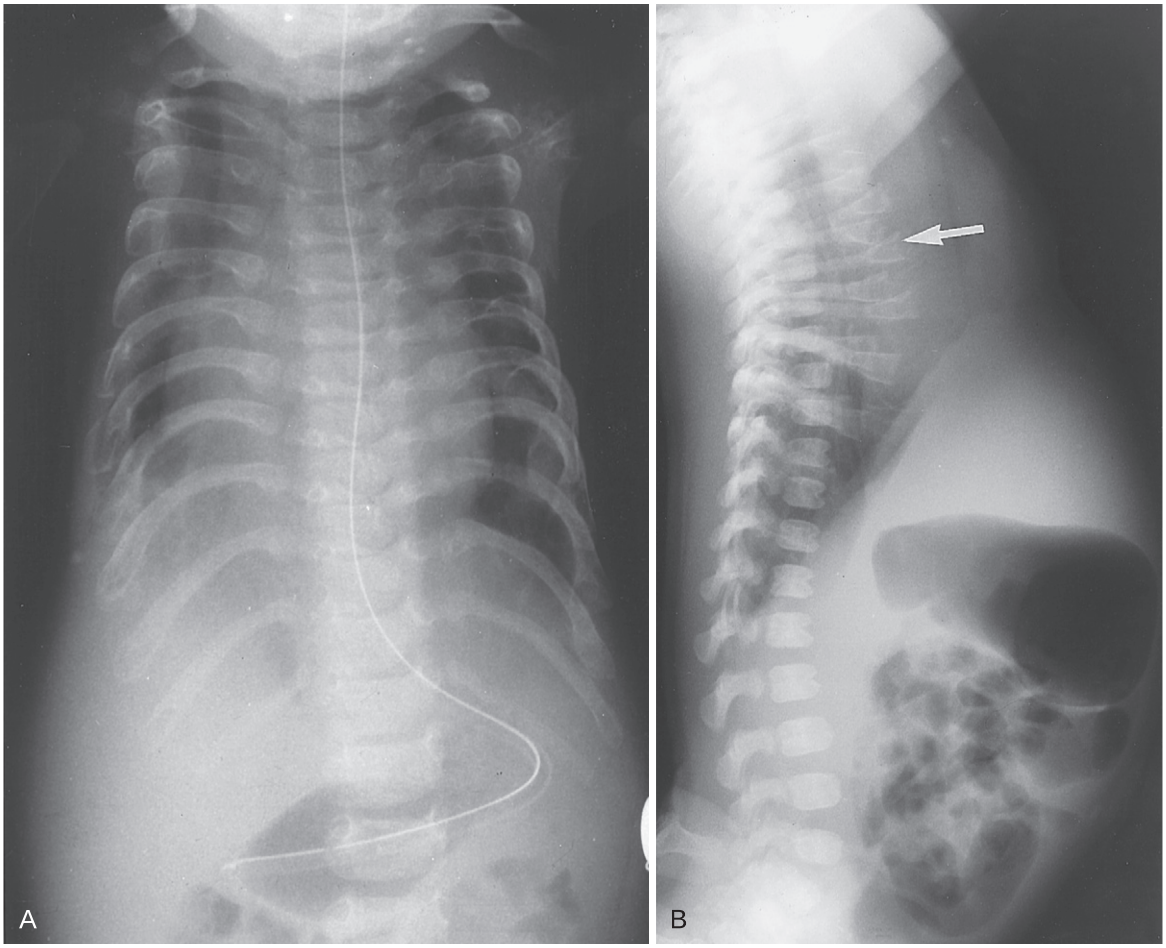



**FIGURE 62-22** **A,** Anteroposterior radiograph shows the short horizontal ribs and narrow chest of an infant with Jeune syndrome (asphyxiating thoracic dystrophy). **B,** Lateral radiograph demonstrates the short rib ends ending at the midaxillary line (*arrow*) and abnormal flaring at the costochondral junction. The infant died of progressive respiratory insufficiency at 1 month of age, and postmortem examination revealed alveolar hypoplasia. (From Shamberger RC: Chest wall deformities. In Shields TW [ed]: General Thoracic Surgery, ed 5. Philadelphia, Lippincott Williams & Wilkins, 2000.)

well, but both of these methods fail to provide progressive enlargement of the chest cavity as the infant grows.[181,182] More recently, use of the vertical expandable prosthetic titanium rib (VEPTR) has been reported in two children with Jeune syndrome.[183] A high-radius curvature device was used to distract the chest wall outward to increase the thoracic volume. The ribs were attached to the device using titanium wire so that the ribs could be distracted laterally. One child with Jeune syndrome, who had carbon dioxide retention, was improved after surgery. No information is available as to how these children have done long-term (Fig. 62-23).

## SPONDYLOTHORACIC DYSPLASIA: JARCHO-LEVIN SYNDROME

Spondylothoracic dysplasia is an autosomal recessive deformity described by Jarcho and Levin[184] in 1938 that is associated with multiple vertebral and rib malformations. Death often occurs in early infancy from respiratory failure and pneumonia. Patients have multiple alternating hemivertebrae that affect most, if not all, of the thoracic and lumbar spine. The vertebral ossification centers rarely cross the midline. Multiple posterior fusions of the ribs and remarkable shortening of the thoracic spine result in a crablike radiographic appearance of the chest (Fig. 62-24). One third of patients with this syndrome have associated malformations, including congenital heart disease and renal anomalies. Heilbronner and Renshaw[185] reported its occurrence primarily in Puerto Rican families. Bone formation is normal in these patients.

The thoracic deformity is secondary to the spinal anomaly, which results in close posterior approximation of the origin of the ribs. Most infants with this entity succumb before 15 months of age, and no surgical efforts have been proposed or attempted.[186]

## CEREBROCOSTOMANDIBULAR SYNDROME

The association of severe rib defects, micrognathia, and other anomalies was first described by Smith and colleagues[187] in 1966 and later by McNicholl and colleagues.[188] Infants with

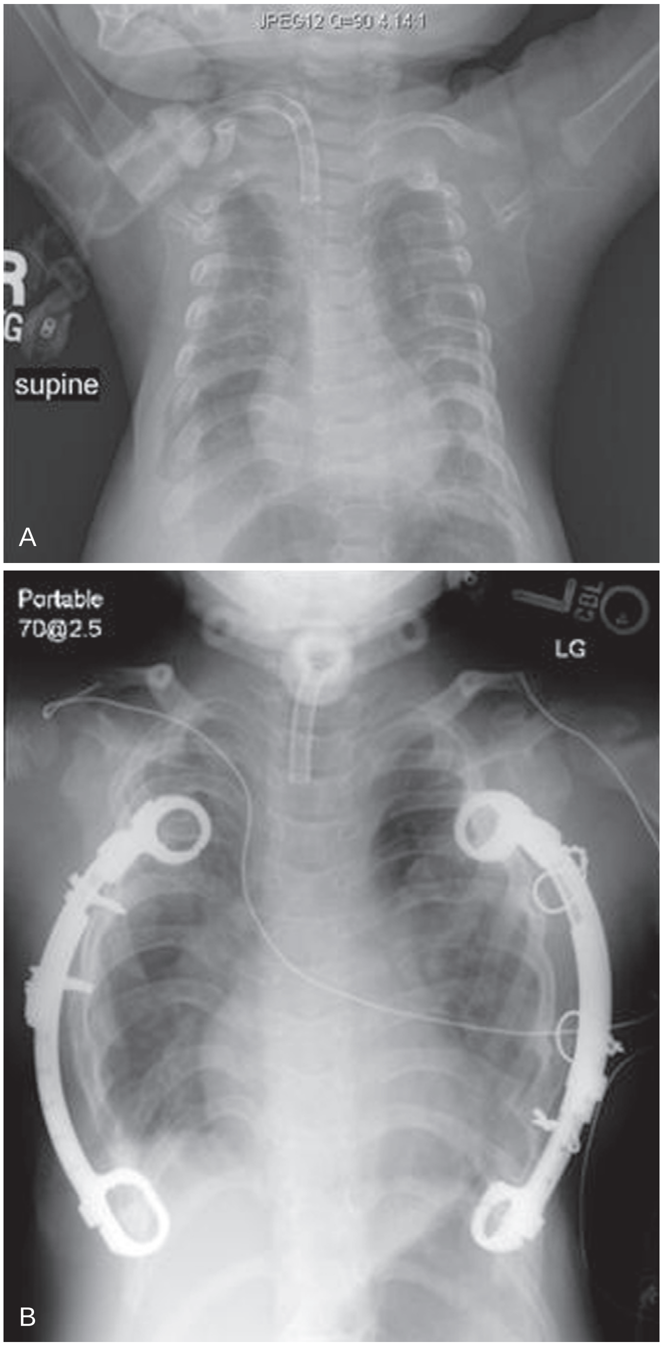



FIGURE 62-23 Vertical expandable prosthetic titanium rib device (VEPTR) in a patient with Jeune syndrome. Preoperative (**A**) and postoperative (**B**) radiographs of a child who required 24-hour ventilatory support before surgery and only nocturnal ventilation after repair. (Courtesy John H.T. Waldhausen, MD.)

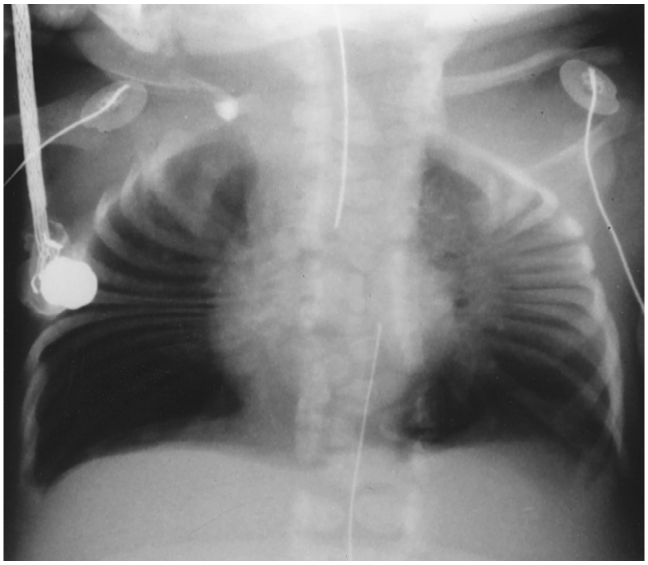


FIGURE 62-24 Chest radiograph of an infant with spondylothoracic dysplasia. Severe abnormality of the spine is apparent, with multiple alternating hemivertebrae and the crablike ribs. (From Shamberger RC: Chest wall deformities. In Shields TW [ed]: General Thoracic Surgery, ed 5. Philadelphia, Lippincott Williams & Wilkins, 2000.)

this constellation of anomalies have ossified ribs with an aplastic segment a short distance beyond the posterior rib angles. They also have micrognathia, abnormal tracheal cartilage, and defects of the soft and hard palates. Mild to moderate mental retardation occurs in 50% of infants surviving beyond the first year of life.[187] The extent of rib defects is variable, both in the number of involved ribs and in the extent of the defect, ranging from a narrow gap to a rudimentary rib. The third to seventh ribs are most frequently involved. The rib gap may contain fibrous tissue, skeletal muscle, or cartilage with variable calcification. The rib gaps produce a flail chest, and the prognosis for these infants is poor. Forty percent die from respiratory failure during the first year of life.[185] The underlying cause and the inheritance pattern are not known, and chromosomal studies are normal.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 63

# Congenital Diaphragmatic Hernia and Eventration

Charles J. H. Stolar and Peter W. Dillon

## History

The earliest English language description of the gross anatomy and pathophysiology associated with congenital diaphragmatic hernia (CDH) in a newborn was by McCauley, an associate of Hunter, as reported in the Proceedings of the Royal College of Physicans, 1754[1]:

> The child was born in the lying-in-hospital in Brownlow Street on the 24th of August, 1752: and was a fully grown boy, remarkably fat and fleshy. He was the fifth child of a healthy young woman who was well during her pregnancy. The child, when first born, started and shuddered; so that the nurse apprehended his going into fits. He breathed also with difficulty and it was some time before he could cry; which when he did, there was something peculiar in its note. He seemed to revive a little in about half an hour and breathed more freely: but soon relapsed and died before he was quite an hour and a half old. Being informed of these particulars by the mother, the matron, and the nurse, I was desirous of examining the body. . . .? I laid open the abdomen and found none of the intestines were contained in that cavity except part of the colon which was distended with meconium. Before I proceeded further with the dissection I sent to acquaint my ingenious friend, Dr. Hunter. We together dissected and examined this curious subject: and at the same time committed to writing the most remarkable appearances.
>
> When the sternum was raised, the stomach with the greatest part of the intestines, with the spleen, and part of the pancreas were found in the left cavity of the thorax; having been protruded through a discontinuation, or rather an aperture of the diaphragm, about an inch from the natural passage of the esophagus.
>
> From the extraordinary bulk of the parts contained in the left side of the thorax, the mediastinum, the heart, the esophagus, and the descending aorta were forced a considerable way to the right side of the thorax; because there was not the least mark of rupture or inflammation about the edges of the chasm: and because it is probable that the diminished size of the left lobes of the lungs, and the heart and mediastinum being pushed to the right side, were gradually affected by the bulk and increase of the viscera.
>
> As the esophagus was pushed to the right side by the stomach and the bowels, in the cavity of the thorax it kept the same course and pierced the diaphragm not in the usual place, but considerably further to the right side: and the aperture through which it passed was backwards and to the right side with respect to that for the vena cava.
>
> I have preserved the heart and lungs to show the disproportioned sizes of the lobes. And I have dried and prepared the diaphragm with its connections to the vertebrae and sternum to show the preternatural aperture through which the bowels passed into the thorax; as also the passage of the esophagus to the right side of the diaphragm. These preparations were at the same time shown to the Society.

Cooper,[2] in 1827, and Laennec,[3] in 1834, not only reported clinical descriptions and gross pathology of CDH but also suggested that laparotomy might be the proper approach for reduction and correction of the hernia. Bowditch,[4] in 1847, was the first to make the bedside diagnosis of CDH and further emphasized the clinical criteria for diagnosis. Although Bochdalek's understanding of the embryology was incorrect, this congenital defect continues to carry his name.[5] He speculated that the hernia resulted from a posterolateral rupture of the membrane separating the pleuroperitoneal canal into two cavities. He also incorrectly speculated that the best way to repair the defect was through the bed of the 12th rib. The record is not clear as to whether this was actually attempted. The earliest, although unsuccessful, efforts to repair CDHs were by Nauman,[6] in 1888, and O'Dwyer, in 1890.[7] The first reports of successful repairs were in an adult by Aue,[8] in 1901, and a child by Heidenhain,[9] in 1905.

The groundwork for treating CDH in the newborn period was laid by Hedblom,[10] whose review of the reported cases as of 1925 showed that 75% of 44 infants diagnosed in the newborn period died. He suggested that earlier intervention might improve survival. Successful repair of CDH remained rare until 1940, when Ladd and Gross[11] reported 9 of 16 patients surviving operative repair, the youngest being 40 hours old. It was not until 1946 that Gross[12] reported survival of the first infant younger than 24 hours old after operative repair of the defect. Until the 1980s, the standard of care remained immediate neonatal surgery followed by postoperative resuscitative therapy (Fig. 63-1).

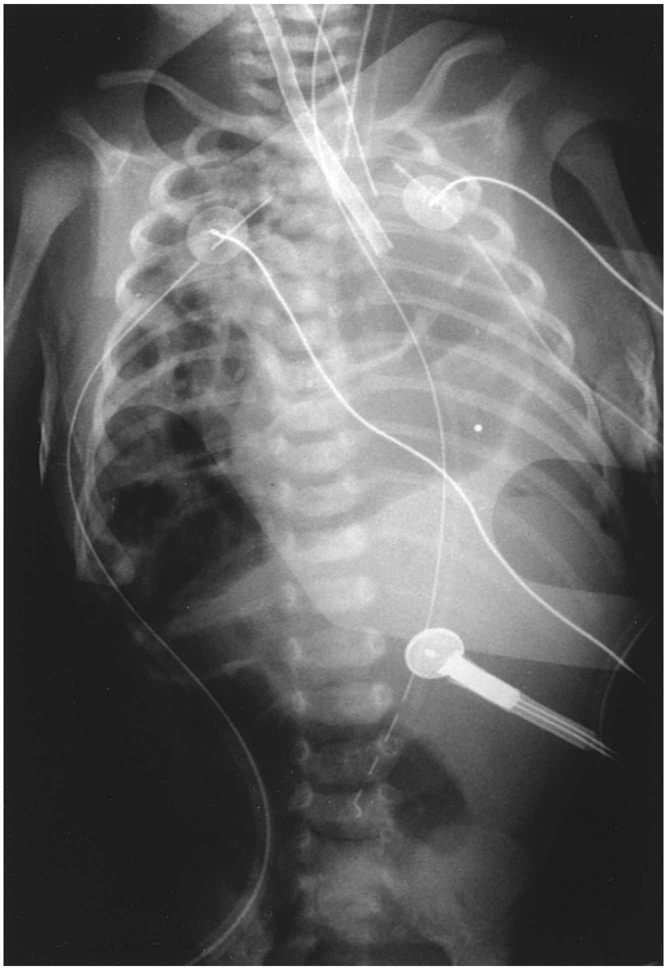


**FIGURE 63-1** Chest radiograph of an infant with a right-sided congenital diaphragmatic hernia demonstrating air-filled loops of intestine in the right hemithorax with contralateral displacement of the mediastinum. The infant has been cannulated for venoarterial extracorporeal membrane oxygenation.

## Epidemiology and Genetics

The reported incidence of CDH is estimated to be between 1 in 2000 to 5000 births. In the United States, approximately 1000 infants per year are affected with this condition, and in a recent study from Atlanta the birth prevalence was found to be 2.4 per 10,000 births.[17] The incidence in stillborns is less well documented. Approximately one third of infants with CDH are stillborn, but these deaths are usually the result of associated fatal congenital anomalies.[18–20] When stillborns are counted with live births, females appear to be more commonly afflicted than males.[13,21,22]

Defects are more common on the left side, with approximately 80% being left sided and 20% right sided. Bilateral CDH defects are rare and have a high incidence of associated anomalies.[103] Infants with isolated CDH are more likely to be premature, macrosomic, and male; and about one third of affected infants may have associated major defects.[24,25] Women who are thin or underweight for their height may have an increased risk of having an infant with an isolated CDH.[26] CDH is thought to represent a sporadic developmental anomaly, although a number of familial cases have been reported.[13,27–31] The expected recurrence risk in a first-degree relative has been estimated to be 1 in 45, or approximately 2%.[30] Structural chromosomal abnormalities have been identified in 9% to 34% of CDH infants and include trisomies, deletions, and translocations.[32] Specific chromosomes with deleted or translocated genes may be candidate loci for CDH development.[33,34] The combination of CDH and an abnormal karyotype has been associated with a poor outcome.[32,35,36]

The cause of CDH is unknown. As with other embryopathies, there is increasing evidence that CDH may be due to the exposure of genetically predisposed or susceptible individuals to environmental factors. Exposure to a number of pharmacologic agents and environmental hazards has been implicated in its development. These include insecticides and drugs, such as phenmetrazine, thalidomide, quinine, cadmium, lead, and nitrofen.[37–40] The clinical findings of vitamin A deficiency in CDH infants and the effects of vitamin A administration in nitrofen-induced pulmonary hypoplasia have strengthened the evolving hypothesis that alterations in retinoid-regulated target genes may be responsible for CDH development.[41]

## Associated Anomalies

Any newborn with a major congenital anomaly, including infants with CDH, has an increased incidence of an additional malformation compared with the general population. Although previously thought to be low, the incidence of associated malformations in infants with a CDH ranges from 10% to 50%.[42–46] Skeletal defects have been noted in as many as 32% of CDH infants and include limb reduction and costovertebral defects.[44,45,47] Cardiac anomalies have been found in 24% of infants.[48] Cardiac hypoplasia involving the left ventricle and often associated with hypoplasia of the aortic arch is frequently described and can be confused with hypoplastic heart syndromes. However, the clinical significance is limited. Most cardiovascular malformations involve the cardiac outflow tract, such as ventricular septal defects, tetralogy of Fallot, transposition of the great vessels, double outlet right ventricle, and aortic coarctation.[25,28,48–51] Anatomic anomalies of the tracheobronchial tree have been found in 18% of patients with CDH and include congenital tracheal stenosis, tracheal bronchus, and trifurcated trachea.[45] The incidence of associated malformations in stillborn infants with CDH is even higher. In one study, 100% of stillborn infants with CDH had associated lethal anomalies.[16,22] Abnormalities noted in this stillborn group were predominantly neural tube defects and included anencephaly, myelomeningocele, hydrocephalus, and encephaloceles. Even in infants who survive to birth but die shortly thereafter, neural tube defects were the most common malformations noted. Cardiac defects were the second most common group and included ventriculoseptal defects, vascular rings, and coarctation of the aorta.[51] Other midline developmental anomalies have also been reported and include esophageal atresia, omphalocele, and cleft palate. A number of syndromes have a CDH as a pathologic finding. These include trisomy 21, 18, and 13, and syndromes such as Frey, Beckwith-Wiedemann, Goldenhar, Coffin-Siris, Fryns, Meacham, and Kabuki.[23,35,50,53–55]

# Embryology

## DIAPHRAGMATIC DEVELOPMENT

The embryologic development of the diaphragm remains incompletely understood and involves multiple, complex cellular and tissue interactions. The fully developed diaphragm is derived from four distinct components: (1) the anterior central tendon forms from the septum transversum, (2) the dorsolateral portions form from the pleuroperitoneal membranes, (3) the dorsal crura evolve from the esophageal mesentery, and (4) the muscular portion of the diaphragm develops from the thoracic intercostal muscle groups. The precursors of diaphragmatic structure begin to form during the fourth week of gestation with the appearance of the peritoneal fold from the lateral mesenchymal tissue. At the same time, the septum transversum forms from the inferior portion of the pericardial cavity. The septum transversum serves to separate the thoracic from the abdominal cavities and eventually forms the central tendinous area of the fully developed diaphragm. It defines the rudimentary pleuroperitoneal canals and allows for the establishment of mesenchymal tissue within these canals that ultimately results in pulmonary parenchymal development.[56]

Closure of the pleuroperitoneal canals with the formation of a pleuroperitoneal membrane occurs during the eighth week of gestation. Several theories have been proposed to explain the formation of this membrane and the subsequent development of a diaphragmatic structure. Progressive growth of the pleuroperitoneal membrane has been one mechanism proposed for canal closure.[57–59] Other researchers have postulated that concurrent hepatic and adrenal organogenesis is crucial to this process.[7a,59,60,71] The involvement of a posthepatic mesenchymal plate in diaphragmatic formation has been proposed.[61]

The pleuroperitoneal folds extend from the lateral body wall and grow medially and ventrally until they fuse with the septum transversum and dorsal mesentery of the esophagus during gestational week 6. Complete closure of the canal takes place during week 8 of gestation. Anatomically, the right side closes before the left.[56] Muscularization of the diaphragm appears to develop from the innermost muscle layer of the thoracic cavity, although it has been proposed that the posthepatic mesenchymal plate is a possible source of muscular tissue.[60,61] Posterolaterally, at the junction of the lumbar and costal muscle groups, the fibrous lumbocostal trigone remains as a small remnant of the pleuroperitoneal membrane and relies on the fusion of the two muscle groups in the final stages of development for its strength. Delay or failure of muscular fusion leaves this area weak, perhaps predisposing to herniation. Bochdalek first described this area of the posterolateral diaphragm in 1848, and it is for this reason that the most common site for CDH bears his name.

## LUNG DEVELOPMENT

Fetal lung development is divided into five stages: embryonic, pseudoglandular, canalicular, saccular, and alveolar.[63] Embryonic lung development begins during the third week of gestation as a derivative of the foregut and is marked by the formation of a diverticulum off of the caudal end of the laryngotracheal groove.[64] The trachea and the two primary lung buds form from this diverticulum by the fourth week of gestation. At 6 weeks, these lung buds have further developed into defined lobar structures. The pseudoglandular phase of lung development takes place during the 7th to 16th weeks of gestation and involves airway differentiation. It is during this period that all bronchial airways develop. From the 16th to the 24th weeks of gestation, fetal lung development enters the canalicular phase of growth. During this period, airspace development occurs, as crude alveolar air sacs begin to take shape. Type 1 pneumocytes begin to differentiate, and the precursors of type 2 pneumocytes ultimately responsible for surfactant production begin to appear. Gas exchange becomes functionally possible at this stage.

Continued maturation of the crude alveolar airspaces takes place during the saccular phase of development that extends from 24 weeks' gestation to term. During this time period, there is continued remodeling of the airspace dimensions and a maturation of surfactant synthesis capabilities.[201] Mature, adult-like alveoli begin to appear shortly after birth.[66,67] Extensive alveolar maturation and multiplication then takes place from birth until approximately 8 years of age, with a 10-fold increase in the number of functioning alveoli.[68–71] Some investigators have proposed that alveolar formation may be completed by 2 years of age.[72]

Pulmonary vascular development follows the stages of airway and alveolar growth and can be divided into two anatomic units based on associated airway structure. The term acinus describes the functional unit of the lung that includes the respiratory bronchioli, alveolar ducts, and alveoli—all structures that evolve during or after the canalicular phase of lung development. Vascular development in this region proceeds concurrently with alveolar growth and multiplication. The preacinar structures include the trachea, major bronchi, and lobar bronchi up to the terminal bronchioles. Preacinar vascular development is completed by 16 weeks' gestational age.[73–76]

It is now recognized that pulmonary development is marked by a series of programmed events regulated by master genes, such as the homeobox genes, nuclear transcription factors, hormones, and growth factors. These processes involve genes regulating epithelial and endothelial interactions as well as temporal and spatial interactions of several hormones and growth factors. Early developmental transcription factors, such as hepatocyte nuclear factor-3β and thyroid transcription factor-1, regulate pulmonary development from the foregut mesenchyme. Additional stimuli of pulmonary development involve the transforming growth factor-β pathway, Sonic Hedgehog pathway, Notch-delta pathway, Wingless-Int pathway, and cytokine receptor pathways. Subsequent signal transduction control of organogenesis includes the apoptotic pathways, nuclear receptor pathways, and interleukin pathways. The angiopoietins and isoforms of vascular endothelial growth factor are involved in pulmonary angiogenesis and vascular development.[77,78] Hormones such as the glucocorticoids, thyroid hormone, and retinoic acid have been shown to regulate several of the crucial cellular interactions required for proper pulmonary organogenesis and differentiation.

Very little is known about the alterations in gene expression, growth factor interactions, and hormone levels associated with airway and vascular development in the hypoplastic CDH lung. A number of factors have been found to be elevated in CDH lung specimens, including epidermal

growth factor, transforming growth factor-α, vascular endothelial growth factor, insulin-like growth factor, tumor necrosis factor-α, angiopoietin-2, and glucocorticoid receptor gene expression.[41,77,79–83] Decreased expression of Sonic Hedgehog, heme-oxygenase-1, and endothelial nitric oxide synthase levels has been found in CDH specimens.[84–86] Abnormal levels of factors that contribute to the regulation of pulmonary vascular tone have also been reported. High plasma concentrations of endothelin-1, a powerful vasoconstrictor, have been found in association with increased expression of its pulmonary artery receptors in CDH infants.[87,88]

Advances in understanding potential mechanisms responsible for the alterations in pulmonary development associated with a congenital diaphragmatic hernia have been limited by the lack of a completely acceptable experimental animal model. Currently, three model systems exist for studying pulmonary maldevelopment: a surgical model of a diaphragmatic defect, a nitrofen model of pulmonary and diaphragmatic hypoplasia, and various gene knockout mice models of pulmonary hypoplasia.[89] Elegant models by de Lorimier and Harrison, in which diaphragmatic defects were surgically created in fetal sheep, showed that long-term compression of abdominal contents into the thoracic cavity resulted in pulmonary maldevelopment and lung hypoplasia.[90,91] The disadvantage of this surgical model is that the defect is created late in the time course of fetal development and may not address early developmental mechanisms. The nitrofen model of experimental CDH coincides with the theory that many developmental defects, including CDH, are embryopathies caused by toxin exposure. Nitrofen is an herbicide with known teratogenic effects. Its administration to pregnant mice results in offspring with pulmonary hypoplasia, diaphragmatic defects, reduced airway branching, excessive muscularization of pulmonary vessels, surfactant deficiency, and respiratory failure at birth. The pulmonary hypoplasia resulting from nitrofen administration has been associated with alterations in a number of growth factors and developmental pathways in embryonic mice.[92] Finally, investigations using specific knockout mice have contributed to the understanding of the role of various factors and pathways in pulmonary and diaphragmatic development.[89]

A number of physical factors may also affect pulmonary growth and development.[63] Adequate intrathoracic space is a prerequisite for normal pulmonary growth. Any intrathoracic or extrathoracic process that results in a decrease of the intrathoracic space and pulmonary parenchymal compression can lead to the development of structurally immature lungs.[90–96] Other physical factors important in lung growth include the maintenance of normal fetal lung liquid and amniotic fluid dynamics.[93,95,98,99,101]

## Pathology

Although the cause of CDH is uncertain, its consequences on pulmonary development and function are well documented. During the early development of the diaphragm, the midgut is herniated into the yolk sac. If closure of the pleuroperitoneal canal has not occurred by the time the midgut returns to the abdomen during gestational weeks 9 and 10, the abdominal viscera herniate through the lumbocostal trigone into the ipsilateral thoracic cavity. The resulting abnormal position of the bowel prevents its normal counterclockwise rotation and fixation. No hernia sac is present if the event occurs before complete closure of the pleuroperitoneal canal, but a nonmuscularized membrane forms a hernia sac in 10% to 15% of CDH patients.[100] Although some claim the herniation can occur late in gestation or be intermittently present as a dynamic process, in most cases the defect is established by gestational week 12.[100a] The subsequent postnatal problems relate to the effects of the herniated viscera on the developing heart and lungs.

The classical left-sided CDH features a 2.0- to 4.0-cm posterolateral defect in the diaphragm through which the abdominal viscera have been translocated into the hemithorax (Fig. 63-2). Herniated contents often include the left lobe of the liver, the spleen, and almost the entire gastrointestinal tract. The stomach is frequently in the chest, which results in some degree of obstruction at the gastroesophageal junction. This obstruction, in turn, causes dilation and ectasia of the esophagus. Occasionally, the kidney may be in the chest tethered by the renal vessels. In instances of a right-sided defect, the large right lobe of the liver can occupy much of the hemithorax in addition to other abdominal viscera. The hepatic veins may drain ectopically into the right atrium, and fibrous fusion between the liver and the lung has been reported. Both of these anatomic findings can significantly complicate attempted surgical repair of the diaphragmatic defect.[89,102]

The diaphragmatic defect usually features a completely open space between the chest and abdomen, although some infants have a membrane of parietal pleura and peritoneum acting as a hernia sac. This finding is to be distinguished from

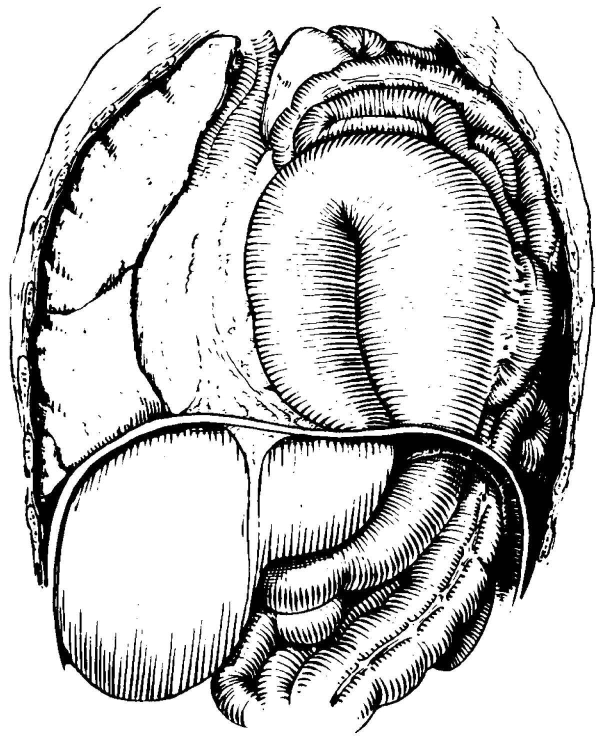


**FIGURE 63-2** Schematic illustration of a left congenital diaphragmatic hernia showing translocation of abdominal viscera through a posterolateral aperture into the chest. (From Spitz L, Coran AG [eds]: Rob & Smith's Pediatric Surgery. London, Chapman & Hall, 1996.)

an eventration of the diaphragm, which results from phrenic nerve or anterior horn cell degeneration. The muscle fibers of the diaphragm are usually present.

Bilateral CDH is an unusual occurrence and is almost always fatal because of bilateral lung growth arrest (Fig. 63-3).[103]

Unilateral visceral herniation affects both ipsilateral and contralateral pulmonary development, although hypoplasia is predictably more severe on the ipsilateral side. This is confirmed by an analysis of lung volumes and weights in human autopsy specimens and animal models.[90,96,104,105] Because the process of CDH herniation occurs at the time of bronchial subdivision, it is at this stage that lung development becomes compromised. Although all major bronchial buds are present in a CDH lung, the number of bronchial branches in the affected lung is greatly reduced. This finding was noted in both ipsilateral and contralateral pulmonary specimens.[104] Alveolar development is severely affected, and it has been reported that few normal alveoli exist in the lungs at term.[106] In addition, the changes in airway structure are quite variable. Infants requiring low ventilatory assistance during treatment had the same airway muscle mass as controls, whereas infants with prolonged ventilatory support had significantly greater muscle thickness throughout the conducting airways.[107]

The pulmonary vascular bed is distinctly abnormal in lungs from patients with CDH. A reduction in the total number of arterial branches in both the ipsilateral and the contralateral pulmonary parenchyma has been reported.[108,109] Structurally, significant adventitial and medial wall thickening has been noted in pulmonary arteries of all sizes in CDH lungs in association with abnormal muscularization of the small preacinar and intraacinar arterioles.[110–112] The physiologic consequence of this abnormal arterial muscularization may be an increased susceptibility to the development of fixed and intractable pulmonary hypertension. No significant changes in pulmonary venous structure have been identified resulting from CDH development. Increased adventitial thickness of pulmonary veins has been noted in CDH infants

FIGURE 63-3 Operative photograph of a left congenital diaphragmatic hernia created in a fetal lamb. The posterolateral defect can be seen looking from the abdomen into the chest. (From Spitz L, Coran AG [eds]: Rob & Smith's Pediatric Surgery. London, Chapman & Hall, 1996.)

but appears to be postnatally derived, perhaps as a result of treatment or secondary to the pathology of pulmonary hypertension.[28,113]

Pulmonary blood flow accounts for only 7% of cardiac output during normal fetal development, and pulmonary vascular resistance remains high. The fetus preferentially shunts oxygenated blood from the placenta through the foramen ovale and ductus arteriosus in a right-to-left direction into the systemic circulation. At birth, a number of hemodynamic changes take place that dramatically alter this circulatory profile. With the institution of breathing, pulmonary vascular resistance falls, as does pulmonary artery pressure allowing for an increase in pulmonary blood flow. Systemic vascular resistance and left atrial pressure rise, causing the foramen ovale to close. Increased arterial oxygen tension induces spontaneous closure of the ductus arteriosus. Transition from a fetal to an adult-type circulatory pattern is accomplished. Persistent fetal circulation may develop if this process is interrupted. After birth and interruption of placental circulatory support, persistently elevated pulmonary vascular resistance results in increased pulmonary artery pressures and decreased pulmonary vascular blood flow. The increased vascular resistance results in right-to-left shunting of blood at either the atrial or the ductal levels with the delivery of unsaturated blood into the systemic circulation. As the blood flow in the shunt increases, the oxygen saturation in the systemic circulation falls and the mixed venous blood returning to the right side of the heart becomes progressively desaturated. The resulting hypoxia further increases pulmonary vascular resistance and compromises pulmonary blood flow while increasing the right-to-left shunt flow. Severe and progressive respiratory failure ensues.

Factors that contribute to the persistence of high pulmonary vascular resistance in CDH lungs are thought to be the structural changes in decreased total arteriolar cross-sectional area in the involved lungs and the increased muscularization of the arterial structures that are present. In the postnatal period, there is failure of the normal arterial remodeling process, further maintaining the abnormal vascular resistance that may be only partly reversed by treatment interventions.[114] Additional exacerbations of pulmonary vascular resistance may be induced by the known stimulators of pulmonary hypertension, including hypoxia, acidosis, hypothermia, and stress.[115] Alterations in the levels of various prostaglandins, leukotrienes, catecholamines, and the renin-angiotensin system have been implicated as mediators of this complex process.[116–118] It can only be surmised at this time whether there is an exaggerated response to these stimuli by the abnormal vascular structures of CDH lungs.[113]

## DIAGNOSIS

The diagnosis of a CDH is often made on a prenatal ultrasound (US) examination and is accurate in 40% to 90% of cases.[119,119a] Although considerable variation in detection rates have been reported, the mean gestational age at discovery is 24 weeks and has been reported as early as 11 weeks.[120] The US may be obtained for routine obstetric care or because of suspicion concerning the presence of polyhydramnios. Polyhydramnios has been reported present in up to 80% of pregnancies with associated CDH.[99a] The mechanism of polyhydramnios is thought to be due to kinking of the gastroesophageal junction

by translocation of the stomach into the thorax with resultant foregut obstruction. The US diagnosis of a CDH is most often suggested by observing the stomach in the fetal thorax at the same cross-sectional level as the heart (Fig. 63-4). Additional US findings suggestive of a CDH include the absence of the stomach in the abdomen and the presence of the liver or other solid viscera in the thorax. The stomach may be small because of interference with fetal swallowing. If the diaphragmatic defect is on the right side, the liver can tamponade the hernia site and obscure the diagnosis. The diagnosis of CDH may be missed because intermittent herniation of abdominal viscera into the thoracic cavity has been reported.[99a] Furthermore, when the stomach is in a normal abdominal position, herniated small bowel loops are not easily distinguishable from lung parenchyma. The misinterpretation of the fetal US scan can be caused by other diagnoses, such as esophageal atresia and cystic lung anomalies. Functional information concerning fetal breathing can be obtained by duplex Doppler examination of amniotic flow at the fetal nares at the time of fetal US. A fetal tidal volume/minute ventilation can be determined that may have a bearing on prognosis.[121]

In addition to diagnosis, prenatal US may also be of benefit in predicting outcome by using quantitative techniques to estimate the severity of pulmonary hypoplasia of the fetal CDH lung. Three-dimensional estimation of the fetal lung volume, calculation of the right lung area to thoracic area ratio, and calculation of the lung to thoracic circumference ratio are three different measurements that may correlate with neonatal outcome,[122–125] but the lung-to-head ratio has been the most widely used prognostic indicator.[126] US can be limited by the poor acoustic contrast between fetal lung and herniated viscera, position of the fetus, and operator experience. As a result, prenatal magnetic resonance imaging (MRI) evaluation is being used with increasing frequency when obstetric sonography has detected a complex fetal anomaly and is ideally suited for fetuses with a diaphragmatic hernia.[127–129] MRI can readily determine liver position in relation to the diaphragm and detect herniated liver into either hemithorax. It may also be used to more accurately assess lung volume and perhaps correlation with outcome.[130–132]

After birth, the spectrum of respiratory symptoms in an infant with a CDH is determined by the degree of pulmonary hypoplasia and reactive pulmonary hypertension. The most severely affected infants develop respiratory distress at birth, whereas a majority demonstrate respiratory symptoms within the first 24 hours of life. Classically, these infants have a scaphoid abdomen and an asymmetric distended chest. The chest may become more distended as swallowed air passes into the stomach and intestines. Gastrointestinal distention further compresses pulmonary parenchyma and affects ventilatory characteristics. It may lead to additional mediastinal compression with impairment of the contralateral lung. Because of the small size of the neonate's chest, breath sounds may or may not be present on the side of the defect. Mediastinal compression with shift into the contralateral thorax may cause deviation of the trachea away from the side of the hernia and also result in obstruction to venous return with the hemodynamic consequences of hypotension and inadequate peripheral perfusion. The signs of respiratory distress may include cyanosis, gasping, sternal retractions, and poor respiratory effort. In babies with a left CDH, heart sounds will be heard best over the right chest; "dextrocardia" accompanied by respiratory distress is a CDH until proven otherwise.

The diagnosis of a CDH can be confirmed by a plain chest radiograph that demonstrates loops of intestine in the chest. The location of the gastric bubble should also be noted, and its position can be confirmed by placement of an orogastric tube. Rarely, a contrast study of the upper gastrointestinal tract is required. The chest radiograph shows angulation of the mediastinum and a shifting of the cardiac silhouette into the contralateral thorax. Although minimal aeration of the ipsilateral parenchyma may be noted, chest radiographs are unreliable for estimating the degree of pulmonary hypoplasia.[58,133–135]

Once the diagnosis of a CDH is confirmed, additional radiographic and US examinations should be carried out to search for associated anomalies. Echocardiography and both renal and cranial US scans should be obtained.

Although most CDHs present in the first 24 hours of life, 10% to 20% of the infants with this defect present later.[136,137] These latter infants present with recurrent mild respiratory

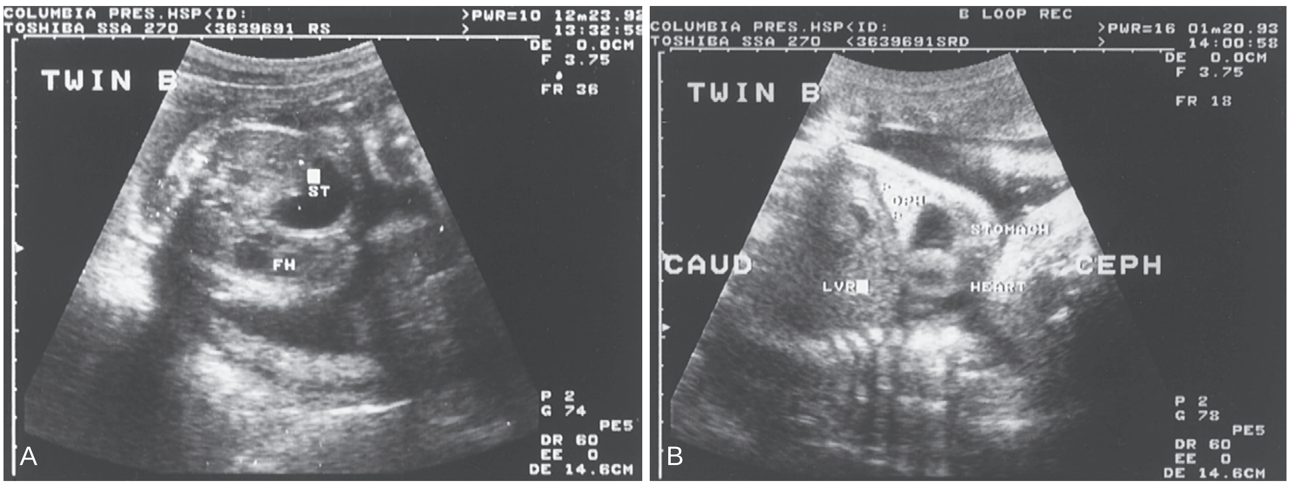



**FIGURE 63-4** **A,** Ultrasound examination of a 28-week gestation fetus (twin B) in cross section demonstrating the fetal heart (FH) and stomach (ST) in the same plane. **B,** Ultrasound examination of the same fetus but in a sagittal plane, demonstrating relationship of the stomach, liver, and heart.

illnesses, chronic pulmonary disease, pneumonia, effusion, empyema, or gastric volvulus. Occasionally, neonatal streptococcal pneumonia may mask a delayed-onset right CDH.[138]

# Differential Diagnosis

The diagnosis of a CDH can be confused with a number of other congenital thoracic conditions, including eventration of the diaphragm, anterior diaphragmatic hernia of Morgagni, congenital esophageal hiatal hernia, congenital cystic disease of the lung, and primary agenesis of the lung. Diaphragmatic eventration has many causes but is seen in the newborn with birth trauma or Werdnig-Hoffmann disease. The eventrated diaphragm can rise as high as the third intercostal space and have the same physiologic consequences as CDH. It can also be completely asymptomatic. The diagnosis is made by fluoroscopy or real-time US with the demonstration of paradoxic movement of the diaphragm. MRI is also useful in determining diaphragmatic structure. Morgagni hernias occur at the hiatus for the internal mammary arteries and are much less common than Bochdalek hernias. Most are diagnosed incidentally on plain radiographs, but some Morgagni hernias can present as a gastrointestinal crisis because of incarceration or volvulus of the colon or small bowel and require immediate operative intervention.

# Prognostic Factors

The search to determine clinically relevant prognostic factors that predict the outcome of infants with CDH has been frustratingly complex, contradictory, and for the most part unsuccessful. Many studies have attempted to examine both anatomic and physiologic parameters that relate to survival, but each has been hampered by its retrospective analysis in the presence of the continuing evolution of new therapies.[139,139a] Whereas consideration of multiple factors may influence one's clinical impression regarding the survival potential of an infant with CDH, such an impression cannot be derived from one measurement alone.

## ANATOMIC FACTORS

With the ability to establish the diagnosis of CDH in utero as a result of the increased use of prenatal US, studies suggested that the antenatal diagnosis of a CDH before 24 weeks' gestational age was associated with a high mortality. Others have shown that antenatal diagnosis, regardless of timing, of an isolated CDH without other associated anomalies is not an indicator of outcome,[140] but more recent reports confirm that antenatal diagnosis is associated with a worse prognosis. A CDH associated with another significant anomaly still has a dismal prognosis. If a CDH is not detected by prenatal US but is subsequently diagnosed after birth, survival rates may be excellent.[122] The Canadian Pediatric Surgery Network (CAPSNet) collected 347 CDH cases between May 2005 and May 2010 (www.capsnetwork.org/resources/annual report 2010); of the 269 patients admitted alive to a pediatric center and with a completed record, 68% had a prenatal diagnosis, with a 74% survival, while the 32% without a prenatal diagnosis had a 96% survival (this drops to 86% when the babies who died in transport are included). Preselection bias prior to transport was not reported.

Antenatal diagnosis and antenatal referral to a full-service children's facility, especially those with maternal/fetal–medicine/lying-in services, has removed much of the postnatal/pretransfer bias and selection. It was also reported that the presence of polyhydramnios was indicative of poor survival.[141] A number of studies, however, have refuted this observation and have shown that the presence of polyhydramnios has no predictive value on the eventual outcome of an infant with CDH.[142,143] The anatomic position of the liver has not been consistently shown to be a reliable predictor of mortality in CDH.[120,126,131,144–146] Nevertheless, there are reports suggesting the presence of liver herniation may be predictive of the need for extracorporeal membrane oxygenation (ECMO) as well as a requirement for prosthetic patch repair for diaphragmatic repair.[15,126,147]

The position of the stomach has been proposed as a prognostic indicator by a number of investigators. Survival rates of infants with CDH with the stomach properly located below the diaphragm at the time of diagnosis have been reported to be as high as 100% but is only 30% when the stomach had herniated into the chest.[148,149] Other studies have shown no predictive value of such positioning.[150] The side of the diaphragmatic defect may be somewhat predictive of outcome. It has been reported that patients with right-sided defects have a worse prognosis than those with left-sided defects.[14,151] A recent study reported no differences in outcomes between the two sides.[152] However, right-sided defects may not become evident in the newborn period and may present with very mild respiratory symptoms at a later age.[153]

A number of different imaging parameters have been reported in an attempt to predict the presence of pulmonary hypoplasia and serve as a prognostic indicator of survival. These include measurements of the fetal thorax and lung, fetal breathing movements, and various calculated blood flow measurements within the pulmonary arteries.[154] The lung–head ratio (LHR) has been the most extensively studied. The LHR is measured using ultrasonography and is the ratio of the area of the contralateral lung (opposite the hernia defect) to the fetal head circumference. The lung area is calculated from perpendicular transverse measurements determined at the plane of the four-chamber view of the fetal heart. This measurement has been suggested to predict prognosis and guide management.[126,155,156] However, there is no consensus as to what value of LHR should serve as a determinant of prognosis or when during gestation that measurement should be made.[157] Because LHR has been proposed to determine the timing of experimental fetal intervention, most studies report LHR measurements before 32 weeks' gestational age.[158] Current data indicate that the strength of association with survival is strongest for those fetuses with LHR greater than 1.0 compared with LHR less than 1.0.[159] A recent report by Aspelund and colleagues of a single-institution experience of all inborn CDH infants managed with a consistent treatment algorithm had significant statistical power to support an LHR less than 0.85 as reliably predicting 100% mortality.[160]

Because LHR changes with gestational age, use of the *observed-to-expected* LHR (O/E-LHR) has been reported.[158,161] A severe left CDH has been characterized by an O/E-LHR of less than 25%.

Prenatal magnetic resonance imaging is being investigated extensively as a method for improving prognostic predictive capability by more accurately determining lung volumes in CDH patients.[162] Measured indices include lung to head ratio as well as relative and absolute fetal lung volumes. The prognostic accuracy appears to be slightly better than sonographic determinations.[146] Signal intensity analysis of fetal lung tissue as part of MRI imaging studies may be a future application of this modality, although a recent report found that lung volumes was a better predictor.[162,163]

The sophisticated analysis of cardiopulmonary structure and function in either the prenatal or postnatal period may also be of prognostic importance.[142,164–166] A number of indices have been reported, including the calculation of the cardioventricular index (left ventricle/right ventricle), the cardiovascular index (Ao/PA), pulmonary artery diameters, the McGoon index (MGI), and pulmonary artery index (PAI).[166–170] The McGoon and pulmonary artery indices are determined shortly after birth by the following formula:

$$\begin{aligned} \text{MGI} &= (\text{RPA diameter} + \text{LPA diameter})/\\ &\quad\ \text{Descending aorta diameter}\\ \text{PAI} &= (\text{RPA area} + \text{LPA area})/\text{BSA} \end{aligned}$$

(RPA and LPA = right and left pulmonary artery, respectively; BSA = body surface area)

MGI scores less than 1.31 have been found to be highly predictive of mortality, while the same has been found for PAI scores less than 90. An analysis of left ventricular mass combined with the simultaneous determination of fractional shortening has also been used to predict outcome, with an index of 1.2 associated with nonsurvival.[171] Advanced echocardiographic measurements with interesting clinical promise include the determination of lung tissue perfusion with the analysis of fractional moving blood volume (FMBV) and the use of pulsed Doppler measurements in the proximal branch of the pulmonary artery to determine the pulsatility index (PI) and the peak end-diastolic reversed flow (PEDRF).[172–174] These measurements may have increasing importance in the search for suitable prenatal predictors of survivability in the setting of fetal therapy.[175]

## PHYSIOLOGIC PARAMETERS

Unfortunately, there are few physiologic parameters that can be measured in the neonate to assess pulmonary function other than $PO_2$, $PCO_2$, and pH. Thus arterial blood gas analysis has been the cornerstone for attempting to establish clinical predictive criteria. Early studies showed differences in pH and $PCO_2$ between survivors and nonsurvivors in response to therapeutic interventions available at that time.[176–178] Infants with a low $PCO_2$ and a $PO_2$ that was initially normal or improved with mechanical ventilation had an excellent outcome, whereas those infants who had high $PCO_2$ levels unresponsive to mechanical ventilation did poorly. These authors noted the importance of measuring both preductal and postductal blood gases to assess the degree of right-to-left shunting. The report by Stolar and colleagues[179] advocated *preductal* oximetry values in the setting of maximal conventional care to identify potential ECMO candidates. In the absence of preductal $SaO_2$ greater than 90%, overwhelming pulmonary hypoplasia was inferred, and ECMO was not offered. This represented less than 5% of all patients, for which there was 100% mortality.

Since these initial reports, investigators have derived a number of formulas using various blood gas components to predict outcome. The most basic concept is the alveolar–arterial oxygen gradient ($AaDO_2$). It is calculated by the formula

$$AaDO_2 = [\{(713 \times FiO_2) - PaCO_2\}/0.8] - PaO_2$$

Although initially used to determine entry criteria for ECMO, its use has been superseded by the development of other indices.

Using blood gas analysis and $PCO_2$ levels in combination with ventilatory data, parameters were determined to predict outcome in CDH infants managed with conventional ventilatory techniques.[110,180–182] To do this, a ventilatory index (VI) was calculated:

$$VI = RR \times (PIP - PEEP)$$

(PEEP = positive end-respiratory pressure; PIP = peak inspiratory pressure; RR = respiratory rate)

When the $PCO_2$ could be reduced to less than 40 mm Hg with a ventilatory index less than 1000, all patients survived. A modified ventilatory index (MVI) was calculated by using peak inspiratory pressure rather than mean airway pressure (MAP):

$$MVI = (RR \times PIP \times PaCO_2)/1000$$

In infants with an MVI less than 40, the survival rate was 96% using conventional therapy. All infants died if the MVI was greater than 80.[183]

The most commonly used calculation is the oxygenation index (OI). It is calculated by the formula

$$OI = (MAP \times FiO_2 \times 100/PaO_2)$$

This formula should be calculated using the *preductal* $PaO_2$, because the postductal one varies tremendously with the amount of shunting.

A 1994 report showed that with conventional ventilatory therapy, an OI less than 6 had a survival rate of 98%, whereas an OI greater than 17.5 had no survivors.[183] The predictive powers of these factors with such therapies as ECMO, high-frequency oscillation (HFO), surfactant, and nitric oxide (NO) have not been determined. Simple preoperative lung function measurements are difficult to obtain but may be of some interest.[184]

In summary, efforts to reliably predict mortality for the fetus or live-born infant with isolated CDH have been fraught with uncertainty. Although a calculated LHR less than 0.85 (or an observed/expected LHR less than 20% to 25%) may have high predictability for mortality, better understanding of prognosis awaits functional evaluation of the fetus. This might include tidal amniotic fluid breathing/lung volumes or response to maternal hyperoxia. Postnatal use of the McGoon index, also because of its functional nature, holds promise.[184a] In the absence of substantiated, reproducible information regarding prognosis, treatment continues to be guided by best clinical judgment.

## PULMONARY FUNCTION TESTS

The analysis of preoperative and postoperative pulmonary function tests has been reported to have predictive value in identifying infants who might require ECMO therapy as well as identifying survivors.[184] Initial studies of respiratory

function in infants with CDH uncovered the detrimental changes in compliance measurements resulting from surgical repair and helped support the hypothesis of medical stabilization and delayed surgical intervention.[185–187] Using the treatment strategies of delayed surgical repair and ECMO, when necessary, infants did not require ECMO when their initial preoperative compliance measurement was greater than 0.25 mL/cm $H_2O$/kg and initial tidal volume was greater than 3.5 mL/kg. An improvement in the tidal volume of 4 mL/kg after repair correlated with survival.[188]

Studies have indicated that preoperative measurement of functional residual capacity may predict fatal pulmonary hypoplasia.[184] In addition, serial measurements of total pulmonary compliance have been found useful in predicting outcome in high-risk infants.[189]

Although no single parameter has proven sufficient as a prognostic factor in managing CDH infants, recent multicenter studies have shown that significant independent predictors of total mortality include prenatal diagnosis, birth weight, low 1- and 5-minute Apgar scores, score for neonatal acute physiology (SNAP-II), and right-sided defect.[139,190–192]

# Treatment

Success in the management of CDH has improved dramatically from 1929 when Greenwald and Steiner[27] wrote, "For the patient in whom the hernia makes its appearance at birth, little or nothing can be done from a surgical standpoint." A number of innovative treatment strategies have been used, although consistent impact on overall survival is still difficult to obtain.

## PRENATAL CARE

The diagnosis of a CDH is being made with increasing frequency by prenatal US examination. This study may be initiated when a discrepancy between size and dates is noted. The prenatal diagnosis of CDH should be complemented by a careful search for other congenital anomalies, particularly those affecting the cardiovascular and nervous systems. Evaluation of fetal karyotype should be accomplished by amniocentesis or chorionic villus or fetal blood sampling. Currently, the standard of care is to support the fetus and mother while bringing them to delivery as close as possible to term. The advantage of prenatal diagnosis is in being able to properly prepare and inform the parents about possible treatments and outcomes. The fetus and mother should be referred to an appropriate tertiary perinatal center where the full array of respiratory care strategies, including NO, oscillating ventilators, and ECMO are immediately available. Anything less may potentially compromise the best possible outcome.[143] Spontaneous vaginal delivery is preferred, unless obstetric issues supervene. The mere diagnosis of a CDH is not an indication for elective cesarean section.

At this time, fetal intervention with attempted in utero correction of the defect is investigational and highly experimental.[105,193–195] In North America, trials of fetal tracheal occlusion for CDH in an effort to promote antenatal lung growth have been abandoned, because they did not show improved survival rates versus contemporary conventional treatments.[193,196] Tracheal occlusion resulted in lung enlargement but did not reverse the pathologic process associated with pulmonary hypoplasia. The selection criteria for the severity of pulmonary hypoplasia to enter the fetal treatment trials has also been questioned.[93,94,193,197–199] The North American trial used an LHR less than 1.4 as entry criterion; the Eurofetus trials have advocated LHR less than 1.0 as entry criterion. Fetoscopic tracheal occlusion trials are ongoing in Europe, with over 200 cases reported,[198] and there are plans for an international prospective randomized trial involving North American centers that participate in NAFTNet (the North American Fetal Treatment Network).

Although prenatal corticosteroids are used to enhance lung development in premature infants, the role of antenatal corticosteroid therapy in CDH patients remains undetermined. The rationale for such therapy to induce pulmonary maturation in a hypoplastic lung is based on animal studies and isolated case reports.[200–203] Balanced against these observations is the growing evidence from premature infant studies that such drugs may also have adverse perinatal and long-term effects.[204,205] The true potential of this therapy in improving CDH outcomes awaits the results of a randomized prospective study.

## PREOPERATIVE CARE

### Resuscitation

After the birth of the infant and confirmation of the diagnosis of CDH, all efforts should be made to stabilize the cardiorespiratory system while inducing minimal iatrogenic injury from therapeutic interventions. It is essential to consider that the CDH is a physiologic emergency and not a surgical emergency. The respiratory distress associated with a CDH in the newborn results from a combination of two factors previously discussed: uncorrectable pulmonary hypoplasia and potentially reversible pulmonary hypertension. The balance between these two factors determines the response to therapy and ultimately the outcome. Clinically, both are manifested by an increase in pulmonary vascular resistance and elevated pulmonary artery pressures, right-to-left shunting at the ductal and foramen levels, and progressive hypoxemia. Because there are no proven therapies to promote pulmonary growth at this time, therapeutic interventions are aimed at governing pulmonary vascular tone.

Resuscitation begins with endotracheal intubation and nasogastric tube insertion. Ventilation by mask and Ambu bag is contraindicated to avoid distention of the stomach and intestines that may be in the thoracic cavity. Arterial and venous access should be acquired through the umbilicus. If the umbilical venous catheter can be passed across the liver into the right atrium, it can be useful for monitoring central venous pressures as well as obtaining mixed venous blood gas samples. Although the umbilical artery is excellent for monitoring systemic blood pressure and obtaining postductal arterial blood gas specimens, additional information can be obtained by monitoring arterial oxygen saturation in a preductal position either with a right radial arterial catheter or a transcutaneous saturation probe. An important part of the treatment algorithm is an attempted estimation as to whether the infant has enough lung capacity for meaningful gas exchange.

It is important to consider this fact before exposing an infant and family to heroic treatment strategies.

As in any neonatal resuscitation, meticulous attention must be paid to maintaining proper temperature regulation, glucose homeostasis, and volume status in the neonate in an effort to maintain adequate oxygen delivery. Any stressful stimulus can further exacerbate already elevated pulmonary pressures and lead to increased shunt flow and further systemic desaturation. Infants should be properly sedated, and any combination of agents, including midazolam, fentanyl, or morphine, can be used. Muscle paralysis is strongly discouraged because of its untoward consequences on ventilatory mechanics and potential morbidity. Infants not “cooperating” with ventilator strategies generally need attention to their discomfort, not muscle paralysis. Systemic hypotension and inadequate tissue perfusion may be observed and reversed with intravenous fluid administration, including crystalloid, blood products, and colloid. Cardiotonic drugs, such as dopamine or dobutamine, may be required. Because of the unstable pulmonary vascular tone and the compromised alveoli, excessive intravenous hydration should be avoided, because it may lead to pulmonary edema, loss of compliance, and further impairment of gas exchange.

Metabolic acid-base disturbances are usually related to hypoperfusion and should be corrected by fluid management or bicarbonate administration. Metabolic acidosis can be reversed with bicarbonate administration if ventilation can be appropriately managed. Severe hypercapnia ($P_{CO_2}$ > 70 mm Hg) should be managed by changing ventilator strategy.

There is no need for a chest tube in the absence of an active air leak, pneumothorax, or hemothorax.[206,207]

## Ventilation

The type of mechanical ventilator needed for the infant with a CDH is a matter of personal and institutional preference. Most infants can be successfully managed with a simple pressure-cycle ventilator, using a combination of high rates (100 breaths per minute) and modest peak airway pressures (18 to 22 cm $H_2O$ and no PEEP) or lower rates (20 to 40 breaths per minute) and higher pressures (22 to 35 cm $H_2O$, 3 to 5 cm PEEP). The goal of such ventilatory support is to maintain minute ventilation while obtaining a preductal $P_{O_2}$ greater than 60 mm Hg ($Sa_{O_2}$ 90% to 100%) with a corresponding $P_{CO_2}$ of less than 60 mm Hg. pH and $P_{CO_2}$ levels have been shown to be important in modifying pulmonary vascular tone.[307b] The successful clinical manipulation of these parameters in therapeutic interventions in neonates with persistent pulmonary hypertension represents an initial treatment strategy. It is now clear, however, that the extremes of hyperventilation with induced alkalosis should be avoided because such therapy compounds the pulmonary problems with serious iatrogenic injury.[208] A respiratory strategy based on permissive hypercapnia and spontaneous respiration has proven to be quite successful.[206] If conventional mechanical ventilatory techniques cannot reverse the hypoxemia or hypercarbia, high-frequency techniques using an oscillating ventilator may be required. This technique may be effective in removing carbon dioxide and temporarily stabilizing an infant in severe respiratory distress. When such techniques have been used as initial therapy, survival results have been quite good.[137,209,210]

## Pharmacology

A broad spectrum of drugs and antihypertensive agents has been used in attempts to modify the pulmonary vascular resistance in infants with CDH and respiratory failure. Experience has been extrapolated from clinical trials of infants with persistent pulmonary hypertension of the newborn (PPHN) and other forms of neonatal respiratory failure.

In the past, agents such as tolazoline,[211,212] which exerts its effects through α-receptor blockade, had been used to lower pulmonary vascular resistance in the face of hypoxemia and respiratory failure.[212,213] Its efficacy in CDH infants was marginal. Other drugs, such as nitroprusside, isoproterenol, nitroglycerin, and captopril, have not been effective.[214] The administration of various prostaglandin derivatives, including prostaglandin $D_2$ ($PGD_2$), prostaglandin $E_1$ ($PGE_1$), and prostacyclin, and of the cyclooxygenase inhibitor indomethacin has also been disappointing.[115,215]

New management strategies for treating persistent pulmonary hypertension now undergoing clinical evaluation include various calcium channel blockers, prostacyclin derivatives, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors such as sildenafil.[216,217]

## Surfactant

Animal models have demonstrated that experimentally induced CDH lungs are surfactant deficient,[218] but such results have not been replicated in human studies. Early reports in infants with CDH demonstrated alterations in surfactant levels and composition.[219,220] However, recent studies have indicated that the surfactant pool in infants with CDH is no different than control patients, even in infants requiring ECMO support.[221–224] There may be alterations in synthetic and metabolic kinetics for individual components.[221] In terms of improving respiratory function and outcomes, clinical and experimental investigations with surfactant administration have been mixed.[224–228] A multicenter review of surfactant administration in CDH patients showed no overall benefit to its use and demonstrated a lower survival rate in preterm infants compared with full-term infants.[229] At this time, there are no clinical data to support the administration of surfactant in the management of CDH infants.

## Nitric Oxide

NO is a potent mediator of vasodilatation and was originally identified as endothelial-derived relaxing factor.[230] Because it is a highly diffusible gas that is rapidly inactivated by binding to hemoglobin, it is particularly suited for administration to the pulmonary vasculature with mechanical ventilatory techniques. In clinical studies, NO was effective in improving oxygen saturation levels in neonates with respiratory failure due to PPHN.[231,232] In an animal model of PPHN, NO decreased pulmonary artery pressures and increased arterial oxygen saturation without discernable side effects.[233] Unfortunately, its effects in CDH infants with respiratory failure have been mixed.[86,231,234–238] There are no data to show that NO administration improves survival or decreases the requirement for ECMO.[239] The variable physiologic response to NO in these infants may be related to the method of its administration.[228,240] NO administered through a nasal cannula has been used for the treatment of late pulmonary hypertension following extubation.[231] The exact role of NO in the treatment

of pulmonary hypertension and respiratory failure in CDH infants has not been defined despite its widespread use.

## SURGICAL MANAGEMENT

### Timing of Surgical Repair

Historically, CDH was considered a surgical emergency. Infants were rushed to the operating room as soon as possible after birth in the belief that reduction of the abdominal contents from the chest would relieve the compression of the lungs. Frequently, after a brief postoperative honeymoon period marked by adequate gas exchange, progressive deterioration in the infant's respiratory status ensued with elevated pulmonary vascular resistance, right-to-left shunting, hypoxemia, and ultimately death resulting from respiratory failure.

As management techniques for neonatal respiratory failure evolved, a period of medical stabilization and delayed surgical repair, in an attempt to improve the overall condition of the infant with CDH, was proposed.[117,180,241–249] At the same time, there was increasing evidence of the potential detrimental effects of early surgical repair on respiratory function.[250] Since then, multiple single-institution studies have reported improved survival rates with delayed surgery as part of their treatment protocols, whereas others have found no changes in overall outcome. Importantly, no study has shown a decrease in survival rates with this technique. Although delayed surgical repair is now widely practiced, there is no statistical evidence that supports this approach over immediate repair at this time.[251]

The optimal timing of operative repair when using a strategy of delayed repair also remains undetermined. The period of preoperative stabilization has varied from several days to several weeks.[186,253–255] Some authors have reported waiting until the infant is successfully weaning off mechanical ventilation and requiring low ventilator settings. Others follow the severity of pulmonary hypertension with serial echocardiographic examinations and wait until the hypertension has abated or at least stabilized.[256–258]

### Operative Repair

Most surgeons approach the defect through a subcostal incision, although the repair can be done through a thoracotomy incision as well. For rare cases in which reduction of the herniated contents is difficult because of an abnormally shaped liver or spleen, a combined approach can be used.[259] Both thoracoscopic and laparoscopic techniques have been used to repair these defects.[260–265a] Although thoracoscopic repairs have application in stable CDH patients[266] and can be accomplished with primary or prosthetic material closure, a recent report by Gander and colleagues[261] suggests thoracoscopic repair is associated with an unacceptably high recurrence rate within 1 year after repair.

After division of the abdominal wall muscles and entrance into the abdominal cavity, the viscera are gently reduced from the defect and completely eviscerated for adequate visualization. The spleen on the left side and the liver on the right are usually the last organs to be mobilized from the chest cavity (Fig. 63-5, *A* and *B*). Mobilization can be difficult and must be done without injury to either organ. On the right side, the kidney and adrenal gland may be found in the chest as well. Abnormal drainage of the hepatic veins on either side may complicate mobilization of the liver.

Once the abdominal contents are reduced, the defect in the diaphragm in the posterolateral position can be examined. In 20% of patients, a hernia sac formed by parietal pleura and peritoneum is present and must be excised to minimize chances of recurrence.[16] Usually, there is an anterior rim of diaphragm of varying size. The posterior rim of diaphragm must be searched for in the retroperitoneal tissue, because it may be rolled up like a window shade by the peritoneum. The peritoneum must be opened over this fold and the diaphragmatic tissue mobilized. When tissue is adequate, a primary repair with interrupted nonabsorbable suture material can be performed (Fig. 63-5, *C*). In some cases, the posterior rim of tissue may disappear along the lateral chest wall. If enough diaphragmatic tissue exists anteriorly, it can be sutured directly to the body wall with sutures placed around the ribs.

If the defect is too large to be closed in a primary fashion, a number of reconstructive techniques have been described using various nearby structures, such as prerenal fascia, rib structures, and various abdominal wall muscle flaps.[267–272] If there is any chance that ECMO support might be required in the management of the infant, however, the use of complex reconstructive techniques requiring extensive tissue dissection is contraindicated because of the risk of bleeding. The use of prosthetic material to complete the diaphragmatic closure has gained widespread acceptance (Fig. 63-5, *D*). A floppy, tension-free diaphragmatic repair can be accomplished, which may lessen the degree of intra-abdominal pressure when closing the abdominal wall.[273] In addition to the risk of infection, the major drawback to using a prosthetic patch closure is the risk of dislodgment and subsequent reherniation.[274] This complication may be lessened by using a cone-shaped patch.[275] Complications of prosthetic patch repair occur in approximately 10% to almost 50% of cases. Patients who develop a recurrent hernia present with bowel obstruction or respiratory distress or may be asymptomatic.[276,277] Recently, the split abdominal wall muscle flap repair was shown to be safe to use on ECMO and was associated with only one recurrence in 23 patients, with a mean follow-up of 4.8 years.[278]

With the loss of intra-abdominal domain, abdominal wall closure may not be possible at all or may result in unacceptable intra-abdominal pressure (i.e., abdominal compartment syndrome), even after extensively stretching the abdominal wall. In these situations, simple closure of the skin can be accomplished with repair of the resultant ventral wall defect some months later. If the skin cannot be closed successfully, temporary closure using prosthetic material, such as a silo, can be used. Biologic closure should then be obtained as soon as safely possible in the postoperative period. Drainage of the chest cavity on the repaired side with a tube thoracostomy is not indicated except for active bleeding or uncontrolled air leak. It has been proposed that such a tube with even a small degree of negative suction may add to the barotrauma and pulmonary hypertension imposed by mechanical ventilation on a hypoplastic lung.[254,279] Additional surgical procedures at the time of the repair, such as correction of the nonrotation as well as appendectomy, are not indicated and should be avoided if ECMO is to be considered.

The repair of recurrent defects can present a formidable surgical challenge. Since the most common organ involved in

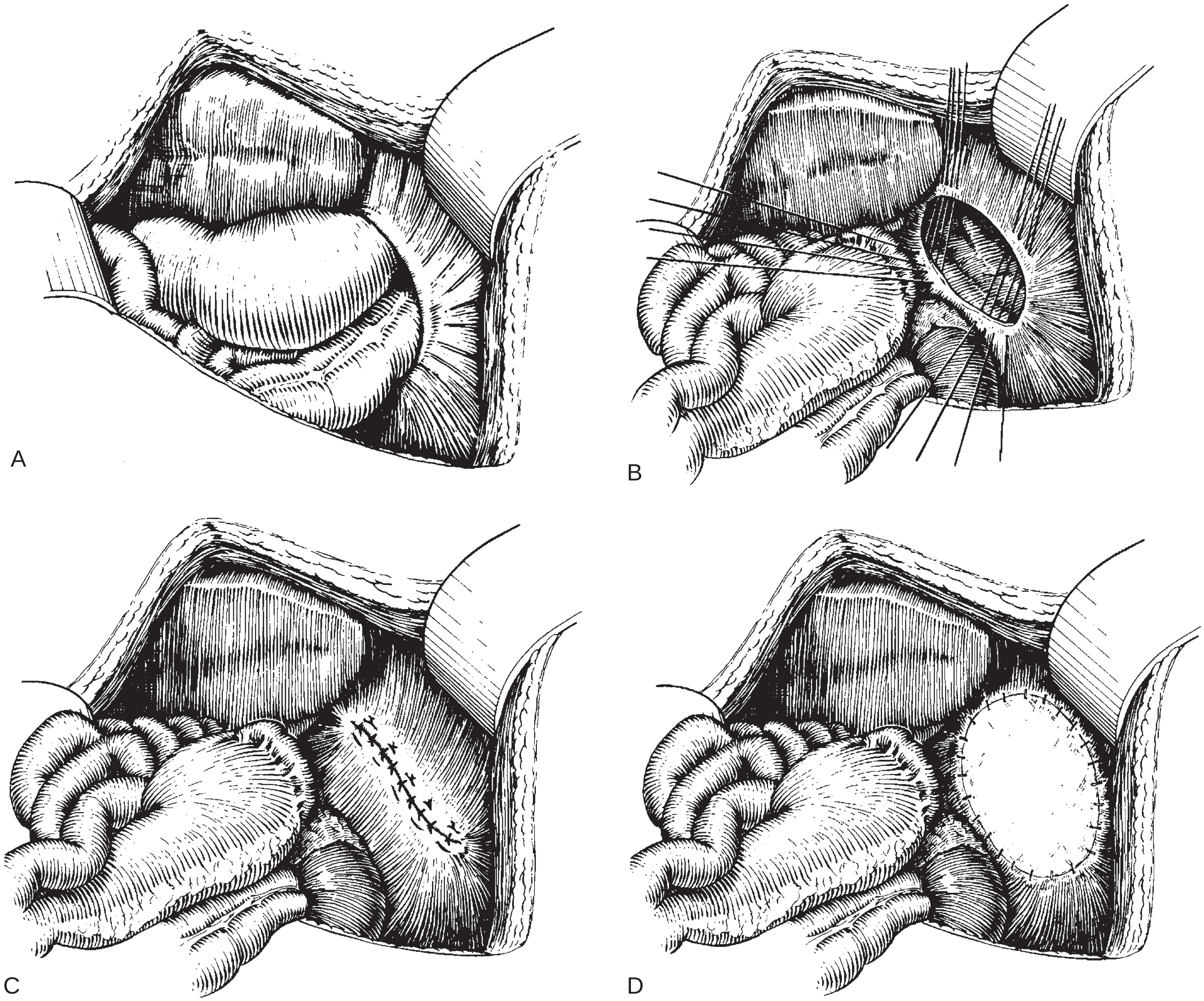



**FIGURE 63-5** **A,** Schematic drawing of an unreduced left congenital diaphragmatic hernia as seen from the abdomen. **B,** The same hernia but now reduced, demonstrating that the spleen is usually the last organ to be reduced from the chest cavity. Sutures have been placed for a primary repair. **C,** Completed primary repair of a left congenital diaphragmatic hernia. **D,** Repaired left congenital diaphragmatic hernia using prosthetic material. (From Spitz L, Coran AG [eds]: Rob & Smith's Pediatric Surgery. London, Chapman & Hall, 1996.)

recurrent herniation is either the small or large bowel, intestinal adhesions to the disrupted diaphragm or intrathoracic organs may compromise attempted closure. Repair is most commonly approached through the abdomen but can be accomplished through a thoracotomy as well. If adequate diaphragmatic tissue is present, then primary reapproximation should be attempted. Otherwise, different techniques for prosthetic material insertion have been tried [269,276,280] Because most recurrent CDH occur after initial patch repair and often well away from the neonatal period, once the baby is more stable, repair using a latissimus dorsi muscle flap through a thoracic approach may provide the best means to prevent further recurrence.[281]

## Anesthesia

To avoid the stresses of transport and sudden changes in ventilation parameters imposed by a trip to the operating room, a number of centers have adopted the policy of performing surgical repair of CDH infants in the neonatal intensive care unit. This change in location allows for the lowest degree of disruption in the neonate's environment. Anesthesia is achieved by intravenous narcotic and muscle relaxant techniques. With intravenous anesthetics, the infant ventilator can be used continuously rather than a conventional anesthesia machine.

## Postoperative Management

Postoperative management should continue the trends and goals established before the operative procedure. Ventilator support should be tailored to keep preductal $Sa_{O_2}$ greater than 90% and $P_{CO_2}$ less than 60 mm Hg.[282] Echocardiograms should be obtained routinely to assess pulmonary hypertension, shunt flow, and ventricular performance. Therapeutic interventions discussed previously may be used if respiratory decompensation develops. Weaning from ventilator support should be slow and deliberate as tolerated by the infant.

Meticulous attention to fluid status must be maintained, particularly in the immediate postoperative period. As a result of surgical intervention, these infants are often hypovolemic and frequently require extra volume administration over time.

## EXTRACORPOREAL MEMBRANE OXYGENATION

Even with recent advances in treatment strategies, overwhelming respiratory failure requiring ECMO support occurs in 10% to 20% of CDH infants.[206,283–285] Initially, infants were placed on ECMO after developing respiratory failure following the immediate repair of the diaphragmatic defect. With the evolution of delayed surgical repair, ECMO is now considered a part of the preoperative stabilization process.

Clinical criteria for determining ECMO use in infants with CDH have been based on factors predictive of at least an 80% mortality rate with mechanical ventilation.[214] A number of parameters have been proposed, including the calculation of the oxygenation index (OI) and the alveolar–arterial oxygen difference $AaDo_2$. For CDH patients, the most common reason for the initiation of ECMO was an OI of 40 or greater, and it is often considered for an OI as low as 25.[283] Generally accepted criteria for initiating ECMO support for neonatal respiratory failure based on $AaDo_2$ criteria include a value of 610 or greater despite 8 hours of maximal medical management. It must be realized that such criteria continue to be institution specific and that no calculations can replace clinical judgment and frequent bedside assessment. Failure to improve in the setting of severe pulmonary hypertension and progressive hypoxemia despite maximum medical intervention remains a valid qualifying criterion for ECMO support.

Controversy still exists as to whether ECMO support should be offered to all infants with CDH and respiratory failure.[32,140,286,287] The issue of severe pulmonary hypoplasia incompatible with life must be kept in mind when ECMO is being considered. This intervention is successful when used to support an infant with a reversible process of pulmonary hypertension. However, it is not a treatment for those infants with irreversible hypoplasia. Differentiating these infants on clinical parameters can be quite difficult. A newborn with a CDH who is unable to reach a preductal oxygen saturation level of at least 90% or a markedly elevated $Pco_2$ level unresponsive to any type of ventilatory intervention during the pre-ECMO course has a high likelihood of having irreversible hypoplasia.[179,289] On the other hand, others have proposed that all infants should be ECMO candidates. Ultimately the decision to use ECMO is a clinical decision. If the infant's tissue oxygen requirements are not being met, as manifest by end-organ failure, despite best conventional care, ECMO is a reasonable consideration.

Although widely accepted as a treatment for the respiratory failure associated with CDH, the impact of ECMO on improving overall survival continues to be debated. Over the past decade, a number of studies have demonstrated improved survival rates in CDH infants with ECMO as part of the treatment strategy.[283,290,291] However, other institutions have either not noted any improvements resulting from ECMO or have been able to manage their infants without it with equivalent success.[137,248,292,293,301] Overall survival rates of infants treated with ECMO vary from 34% to 87% and are clearly dependent on a number of variables, including gestational age and birth weight, respiratory function, and the degree of pulmonary development and associated pulmonary hypertension.[219,256,292,294] The impact of barotrauma and oxygen toxicity from overly aggressive respiratory care strategies on outcome cannot be overemphasized. As conventional treatment strategies continue to improve, ECMO use and concomitant survival rates following ECMO may decrease.

A number of surgical issues are relevant in the management of CDH infants while on ECMO. Both venovenous and venoarterial techniques have been reported to be equally effective in supporting patients while on bypass.[284,295] With venovenous bypass, severe right-sided heart failure can be managed temporarily with a $PGE_1$ infusion to keep the ductus open until the pulmonary hypertension resolves or by converting to venoarterial support. The timing of the surgical repair of the defect in relation to ECMO support remains variable. As a result of the acceptance of delayed surgical repair as a treatment strategy, more than 90% of CDH infants requiring ECMO support are placed on bypass before undergoing surgical repair.[242] Surgical repair of the defect while on ECMO can then be accomplished but has been associated with hemorrhagic complications in 60% of the patients.[244,296] Survival rates after surgery on ECMO have varied from 43% to 80%.[287,297,298] To minimize the risk of hemorrhagic complications, a number of techniques have been proposed, including the use of heparin-bonded ECMO circuits, performance of the surgical repair just before expected decannulation, and aggressive management of the anticoagulant status of the infant, including the use of antifibrinolytic therapy. Because of the coagulation problems, less than 20% of infants are reportedly repaired while on ECMO.[299] The majority undergo repair after the completion of ECMO. This delayed operative approach, sometimes not occurring until several days after decannulation, has been extremely successful, with survival rates of almost 80% and higher.[258,284,300] However, there are currently no available studies comparing either pathway.

## OUTCOME

Survival rates for infants born with a CDH vary from approximately 60% to 90% because of the use of more physiologic treatment strategies, including "gentle ventilation" techniques, high-frequency ventilation, cardiovascular pharmacologic support, and ECMO.* With the gradual improvement in survival rates over the past 2 decades, there is a greater appreciation for issues related to the long-term development of CDH survivors and the frequency of associated morbidities, as a greater number of physiologically compromised infants are surviving beyond the neonatal period. It is now recognized that CDH survivors are at significant risk for chronic neurologic, developmental, gastrointestinal, nutritional, pulmonary, musculoskeletal, and other disorders. Late deaths have been reported in approximately 10% of initial survivors, mainly because of the consequences of persistent pulmonary hypertension or iatrogenic complications.[19,39,306,307] The requirement for coordinated long-term follow-up and care of these patients has become evident from studies carried out over the past decade.[303,307a,308]

Pulmonary issues are the most common long-term problems in the postnatal period and include chronic lung disease or bronchopulmonary dysplasia, reactive airway disease,

*References 191, 206, 211, 241, 287, 301–305.

pulmonary hypertension, and pneumonia. Pulmonary developmental studies have shown that alveolar multiplication continues for several years after birth. However, a normal number is never achieved in CDH hypoplastic lungs. Over time, the alveoli in both lung fields may become emphysematous, as the contralateral lung may herniate across the mediastinum on chest radiographs. Gradual remodeling of the pulmonary vascular bed occurs. However, vascular growth may not match alveolar growth.[309,310] Pulmonary function testing remains the most useful test, because ventilation-perfusion studies have been associated with conflicting reports on pulmonary growth.[311]

Immediately following surgical repair of the hernia and for the first 6 months of life, abnormalities in pulmonary function values have been reported in such measurements as functional residual capacity (FRC), compliance (C), airway resistance (R), and maximum expiratory flow rate at FRC.[151,312,313] Significant improvements in lung function become evident during the first year of life, with only mild abnormalities in subsequent tests noted after 2 years of age, indicating that lung function does improve over time. These improvements in lung function parameters, such as compliance and airway resistance, correlate with the growth of the infant, and any compromise of the nutritional status of a CDH infant should raise concern about lung growth and development.[19] Chronic lung disease has been reported in CDH survivors, particularly in those requiring ECMO support.[314,315] Whether this finding is related to the pathology of the disease or has been induced iatrogenically resulting from techniques of ventilation is unclear.[250] Treatment strategies for these patients have included the use of supplemental oxygen, bronchodilator therapy, corticosteroids, diuretics, and appropriate immunizations. Prolonged ventilator support and tracheostomy may be required in a small percentage of patients.[316]

In long-term studies of pulmonary function in survivors, many adolescents and adults have been found to have nearly normal exercise capacity and cardiorespiratory response to exertion.[151,315,317–321] Abnormalities in such parameters as forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), and maximum midexpiratory flow and peak expiratory flow rates indicate that obstructive and restrictive ventilatory impairments are present in up to 50% of survivors.[311,318,320,322] The functional consequences of these flow abnormalities are reportedly minimal.

The risk of pneumonia in CDH survivors, particularly in infancy and early childhood, is significant and has been reported in up to 35% of patients by the age of 12. Viral bronchiolitis, particularly with respiratory syncytial virus (RSV), is a concern in the first 3 years of life.[151,323]

Although it is known that patients with congenital heart disease and CDH have a poor prognosis, the long-term consequences of structural cardiac abnormalities in survivors are unknown. Although the frequency of cardiovascular malformations ranges from 11% to 17% and includes major structural defects, such as atrial and ventricular defects, conotruncal defects, and left ventricular outflow tract obstructive defects, the risk of death in these patients can be as high as 3 times that for patients with CDH alone.[48,324] Prolonged elevation in pulmonary artery pressure, whether it results from pulmonary hypoplasia, bronchopulmonary dysplasia, or structural cardiac disease, impacts survival, and late deaths have been associated with persistent pulmonary hypertension. Pulmonary artery pressures determined by echocardiography normalize in approximately 50% of all patients with CDH by 3 weeks of age but can remain elevated for months in up to one third of surviving infants.[256,307,325]

A high incidence of neurodevelopmental abnormalities have been detected in CDH survivors. Developmental delay has been reported in a number of surviving infants as well as abnormalities in motor and cognitive skills.[314,326] Both motor and language problems are evident within the first 3 years of life, and infants with motor problems detected at age 1 year were more likely to have abnormal postnatal neuroimaging studies.[327–329] Progressive sensorineural hearing loss has been demonstrated in up to 50% or more of CDH survivors with no discernable etiology. Its onset appears to be within the first 2 years of life, but late onset deficits in patients with previously normal audiology tests have been reported.[62,330] It is a progressive abnormality and requires frequent audiology follow-up. Aggressive use of aminoglycoside antibiotics and furosemide diuretics may be part of the etiology. Other neurologic findings reported in CDH survivors include visual disturbances, seizures, and abnormal computed tomography (CT) and MRI studies.[314,331] Most studies have implicated ECMO as a factor in these neurologic problems, but infants treated without ECMO are also at risk.[332–334]

CDH survivors have a high incidence of gastrointestinal conditions, of which gastroesophageal reflux is the most significant (Fig. 63-6).[52,314,335,336] The condition may occur in as many as 80% of patients after CDH repair and in 60% of long-term survivors.[337] Infants requiring patch closure of the defect, having an intrathoracic position of the stomach at the time of repair, or requiring ECMO support are at higher risk for developing symptomatic reflux.[52,336a–338] Antireflux surgery for severe disease is required in 15% to 35% of cases. Nutritional and growth-related problems have been found in a significant number of survivors.[92,339,340] Aggressive nutritional management using gastrostomy feedings may be required.[303]

A number of skeletal disorders have been reported, including chest wall deformities and scoliosis.[341,342] Chest wall

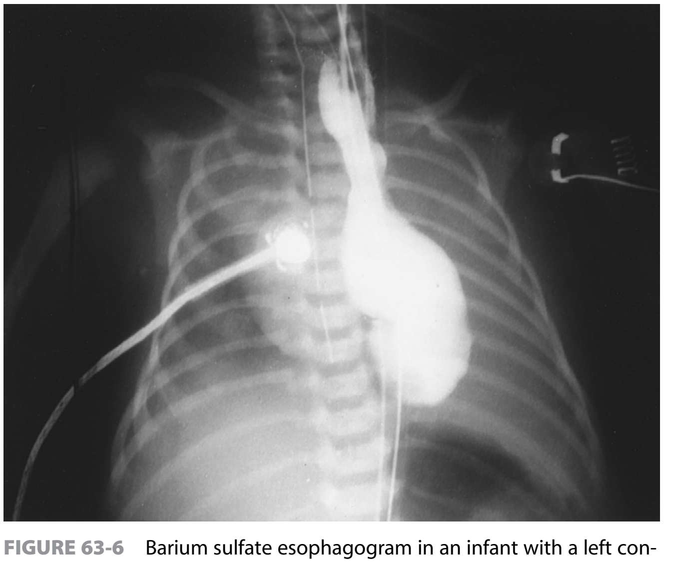


**FIGURE 63-6** Barium sulfate esophagogram in an infant with a left congenital diaphragmatic hernia demonstrating a dilated, ectatic esophagus. The stomach was oriented vertically and emptied slowly.

deformities have been associated with patch repair of the defect. Most defects are minor, and treatment of these problems has included initial attempts at bracing followed by surgical correction if progressive.

Recurrent diaphragmatic hernia and small bowel obstruction are the dominant surgical challenges following initial repair. Recurrent hernias may occur in up to 50% of infants undergoing patch repair of the defect and in 10% of primary repairs, and they tend to occur in the first 4 years of life.[342–344] A small bowel obstruction may occur in a small percentage of patients and may be related to adhesions, reherniation, or, rarely, a volvulus. Chylothorax can also occur after both primary and patch closure and may require surgical intervention if conservative management is unsuccessful.[65]

There is a growing realization that infants with a right-sided diaphragmatic defect may present with management challenges and outcomes different from those with left-sided defects. Herniation of the liver into the right chest can be a surgical challenge in diaphragmatic repair, and cases of hepatopulmonary fusion have been reported.[345–347] Infants with right-sided defects may have a higher requirement for patch repair of the diaphragm as well as for ECMO support.[348,349]

Over the last decade, it has become clear that CDH survivors present many complex management challenges and require lifelong medical surveillance and follow-up. Comprehensive multispecialty clinics that provide specialty physician and support services, along with evidence-based guidelines, are important in advancing the care of these patients.[307a,342]

## FUTURE THERAPIES

Despite the advancements that have been made in treating infants with CDH, it still represents a frustrating and complex clinical problem. As the striking variance in survival rates attests, no currently used therapeutic intervention or management strategy has emerged for widespread successful application. Even with the increasing success of current treatment strategies, such as permissive hypercapnia, delayed operative repair, antihypertensive pharmacology, and advanced ventilatory techniques, a cohort of infants refractory to these interventions continue to be candidates for novel treatments.

Fetal intervention in the management of CDH remains highly controversial. The concept of fetal surgical intervention evolved from the experimental observations in lambs that the reduction of compressive forces on the lung resulted in continued pulmonary growth and development.[91,98,101,194,350] With the development of fetal surgical techniques, initial studies attempted direct surgical repair of the defect with reduction of the herniated contents.[351,352] When no clinical advantage in survival was demonstrated, this approach was terminated. Experimental evidence for the important role of lung fluid dynamics in fetal lung development[101,353–355] has subsequently triggered interest in the role of tracheal occlusion (TO) as a fetal intervention to promote in utero lung growth.[175,356–359] The clinical technique has evolved from the open or fetoscopic placement of extraluminal clips on the trachea to the insertion of an endoluminal device with either a foam plug or detachable balloon. Experimentally, lung growth was further enhanced using intraalveolar fetal albumin administration.[360] Although TO has been shown in some studies to induce changes in pulmonary morphology, pathologic changes, such as a decrease in type II (surfactant-producing) pneumocytes, have also been noted.[356,361–365] Improvement in physiologic lung function was seen in some studies but not in others.[252,310,358,366] Local effects on tracheal structure have included tracheomegaly.[367,368] Although this intervention in the prenatal management of fetuses with CDH has been reported in several institutional studies,[197–199] there are no randomized trials in the North American setting demonstrating a clinical benefit in improving postnatal survival in a cohort of CDH fetuses with agreed upon prohibitive mortality.[193,196,352] The role of tracheal occlusion in the treatment of CDH remains experimental and unproven. Continued evolution in the techniques of this procedure as well as bona fide, randomized clinical trials will continue to generate interest and perhaps validation of this intervention.

Liquid ventilation techniques have been attempted in CDH infants while on ECMO (Fig. 63-7).[369,370] After perfluorocarbon administration, significant increases were reported in $Pa{O_2}$ levels and in static total pulmonary compliance measurements accompanied by a fall in $Pa{CO_2}$ levels. No adverse side effects were noted. Extensive studies are required to examine this newest form of ventilation before its efficacy can be judged.

Based on the observations of fetal lung growth induced by tracheal occlusion, inducement of postnatal lung growth with static distention has also been investigated. During the course of the liquid ventilation experiments, pulmonary distention as a result of perfluorocarbon administration was observed. Its use as a potential treatment to induce postnatal lung growth in CDH patients was then reported.[371–373] Preliminary studies have shown significant radiographic enlargement of the lung and improved gas exchange. Animal studies have supported the concept of accelerated postnatal lung growth using perfluorocarbon distension.[374] Further study of this potential intervention is required.

Lung transplantation has also been used anecdotally in the surgical treatment of CDH.[375,376] Both unilateral and bilateral

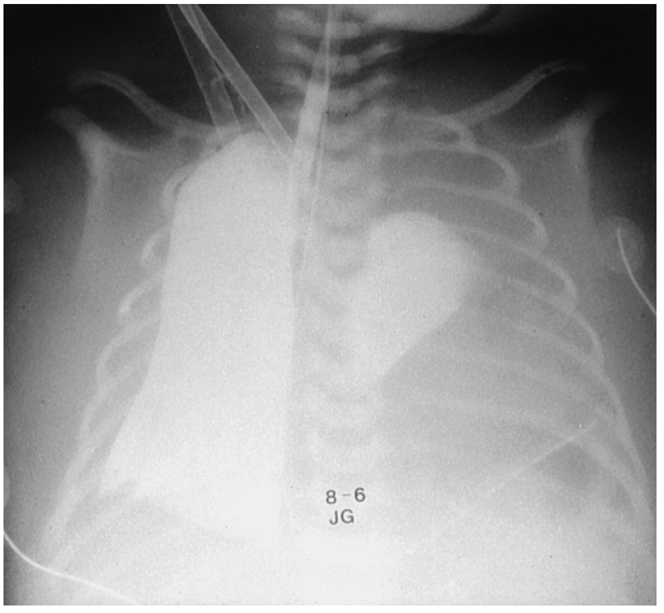



FIGURE 63-7 Chest radiograph of a left congenital diaphragmatic hernia being supported with extracorporeal membrane oxygenation. The lungs have been opacified with perflubron for liquid ventilation. The pulmonary hypoplasia can be appreciated. (Courtesy R. B. Hirschl, MD.)

transplants have been attempted. Currently, not enough experience exists to recommend this form of treatment.

The potential role of pharmacologic augmentation of pulmonary growth and development is currently being investigated. The combined administration of thyrotropin-releasing hormone and glucocorticoid therapy has been studied in a chemically induced rat model of CDH, with positive effects on lung growth.[24,377] It is also known that a number of growth factors are crucial to normal pulmonary development. It has been proposed that perhaps selected administration of one or several of these pharmacologic agents or growth factors may be able to reverse the pulmonary hypoplasia of CDH.[60,377] Continued experimental work using the nitrofen model of CDH may uncover new candidates to promote lung growth and development either prenatally or after birth.

Finally, given the current wide-ranging survival rates at various institutions, an in-depth study and evaluation of current management techniques and outcomes must be made. The efforts of the CDH Study Group, Extracorporeal Life Support Organization (ELSO),[378] and the Canadian Pediatric Surgery Network to interpret very heterogeneous data are an encouraging beginning. Such studies might result in the refinement and consolidation of current practices into a universally effective treatment strategy.

# Foramen of Morgagni Hernia

The diaphragmatic hernia of Morgagni is located anteromedially on either side of the junction of the septum transversum and the anterior thoracic wall. The defect occurs through the embryologic space of Larrey. Occasionally, bilateral Morgagni hernias communicate in the midline, constituting a large anterior diaphragmatic defect extending all the way across the midline from right to left. Typically, a sac is present, and herniation of the colon or small bowel is usually discovered to the right or left of the midline. Morgagni hernias account for less than 2% of diaphragmatic defects. Although this defect may be observed in neonates, it usually presents more commonly in older children or adults. Associated anomalies may be present and include malrotation, cardiac defects, and trisomy 21.[379,379a] An anterior midline deficiency in the diaphragm, with or without the other elements of the pentalogy of Cantrell, with free pericardial and peritoneal communication may allow herniation of intestine into the pericardium. The hernia is often discovered incidentally as a mass or air–fluid level on a chest radiograph. A barium enema or a CT scan may confirm the diagnosis.

Operative correction is easily performed through an upper transverse abdominal incision. The diaphragm is sutured to the underside of the posterior rectus sheath at the costal margin after reduction of the hernia and resection of the sac. Laparoscopic and thoracoscopic techniques have also been used to repair this defect, but the laparoscopic approach is generally favored.[380–384]

# Eventration of the Diaphragm

Eventration of the diaphragm may be either congenital or acquired. The congenital form may be indistinguishable from a diaphragmatic hernia with a sac, and symptoms may be similar for the most severe forms, while small localized eventrations are usually discovered incidentally on chest radiographs. A lateral chest radiograph is essential to the evaluation of eventration, especially on the right side. A modest posteromedial eventration that looks much more significant on an anteroposterior view is unlikely to benefit from surgical intervention. The acquired lesion is due to paralysis of the phrenic nerve, which may occur from injury during repair of congenital heart defects or through brachial plexus injury at birth (Erb palsy).[385] In these cases, the diaphragmatic muscle is usually present in its normal distribution, but it is attenuated and inactive.

There may be no symptoms whatsoever, even in the presence of a large eventration, although the findings may range from wheezing, frequent respiratory infections, and exercise intolerance to extreme respiratory distress. Diagnosis is usually made on fluoroscopy of the chest or with ultrasound examination. In such cases, the diaphragm moves paradoxically with respiratory motion. This paradoxic movement may be so marked that it results in severe compromise of gas exchange. Although pneumoperitoneum was used frequently in the past as a diagnostic modality, CT or MRI is used more often today. A right diaphragmatic eventration may be difficult to differentiate from a CDH, because the liver may block the defect; sometimes thoracoscopy is required for diagnosis.

A small eventration may be left untreated. Repair is indicated when a large functional deficit in the function of the ipsilateral lung on ventilation/perfusion studies is found in an apparently asymptomatic patient. In such cases, the compressed lung will not grow well. Repair may be performed either through the abdomen or the chest, but, in most cases, a low thoracotomy is recommended, because this approach allows identification and preservation of phrenic nerve fibers in case the damaged nerve recovers. A thoracic approach is especially preferred for right diaphragmatic eventration, because the liver would make an abdominal approach more difficult. Through this approach, the diaphragm is best plicated with nonabsorbable interrupted 2-0 sutures. A radial or peripheral incision may also be made in the diaphragm and the edges overlapped and sutured. It is important to reef up and overlap the diaphragm so that it is taut—overcorrecting it somewhat, because invariably, the muscle will stretch and the eventration will recur if this is not done. Although phrenic nerve injury may spontaneously recover, diaphragmatic plication for acquired eventration is frequently necessary to wean infants from ventilatory support. Plication can also be accomplished by either a laparoscopic or thoracoscopic approach. This operation does not preclude normal diaphragmatic function, should phrenic nerve function return.

### *Acknowledgments*

For Carol and Judy, who wait . . . and wait. . . .

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 64

# Cysts of the Lungs and Mediastinum

N. Scott Adzick and Diana L. Farmer

Familiarity with normal variations and potential pathologic abnormalities in the lung and mediastinum is necessary, because questions frequently arise on evaluation of chest radiographs. The possibility of infection, respiratory difficulty, and airway obstruction from space-occupying lesions makes mandatory the expeditious evaluation and treatment of children with a mediastinal or pulmonary cystic mass. The prognosis of mediastinal and lung cysts in most children is good.

## Embryology

Mediastinal and lung cysts are developmental in origin. Embryologic development pertinent to mediastinal masses is mostly related to the foregut and the thymus. The foregut is first recognizable as an epithelial-lined tube late in the third postconceptual week, by which time the respiratory groove (tracheal bud) is visible. Septation of the esophagus and the trachea occurs over the ensuing 2 weeks by a process of cephalocaudal growth of both structures, lateral infolding of the foregut, and caudocranial septation of the trachea and esophagus. During this interval, there is proliferation of foregut epithelium that almost completely obliterates the esophageal lumen before subsequent tubularization. Differentiation of both esophageal and tracheal epithelium is recognizable in the fourth week. The process is largely completed by day 32 to 34. It is presumed that incomplete tubularization after the epithelial proliferative phase results in foregut duplication cysts.[1]

The thymus develops as paired primordia from the ventral third pharyngeal pouch. During the seventh postconceptual week, the primordia elongate caudad and ventromedially to their normal position anterior to the aortic arch. At that time, the two thymic lobes attach to each other by connective tissue but not parenchyma. Initially, thymic primordia contain a thymopharyngeal duct, which is obliterated after complete descent. Incomplete descent may result in solid or cystic masses in the neck. Lack of obliteration of the thymopharyngeal duct results in congenital cysts of the thymus.[2]

Prenatal lung development is described in Chapter 63. A mixed lung lesion consisting of a combination of bronchogenic cyst, bronchopulmonary sequestration, and congenital cystic adenomatoid malformation suggests a common embryologic link for these malformations, but the precise embryologic causes are unknown.[3]

## Cystic Lung Lesions

### DIAGNOSIS AND TREATMENT

The true incidence of cystic lung lesions is unknown, because there are no population-based studies in the literature. Congenital cystic adenomatoid malformation was first described as a distinct pathologic entity by Chin and Tang in 1949.[4] Before then, congenital cystic adenomatoid malformation was grouped under the general diagnosis of congenital cystic lung disease, along with bronchopulmonary sequestration, congenital lobar emphysema, and bronchogenic cyst.

Prenatal diagnosis provides insight into the in utero evolution of fetal lung lesions, such as congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS), and congenital lobar emphysema. Serial sonographic study of fetuses with lung lesions has helped define the natural history of these lesions, determine the pathophysiologic features that affect clinical outcome, and formulate management based on prognosis.[5–10] A decade ago, we reported a series of more than 175 prenatally diagnosed cases from the Children's Hospital of Philadelphia and the University of California, San Francisco, and our clinical experience over the last 15 years at the Center for Fetal Diagnosis and Treatment at the Children's Hospital of Philadelphia now extends to more than 700 cases. We found that the overall prognosis depends on the size of the lung mass and the secondary physiologic derangement: A large mass causes mediastinal shift, hypoplasia of normal lung tissue, polyhydramnios, and cardiovascular compromise, leading to fetal hydrops and death (Fig. 64-1).[11]

Huge fetal lung lesions have reproducible pathophysiologic effects on the developing fetus. Esophageal compression by the thoracic mass causes interference with fetal swallowing of amniotic fluid and results in polyhydramnios. Polyhydramnios is a common obstetric indication for ultrasonography; so, a prenatal diagnostic marker exists for many large fetal lung tumors. Support for this concept comes from the absence of fluid in the fetal stomach in some of these cases and the

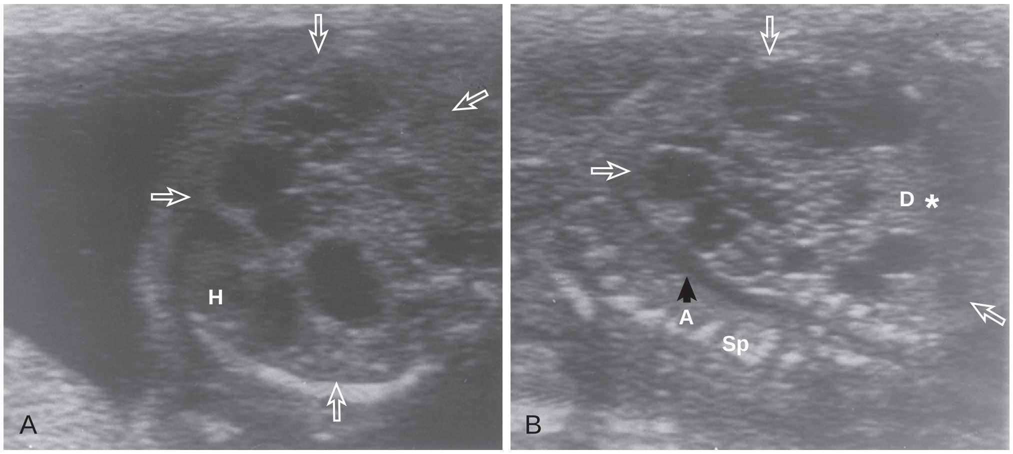



**FIGURE 64-1** **A,** Transverse ultrasonographic scan of the fetal thorax at 22 weeks' gestation. A large multicystic mass in the left hemithorax (*open arrows*) displaces the mediastinum to the right. H, Heart. **B,** Sagittal ultrasonographic scan of the fetal thorax and abdomen shows a mixed cystic/echogenic mass (*open arrows*) of the left hemithorax that flattens the left hemidiaphragm (*D*)*. A, Aorta; Sp, spine. This lesion grew and resulted in fetal hydrops. Fetal surgical resection of the affected lobe was performed successfully at 23 weeks' gestation, delivery occurred at 35 weeks' gestation, and the infant survived.

alleviation of polyhydramnios after effective fetal treatment.[11] The hydrops is secondary to vena caval obstruction and cardiac compression from large tumors, causing an extreme mediastinal shift. Like CCAMs, a fetal BPS can also cause fetal hydrops, either from the mass effect or from a tension hydrothorax that is the result of fluid or lymph secretion from the BPS.[11] Hydrops is a harbinger of fetal or neonatal demise and manifests as fetal ascites, pleural and pericardial effusions, and skin and scalp edema. Although there is some association of both polyhydramnios and hydrops with fetal lung lesions, experience indicates that either can occur independently of the other.

Smaller thoracic lesions can cause respiratory distress in the newborn period, and the smallest masses may be asymptomatic until later in childhood when infection, pneumothorax, or malignant degeneration may occur. Large fetal lung tumors may regress in size on serial prenatal sonography illustrating that improvement can occur during fetal life.[12–14] In particular, many noncystic BPSs dramatically decrease in size before birth and may not need treatment after birth.[11] However, fetal lung lesions that seem to disappear on prenatal ultrasonography and are not seen on neonatal chest radiograph still require evaluation by chest computed tomography (CT) scan, which will frequently detect a lesion.[15]

Recently, fetal CCAM volume has been determined by sonographic measurement using the formula for a prolate ellipse (length × height × width × 0.52). A CCAM volume ratio (CVR) is obtained by dividing the CCAM volume by head circumference to correct for fetal size. A CVR greater than 1.6 is predictive of increased risk of hydrops, with 80% of these CCAM fetuses developing hydrops. The CVR may be useful in selecting fetuses at risk for hydrops and thus needing close ultrasound observation and possible fetal intervention.[16] Serial CVR measurements have shown that CCAM growth usually reaches a plateau by 28 weeks' gestation. For fetuses at less than 28 weeks' gestation, the recommendation is twice-weekly ultrasound surveillance if the CVR is greater than 1.6 and initial weekly surveillance for fetuses with smaller CVR values.

The finding that fetuses with hydrops are at very high risk for fetal or neonatal demise led to the performance of either fetal surgical resection of the massively enlarged pulmonary lobe (fetal lobectomy) for cystic/solid lesions or thoracoamniotic shunting for lesions with a dominant cyst.[11,17,18] It is possible that administration of a short course of maternal betamethasone may impair CCAM growth in some cases and lead to amelioration of hydrops; so, we recommend this therapy for fetal CCAM cases with a CVR greater than 1.4.[19] Lesions with associated hydrops that are diagnosed late in gestation may benefit from resection using an ex utero intrapartum therapy (EXIT) approach.[20] The fetus with a lung mass but without hydrops has an excellent chance for survival with maternal transport, planned delivery, and neonatal evaluation and surgery.

Neonates with respiratory compromise resulting from a cystic lung lesion require prompt surgical resection, usually by lobectomy. In the most severe cases, ventilatory support with high-frequency ventilation or extracorporeal membrane oxygenation may be required. In asymptomatic neonates with a cystic lung lesion, we believe that elective resection is warranted because of the risks of infection and occult malignant transformation.[21] Malignancies consist mainly of pulmonary blastoma and rhabdomyosarcoma in infants and young children and bronchioloalveolar carcinoma in older children and adults.[22–26] After confirmation of CCAM location by postnatal chest computed tomography with intravenous contrast, we recommend elective resection at 1 month of age or older. An experienced pediatric surgeon can safely perform a thoracotomy and lobectomy in infants with minimal risk of morbidity,[27] and experience with thoracoscopic resection has been growing.[28] Early resection also maximizes compensatory lung growth; long-term follow-up has shown normal pulmonary function.[29,21] In contrast, we have usually followed patients with a tiny, asymptomatic, noncystic extralobar bronchopulmonary sequestration if we are confident of the diagnosis based on postnatal imaging studies. We do not favor the approach of catheterization and embolization for the treatment of larger bronchopulmonary sequestration lesions but instead opt for surgical resection.

## CONGENITAL CYSTIC ADENOMATOID MALFORMATION

CCAM is characterized by an "adenomatoid" increase of terminal respiratory bronchioles that form cysts of various sizes. Grossly, a CCAM is a discrete, intrapulmonary mass that contains cysts ranging in diameter from less than 1.0 mm to more than 10.0 cm. Histologically, CCAM is distinguished from other lesions and normal lung by (1) polypoid projections of the mucosa, (2) an increase in smooth muscle and elastic tissue within cyst walls, (3) an absence of cartilage (except that found in "entrapped" normal bronchi), (4) the presence of mucus-secreting cells, and (5) the absence of inflammation.[30] Although the tissue within these malformations does not function in normal gas exchange, there are connections with the tracheobronchial tree, as evidenced by air trapping that can develop during postnatal resuscitative efforts. Cha has identified two histologic patterns of fetal CCAM: pseudoglandular and canalicular.[31] Stocker defined three types of CCAM (types I to III) based primarily on cyst size,[30,32] but this categorization has little clinical relevance. Prenatally diagnosed CCAMs are divided into two categories based on gross anatomy and ultrasound findings.[5] Macrocystic lesions contain single or multiple cysts that are 5.0 mm in diameter or larger on prenatal ultrasonography, whereas microcystic lesions appear as a solid echogenic mass on sonography.

The overall prognosis for prenatally diagnosed lesions depends primarily on the size of the CCAM rather than on the lesion type, and the underlying growth characteristics are likely to be important. Resected large fetal CCAM specimens demonstrate increased cell proliferation and markedly decreased apoptosis compared with gestational-age-matched normal fetal lung tissue.[33] Examination of factors that enhance cell proliferation or down-regulate apoptosis in CCAM may provide further insights into the pathogenesis of this tumor and may suggest new therapeutic approaches. Fetal CCAMs that grew rapidly, progressed to hydrops, and required in utero resection showed increased platelet-derived growth factor *(PDGF)* gene expression and PDGF protein production compared with either normal fetal lung or term CCAM specimens.[34] Flake's group showed that transuterine ultrasound-guided microinjections of adenoviral vector encoding the *RFGF10* transgene leads to fibroblast growth factor (FGF)10 overexpression and consequent CCAM lesions in fetal rat lung. Remarkably, FGF10 overexpression in the proximal tracheobronchial tree during the pseudoglandular stage of rat lung development resulted in large cysts, whereas FGF10 overexpression in the distal lung parenchyma during the canalicular stage resulted in small cysts, and the lesions showed the pathologic spectrum of human CCAM. These findings support a role for FGF10 in the induction of human-like CCAMs.[35]

CCAM usually arises from one lobe of the lung, with the lower lobes being the most common site. Bilateral lung involvement is rare. CCAM lesions have an equal left- and right-sided incidence. For those children who are not diagnosed as a fetus or newborn, the usual clinical presentation is with infection in the CCAM area, probably because of failure of clearance of environmental bacterial pathogens. Other presentations include pneumothorax, reactive airway disease, and failure to thrive. There is no gender predominance. Associated anomalies in our experience are very uncommon.

## BRONCHOPULMONARY SEQUESTRATION

A BPS is a mass of nonfunctioning lung tissue that is supplied by an anomalous systemic artery and does not have a bronchial connection to the native tracheobronchial tree. There are two forms of sequestration: extralobar and intralobar. Extralobar sequestrations are completely separate from the normal lung and are surrounded by a separate pleural covering, whereas intralobar sequestrations are incorporated into the normal surrounding lung. An extralobar sequestration may reside in the chest, within the diaphragm, or in a subdiaphragmatic location. Intralobar and extralobar sequestrations can occur simultaneously. An entire lung can be sequestered, and bilateral sequestrations have been reported but are very rare.[36,37] Because of the foregut derivation, communication between the esophagus or the stomach and a BPS may occur and, if suspected, should be delineated preoperatively by upper gastrointestinal series.[38] Arterial blood supply to the BPS can arise from below or above the diaphragm, and venous drainage can be to either the pulmonary or the systemic venous circulation. The anomalous blood supply can result in high-output cardiac failure because of substantial arteriovenous shunting through the BPS[39] or bleeding with massive hemoptysis or hemothorax.[40]

On prenatal ultrasonography, a BPS appears as a well-defined echodense, homogeneous mass. Detection by color-flow Doppler of a systemic artery or arteries from the aorta to the fetal lung lesion is a pathognomonic feature of fetal BPS (Fig. 64-2).[41] However, if this Doppler finding is not detected, then an echodense microcystic CCAM and a BPS can have an identical prenatal sonographic appearance. Ultrafast fetal magnetic resonance imaging (MRI) may help differentiate CCAM from BPS.[42] Furthermore, there are prenatally diagnosed lung masses that display clinicopathologic features of

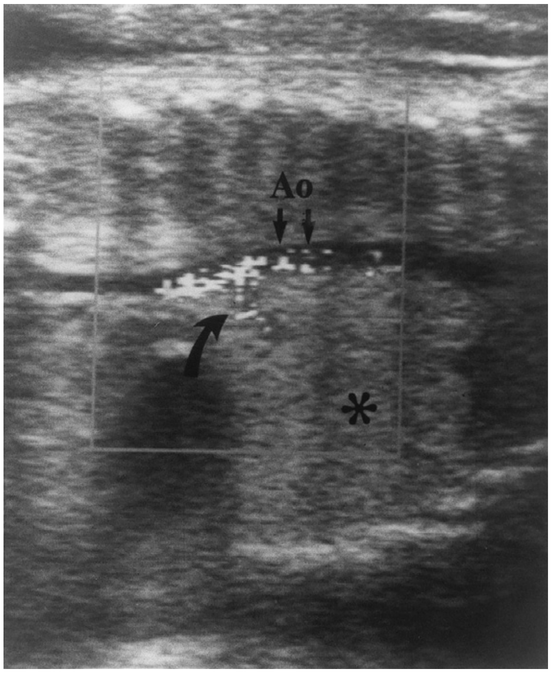



**FIGURE 64-2** By Doppler studies, a systemic artery (*curved arrow*) from the descending aorta (*Ao*) supplies the mass (*), consistent with the prenatal diagnosis of pulmonary sequestration.

both CCAM and sequestration-hybrid lesions, which suggests a shared embryologic basis for some of these lung masses.[43–45] The ability to differentiate intralobar and extralobar sequestration before birth is limited unless an extralobar sequestration is highlighted by a pleural effusion or is located in the abdomen (usually close to the left adrenal gland). There are no diagnostic hallmarks for the specific prenatal diagnosis of an intralobar sequestration.

Extralobar BPS has a predominance in males (3:1), is more common on the left side, and can be associated with conditions such as congenital diaphragmatic hernia, vertebral deformities, and congenital heart disease. Approximately 5% of neonates with a congenital diaphragmatic hernia will have an extralobar BPS, which is usually an incidental intraoperative finding. An isolated, tiny noncystic extralobar BPS rarely requires treatment. An intralobar BPS is most commonly seen in the medial basal or posterior basal segments of the lower lobes, left side more frequent than the right side. Upper lobe involvement is present in only 10% to 15% of cases. For those cases that are not prenatally diagnosed, the usual postnatal presentation of an intralobar BPS is recurrent pneumonia and even abscess formation within the BPS; thus resection (usually by lobectomy) is warranted. It is mandatory to identify and ligate the feeding systemic arterial vessel(s), which usually is found within the inferior pulmonary ligament.

## CONGENITAL LOBAR EMPHYSEMA

Several causes for congenital lobar emphysema (CLE) have been described,[46] but the fundamental mechanism is that the affected bronchus allows passage of air on inspiration but only limited expulsion of air on expiration leading to lobar overexpansion. Air trapping in the emphysematous lobe may be the result of (1) dysplastic bronchial cartilages creating a ball-valve effect or a complete bronchial atresia[47,48]; (2) endobronchial obstruction from inspissated mucus[49] or extensive mucosal proliferation and infolding[50]; (3) extrinsic compression of the bronchi from aberrant cardiopulmonary vasculature or enlarged cardiac chambers[51]; and (4) diffuse bronchial abnormalities that may or may not be related to infection.[52] Careful preoperative bronchoscopy may help delineate an intrinsic obstructive lesion.[47] The most common site of involvement for CLE is the left upper lobe (40% to 50%), followed by the right middle lobe (30% to 40%), right upper lobe (20%), lower lobes (1%), and multiple sites for the remainder.

Barotrauma associated with the treatment of bronchopulmonary dysplasia in preterm infants can result in acquired emphysema in which multiple areas of hyperinflation may be present.[53] Because of endotracheal tube positioning, right lower lobe involvement is common in these cases, which helps to differentiate acquired from congenital disease. Polyalveolosis, or the polyalveolar lobe first described by Hislop and Reid, has been found in some cases of congenital lobar emphysema.[54] The total alveolar number is increased several-fold in this condition, but the airways and arteries are normal for age in number, size, and structure. The polyalveolar lobe becomes overinflated and hyperlucent on chest radiography because of impaired air exchange in the affected lobe. Because clinical presentation and imaging cannot differentiate between true CLE and polyalveolar lobe, the term "congenital lobar overinflation" has been used to include both entities.[55]

Congenital lobar emphysema can be distinguished prenatally from other cystic lung lesions on ultrasonography by increased echogenicity and reflectivity compared with a microcystic CCAM, and the absence of systemic arterial blood supply compared with a BPS.[56,57] Progressive enlargement of these lesions prior to 28 weeks' gestation may be due to fetal lung fluid trapping in the lobe, analogous to the air trapping seen postnatally. Late in gestation, lobar emphysema may regress in size and echogenicity, rendering it indistinguishable from adjacent normal fetal lung.[57] Postnatal assessment is important because of the risk of postnatal air trapping in the emphysematous lobe. At the time of birth, the affected lobe may be radiopaque on chest radiography because of delayed clearance of fetal lung fluid. Prenatally diagnosed mainstem bronchial atresia results in massive lung enlargement, hydrops, and fetal death; ultrafast fetal MRI demonstrates that the entire lung is involved and that there are dilated bronchi distal to the mainstem atresia.[58] Congenital lobar emphysema is diagnosed at birth in about 25% of cases and by age 1 month in about 50%. The diagnosis is sporadic after 6 months of age. The earlier the onset of symptoms, the more likely the progression of lobar emphysema and the need for resection. Nevertheless, some infants have very mild symptoms that do not progress, and the emphysematous lobe remains stable and does not encroach on adjacent lung; so, resection is not required in these cases.[59] Besides chest radiography and CT (Fig. 64-3), a ventilation-perfusion scan can demonstrate delayed uptake and washout of the xenon radioisotope from the affected lobe and little blood flow through it. If the presentation is respiratory distress and pulmonary lobar hyperinflation, then the mainstay of management is resection of the emphysematous lobe. Positive-pressure ventilation may result in abrupt exaggerated air trapping in the lobe, with sudden cardiopulmonary decompensation; so, it is important for the surgeon to be present during anesthetic induction in the event that urgent thoracotomy is needed. At operation, the

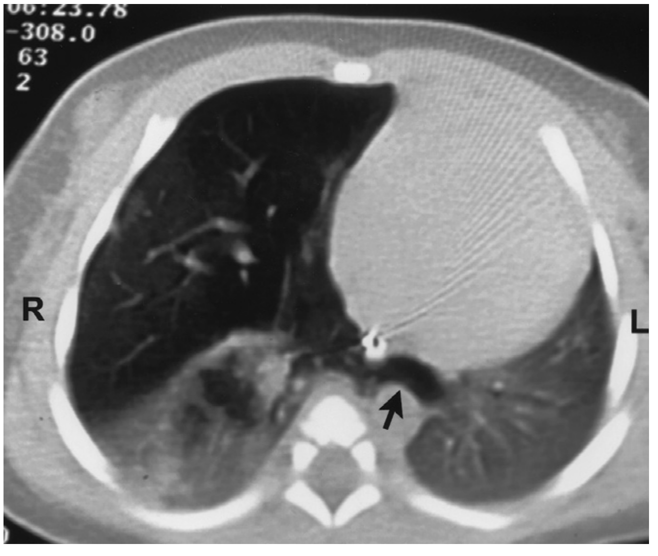



**FIGURE 64-3** Chest computed tomography (CT) scan from a neonate with congenital lobar emphysema involving the right middle lobe. There are dilated airspaces in the right middle lobe with compressive atelectasis of the right lower lobe. The mediastinum is shifted to the left, and a portion of the emphysematous lobe herniates across the midline posterior to the heart (*arrow*).

affected lobe will characteristically "pop out" through the thoracotomy wound. High-frequency ventilation,[60] selective bronchial intubation,[61] and endoscopic decompression of the emphysematous lobe[62] may be useful adjuncts in the preoperative management of patients with respiratory distress. Long-term pulmonary growth and function after lobectomy for congenital lobar emphysema is excellent.[63]

# Cystic Mediastinal Lesions

## CLINICAL FEATURES

The clinical manifestations of mediastinal lesions are the result of mass effects and are influenced by the location of the lesion within the chest. Many are asymptomatic, although the most important symptom of anterior and middle mediastinal masses is respiratory distress, particularly in infants when noisy, stridorous breathing or cyanosis while feeding is observed.[64] In older children, cough, chest pain, dyspnea, orthopnea, or, rarely, hemoptysis occurs.[65] Respiratory distress may be life threatening in all age groups.[66–69] Rapid onset of respiratory distress or symptoms of superior vena caval obstruction suggest lymphoma.[64,70] Although rare, infected teratomas have been reported to rupture into the bronchus, pleura, pulmonary artery, and pericardium.[65,71,72] Posterior mediastinal masses can be quite large and yet asymptomatic, often discovered incidentally on a chest radiograph taken for other indications. Less frequently, pain or symptoms of spinal cord compression lead to recognition.[73,74]

Reports from individual institutions regarding mediastinal masses may be biased by selection. If more recent series are compared with those published before 1967 (Table 64-1), an increase in malignancy, particularly of lymphomas and neuroblastoma, is evident.[64,70,72,74–79] Such is the case in a single large institutional series from Walter Reed Army

**TABLE 64-1**

**Incidence of Various Mediastinal Tumors**

| *Cyst/Neoplasm* | *King et al, 1982*[64] | *Simpson and Campbell, 1991*[81] | *Saenz et al, 1993*[131] | *Cohen et al, 1991*[80] | *Grosfeld, 1994*[89] | *Total* | *%* |
|---|---|---|---|---|---|---|---|
| **Neurogenic Tumors** | | | | | | | |
| Neuroblastoma/ganglioneuroblastoma | 20 | 16 | 32 | 13 | 50 | 227 | 33 |
| Ganglioneuroma | 17 | 9 | 14 | 8 | 14 | | |
| Neurofibroma | 4 | 4 | 3 | | 2 | | |
| Neurilemoma/schwannoma | 6 | 1 | 3 | 1 | 5 | | |
| Paraganglioma (pheochromocytoma) | 1 | | 2 | | | | |
| Primitive neuroectodermal tumor/ neurosarcoma | | | 2 | | | | |
| **Lymphomas** | | | | | | | |
| Hodgkin disease | 33 | 29 | 34 | 1 | 49 | 281 | 41 |
| Non-Hodgkin lymphoma | 54 | 34 | 6 | 3 | 38 | | |
| **Germ Cell Tumors** | | | | | | | |
| Teratodermoid | | | | | | | |
| Benign | 8 | 7 | 2 | 4 | 18 | 50 | 7 |
| Malignant | 7 | | | | | | |
| Seminoma/embryonal carcinoma | 1 | | | | 3 | | |
| **Mesenchymal Tumors** | | | | | | | |
| Lymphangioma/cystic hygroma | 3 | 3 | 1 | 3 | 11 | 50 | 7 |
| Hemangioma | 2 | | | | 1 | | |
| Fibroma/fibrosarcoma | 1 | | | | 1 | | |
| Lipoma/liposarcoma/sarcoma | 12 | | 3 | 1 | 3 | | |
| Rhabdomyosarcoma | 5 | | | | | | |
| **Cysts** | | | | | | | |
| Pericardial | | 1 | | 1 | | 35 | 7 |
| Bronchogenic | 6 | 7 | | 7 | | | |
| Enteric | 2 | 3 | | 5 | | | |
| Neurenteric/miscellaneous cyst | | | | 3 | | | |
| **Thymic Lesions** | | | | | | | |
| Thymic cyst | 2 | 1 | | 2 | | 17 | 2.5 |
| Hyperplasia | | | | 3 | | | |
| Thymoma | 2 | | | 2 | 3 | | |
| Thymic carcinoma | | 1 | | 1 | | | |
| **Miscellaneous** | | | | | | | |
| Granulomas, abscess, fibrosis | 2 | 5 | 3 | 4 | 3 | 17 | |
| Total | 188 | 121 | 105 | 62 | 201 | 677 | |

Hospital[80] in which a retrospective review compared the 60-year experience before and after 1970. The best estimate of prevalence of mediastinal masses is provided by a retrospective pathology study of mediastinal masses from Victoria in Australia, which had an estimated pediatric population of 900,000. In that series, 50% of mediastinal masses were lymphomas, followed by 20% of neurogenic origin, 8% foregut duplication cysts, and 6% teratomas.[81] This prevalence is similar to U.S. series (see Table 64-1).

## ANATOMIC CONSIDERATIONS

A clear understanding of the anatomic subdivisions of the mediastinum is useful in differential diagnosis and selection of diagnostic studies. The mediastinum is the central thoracic space bounded laterally by the right and left parietal pleura, anteriorly by the sternum, posteriorly by the vertebral bodies to include the transverse processes, superiorly by the thoracic inlet, and inferiorly by the diaphragm. Although several classifications for subdividing the mediastinum exist, the classical anatomic description is used here.[82] The value of any system of anatomic subdivision is to provide insight into the contents of that region, which simplifies differential diagnosis.

The superior mediastinum is delimited by the thoracic inlet superiorly and the plane between the sternomanubrial junction and the inferior limit of the fourth thoracic vertebra inferiorly. The lateral boundaries are the parietal pleurae. Normal anatomic contents of this subdivision are the thymus, other lymphatic structures, and mesenchymal derivatives, including vasculature, diffusely found throughout the entire mediastinum.

The anterior mediastinum is the zone posterior to the sternum, anterior to the pericardium, superior to the diaphragm, and inferior to the plane through the sternomanubrial junction. This space normally contains mesenchymal derivatives, fat, and connective tissue.

The middle mediastinum is delimited by the pericardium and origins of the great vessels. Therefore its normal contents are the pericardium, heart, great vessels, lymphatics, and mesenchymal derivatives.

The posterior mediastinum is outlined by the pericardium and great vessels anteriorly, the vertebral column posteriorly, and, as in each of the prior subdivisions, the parietal pleurae laterally. Its contents include the trachea and main bronchi, esophagus, widely distributed lymphatic structures, sympathetic nervous ganglia, descending aorta, azygous venous system, and thoracic duct.

Large masses or diffuse processes may transgress multiple subdivisions. An additional caveat to aid in differential diagnosis is age. With the exception of posterior mediastinal neuroblastoma, mediastinal masses in young children are most likely to be developmental in origin. Mediastinal masses that are not cystic will also be mentioned.

## DIAGNOSIS AND TREATMENT

Recognition of cystic mediastinal masses may first occur on fetal ultrasonography.[83–85] The fetus who develops progressive nonimmune hydrops, cardiac failure, or mediastinal shift with compression of developing lung tissue may benefit from in utero decompression or resection of a cystic mediastinal lesion.[86]

For cystic mediastinal masses, the initial postnatal diagnostic study should be anteroposterior and lateral chest radiographs. A presumptive diagnosis can often be made based on the location of the lesion on the plain radiograph. CT has now largely replaced endoscopy and esophagograms as part of the preoperative evaluation. Several studies comparing contrast medium-enhanced CT with MRI suggest that CT is superior, given its ability to define calcification within a mass.[87,88] MRI is useful if spinal involvement is in question or if vascular lesions are being considered. An esophagogram reveals the characteristic extrinsic mass effect of a foregut duplication cyst, but CT is probably the most useful study for this diagnosis. Echocardiography has value in defining the rare intrapericardial teratoma in the neonate with an enlarged pericardial silhouette[89] and can detect congenital heart disease if present.

The goal of the preoperative diagnostic workup is to help define the optimal surgical approach. When the nature of a mediastinal mass is uncertain or if the potential of malignancy exists, a preoperative serum sample should be drawn for determination of alpha fetoprotein or beta-human chorionic gonadotropin levels, particularly in the case of anterior mediastinal tumors. Similarly, urinary catecholamine catabolites should be obtained in suspect posterior mediastinal masses.

Surgical resection at the time of diagnosis is the preferred treatment of most benign mediastinal cysts and tumors. When indicated, thoracoscopic resection or biopsy can be performed with adequate results and minimal morbidity.[90,91] Large anterior mediastinal masses are best approached through median sternotomy, and middle and posterior mediastinal masses are best approached through posterolateral thoracotomy.

# Anterior and Superior Mediastinum

The anterior and superior mediastinum contains the thymus, great vessels, and a network of lymphatic structures, as well as connective and adipose tissue. Lymphomas are the most common tumors, followed by teratomas, germ cell tumors, cystic lymphangiomas, and thymic lesions (Fig. 64-4). Anterior mediastinal masses in infants are usually either a teratoma or a thymic enlargement.

Foremost in evaluation of masses of the anterior mediastinum is assessment of the risk of malignancy. Malignant disease, such as lymphoma, generally presents in the older child, is often associated with systemic symptoms and adenopathy elsewhere, and is frequently associated with symptoms of airway compromise. When possible, the diagnosis should be sought from nonmediastinal sources, such as bone marrow, pleural fluid, or other nodal tissues, thus avoiding a general anesthetic.[77,79] If a diagnosis is still lacking in the presence of airway compromise, corticosteroid administration reduces the risk of open biopsy yet does not affect diagnostic accuracy. Lymphomas are discussed in Chapter 38.

## THYMUS

Thymic cysts are seen in the anterior mediastinum and the neck (Figs. 64-5 and 64-6). They are usually asymptomatic but can become infected or hemorrhagic or produce

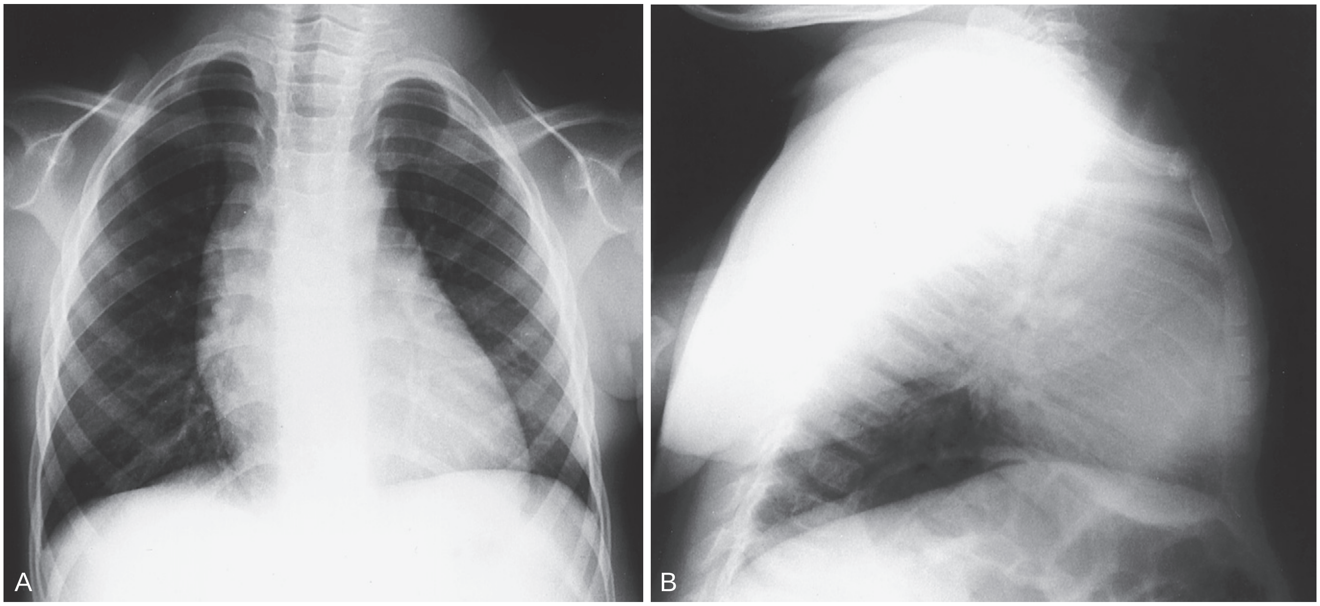



**FIGURE 64-4** A 5-year-old boy presented with a superoanterior mediastinal mass noted to be separate from the pericardial silhouette on an anteroposterior chest film (**A**). Lateral chest radiograph (**B**) reveals sternomanubrial prominence and a mass anterior to the trachea. This mass turned out to be a teratoma.

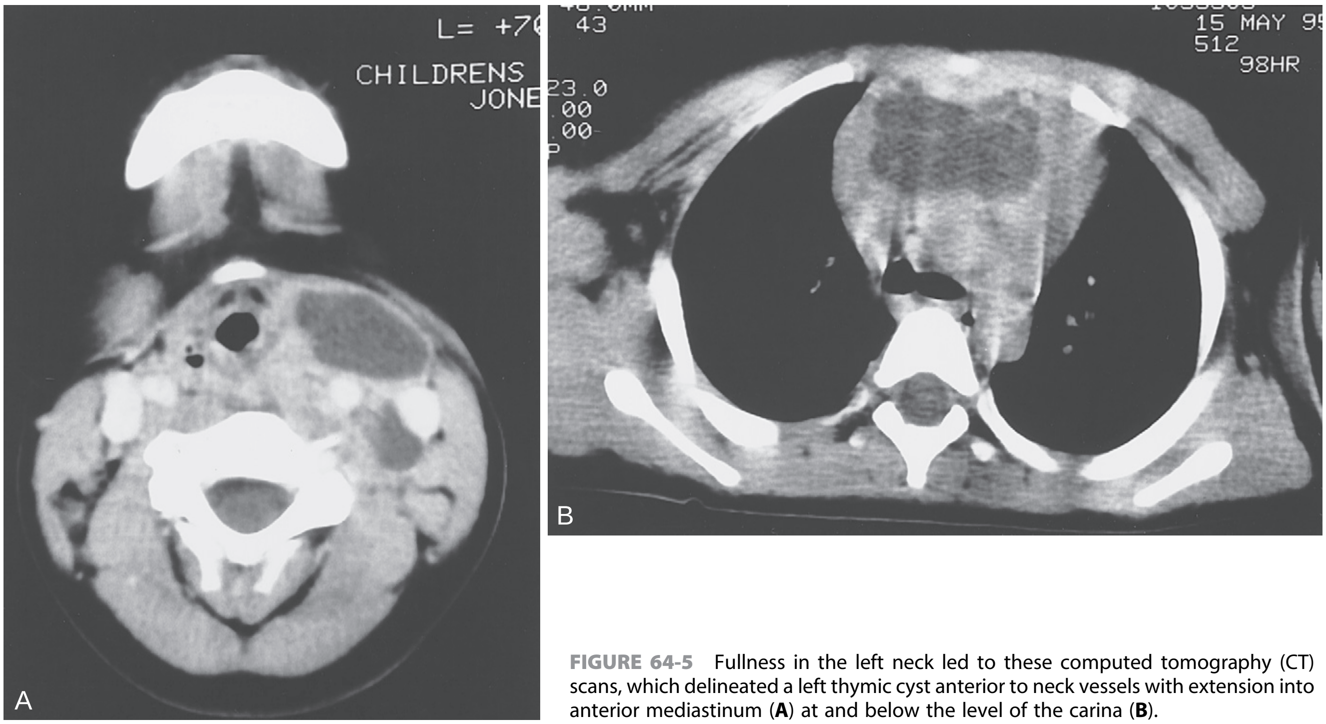



**FIGURE 64-5** Fullness in the left neck led to these computed tomography (CT) scans, which delineated a left thymic cyst anterior to neck vessels with extension into anterior mediastinum (**A**) at and below the level of the carina (**B**).

symptoms because of mass effects and can create a cosmetically unacceptable appearance. The cysts are lined with ciliated, respiratory epithelium; contain lymphocytes as well as normal thymic tissue; and often show inflammatory and granulomatous changes. Thymolipoma is a benign tumor, possibly hamartoma, of mixed fatty and thymic tissue. Resection results in diagnosis and cure.

Thymomas are rare in children, accounting for less than 1% of mediastinal tumors, with only 20 well-documented cases of malignant thymoma in children in the literature.[92–95] These tumors originate in the thymic epithelium and are usually aggressive.[96] Treatment is multimodal, but outcome is poor.

Although the thymus is located in the anterior and superior mediastinum, ectopic thymic tissue can be found in the

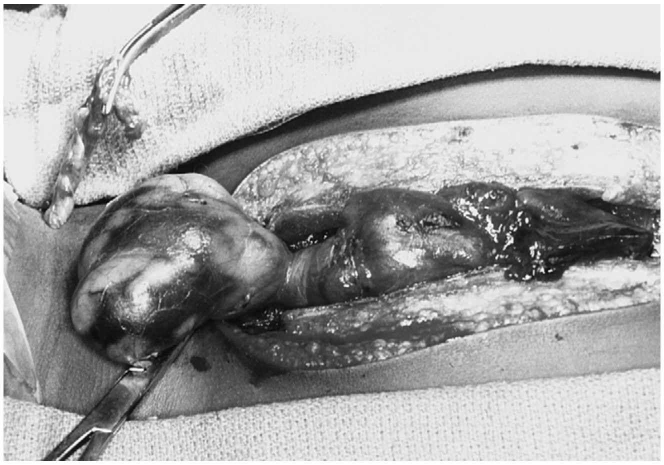


**FIGURE 64-6** Thymic cyst mobilized from the mediastinum through sternotomy before removal of the cervical extension in the same patient as in Figure 64-5.

neck and posterior mediastinum as well.[97–99] Benign thymic hyperplasia is a physiologic enlargement of the thymus gland no longer believed to cause respiratory embarrassment, although rapid enlargement has led some authors to recommend resection.[100,101] If necessary, a short course of prednisone shrinks the normal thymus gland and helps differentiate it from nonlymphoid mediastinal masses. MRI can also be helpful.[99,102] Mediastinal radiation is of historical interest, only because it had an unacceptably high association with thyroid carcinoma. Exploration is recommended only when malignancy cannot be ruled out, as in benign nodular thymic hyperplasia. Nodular thymic hyperplasia is usually asymptomatic and is usually recognized as a superior mediastinal mass on an incidental chest film. CT reveals a solid, asymmetric, nonenhancing mass within a thymic lobe. Peripheral blood and bone marrow studies are normal. Operation in these instances reveals a lymphoid mass within one lobe of the thymus with histologic compression of adjacent normal thymus. Analysis of lymphocytes in the mass reveals a normal ratio of T and B lymphocytes. Today, most thymic lesions can be resected using thoracoscopic techniques.

### TERATOMAS, DERMOID CYSTS, AND GERM CELL TUMORS

After lymphoma, teratomas are the most common tumors of the anterior mediastinum. They also have been reported in other subdivisions of the mediastinum.[103] These tumors are discussed in Chapter 37.

## Middle Mediastinum

In the classical anatomic description, the middle mediastinum is circumscribed by the pericardium.[82] As such, pericardial cysts may be the only true common middle mediastinal cysts. Pericardial cysts are benign, thin-walled, fluid-containing cysts lined with mesothelium. It is postulated that the pericardium forms from a series of disconnected lacunae in the mesenchyme that later coalesce to form the pericardial sac. Occasionally, one of these lacunae persists as a pericardial cyst. They are nearly always asymptomatic and are often discovered on routine chest films or at autopsy. The classical description is that of a cystic mass lying anteriorly in the chest at either cardiophrenic sulcus, although the right side is more common. Historically, thoracotomy was recommended to establish a definitive diagnosis. Currently, CT provides a sufficiently characteristic appearance to allow accurate diagnosis, thus allowing nonintervention unless the cyst is large. If the diagnosis is uncertain, these can be excised or unroofed thoracoscopically as well.

## Posterior Mediastinum

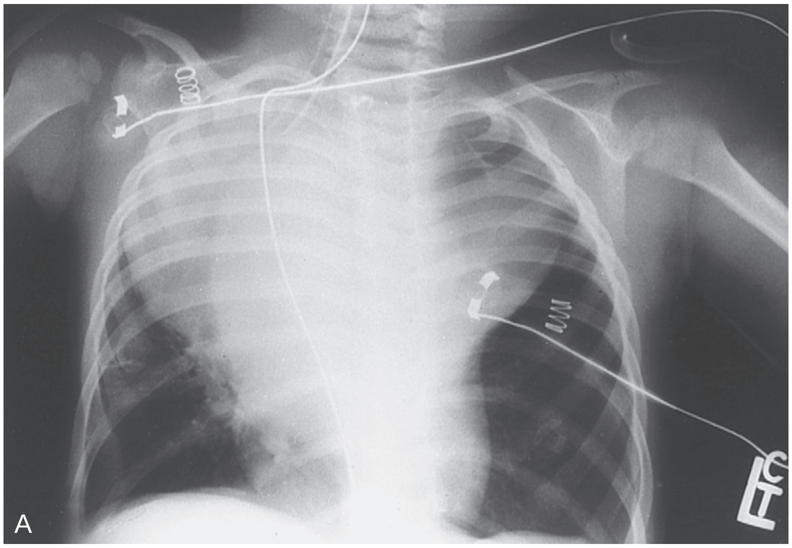
The posterior mediastinum lies behind a plane passing in front of the tracheal bifurcation and extending posteriorly to the paravertebral sulci.[82] The posterior mediastinum is the site of a heterogeneous group of cysts, neoplasms, and inflammatory processes in children. Most common of these lesions is the spectrum of benign to malignant neurogenic tumors of the sympathetic nervous system. In the young, the most common tumor is a malignant neuroblastoma, and in the older child, the most common tumors are benign ganglioneuromas; both of these lesions are discussed in Chapter 31.

### FOREGUT DUPLICATION CYSTS

Foregut duplication cysts are reasonably common in pediatric specialty centers. The nomenclature of these lesions varies considerably. They can be subdivided clinically and pathologically into (1) enteric duplications and cysts (lined by intestinal epithelium), (2) bronchogenic cysts (lined by respiratory epithelium), and (3) neurenteric cysts (associated with vertebral anomalies or having a connection with the nervous system). Enterogenous is a confusing historical term and in various reports has included each of the aforementioned categories. The generic term foregut duplication cyst is a more accurate embryologic description with subdivision into bronchogenic or enteric cysts determined by the histology of the mucosa lining the cyst wall.[104] In fact, all three endodermal derivatives may be found in the occasional foregut duplication, supporting a common embryologic derivation for foregut duplication cysts.

### BRONCHOGENIC CYSTS

Bronchogenic cysts (Fig. 64-7) develop from abnormal budding of the tracheal diverticulum or ventral portion of the foregut. These cysts can be found in a variety of locations from paraesophageal to paratracheal, perihilar, or intraparenchymal,[105] depending on the level at which the abnormal budding occurred in the development of the foregut or tracheobronchial tree. It has been reported that about two thirds of bronchogenic cysts are located within the lung parenchyma, with the remainder in the mediastinum, but this distribution varies between different reports. Rarely, they can be found in remote locations, such as the tongue, neck, back, and even below the diaphragm [78,106–109]



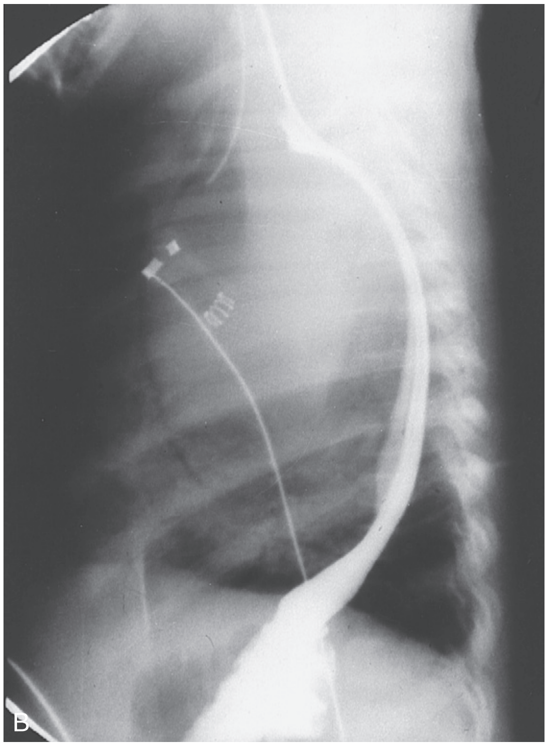


**FIGURE 64-7** **A,** Bronchogenic cyst. Central tracheobronchial compression with respiratory distress was demonstrated in this 15-month-old boy transferred to the intensive care unit in critical condition. He had been treated for a year for symptoms of asthma. **B,** Lateral view shows remarkable tracheal compression with tracheoesophageal separation confirmed by contrast agent in the esophagus.

Histologically, bronchogenic cysts are thin walled, lined with bronchial epithelium, and filled with mucus. They can be single or multiple and are white or pinkish. Cartilage has been reported in the wall of these cysts, and air-fluid levels may be present. The cysts have no predilection for the right or left side. Although they do not usually communicate with the tracheobronchial tree, they may do so from inception or the communication may be acquired from superinfection.

Diagnosis in older children often results from identification of an incidental mass on chest radiograph obtained for an unrelated reason. Infants usually present with respiratory symptoms, and the mass may be obscured on plain film by associated atelectasis and infection (Figs. 64-8 and 64-9).[110–112] In this case, the diagnosis can be delayed, but CT usually confirms the diagnosis. Bronchogenic cysts have also been recognized on antenatal ultrasonography[113] and on esophagogram for other indications. The differential diagnosis includes foreign body, lobar emphysema, pneumonia, bronchial stenosis, and pneumothorax.

Bronchogenic cysts should be excised to avoid the complications of infection, hemorrhage, or sudden death from rapid expansion under tension. A risk of malignant transformation does exist, as malignancy has been reported in two adult patients with bronchogenic cysts and adenocarcinoma has been reported arising from a bronchogenic cyst in an 8-year-old girl.[114] Excision should be accomplished without injury to the bronchial or esophageal wall. Small cysts in the pulmonary hilum may not be visualized until the mediastinal pleura is opened. Cyst resection is usually straightforward, but occasionally, limited parenchymal lung resection or lobectomy may be required. In the majority of patients, bronchogenic cysts are amenable to thoracoscopic resection.[115,116] An error in recognition may lead to unnecessary resection of emphysematous lung tissue rather than removal of a cyst producing bronchial obstruction. Complete excision is recommended; recurrence 25 years after incomplete resection has been reported.[117] Although there are reports of transbronchial drainage, we do not recommend that approach.[118]

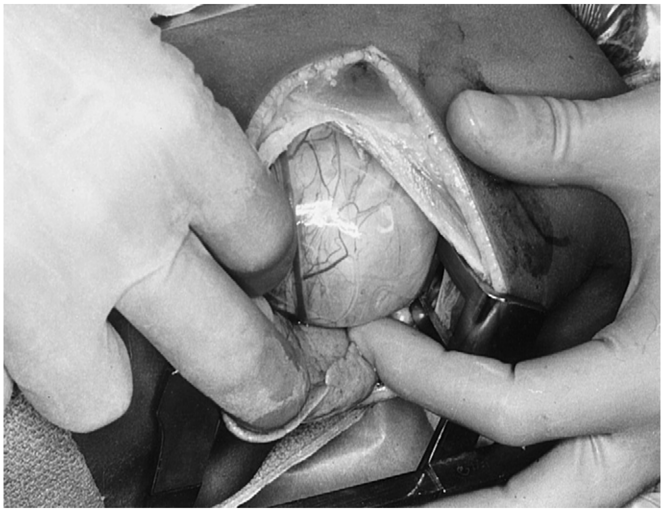


**FIGURE 64-8** Urgent thoracotomy in the same patient as in Figure 64-7 showed a large unilocular cyst. It was aspirated of infected mucus to relieve bradycardia and then removed from its attachment to the posterior trachea. The microscopic appearance is shown in Figure 64-9.

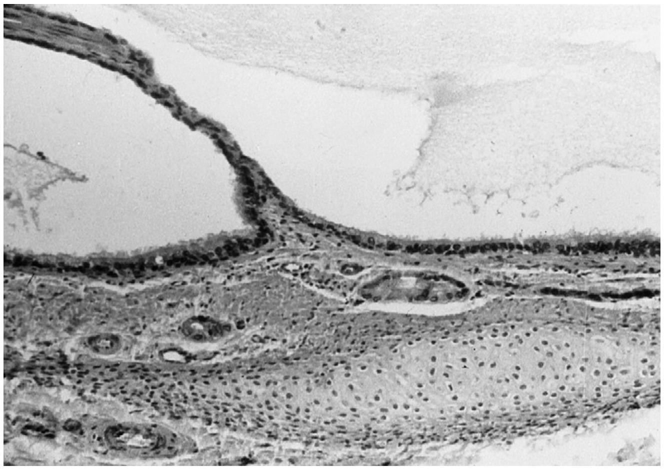


FIGURE 64-9 Microscopically, this bronchogenic cyst wall is lined by ciliated respiratory epithelium and contains bronchial cartilage, characteristic of bronchogenic cysts and evidence that they are central bronchial developmental anomalies (in contrast to cystic adenomatoid malformation, which is a peripheral parenchymal anomaly).

## ENTERIC DUPLICATION CYSTS

Enteric cysts arise from failure of coalescence of vacuoles early in development of the foregut. They are lined by esophageal or gastric epithelium surrounded by smooth muscle. They have been called variously enterogenic or enterogenous cysts, esophageal cysts, enteric cysts, and esophageal duplications. Gastric mucosa is often seen, and intramural adrenal cortical rests have been reported.[119] Enteric cysts may be located throughout the posterior mediastinum and in the neck. Although most commonly integral to the wall of the esophagus, they may communicate with the lumen of the esophagus or exist completely separate from the structure of origin. A number of large thoracoabdominal enteric cysts have been reported, either ending blindly in the abdomen or connecting with the lumen of the stomach, jejunum, ileum, or pancreatic duct.[78,120] Biliary reflux during bronchoscopy was reported in a case of an enteric duplication cyst that penetrated the diaphragm and connected the carina with the biliary tree.[111] There is a 12% incidence of associated malformations. Most of these are additional enteric duplications.[104,121] Two cases of prenatally diagnosed intrathoracic enteric duplication cyst associated with hydrops have been treated with placement of a thoracoamniotic shunt in utero.[122]

In most series, enteric cysts are asymptomatic at presentation. Chest radiograph and CT are the mainstays of diagnosis (Figs. 64-10 and 64-11). Although $^{99m}$Tc pertechnetate, abdominal ultrasonography, barium swallow, or MRI may occasionally be useful adjunctive procedures; the goal of preoperative studies is less an attempt to make a definitive diagnosis than to provide information to aid in operative planning. Treatment consists of complete surgical excision either by thoracotomy or thoracoscopy. If necessary, as in long tubular duplications, the mucosal lining of a foregut duplication

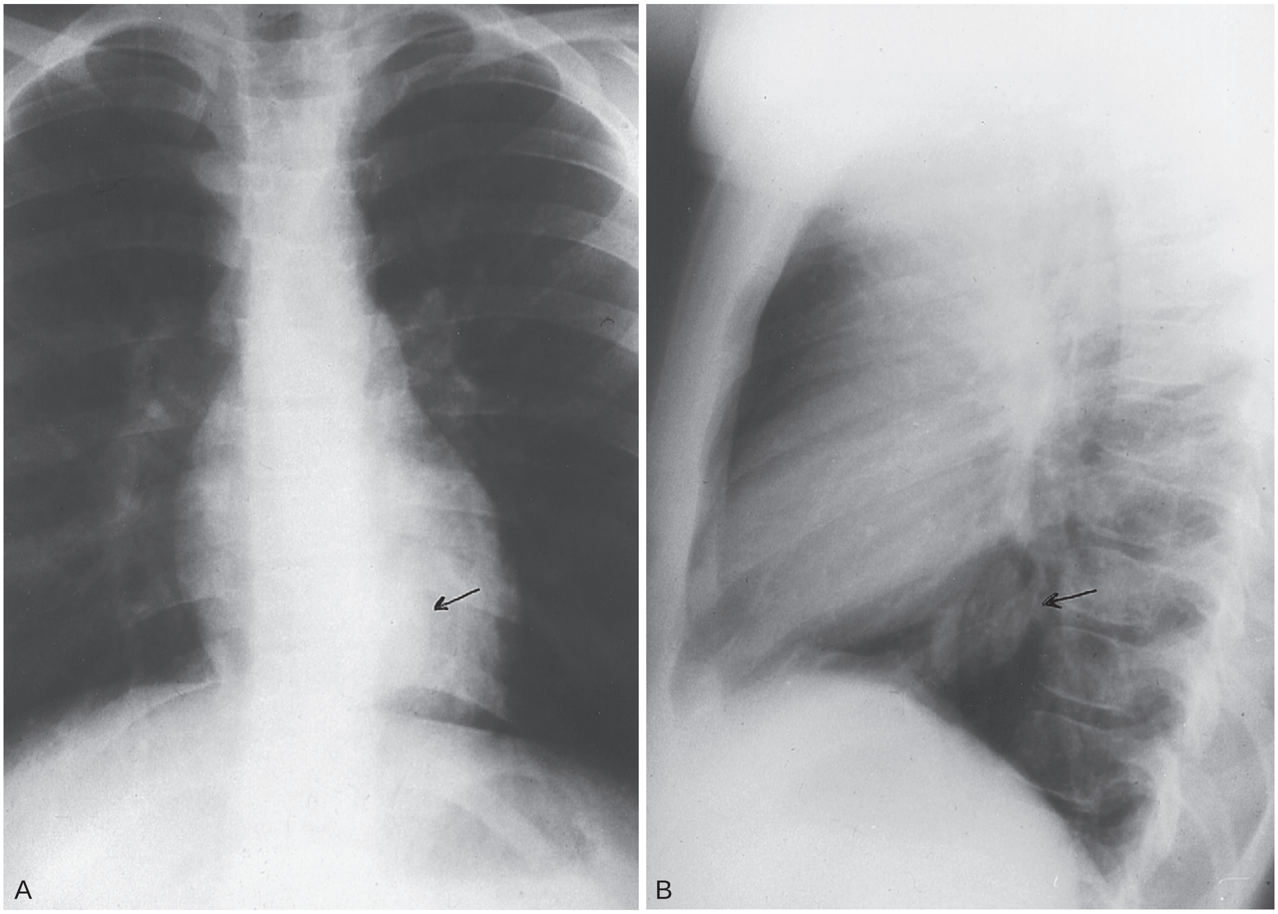
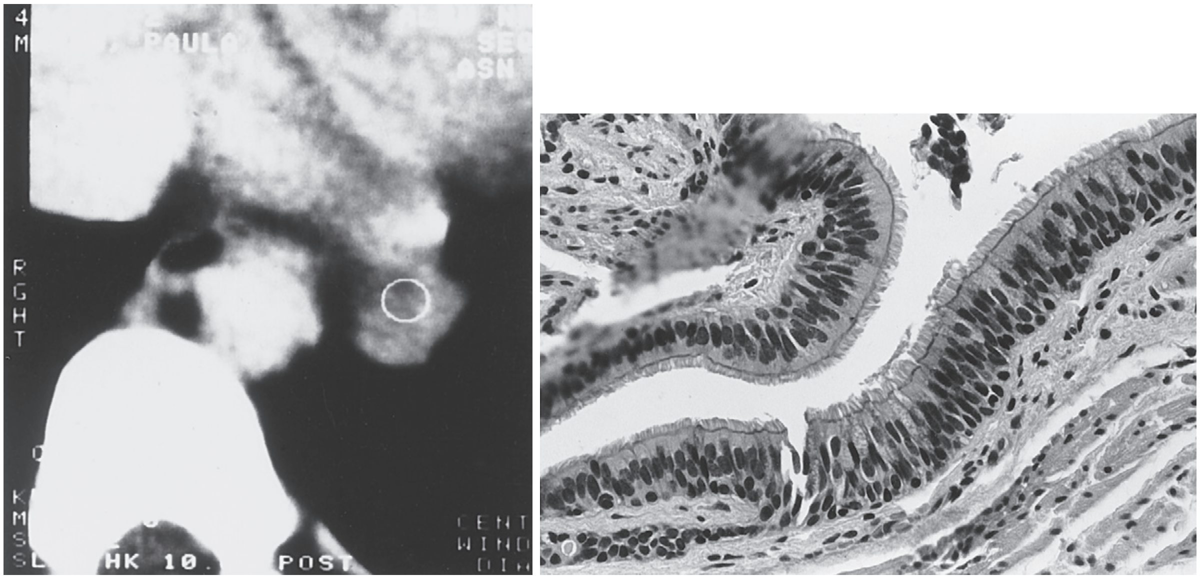



FIGURE 64-10 **A,** Incidental finding of an asymptomatic mediastinal mass behind the cardiac silhouette on anterior chest radiograph (*arrow*). **B,** On lateral film, the lesion was located just inferior and posterior to the base of the heart (*arrow*) and adjacent to the esophagus.




A B

**FIGURE 64-11** **A,** Computed tomography (CT) scan further delineates the lesion in the patient shown in Figure 64-10 (*ring marker*). CT is probably the most useful imaging approach for patients with mediastinal tumors. **B,** Operative findings revealed a single cyst with esophageal mucosal lining, and microscopic examination confirmed the presence of esophageal mucosa.

may be stripped, leaving the common muscular wall intact.[123] Marsupialization is no longer recommended. These are benign lesions, and esophageal integrity should be preserved.

## NEURENTERIC CYSTS

Neurenteric cysts are rare foregut duplications that also have connections to the spinal canal, sometimes with the dura. Although they most commonly present as intrathoracic masses, they may also present as an intraspinal mass. The coexistence of a cystic posterior mediastinal mass with adjacent hemivertebrae should raise suspicion of a neurenteric cyst as well as anterior myelomeningocele.[124] Neurenteric cysts are thought to form early in development when the notochord and foregut are in apposition, either by failure of complete separation or by herniation of foregut endoderm into the dorsal ectoderm.[125,126]

Histologically, neurenteric cysts have alimentary tract mucosa, well-developed muscle walls, and no serosa. Gastric mucosa may be present, so signs of inflammation and ulceration may occur.[125] Symptoms often include pain or neurologic findings (or both). MRI is indicated when a posterior mediastinal mass is associated with vertebral anomalies. Prompt excision is mandatory. Paraplegia and death owing to meningitis have been reported.[118] Although some authors report leaving the neural connections intact, most recommend total excision with simultaneous laminectomy if necessary.[124,127,128]

Other miscellaneous entities enter into the differential diagnosis of rare posterior mediastinal cystic masses. Anterior thoracic meningoceles are seen in older children and are thought to be progressive degenerative lesions associated with vertebral anomalies.[27] MRI should distinguish this lesion from a neurenteric cyst.

## MISCELLANEOUS MESENCHYMAL CYSTIC TUMORS

Mesenchymal tumors may occur throughout the mediastinum and may compromise the airway. They originate from connective tissue, lymphatic tissue, smooth and striated muscle, fat, and blood vessels. As a group, they constitute less than 5% of mediastinal masses in children.

Mesenchymal tumors derived from blood and lymph vessels are the most common varieties in children, especially lymphangiomas. In most patients, lymphangioma presents as a superior or posterior mediastinal extension of a cervical lesion; however, primary mediastinal lymphangiomas do occur.[129,130] Hemangiomas are even less common. The pathophysiology and management of both lesions are discussed in Chapter 125. The most common complication after surgical resection of mediastinal lymphangioma is lymphatic fluid leak. Treatment of this complication by aspiration, chest tube drainage, and fibrin glue application (if drainage alone fails) is usually effective. Lymphangiomas recur in at least 15% of cases after resection; so, long-term follow-up is important.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 65

# Lesions of the Larynx, Trachea, and Upper Airway

Dana Mara Thompson, J. Paul Willging, and Robin T. Cotton

Lesions of the upper airway, namely the larynx and trachea, can present with life-threatening airway obstruction. The etiology of obstructive airway disease is often multifactorial and includes anatomic, congenital, and inflammatory problems, many of which are managed by surgical intervention. A variation of clinical signs and symptoms are associated with airway obstruction. Signs of acute airway obstruction are stridor, respiratory distress, apnea, cyanosis, pallor, tachypnea, use of accessory muscles of respiration and retractions, and mental status changes. Chronic airway obstruction may present with similar signs and symptoms and may develop long-term complications of airway obstruction and hypoxia, such as failure to thrive, poor weight gain, pulmonary hypertension, and pectus excavatum. Regardless of whether the airway is acutely or chronically obstructed, stridor is the most useful noninvasive clinical examination finding for determining location of the obstruction in the airway. Stridor occurs as a result of turbulent air flow through a narrowed lumen and is present in virtually all children with airway obstruction, except those on the brink of complete asphyxia. The phase of respiration in which the stridor is heard will help the astute examiner to better determine the location of the lesion. Inspiratory stridor typically occurs in obstructive lesions above the glottis, such as laryngomalacia and vocal cord paralysis. Biphasic stridor is heard in a fixed obstruction below the glottis in the subglottis or trachea. Expiratory stridor usually represents an obstruction in the intrathoracic airway, such as tracheomalacia. Obstructive lesions of the airway may be mistakenly diagnosed as asthma on the basis of a respiratory "wheeze;" therefore a high index of suspicion and correlation with other clinical examination findings are essential so that a potentially critical or surgically correctable cause of airway obstruction is not overlooked.

Endoscopic evaluation of the airway has revolutionized the diagnosis and management of the obstructed airway. Endoscopic evaluations are divided into those done with the child awake and those done with the child under sedation or general anesthesia. Flexible fiberoptic nasopharyngoscopy and laryngoscopy is done with the child awake. This technique permits safe, rapid examination of the nose, hypopharynx, supraglottis, and glottis in virtually all children, despite age or lack of cooperation. The awake state allows for evaluation of the dynamics of supraglottic tone, vocal fold mobility, and the impact of fixed obstructing lesions of the larynx. Examination under the influence of sedation or general anesthesia can alter the findings; therefore a significant cause of airway obstruction, such as laryngomalacia or vocal cord paralysis, could be overlooked. Direct examination of the airway under general or sedated anesthesia remains the mainstay in diagnosis and confirmation of lesions that obstruct the airway, particularly those below the glottis that cannot be accurately evaluated by awake fiberoptic examination. Airway endoscopy confirms the presence of suspected laryngotracheal pathology, such as subglottic stenosis and tracheal stenosis.

The goal of any evaluation and management of airway obstruction caused by laryngeal or tracheal disease is to establish and maintain a safe and stable airway. The number of children that require surgical intervention for airway obstruction has increased. This is due in part to the development of long-term intubation and ventilation techniques in the 1960s, which allowed increased survival rates for critically ill premature newborns. As a result of prolonged intubation, these infants were able to survive, however, with an entirely new spectrum of long-term health problems, including those of the airway, particularly the larynx and trachea.

## Airway Pathophysiology and Diagnostic Considerations

The larynx is the entry point for air into the tracheobronchial tree and respiratory system. Without a functioning larynx, the remainder of the respiratory system is compromised. The phylogenetic purposes of the larynx are respiration and protection of the lower airway from aspiration. Voice is an evolutionary and secondary function of the larynx. The pediatric airway differs from the adult airway in structure and function. The infant larynx is approximately one third of its adult size, measuring approximately 7 mm in the sagittal dimension and 4 mm in the coronal plane. The vocal cords are 6 to 8 mm long. The subglottic space is approximately 4.5 mm across

and is the narrowest portion of the upper airway, bounded by the cricoid cartilage, the only complete ring of cartilage in the upper airway. Therefore only 1 mm of mucosal edema in this portion of the infant airway can obstruct the airway by 40%. As the airway space and dimensions grow with age, mucosal edema causes less compromise of the airway. The cartilaginous framework of the larynx and trachea is softer and more pliable in infancy. This can lead to a tendency to collapse under external compression or air pressure gradients, which may lead to airway obstruction as seen in laryngomalacia and tracheomalacia. As the infant grows and the cartilage matures, symptoms of these conditions often spontaneously improve and resolve without intervention. In the infant, the larynx sits high in the neck at the level of vertebrae C2 and C3, directly behind the nose, with approximation of the velum, tongue, and epiglottis, thereby functionally separating respiration from swallowing. Because neuromuscular function for airway protection is not fully developed at this stage, this intended anatomic relationship allows the infant to safely breathe and feed at the same time without aspirating. With this anatomic relationship, however, any obstruction of the nasal cavity can cause significant obstruction of the airway, which also causes feeding difficulty. In conjunction with neuromuscular maturation, the position of the larynx descends in the neck. By 2 years of age, the larynx descends to C4, thereby creating less of a separation between the functions of breathing and swallowing. By age 6 years, the larynx has descended to its adult location directly behind C6. Airway and swallowing symptoms tend to be exaggerated if neuromuscular function is compromised or has not matured in conjunction with descent of the larynx.

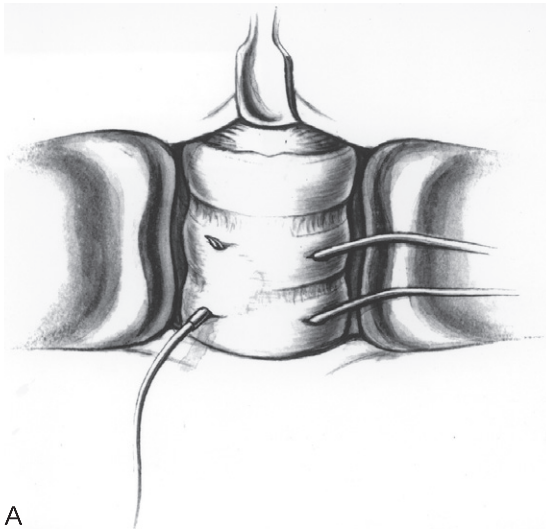
# Tracheotomy

Tracheotomy is a means of managing severe airway obstruction caused by nearly all the airway lesions discussed in this chapter. Because it is the sine qua non procedure to bypass an obstruction in the airway, indications, technique, and complications will be discussed prior to the review of specific obstructive laryngotracheal lesions. The three major indications for long-term tracheotomy in children are airway obstruction, ventilatory support, and pulmonary toilet. Most children with tracheotomy tubes in place for airway obstruction undergo the procedure as very young infants, either for acquired subglottic stenosis related to prolonged endotracheal intubation or for congenital lesions that compromise the airway. Because of its morbidity and the tremendous psychosocial and developmental implications of a child with a tracheotomy, all alternative interventions before proceeding to tracheotomy should be explored and exhausted.

## TRACHEOTOMY TECHNIQUE

The technique of pediatric tracheotomy preferred by the authors is as follows. The patient is taken to the operating room, and the airway is secured with an endotracheal tube. Because the typical landmarks for tracheotomy may be difficult to identify because of the small size of the larynx and cricoid, tracheotomy in the emergent setting is best done with a secured airway, either by intubation or rigid bronchoscopy. A vertical incision is made over the midline of the neck, its superior extent at the cricoid cartilage. Subcutaneous fat is removed with electrocautery, and the fascia is divided in layers in the midline. The strap muscles are separated at the raphe, and the thyroid isthmus is divided with the electrocautery. Vertical 4-0 nonabsorbable "stay sutures" are placed though the third and fourth tracheal cartilage rings on the right and left sides just off the midline and tied loosely. Gentle tension is applied to these sutures to elevate the tracheal rings, and then the airway is entered with a blade in the midline between the third and fourth rings. As seen in Figure 65-1, the stoma is created by placing 4-0 chromic gut sutures through the cut edge of the trachea and sewn to skin. Some authors note that this technique fashions a more "permanent" stoma and may result in a persistent tracheocutaneous fistula after decannulation. Because the major sources of mortality in pediatric tracheotomy are accidental decannulation or inability to replace an obstructed tube, the authors feel that the added margin of safety, particularly in the first few days, is justification for the approach outlined. In addition, pediatric tracheotomies are rarely short term, and even without the skin sutures, the tract tends to epithelialize over time.

The endotracheal tube (or bronchoscope) is withdrawn, an appropriate-sized tracheotomy tube is inserted, and ventilation is assured bilaterally. As seen in Figure 65-2, the previously placed stay sutures are labeled specifically for the right and left sides and then taped to the anterior chest wall to serve as emergency traction lines in the event of accidental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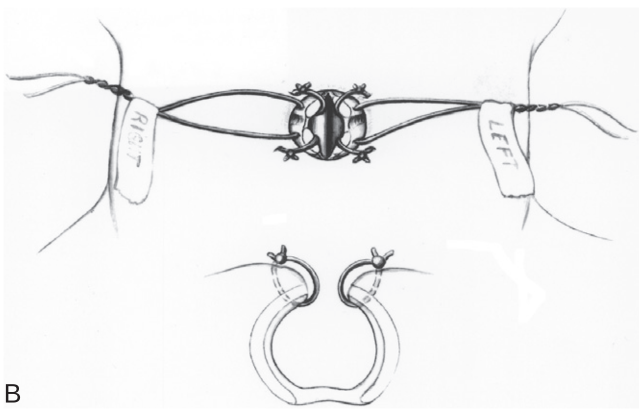


B

**FIGURE 65-1** **A,** Placement of stay suture. **B,** Creation of immediate stoma.

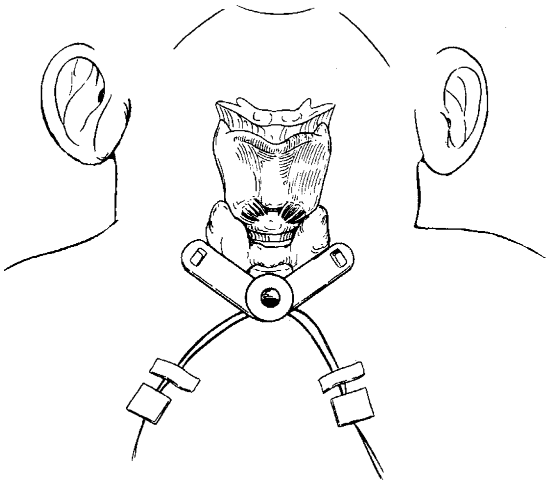


FIGURE 65-2 Labeling stay sutures.

decannulation. The tracheotomy tube is secured around the neck with cotton twill ties. A tracheotomy tube, particularly if it does not have an inner cannula, should never be directly sewn to the skin of a child. In the scenario of a life-threatening mucous plug obstructing the tube, particularly in the immediate postoperative period when the tract has not fully epithelialized, having a tube secured to the skin presents a significant challenge for removal and replacement with a patent clean tube. Postoperative deaths have occurred in this scenario. Ideally, the position of the tracheotomy tube is evaluated by passing a telescope through the glottis, along the tracheotomy tube. This allows the surgeon to ensure that the tip of the tube is proximal to the carina. This technique also allows the surgeon to evaluate the fit of the tube within the lumen of the trachea. This relationship is ideally co-linear and co-centric without any rubbing or encroachment on the anterior or posterior tracheal wall. If assessment by this method is not possible, a flexible bronchoscope can be passed through the tube to verify that the tip is proximal to the carina. The tracheotomy tube is changed, and the stay sutures are removed in 5 days once the tract has epithelialized. These patients should be managed in a monitored in-hospital setting, at least until the tract has epithelialized and a successful change of the tracheotomy tube has occurred.

## TRACHEOTOMY COMPLICATIONS

There are perioperative, postoperative, and long-term complications of tracheotomy, many of which can occur at any time a tracheotomy tube is in place. Perioperative complications following tracheotomy tube placement are rare. The most serious perioperative complications are pneumothorax and major vessel bleeding, particularly from an innominate artery that may be just below the sternum in an infant. A chest radiograph should do be done at the end of the procedure to ensure that there is no pneumothorax or pneumomediastinum. The most common immediate postoperative complications can be life threatening and include mucus plugging and accidental decannulation. The diameter size of tracheotomy tube cannulas for children are significantly smaller than for adults; therefore any occlusion of the tube by mucus could lead to complete airway obstruction, particularly in the child who is totally dependent on the tracheotomy to breathe. Likewise, the stoma into the airway for the tracheotomy tube is much smaller in the child. If the tube were to accidentally dislodge, the increased work of breathing causes further collapse, and a "sucking-in"–like closure at the stoma that makes it difficult to breathe through, and challenging to replace the tube. This effect is even more dramatic in the immediate postoperative time, when the stoma has not fully matured. Because these complications are life threatening, every precaution should be done to ensure that the tracheotomy tube is patent and carefully suctioned and, at the same time, secured around the neck to prevent accidental decannulation.

Any child with a tracheotomy tube for a prolonged time period is likely to develop a minor or major complication. As in the immediate postoperative period, mucous plugging and accidental decannulation are the most serious and life-threatening complications that can occur. Accidental decannulation remains a major concern throughout the time a child has a tracheotomy tube. It is particularly concerning as a young child develops the manual dexterity to remove his or her own tube. Accidental removal could prove to be a fatal event in the child with near-total obstruction of the airway above the tracheotomy tube. Although not universally adopted, many recommend a home apnea monitor or a pulse oximeter to assist caregivers in detecting such a situation. In many cases, the child will still be able to breathe comfortably through the stoma and care should be taken with replacing the tube rapidly, but safely. Hastily performed insertion of the tracheotomy tube may result in creation of a false tract leading to airway compromise where none existed.

Complications related to local infection of either the skin or soft tissue surrounding the stoma (cellulitis), the tracheal mucosa (tracheitis), or the tracheal cartilage (chondritis) are rare in the mature tracheotomy tract. By adapting the skin directly to the cut edge of the tracheal cartilage, epithelialization of the tract is accelerated and healing promoted. Nevertheless, some patients may develop local infections after the perioperative period. Typically, these individuals have some underlying predisposition to breakdown and bacterial invasion, such as drug-induced immunosuppression, primary immunodeficiency, or diabetes. Treatment is with local antimicrobial packing, frequent dressing and cannula changes, and systemic antibiotics. The choice of antibiotics is dictated by culture. Staphylococcal and pseudomonal infections are frequently seen in the intensive care unit setting. Aggressive infections can lead to chondritis, with breakdown of the wound, exposure of the great vessels, and extension of infection into the mediastinum.

Suprastomal granuloma formation is a nearly universal consequence of the presence of a chronic foreign body in the airway. Although some authors recommend routine removal of this tissue at regular intervals, this is not necessary in all patients. Overly aggressive removal of granulomas leads to more frequent recurrences, further arguing against routine excision.[1] Granulomas that completely obstruct the suprastomal airway require removal because of the potential for complete airway obstruction if the tube becomes blocked or displaced as well as to preserve phonation. Parents are usually the first to note symptoms or findings that may suggest suprastomal granuloma formation. Most common are progressive loss of voice and difficulty changing the tracheotomy tube. The most lethal of all late tracheotomy complications is that

of innominate artery erosion at the level where the artery crosses the anterior tracheal wall. This complication can occur as a result of increased pressure from the tip of the tracheotomy tube against the anterior tracheal wall, which leads to granulation tissue formation, weakening of the cartilage, and eventual erosion if not identified. Rigid and inappropriately curved tubes are notorious for causing this, thus emphasizing the importance of appropriate tracheotomy tube size selection. Often, a sentinel bleed of bright red blood will alert the clinician to impending arterial rupture. For this reason, even small amounts of suctioned blood should be evaluated fully by a surgeon.

In the same manner that the anterior wall of the trachea can be eroded by the continued pressure of a tracheal cannula, the posterior wall can break down as well. This is fairly uncommon as a late complication, although the presence of an indwelling nasogastric tube worsens the situation by trapping the posterior wall between two rigid foreign bodies. The diagnosis is suspected in patients with unexplained recurrent pneumonia or pneumomediastinitis. In a ventilated patient, eructation will occur with each inspiratory breath. This complication is traditionally managed by an open surgical procedure, with interposition of healthy muscle between the trachea and the esophagus.

With increased surgical experience, improved surgical techniques, identification, and management of comorbidities that affect outcomes, and improvement in postoperative care, the indications for airway expansion surgery have been extended to patients with laryngotracheal stenosis as the primary definitive operation, thus avoiding tracheotomy[2–7] for many of the airway lesions that may have traditionally required one for initial management.

# Lesions of the Larynx and Subglottis

## LARYNGOMALACIA

Laryngomalacia (LM) is the most common laryngeal anomaly and cause of stridor in infancy. The clinical presentation is that of inspiratory stridor that is worse with feeding, agitation, and supine position. The symptoms are usually present at birth or shortly thereafter. Symptoms peak at 4 to 8 months of age and usually resolve between 18 to 24 months of age.[8,9] Mild forms of the disease present with inspiratory stridor and usually no other constitutional symptoms. Those with moderate disease usually have feeding problems, because it can be difficult for infants to coordinate the suck/swallow/breath sequence in the setting of airway obstruction. Many of these infants who fall into this category have gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux (LPR) and benefit from antireflux treatment and measures.[9–11] Why there is such a high incidence of GERD in this patient population is poorly understood. One theory is that increased intrathoracic airway pressure from the proximal airway obstruction promotes reflux. Another contributing factor could be immature reflexes that regulate esophageal motility causing poor esophageal clearance. GERD in this patient population, as in other infant populations with airway problems and apnea, may be related to frequent relaxation events of the lower esophageal sphincter.[12] Infants with severe laryngomalacia develop life-threatening complications of airway obstruction that can lead to pectus excavatum formation, failure to thrive, chronic hypoxia, pulmonary hypertension, and cor pulmonale. These patients require surgical intervention.[9,13–16] The diagnosis is suspected by auscultation of the stridor but must be confirmed by flexible laryngoscopy. This examination must be done with the infant awake, in order to demonstrate the cyclic collapse of the supraglottic tissues into the laryngeal inlet. The influence of general anesthesia can obscure these findings. Other typical findings are that of an omega-shaped epiglottis and forward prolapsing arytenoid cartilages obstructing airflow and a complete view of the vocal folds. This examination is also done to ensure that there is no other significant supraglottic pathology contributing to the stridor. The etiology of this condition remains elusive. Proposed theories include abnormal airway anatomy,[17,18] immature cartilage formation, delay in neuromuscular maturation, and abnormal integration of the peripheral and central neuromuscular reflexes responsible for laryngeal tone and function.[9]

Laryngomalacia is usually a self-limiting disease that rarely requires surgical intervention. Surgical intervention is recommended in those who develop life-threatening episodes of airway obstruction or complications of hypoxia as described previously. Tracheotomy was the treatment of choice for this condition until the mid-1980s when techniques of supraglottoplasty were introduced.[15,19,20] Tracheotomy bypasses the site of laryngeal obstruction until the condition resolves spontaneously, usually after 18 to 24 months. Tracheotomy can be avoided by performing a supraglottoplasty. As seen in Figure 65-3, this is accomplished by microsurgical removal of the redundant prolapsing tissue seen in the area of the arytenoid cartilages and release of the aryepiglottic folds tethering the position of the epiglottis.[15] Long-term results with this approach have generally been excellent, with reversal of symptoms in 80% to 100% of cases.[9,13,15,16,21–24] Outcomes, however, are dependent on the number of medical comorbidities present. Up to 45% of patients with severe laryngomalacia that require surgery have at least one major medical comorbidity (neurologic disease, cardiac disease, a syndrome, or anomaly) in addition to GERD/LPR that may affect outcomes of surgical intervention.[9,25,26] Most infants who have two medical comorbidities or less, including GERD/LPR, benefit from supraglottoplasty where symptom improvement rates range from 70% to 100%, and revision rates or complications are less than 8%.[9,25,26] Revision supraglottoplasty or tracheostomy will be required in 19% to 45% of infants and is directly influenced by the number and type of medical comorbidity.[9,23–26] Infants younger than 2 months of age who do not have significant comorbidities also have higher supraglottoplasty revision rates.[26] The authors' experience is that if two of these medical comorbidities are present, in addition to LPR, the infant is 5 times more likely to require revision supraglottoplasty, and if all three comorbidities are present, the infant is 10 times more likely to require a tracheostomy for management despite aggressive management of reflux disease.

Infants with laryngomalacia and syndromes associated with micrognathia, such as the CHARGE association (colobama, heart disease, atresia choanae, retarded growth or development or central nervous system anomalies, genital hypoplasia, ear anomalies and/or deafness) and the Pierre Robin sequence, will do worse because of the retrodisplacement of the tongue base collapsing on the epiglottis, in addition to supraarytenoid tissue redundancy and short aryepiglottic folds. Supraglottoplasty or epiglottic suspension procedures usually are unsuccessful.[27]

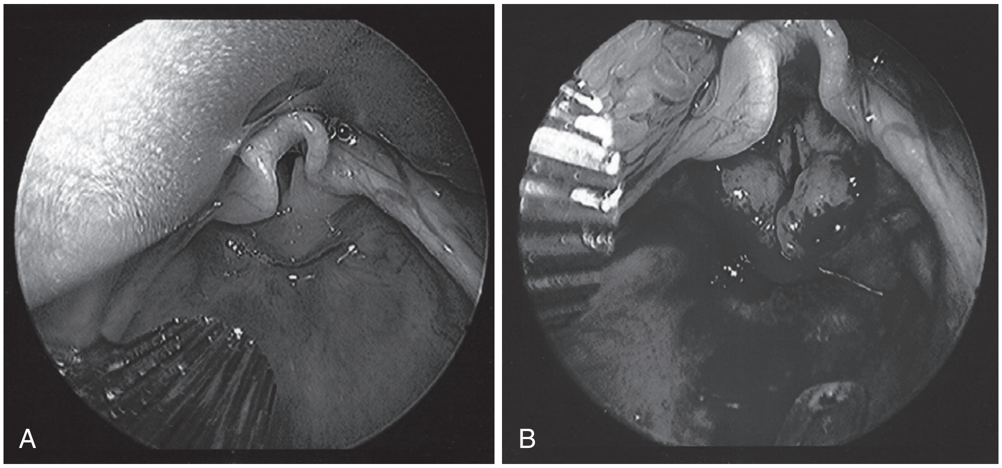



FIGURE 65-3 Laryngomalacia before (**A**) and after (**B**) supraglottoplasty.

Because of the severity of airway obstruction, this patient group is traditionally managed by tracheostomy placement until they grow out of the micrognathia or it is corrected by mandibular distraction, although subperiosteal release of the floor of the mouth muscles provides an attractive alternative.[28,29]

Supraglottic stenosis is the most severe complication of this operation and can occur after overzealous removal of tissue or failure to control for acid reflux disease, which may enter the airway and cause injury to tissues, leading to haphazard scarring.

## LARYNGEAL ATRESIA AND WEBS

Laryngeal webs are congenital (Fig. 65-4, *A*) or acquired (see Fig. 65-5). Congenital laryngeal webs and atresias are rare. The embryologic origin is failure of recanalization of the larynx during prenatal development. A child born with velocardiofacial syndrome or a 22q11.2 deletion that presents with respiratory distress and a weak cry will likely have a laryngeal web that will require surgical intervention.[30] An atresia or a web of sufficient size will present at birth as aphonia and rapid asphyxia if not immediately addressed. A thin web with a small residual airway may be ruptured by intubation. Often this is the only treatment needed; however, these infants should be followed closely so that appropriate intervention occurs if airway obstruction develops. Thick webs and atresias make emergent intubation by standard techniques difficult if not impossible. In this setting, survival of the infant may be dependent on securing the airway with a 2.5 rigid bronchoscope and, if that is not possible, obtaining a surgical airway. Surgical management of thick webs and atresias requires a tracheostomy tube until the larynx is larger and more amenable to surgical intervention.[31] Surgical correction usually requires a laryngofissure (vertical split of the thyroid cartilage on the anterior midline) with anterior airway division across the atretic region and placement of costal cartilage in the anterior cricoid and cervical trachea, similar to a laryngotracheal reconstruction for subglottic stenosis, which is discussed later in this chapter. Timing of reconstruction is dependent on many factors, including age of the child and surgeon experience.

Thin and moderate anterior webs are not usually diagnosed or suspected at birth and may or may not have airway

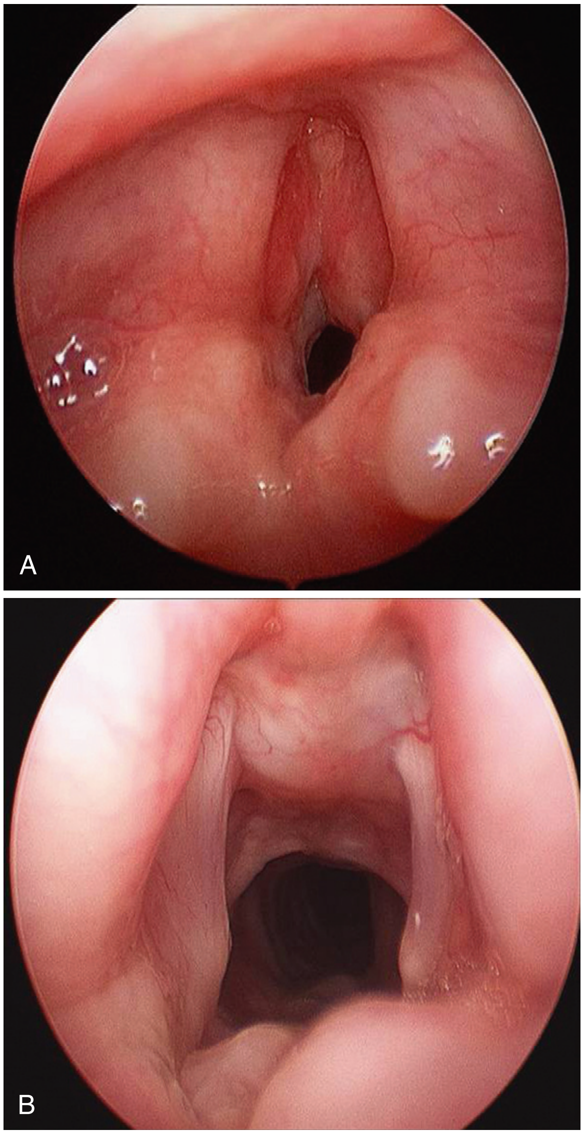



FIGURE 65-4 Congenital web in child with velocardiofacial syndrome. **A,** Before anterior graft reconstruction. **B,** After anterior graft laryngotracheal reconstruction with placement of the graft between the vocal cords. *(See Expert Consult site for color version.)*

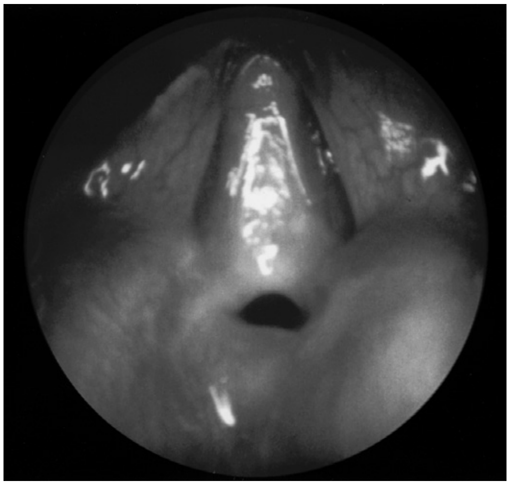


FIGURE 65-5 Acquired web.

obstructive symptoms. The most common presenting symptom is hoarseness. The primary goals of management are to provide a patent airway and to achieve a good voice quality. This is challenging, because vocal cords have a tendency for fibrosis and granulation tissue formation after surgical interventions. Traditionally, the treatment of choice for these thin and moderate laryngeal webs is laryngofissure and placement of a stent or keel, when the surgeon feels the child has grown appropriately. Select laryngeal webs can be managed with endoscopic lysis and off- label topical mitomycin-C application, even in infants under 1 year of age.[32] This technique may allow congential webs to be successfully managed at a younger age. However, long-term outcomes of this technique are not available, and it is unknown if infants treated by this method eventually need laryngotracheal reconstruction to maintain a patent airway. Moderate and severe webs that have a thick plate extending into the immediate anterior subglottis just below the vocal cords are difficult to successfully manage with endoscopic techniques or laryngofissure and keel placement. Because these webs often present with airway obstruction, aggressive intervention is required, such as tracheotomy or airway reconstruction, whereby the web is divided and a cartilage graft placed between the vocal cords (Fig. 65-4, *B*). Long-term results in the management of webs depend on the severity of the original lesion. Surgically treated thin webs often heal with minimal disruption of phonation, while thicker plates with associated subglottic stenosis have less satisfactory results, particularly those that require cartilage grafting.[33]

Acquired laryngeal webs are also uncommon (Fig. 65-5). Etiology is usually from direct laryngeal trauma, where the medial surfaces of both vocal cords are disrupted, and they heal together, forming a web. This is most commonly seen in the management and treatment of laryngeal papillomas, usually caused by overzealous removal of papilloma disease at the anterior glottic commissure, particularly in the setting of laryngopharyngeal reflux.[34]

## VOCAL CORD IMMOBILITY: VOCAL CORD PARALYSIS AND VOCAL CORD FIXATION

Vocal cord movement requires intact neurologic function of the vagus nerve and free rotation of the cricoarytenoid joint. The action of abduction of the vocal cords from the midline opens the glottic inlet for airflow into the tracheobronchial tree. Airflow is restricted if vocal cord abduction does not occur. Vocal cord immobility is caused by failure of the vocal cords to abduct. There are two primary etiologies of vocal cord immobility, vocal cord paralysis, and vocal cord fixation. Injury of the vagus nerve anywhere along its course from the skull base to the thoracic cavity or injury of the recurrent laryngeal nerve causes neurogenic vocal cord paralysis. Paralysis can be congenital or acquired. Acquired immobility is usually caused by a stretch injury, pressure encroachment, inflammatory insult, trauma, or sectioning of the nerve itself. In this setting, the cricoarytenoid joint is mobile, but the neuromuscular function is compromised. A traumatic or inflammatory process in the cricoarytenoid joint causes vocal cord fixation. In this setting, the function of the joint that is required for mobility is fixed, but the neuromuscular function is intact. Fixation and paralysis can coexist. Regardless of the etiology of immobility, failure of one or both of the vocal cords to abduct can lead to stridor and airway obstruction.

Unilateral vocal cord immobility rarely causes stridor or airway obstruction, except occasionally in very young infants, particularly in the setting of mucosal edema, where the cross-sectional diameter of the airway is already small. In the setting of bilateral vocal cord immobility, both cords lie in the midline, thereby limiting air flow through the glottis. This may present with severe life-threatening symptoms and airway obstruction, requiring an immediate artificial airway. Some infants and children have mild symptoms, occurring only during periods of upper respiratory tract infection, and may not require a tracheotomy. Most children with bilateral vocal cord immobility require tracheotomy early in the course of the disease, prior to definitive surgical therapy. Because it is bilateral immobility that most commonly leads to airway obstruction, the discussion of surgical treatment will be limited to management of bilateral immobility.

Management and treatment of airway symptoms of bilateral cord immobility is based on the etiology and site of involvement along the vagus nerve. In neonates and infants, bilateral vocal cord paralysis may have a central etiology, most commonly a Chiari malformation or hydrocephalus. Caudal displacement of the brainstem as seen in a Chiari malformation causes pressure on the brainstem at the site of origin of the vagal nuclei and nerves. Recognition and diagnosis of this is important to prevent other complications of a Chiari malformation. Vocal cord paralysis can be cured once the Chiari malformation is decompressed if done in a timely fashion. Hydrocephalus leads to increased compression of the fourth ventricle. This can also cause compression of the vagal nuclei and nerves. Decreasing the intracranial pressure by shunt placement is often curative[35,36] and should be the initial management prior to consideration of tracheotomy or airway surgery. Infants with a central etiology of bilateral vocal cord paralysis and who fail central decompressive procedures will require a tracheotomy for airway safety. These groups of patients often go on to develop other lower cranial nerve problems and aspiration that keep them tracheotomy tube dependent; they are generally not good candidates for other surgical procedures to achieve decannulation. If the vagal nerves are intact, and the etiology of bilateral vocal cord paralysis is a localized insult to the vagal nerves, such as a stretch injury from obstetrical trauma, infection, or extrinsic compression, an observational period is often warranted if there are no acute

symptoms of airway obstruction. The paralysis is frequently transient in these patients who are otherwise healthy. If the etiology of vocal cord paralysis is traumatic with direct nerve injury where function is not expected to return, a tracheotomy is required until another procedure can be done to expand the glottic opening. This situation may be seen in "fixed wire" neck trauma with nerve injury[37] or nerve injury as a complication of thyroid surgery.

Bilateral vocal fold immobility resulting from fixation occurs when the synovial joint surfaces of the cricoarytenoid joint become fixed, thereby not allowing vocal fold abduction or adduction. In this setting, the vagal nerve is usually fully functional and physically intact. The most common cause of fixation of the joint is some type of direct trauma to the joint area itself, such as intubation or neck trauma dislocating the cricoarytenoid joint. Once the joint is injured, an inflammatory process occurs, causing an arthritic-like process. Juvenile rheumatoid arthritis can also cause bilateral immobility.

Whether the cause of vocal fold immobility is paralysis or fixation, surgical approaches for treatment in children are similar. The fact that there is a wide variety of surgical approaches suggests that no one procedure is ideal. The goal is to open the posterior glottic airway enough to allow adequate airflow without exposing the patient to increased risk of complications from aspiration. The procedures described are often done after the airway has been secured and is stable with a tracheotomy tube. More recently, many of these surgical techniques have been used as the primary surgery, with the goal of avoiding a tracheotomy. The decision to do definitive primary surgery depends on the acuity of airway obstruction, age of the child, and ability to protect the airway against aspiration.

Repositioning or removal of structures and tissue in the posterior glottis, namely the arytenoid cartilage and mucosa, are well-described techniques of opening the airway in the setting of bilateral vocal cord immobility. These include arytenoid lateralization, arytenoidopexy, partial arytenoidectomy, and cordotomy.[38–41] These procedures can be done alone or in combination with the goal of decannulation. The surgical approach can be external through a laryngofissure or endoscopic using a carbon dioxide ($CO_2$) laser or a combination of both. Endoscopic $CO_2$ laser removal of the vocal process of the arytenoid and a portion of the posterior vocal cord has been successfully used in some series.[41,42] The management challenge of this technique is treatment of postoperative granulation tissue formation, which may lead to airway obstruction.[43] Recent meta-analysis and retrospective studies evaluating outcomes of surgically managed bilateral vocal cord paralysis in children suggest that laryngofissure with partial arytenoidectomy, combined with a vocal cord lateralization procedure, results in the highest decannulation rates when compared with $CO_2$ arytenoidectomy and cordotomy procedures or arytenoidopexy procedures alone.[44,45] These same studies conclude that open external procedures appear to be more effective as a first-line treatment in pediatric vocal cord paralysis, with arytenoidopexy with or without partial arytenoidectomy offering an attractive first-line surgical option. They also conclude that $CO_2$ laser procedures, although having limited success as a primary procedure, are effective for revision. Although these procedures have been effective in achieving decannulation and maintaining airway patency, long-term outcomes on aspiration and voice are unknown. Recent reports suggest that endoscopic placement of sutures to lateralize the vocal cords is an option to achieve a patent glottic airway.[46–48] Short-term results suggest the technique is more successful in adolescents and adults. The authors' experience with this technique in infants and children has resulted in variable outcomes. Long-term outcomes are unknown.

Posterior graft laryngotracheoplasty is another effective technique to open the posterior glottis.[49,50] Through a laryngofissure with extension into the first two rings of the trachea, the posterior cricoid lamina is incised and distracted, thereby separating the arytenoid cartilages. Inserting a costal cartilage graft into the distracted posterior cricoid lamina stabilizes the position of the arytenoid cartilages. Although published series of this procedure are small, the decannulation rate after posterior approaches is near 100%.[44] Endoscopic posterior cricoid split and rib graft insertion has been successfully accomplished in selected children with bilateral vocal cord paralysis, thereby avoiding the need for a tracheotomy or other endoscopic vocal cord ablation procedures that could compromise voice.[6,51]

## RECURRENT RESPIRATORY PAPILLOMATOSIS

Recurrent respiratory papillomatosis (RRP) is the expression of human papillomavirus (HPV) infection in the mucosa of the upper aerodigestive tract. Papillomas involving the larynx are the most common laryngeal tumor in children, and the larynx is the most common site of occurrence in the aerodigestive tract (Fig. 65-6). Adult laryngeal papilloma disease is usually solitary, whereas papillomas of childhood tend to occur in clusters and have an incredible propensity for recurrence. Clinical presentation of laryngeal papilloma is progressive airway obstruction, dysphonia, and possible progression to aphonia. RRP is most commonly associated with HPV-6 and HPV-11 subtypes. Subtypes 16 and 18 are rarely associated with RRP but, if present, have a higher risk of malignant transformation. These viral particles are present in adjacent and clinically normal sites of the respiratory tract but are expressed primarily in anatomic locations of juxtaposed epithelium, hence the high predilection for the vocal cords.[52] The other common location is at an area of mucosal injury, such as a tracheotomy site.[52] The vector of transmission is controversial. Pediatric RRP and vaginal condyloma acuminata are

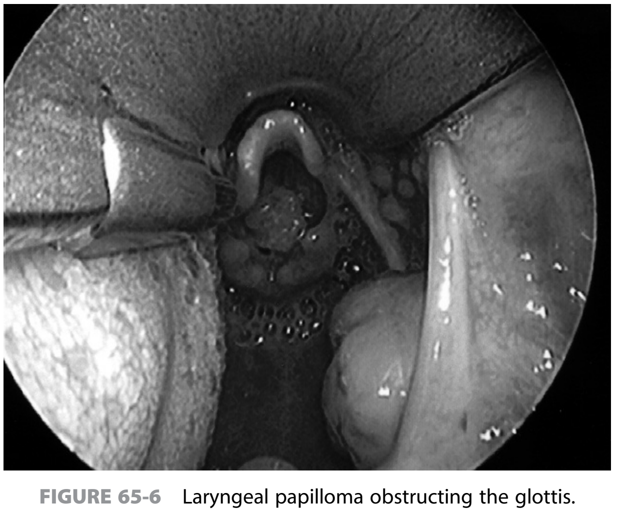


FIGURE 65-6 Laryngeal papilloma obstructing the glottis.

both caused by HPV subtypes 6 and 11, thus leading most researchers to believe that vertical transmission from mother to child is taking place in most cases. Although unusual, vertical transmission to children born by cesarean section of mothers with vaginal warts has also been documented.[53]

The natural course of RRP is extremely variable, with no obvious patient-related risk factors to aid in prognosis. The estimated mean number of procedures per child for their disease is 19.7, with an average of 4.4 procedures per year. Many cases have been seen to regress spontaneously in adolescence, but others go on to extensive disease involving the trachea and bronchial tree, with a high fatality rate from untreatable airway obstruction. Less commonly, the papilloma may undergo malignant degeneration to squamous cell carcinoma. For this reason, interval histologic examination of the obstructing tissue is important.

Pediatric RRP continues to be an extremely difficult management problem for otolaryngologists. The goal of surgical treatment is to maintain a patent airway while providing a usable voice and to prevent spread of disease into the distal airway.

Although the mainstay of surgical management has traditionally been the $CO_2$ laser, newer surgical techniques have demonstrated efficacy in the management of pediatric RRP patients, including powered instrumentation, the laryngeal shaver,[54] and the pulse-dye laser.[55,56] In comparison with the $CO_2$ laser, the pulse-dye laser is thought to not cause damage to the vocal fold epithelium; thus some propose that more aggressive surgical excision to the vocal structures is possible while minimizing compromise to voice.[55] Removal of papillomas using the microdebrider results in improved perceptual and objective voice outcomes in comparison with the $CO_2$ laser ablation.[57] Regardless of the surgical technique used, scarring, stenosis, and web formation in the larynx are all the results of overly aggressive or inexpertly performed endoscopic removal of the disease. Care must be taken to avoid injury to vital structures. The papillomas can be removed down to the level of the vocal ligaments, but the cords themselves should not be incised. When working in the anterior commissure, the far anterior glottis where the vocal cords meet, bilateral resection should not be done to avoid web formation. Even in experienced hands, the incidence of minor scarring in the anterior glottis may be as high as 25%.[58] Aggressive resection beyond that necessary to maintain a safe airway will not improve the long-term prognosis for remission, but may contribute to late morbidity.

The role of tracheotomy in the surgical management of laryngeal papillomatosis is controversial. Most surgeons try to avoid tracheotomy if at all possible. The mucosal injury at the tracheotomy site encourages growth of papillomas outside of the larynx, thereby increasing the probability of distal spread of the disease. The rate of tracheal spread in patients requiring tracheotomy has been reported as high as 50%.[59] It is possible, given the variable degree of aggressiveness of RRP, that patients who have distal spread of disease represent a subset of the patient population with a predetermined propensity to disseminate beyond the larynx who would require a tracheotomy regardless. Patients who develop life-threatening airway obstruction from aggressive disease within or beyond the larynx, which cannot be managed by endoscopic procedures, should have a tracheotomy placed until the disease can be controlled with further surgical intervention and adjunctive therapy. If a tracheotomy is placed, the clinician should make every attempt possible to decannulate as soon as possible, both to limit potential distal airway dissemination and to relieve the child of the burden of tracheotomy. The traditional adjuvant medical therapies used for pediatric RRP are interferon-alpha 2a, retinoic acid, and indol-3-carbinol/diindolylmethane (I3C/DIM). The most recently introduced adjunctive therapy is cidofovir. Cidofovir is an acyclic nucleoside phosphonate derivative with antiviral activity used for the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. Off-label use of cidofovir injected directly into the region after removal of laryngeal papilloma has demonstrated efficacy in selected patients. In addition, promising research efforts are being done to develop vaccination therapy for pediatric RRP.

Gardasil (Merck) and Cervarx (Glaxo-Smith-Kline) are two vaccines shown to be effective against the human papilloma virus. Gardasil is a quadrivalent vaccine, protecting against HPV types 6, 11, 16, and 18, while Cervarx stimulates a response only to HPV types 16 and 18. These vaccines were developed with virus-like particles (VLP) that simulate the surface of the HPV. The vaccines are manufactured in the yeast *Saccharomyces cerevisiae*. Yeast-derived vaccines have a long safety record after administration in both adults and children.

Vaccination trials show excellent response rates to the recommended three-injection series, with 99.7% of those vaccinated developing an antibody response. Vaccination to the HPV provides protection to those not previously infected with the virus. The vaccination does not appear to have any effectiveness for treating established chronic HPV infections.[60] The vaccine is currently recommended for females 9 to 15 years of age. This is treating them before their first sexual encounter and during a time when their immune response is higher, compared with women aged 18 to 26. Older women were found to have lower immune response rates to the vaccine and have the added potential for previously contracting the HPV through sexual contact.[61] Older women may benefit from the vaccine if they have not been previously infected with the viral subtypes in the vaccine.

The quadrivalent vaccine, Gardasil, has the potential to significantly reduce the incidence of RRP in children. Encouraging primary care physicians to offer the vaccination to females prior to their becoming sexually active will be important. Encouraging families to vaccinate their young girls will also take significant time to explain the benefits. The question of whether males should be vaccinated has yet to be determined. It is reasonable to consider reducing the overall exposure of individuals to HPV by treating males as part of an overall societal strategy for reducing the impact of this disease on society.

## LARYNGOTRACHEAL STENOSIS AND SUBGLOTTIC STENOSIS

Laryngotracheal stenosis may be characterized by etiology and area involved. Areas of involvement include the supraglottis, glottis, subglottis, and upper trachea. A single area or multiple areas can be involved. Stenosis of the larynx is congenital (Fig. 65-7) or acquired (Fig. 65-8). Congenital stenoses are believed to be the result of failure or incomplete recanalization of the laryngeal lumen that occurs by the 10th week of gestation. Congenital subglottic stenosis is

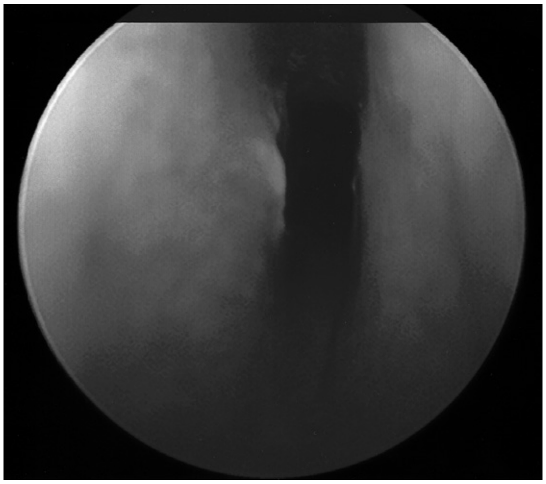


**FIGURE 65-7** Congenital subglottic stenosis with an elliptically shaped cricoid.

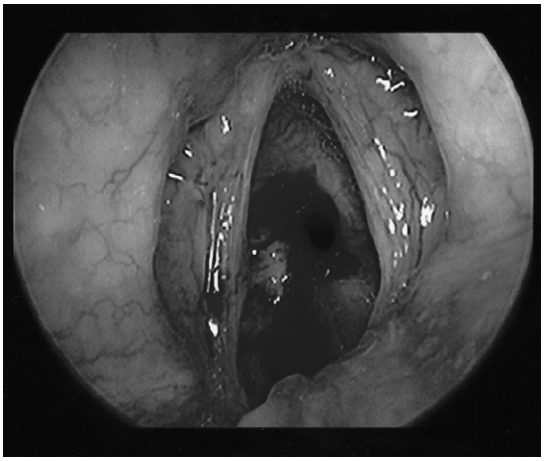


**FIGURE 65-8** Acquired subglottic stenosis.

histopathologically divided into a membranous stenosis and a cartilaginous stenosis (Table 65-1).

A congenital stenosis exists when the lumen of the cricoid region of the airway measures less than 4 mm in a full-term infant or 3 mm in a premature infant with no prior history of intubation. As seen in Figure 65-7, the typical appearance of a congenital cartilaginous stenosis is that of an elliptic-shaped cricoid cartilage. The definition of what may be a congenital or an acquired stenosis can be somewhat arbitrary, because children with congenital subglottic stenosis may develop secondary soft tissue stenosis and scarring from injury, thereby developing an acquired stenosis. This most commonly occurs from prolonged intubation; so, the true incidence of congenital subglottic stenosis is difficult to determine. Of the areas involved in stenosis, the subglottis is the most common. Most subglottic stenoses that require surgical management are acquired. An example of acquired stenosis is seen in Figure 65-8. The principles of surgical management discussed are applicable to both congenital and acquired disease.

Subglottic stenosis (SGS) essentially did not exist until after 1965 with the introduction of prolonged endotracheal intubation and ventilation of neonates.[62] As very-low-birthweight infant survival increased, so did the number of patients with secondary laryngotracheal stenosis, with the incidence of SGS in surviving neonates as high as 97%.[63] Fortunately, advances in the technique of endotracheal intubation and tube stabilization, along with the implementation of softer materials for endotracheal tubes, have decreased the incidence of laryngotracheal stenosis in surviving neonates to 0.9% to 8.3%.[64] With the proliferation of lifesaving advancements in medicine and surgery, we are seeing children survive disease processes who would have not survived 20 years ago. These children also develop other chronic diseases as a result of treatment, with subglottic stenosis being one of them. The numbers of toddlers, children, and adolescents who are now developing stenosis of the larynx has increased, but the exact percentages are unknown. The nature of the stenosis can be soft or firm, or commonly a combination of both. Causes of soft tissue stenosis are submucosal mucous gland hyperplasia, ductal cysts, fibrous and granulation tissue, and laryngopharyngeal reflux of gastric acid causing mucosal edema. Firm stenoses are usually associated with an abnormally shaped or thickened cricoid cartilage, or mature scar tissue. The Myer-Cotton grading system is the most widely used for documentation of the degree of obstruction (Fig. 65-9). Endotracheal tube sizing has become the most widely used means of grading and assessing the degree of stenosis.[65]

**TABLE 65-1**
**Classification of Congenital Subglottic Stenosis**

| *Cartilaginous Stenosis* | *Soft Tissue Stenosis* |
|---|---|
| Cricoid cartilage deformity | Granulation tissue |
| Normal shape | Submucosal fibrosis |
| Small for infant's size | Submucosal gland hyperplasia |
| Abnormal shape | |
| Large anterior lamina | |
| Large posterior lamina | |
| Generalized thickening | |
| Elliptical shape | |
| Submucous cleft | |
| Other congenital cricoid stenoses | |
| Trapped first tracheal ring | |

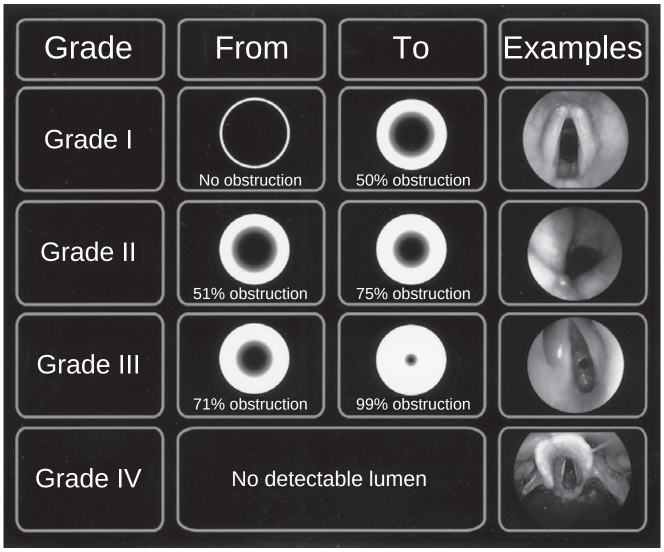



**FIGURE 65-9** Myer-Cotton subglottic stenosis grading system.

Successful laryngotracheal reconstructive surgery requires a carefully formulated plan. This plan includes identification and management of significant medical comorbidities that have the potential to contribute to poor outcomes. The plan also requires accurate identification of the type of stenosis in all areas of the larynx and upper trachea involved, because the stenosis can be multilevel and require more than one type of intervention. The treatment plan is tailored to the specific patient, his medical comorbidities, and the anatomic problem. This treatment plan is best developed by a multidisciplinary team approach, including the pediatric otolaryngologist, pediatric surgeon, pulmonologist, gastroenterologist, anesthesiologist, intensivist, and appropriate allied health personnel.

Any laryngeal stenosis can be effectively managed by placement of a tracheotomy. Long-term morbidity and mortality associated with tracheotomy tube placement has encouraged advancements in laryngotracheal reconstructive procedures (LTR) to either avoid tracheotomy tube placement or to achieve decannulation.

Associated medical comorbidities, particularly cardiopulmonary disease, must be addressed, stabilized, and managed prior to considering surgical intervention. Children who require significant ventilatory support or medical support are not good candidates for laryngotracheal reconstruction. Evaluation of swallowing function is essential to help determine airway protection ability and aspiration risk so that preoperative and perioperative accommodations can be made to minimize the complications of aspiration. Patients with significant aspiration are usually not good candidates for LTR.

The influence of gastroesophageal reflux on laryngotracheal stenosis cannot be overemphasized. GERD is an etiologic factor in acquired subglottic stenosis. Clinical and animal studies demonstrate that the presence of acid in the region of the larynx negatively affects healing.[66–72] Perioperative and postoperative aggressive medical and sometimes even surgical[70] antireflux therapy is recommended in the setting of LTR surgery. Prospective and retrospective studies evaluating long-term outcomes of reflux control in LTR surgery are not available.

Surgical management of laryngotracheal stenosis is individualized to the patient, and no single operative approach will work for all patients. Each patient presents with multiple variables that must be considered and include the location and extent of the stenotic area, medical comorbidities, airway protection and swallowing function, age, and weight. Surgical options include endoscopic techniques, expansion surgery, and resection surgery. Methods used are dependent on the degree and location of the stenosis. In general, grade I stenoses are usually managed by endoscopic techniques. Grade II stenoses may be approached with either endoscopic or open techniques, depending on location and extent of the lesion. Grade III and IV lesions almost always require open surgical reconstruction.

## Endoscopic Airway Surgery for Laryngotracheal Stenosis

Grade I and II stenoses can be approached with endoscopic techniques. Over the past 5 years, with advances in endoscopic techniques and the introduction of improved instrumentation, endoscopic techniques are also being applied to selected grade III stenoses. The $CO_2$ and potassium-titanyl-phospate (KTP) lasers, because of their precise tissue characteristics, have been the most widely used modalities. The laser is useful for treating early intubation injury with granulation tissue accumulation, subglottic cysts, thin circumferential webs, and crescent-shaped bands. Predisposing factors to failure of endoscopic laser treatment of SGS are previous failed endoscopic procedures, significant loss of the cartilaginous framework, thick, circumferential cicatricial scarring greater than 1 cm in length, and posterior commissure involvement. A complication of laser treatment of SGS is exposure of perichondrium or cartilage causing perichondritis and chondritis, which may lead to further scar formation.

Airway dilation techniques have been applied for the management of airway stenosis since the advent of bronchoesophagology. The traditional methods involved bougienage techniques, including cattail dilators and endotracheal tubes. Although these techniques are effective and still used by many surgeons, the sheering forces generated across the area of stenosis may lead to scarring and require ongoing serial dilations[73] or more aggressive open airway surgical management. The introduction of balloon dilation of the airway has shown promising outcomes. As seen in Figure 65-10, airway specific balloon catheters are designed to exert a radial pressure at the site of stenosis; the diameter is selected based on the anticipated normal age-related size of the airway. Unlike traditional dilation techniques, the radial pressure applied to the stenosis has shown less scarring and better long-term results, often obviating the need for tracheotomy or open airway reconstruction.[74,75] Balloon dilation is also effective for emergent stabilization of a patient's airway until a definitive open procedure can be performed. As seen in Figure 65-10, balloon dilation is also used as an adjunct to recurrent airway stenosis after successful open airway reconstruction.[76]

Another adjunctive tool used in the management of laryngotracheal stenosis is the microdebrider. In contrast to the blades used for the management of laryngeal papilloma, a number of more aggressive cutting blades have been designed for management of laryngeal and tracheal stenosis and granulation tissue. The theoretical advantage of the blade compared with a laser is less thermal damage with potentially less scar formation.[77,78]

Moderate and severe cases of laryngotracheal stenosis, in particular those involving the posterior glottic and posterior subglottic areas, can be successfully managed endoscopically

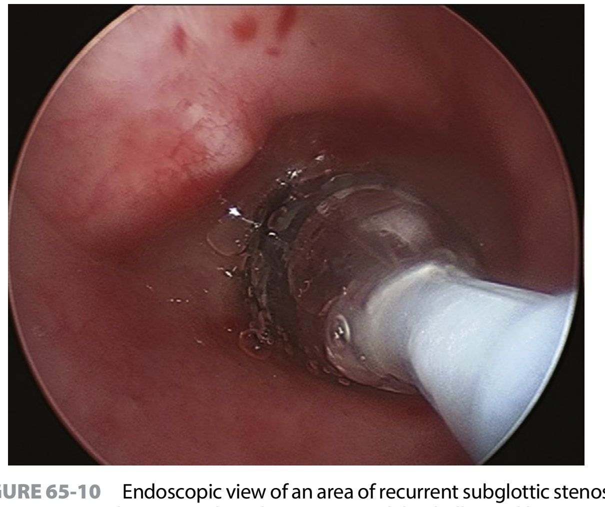


**FIGURE 65-10** Endoscopic view of an area of recurrent subglottic stenosis following open laryngotracheoplasty managed by balloon dilation. *(See Expert Consult site for color version.)*

by performing $CO_2$ laser–assisted endoscopic cricoid split and placement of a posterior costal cartilage graft between the distracted cricoid plate as previously described for the management of bilateral vocal cord paralysis.[6,51] This evolutionary technique is becoming a viable alternative to open airway surgery or tracheotomy as more surgeons gain experience and endoscopic instrumentation continues to evolve.

Achieving optimal results for endoscopic procedures often involves the use of adjunctive therapies to minimize scarring and stenosis. Mitomycin C is a potent antibiotic derived from the *Streptomyces caespitosus* bacteria shown to modify wound healing at the molecular level and minimize postsurgical scar formation. Off-label topical application of mitomycin C is a well-described adjunct that has been shown to minimize recurrent tracheal granulation tissue formation and cicatrix formation after manipulation. The mechanism of the drug's anticellular action has not been definitively characterized. It is known, however, that mitomycin C is a prodrug that is activated into toxic forms that produce oxygen free radicals, creates single-strand DNA breaks, and cross links DNA.[79] Another adjuvant is the intralesional injection of steroid preparations into the stenotic area to minimize inflammation, granulation, and scarring.

### Open Airway Surgery for Laryngotracheal Stenosis

Open surgical reconstruction is recommended when the endoscopic methods to establish a patent airway are inappropriate or have failed. Anterior cricoid split is considered one of the expansion surgical techniques. It is used predominantly in a neonate with anterior subglottic narrowing who fails multiple attempts at extubation despite adequate pulmonary reserve. In this setting, the narrowing at the level of the cricoid cartilage is corrected by dividing the cricoid ring in the midline. This decompresses the mucosal edema and expands the cricoid lumen when an endotracheal tube is placed through the area. The endotracheal tube is left in place for 5 to 10 days. Dexamethasone sodium phosphate is initiated 24 hours before extubation and continued for 5 days after extubation. This technique leads to successful extubation in 66% to 78% of patients.[80] As seen in Table 65-2, before considering using this technique in a neonate, several clinical criteria must be met to increase the probability of successful extubation following anterior cricoid split.

In the authors' hands, this technique has nearly been replaced by anterior cricoid split with the placement of a small auricular cartilage or thyroid alae graft, followed by endotracheal intubation for 3 to 7 days. Outcomes comparing decannulation rates of cricoid split versus cricoid split with placement of the cartilage graft have not been formally reviewed.

**TABLE 65-2**

| Criteria for Performing an Anterior Cricoid Split |
|---|
| Extubation failure on at least two occasions secondary to subglottic laryngeal pathology |
| Weight greater than 1500 g |
| No ventilator support for at least 10 days before repair |
| Supplemental $O_2$ requirement less than 30% |
| No congestive heart failure for 1 month before repair |
| No acute respiratory tract infection |
| No antihypertensive medication for 10 days before repair |

Multiple open procedures have been described and are used to expand the stenosed airway. These procedures and their applications have evolved over the past 30 years. Fearon and Cotton[80a] introduced laryngotracheal reconstruction (LTR) with cartilage interpositional grafting in 1972 with placement of a cartilage graft between a split anterior cricoid and upper trachea. This method has become one of the most common techniques of expanding stenotic airway segments. Anterior grafting alone is typically used in grade II and grade III stenoses that do not involve the posterior glottis or posterior subglottis. With involvement of the posterior glottis or subglottis, the posterior cricoid plate lamina is split with or without the placement of an interpositional graft, depending on the degree of the stenosis. The grafts may be placed anteriorly, posteriorly, or in both locations depending on the degree of stenosis. This problem is more commonly seen in grade III and grade IV stenosis. Partial cricotracheal resection (CTR) has evolved into another option for surgical management of selected grade III and IV stenosis.[81–86] In this operation, the stenotic region of the anterior cricoid plate and any involved tracheal stenotic segment is resected, and the trachea is mobilized to allow an end-to-end anastomosis. As seen in Figures 65-11 and 65-12, the posterior trachea and trachealis muscle is anastomosed with the posterior cricoid plate and its mucosa. The anterior wall of the trachea is then mobilized superiorly, and secured to the thyroid cartilage.[81–83,86]

The traditional approach to LTR surgery involves several stages of reconstruction[87–90] where the expansion operation is done, and a stent (Silastic sheeting or Teflon) is placed to

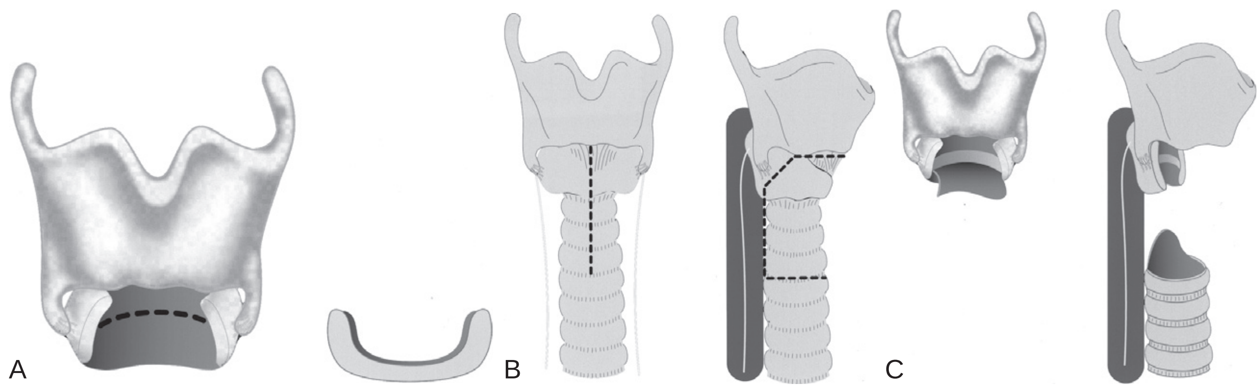



**FIGURE 65-11** Cricotracheal resection. **A,** Resection of the anterior cricoid with a mucosal incision in the posterior cricoid. **B,** View of resection of a scarred airway with preservation of the recurrent laryngeal nerves. **C,** Resection complete with a cuff of posterior tracheal mucosa.

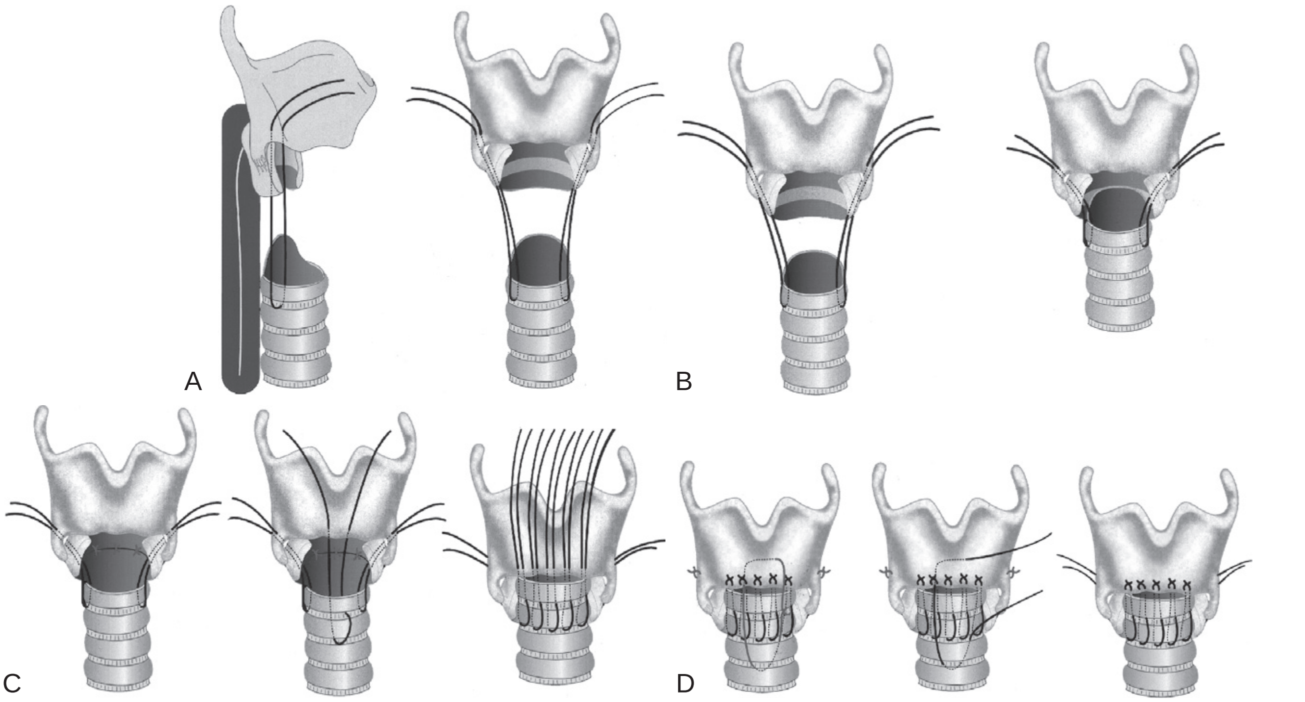



**FIGURE 65-12** Reanastomosis of a resected airway. **A,** Detensioning suture. **B,** Mobilization of the trachea. **C,** Posterior anastomosis complete; anterior anastomotic sutures placed. **D,** Anastomosis complete.

stabilize the reconstruction. The stent is left in place above a tracheotomy stoma (suprastomal stent) for 4 to 6 weeks. After removal of the stent, and once the surgical site has healed with a patent subglottis, the tracheotomy tube is downsized until the child tolerates and is able to breathe around a plugged tracheotomy tube. Once this is accomplished, the tracheotomy tube is removed. This process of reconstruction and decannulation can take weeks to several months. The morbidity and potential mortality of a tracheotomy tube is well recognized in children. With staged reconstruction and stent placement, the child is left with little or no airway above the tracheotomy tube, which is life-threatening if the tube accidentally falls out or becomes occluded. Long-term stenting has additional morbidities of granulation tissue formation, infection, dislodgment of the stent, dysphagia, and aspiration. To address these risks and circumvent some of these problems, single-stage LTR (SSLTR) evolved. In the authors' hands, staged procedures are still done in children with compromised pulmonary reserve or complex multilevel stenosis that require prolonged stenting.

Single-stage LTR (SSLTR) involves surgical correction of the stenotic airway with a short period of endotracheal intubation, thus avoiding the need for prolonged laryngotracheal stenting and tracheotomy tube dependency. The airway must have adequate cartilaginous support to consider SSLTR as a surgical option. SSLTR requires a comprehensive understanding of the principles of airway reconstruction and extensive experience on the part of the surgeon, anesthesiologist, intensivist, and nursing staff. Postoperative care of these patients can be complicated.[2,91,92] The experience at our institution of 200 SSLTR cases showed that 29% of patients were reintubated, and 15% required postoperative tracheostomy. The overall decannulation rate was 96%. We also found that the use of anterior and posterior costal cartilage grafting, age less than 4 years, sedation for more than 48 hours, a leak pressure around the endotracheal tube of greater than 20 cm $H_2O$, and moderate/severe tracheomalacia significantly increased the rate of reintubation. The duration of stenting did not affect outcomes. Children with anterior and posterior grafts and those with moderate or severe tracheomalacia were more likely to need a postoperative tracheostomy. SSLTR can be effectively used in the treatment of pediatric laryngotracheal stenosis. However, diligent preoperative assessment of the patient's airway and comorbidities, surgical skill and experience, and meticulous postoperative care are important to the success of this operation. The ultimate goal of laryngotracheal reconstruction is tracheotomy decannulation or prevention. The rate of decannulation varies with the severity of stenosis and the method of reconstruction. Surgical management of pediatric subglottic stenosis is challenging. Multiple operations may be required to achieve eventual extubation or decannulation. There is no specific model to predict the outcome of pediatric airway reconstruction surgery. A review of the experience at our institution shows that decannulation rates for double-stage laryngotracheal reconstruction for Myer-Cotton grades II, III, and IV are 95%, 74%, and 86%, respectively. Decannulation rates for SSLTR for Myer-Cotton grades II, III, and IV are 100%, 86%, and 100%, respectively. Our experience is that children with Myer-Cotton grade III or IV disease represent a significant challenge, and refinements of techniques are needed to address this subset of children.

Surgical management of grade IV stenosis represents the most difficult group to obtain good results. We have found that refinements in surgical technique and application of cricotracheal resection (CTR) as the primary operation for grade IV stenosis has improved the decannulation rates from 67% in the 1980s to 86% in the 1990s.[93] Our experience also shows that patients who undergo CTR have higher decannulation

rates than patients who have laryngotracheal reconstruction (LTR) with anterior and posterior costal cartilage grafting (92% vs. 81%). CTR patients are less likely to need additional open procedures to achieve decannulation (18% vs. 46%).[93] Patients with grade IV stenosis and other areas of the larynx and trachea involved often require extended CTR with the application of cartilage grafting and arytenoid procedures. Extended CTR procedures are those beyond isolated resections and anastomosis. Interposition grafts can be incorporated into the closure of a CTR. Arytenoidectomy, vocal cord lateralization, and epiglottic repositioning procedures are common extended CTR procedures.

## HEMANGIOMA

Subglottic and tracheal hemangiomas are benign congenital vascular tumors that are derived from mesodermal rests. The lesions are relatively uncommon, accounting for 1.5% of all congenital laryngeal anomalies, with a 2:1 female predominance.[8] Patients are usually asymptomatic at birth but present with stridor or "croup" within the first few months of life; 85% present in the first 6 months,[94] and 50% have cutaneous hemangiomas present at the time of diagnosis.[95] Infants with a subglottic hemangioma and cutaneous facial hemangiomas in a "beard" distribution should be evaluated for PHACES syndrome, which is the acronym for posterior fossa malformations (P), segmental facial hemangiomas (H), arterial anomalies (A), cardiac defects (C), eye abnormalities (E), and sternal defects (S). An infant who presents with stridor and a cutaneous hemangioma warrants an airway evaluation to detect the presence of a hemangioma. Asymmetric subglottic narrowing is the classic finding on soft tissue neck radiographs. Endoscopic diagnosis is usually made without biopsy because of the lesion's typical appearance of a compressible, asymmetric, submucosal mass with bluish or reddish discoloration most often found in the posterolateral subglottis (Fig. 65-13,*A*). Because the lesion may be the "tip of the iceberg" and extend into the thoracic cavity, select cases should have imaging either by magnetic resonance imaging (MRI) or computed tomography (CT) angiogram before treatment is initiated.

Subglottic and tracheal hemangiomas will have a rapid growth phase that slows by 12 months, followed by slow resolution over the subsequent months to years. Most will show complete resolution by 5 years. However, subglottic hemangiomas are associated with 30% to 70% mortality when left untreated. Therapeutic and surgical management of this problem is directed at maintaining the airway, while minimizing potential long-term sequelae of the treatment itself. Historical methods of management include external beam radiation, radium and gold implants, and sclerosing agents, and they are no longer used because of the associated morbidity. Current management options include tracheotomy, laser partial excision, systemic or intralesional steroids, open surgical resection, systemic interferon alpha-2A, and systemic propranolol. Bypassing the obstructing lesion with a tracheotomy and waiting for the expected involution will provide for the optimal anatomic result and is considered by many to be the standard of care by which all other treatment options need to be measured. However, as previously discussed in this chapter, there are risks associated with a tracheotomy as well

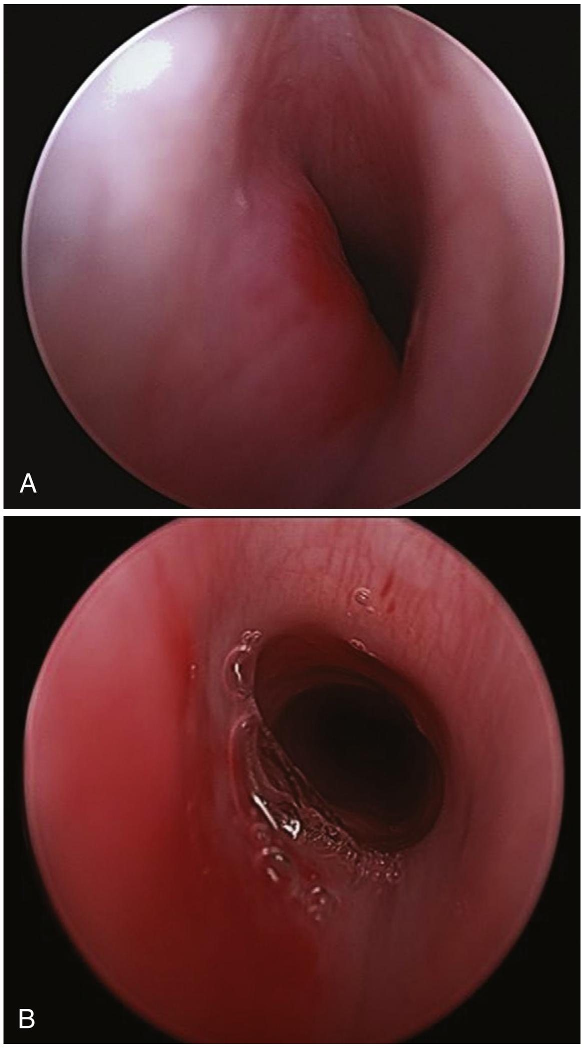



**FIGURE 65-13** Subglottic hemangioma in a 4-month-old infant. **A,** Before propranolol therapy. **B,** Two months after propranolol therapy. *(See Expert Consult site for color version.)*

as the delay in speech and language that is routinely encountered when children require a tracheotomy at a young age. Additionally, scarring in the subglottis often occurs as a result of the involution process that may require an endoscopic or open surgical reconstruction to manage the resultant subglottic stenosis to achieve decannulation.

Systemic corticosteroids for treatment of subglottic hemangiomas were introduced in 1969 by Cohen[96] and are used both as primary and adjuvant therapy. Steroids decrease the size of the hemangioma and accelerate involution by an unknown mechanism. Steroids are thought to decrease hemangioma size by blocking estradiol-induced growth[97] or by directly increasing capillary sensitivity to vasoconstrictors. Systemic steroids are shown to reduce the size of the hemangioma, but only approximately 25% of cases resolve completely with this treatment alone.[98] Risks of long-term steroid use include growth retardation, cushingoid face, and increased susceptibility to infection, including life-threatening *Pneumocystis carinii* pneumonia.[99] Using an alternate-day dosing regimen in the smallest possible doses may reduce these effects. Successful avoidance of tracheotomy can be achieved by endoscopic intralesional injection of corticosteroids into the hemangioma, with or without

short-term intubation.[100] This approach, however, often requires 30 to 50 days of total intubation time while the patient is undergoing serial injections, thereby increasing intubation-related morbidity and cost.[101]

Endoscopic surgical management with the $CO_2$ laser was first reported in 1980 by Healy and colleagues.[102] Isolated unilateral subglottic hemangiomas are usually the best type and location for $CO_2$ laser treatment. In carefully selected patients, partial resection of the hemangioma with $CO_2$ laser, with or without systemic corticosteroids, is successful.[103] The authors' experience is that systemic steroids are usually a necessary adjunct. Other reports show that the KTP laser is a good tool for management of subglottic hemangiomas, with a low incidence of complications.[104,105] The KTP laser is preferentially absorbed by hemoglobin, making this laser system well suited for the treatment of vascular tumors such as a hemangioma. Long-term outcomes of this technique are not available.

Interferon alpha-2A has been used in children with obstructing hemangioma who were unresponsive to laser and/or corticosteroid therapy, achieving a 50% or greater regression of the lesion in 73%.[106] Interferon alpha-2A requires prolonged therapy, because it does not promote involution but inhibits proliferation by blocking various steps in angiogenesis. The side-effect profile of neuromuscular impairment, spastic diplegia, neutropenia, skin slough, fever, and liver enzyme elevation,[106] limits its use to therapy of last resort and will likely relegate it to a historical treatment option in the near future.

To avoid the complications of the previously mentioned management strategies, open excision of subglottic hemangiomas was revisited in the late 1990s to the mid-2000s to provide a more definitive treatment. Several studies show that this strategy is effective for selected patients and should be considered in corticoresistant or corticodependent, circular or bilateral hemangiomas,[3] large life-threatening hemangiomas[4,5] and is even an alternative to tracheotomy placement.[101,107,108] The surgical technique is similar to SSLTR. The airway is opened at the level of the cricoid cartilage, followed by a submucosal dissection with or without microscopic dissection to excise the hemangioma. An anterior cartilage graft is usually placed, and the patient is intubated for 5 to 7 days.[107,109] Similar to airway reconstruction surgery for subglottic stenosis, appropriate institutional resources and a team is required for successful outcomes.

Propranolol, a nonselective beta blocker was serendipitously discovered as a treatment option by noting rapid regression of hemangiomas in infants treated with propranolol for cardiopulmonary conditions. Since this landmark report of Léauté-Labrèze and colleagues in 2008,[110] it has become the emerging treatment option for hemangiomas. Beta-2 receptors for propranolol are expressed in hemangioma endothelial cells. The mechanism of action of propranolol in the treatment of hemangiomas remains unclear, but it is hypothesized to work through antiangiogenesis, with decreased production of vascular endothelial growth factor and fibroblast growth factor-β (VEGF and FGF-β, respectively) or by inducing cellular apoptosis.[110] Since that initial report, others have reported successful management of subglottic hemangiomas,[111–118] including those that extend into the mediastinum,[114] at a dose of 2 mg/kg/day, with near immediate response (Fig. 65-13, *B*). The duration of treatment required is not known, but published reports suggest a mean duration of 6 months; however, the treatment course may need to extend through the expected rapid growth phase until the early involution phase.[115,119] Up to 47% of patients may be partial responders,[119] whereby adjunctive therapies, including steroids, endoscopic laser excision, or open surgery may be required.[119,120] Propranolol is an attractive therapeutic alternative, because it may avoid the risk of surgery and can avoid the common adverse effects of prolonged high-dose steroid use, but it is not without its own potential risks, which include bradycardia, hypotension, hypoglycemia, as well as potential exacerbation of reactive airways disease.[119] Routine monitoring of blood pressure and glucose is required. Further clinical experience with this treatment modality is required to determine if it may render surgical treatment of subglottic hemangiomas obsolete.

## LARYNGEAL AND LARYNGOTRACHEOESOPHAGEAL CLEFTS

Congential laryngeal and laryngotracheoesophageal clefts are rare conditions that can be characterized by a posterior midline deficiency in the separation of the larynx and trachea from the hypopharynx and esophagus (Fig. 65-14). The incidence is less than 0.1%, and the majority of cases are sporadic. There is a strong association with other anomalies (56%), most commonly esophageal atresia and tracheoesophageal fistula (EATEF) in 20% to 27%.[121] Six percent of children with EATEF have a coexisting laryngeal cleft. In these patients, the laryngeal cleft goes undetected in three quarters until persistent aspiration, despite successful EATEF repair, prompts further investigation.[121] Laryngeal or laryngotracheoesophageal clefting is commonly associated with a syndrome, most commonly G syndrome, VACTERL association (vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula and/or esophageal atresia, renal agenesis and dysplasia, and limb defects), and Pallister-Hall syndrome.[122]

The degree of clefting may be relatively minor, involving only a failure of interarytenoid muscle development, or can extend to the carina and even into the mainstem bronchi. Multiple classification systems have been used to describe laryngeal clefts, differentiating them by the length of the cleft. The most commonly accepted classification system is the

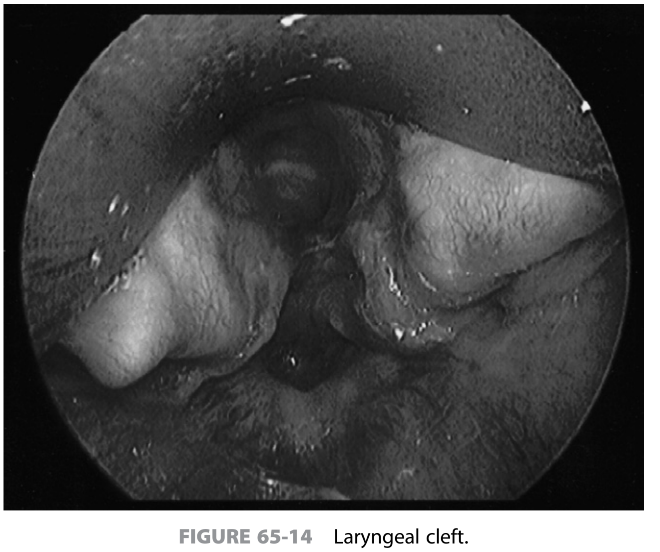


**FIGURE 65-14** Laryngeal cleft.

Benjamin-Inglis classification,[123] describing a type I cleft as interarytenoid to or below the level of the vocal process, type II as having partial extension through the posterior cricoid plate, type III as extending completely through the cricoid plate, and type IV as extending through the larynx and into the cervical or intrathoracic trachea and esophagus. The range of symptoms will vary depending on the length of the cleft. Patients with any degree of clefting may present with stridor, cyanosis associated with feeding, aspiration, and recurrent pulmonary infections. Type IV clefts, if not addressed immediately, are incompatible with life. Although radiographic contrast studies may suggest aspiration, the best single study for identifying a laryngeal cleft is careful endoscopic examination. The arytenoids need to be parted to obtain adequate visualization, because the larynx may be obscured by redundant esophageal mucosa prolapsing into the glottic and subglottic lumen. Most type I clefts do not require surgical intervention, unless significant swallowing or respiratory symptoms are present.[124,125] Most of these can be managed conservatively with aggressive medical management of gastroesophageal and laryngopharyngeal reflux and swallowing therapy.[121,125] When surgical intervention is required for these small clefts, endoscopic repair is successful in over 80%, with open repair reserved for endoscopic failures.[121,126,127]

In contrast to the type I clefts, surgical repair is required in nearly all type II to IV clefts. An anterior approach through a laryngofissure is historically the most commonly approach used. The advantage of this approach is excellent exposure of the entire defect without risk to the laryngeal innervation. Complete laryngotracheoesophageal clefts (type IV) that extend to the carina may require a posterolateral approach to allow for a two-layer closure and may require extracorporeal circulation. Some surgeons choose to place a tracheotomy if not present prior to surgical repair. Single-stage repair using endotracheal intubation as a short-term stent without tracheotomy is the preferred technique by the authors.

As more surgeons gain experience with endoscopic airway surgery, endoscopic techniques are being applied to repair type II and type III clefts.[125,127–129] Through an operating laryngoscope, the edges of the cleft are demucosalized with either sharp dissection or a $CO_2$ laser and a one-layer or two-layer closure is completed with absorbable suture. There is general agreement that a successful endoscopic repair is preferable to a successful open repair, primarily because the former preserves the anterior commissure and thus results in better voice outcomes. Robotic surgical applications may even further the endoscopic surgical options, but more experience is needed to determine if robotic techniques prove to be better than standard techniques.[128]

# Tracheal Lesions

## TRACHEOMALACIA

Tracheomalacia is a condition where the tracheal wall cartilage is soft and pliable. The cardinal symptom of tracheomalacia is stridor with increased respiratory effort that leads to dynamic collapse of the airway. Tracheomalacia is usually congenital, and the congenital forms are either primary tracheomalacia or secondary. The etiology of primary tracheomalacia is unknown. It is a common cause of stridor in infancy. It is differentiated from laryngomalacia in that the phase of stridor is in expiration; however, laryngomalacia and tracheomalacia can coexist, and the child may have both inspiratory and expiratory stridor. Most infants with primary or isolated tracheomalacia outgrow the condition by 18 months of age. Secondary tracheomalacia occurs as a result of another coexisting condition.

The most common congenital condition that causes secondary tracheomalacia is extrinsic compression from a vascular anomaly, such as a vascular ring or innominate artery (Fig. 65-15, *A*). Severe airway symptoms resulting from such vascular anomalies include acute life-threatening events (ALTEs), infant apnea, recurrent pneumonia, stridor with severe airway obstruction leading to hypoxia, respiratory distress, and pectus excavatum. These life-threatening indications warrant surgical intervention. Surgically addressing the compressing innominate artery by aortopexy, innominate artery suspension or innominate artery repositioning, or correcting the causative vascular ring will often improve, if not reverse, the airway symptoms. (see Fig. 65-15)

Because of the embryologic development of the esophagus and tracheobronchial tree, there is a high probability that a child with EATEF will have some degree of tracheomalacia. In these patients, the tracheomalacia is most often found at the level of the fistula site. After repair of the TEF, a resultant

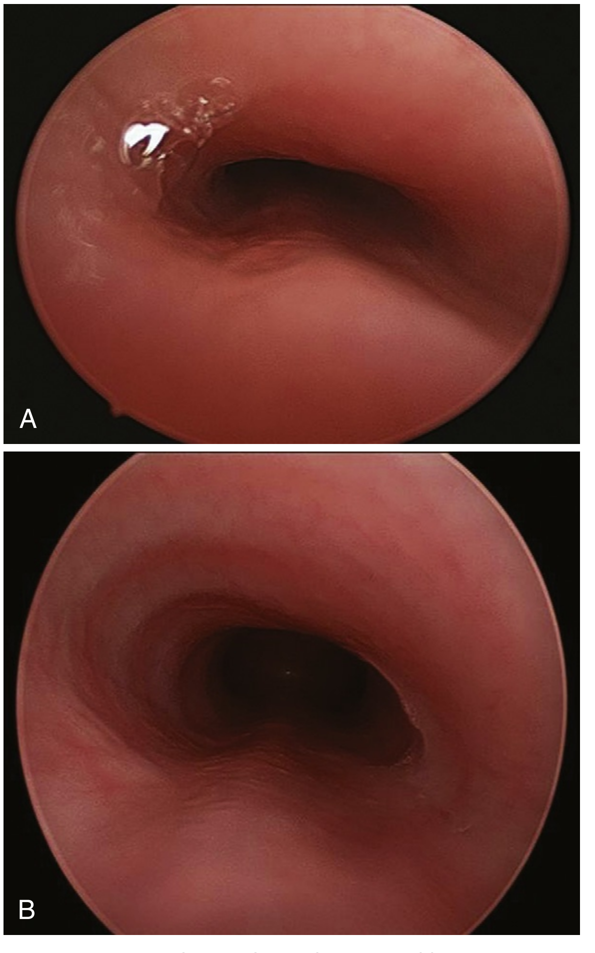



**FIGURE 65-15** Secondary tracheomalacia caused by innominate artery compression. **A,** Before aortopexy. **B,** After aortopexy. *(See Expert Consult site for color version.)*

tracheal pouch is often present. Some of these pouches will require intervention as discussed in the following section.

Acquired tracheomalacia may also develop in infants who require long-term ventilatory support with high-pressure endotracheal tubes or cuffed tracheotomy tubes. There is no good treatment for severe or life-threatening diffuse tracheomalacia other than bypassing and stenting the area with a tracheotomy tube and waiting for the child to grow. Methods of endotracheal stenting with angioplasty and Palmaz stents have been attempted in life-threatening cases with some success; however, stenting is associated with significant morbidity and mortality.[130]

## TRACHEAL POUCH

An acquired tracheal pouch is typically a sequela of TEF repair. Shallow, wide-mouthed pouches in the region of the carina are common, usually asymptomatic, and do not require surgical repair. In contrast, pouches that occur more proximally are more likely to be large, symptomatic, and require surgical intervention to alleviate associated respiratory symptoms or the risk of inadvertent intubation of the pouch with endotracheal or tracheotomy tubes, with a resultant inability to ventilate. The repair is generally based on division of the shared diverticular and tracheal wall. Various techniques for repair have been described, including endoscopic and open transcervical or transthoracic approaches. Johnson and colleagues[131] describe an endoscopic approach to divide the pouch using a Clickline biopsy forceps (Karl Stortz Endoscopy, El Segundo, Calif.), which is a True-Cut laparoscopic instrument with incorporated suction and cautery as a minimally invasive option for symptomatic tracheal pouches resulting from TEF repair.

## CONGENITAL TRACHEAL STENOSIS

Congential tracheal stenosis is a rare, potentially life-threatening anomaly that usually involves complete cartilaginous tracheal rings, and has proven to be difficult to treat. In 1964, Cantrell and Guild[132] classified congential tracheal stenosis into three categories: long-segment stenosis with generalized hypoplasia (22%), funnel-like stenosis (37%), and segmental stenosis (41%). Associated anomalies in children with congenital tracheal stenosis are common, with 24% having coexistent vascular anomalies, most commonly a pulmonary artery sling.[133]

Congenital tracheal stenosis usually presents with a history of biphasic stridor and possibly acute respiratory distress. Severe cases in neonates may require extracorporeal membrane oxygenation until a definitive surgical procedure can be executed.[134] A definitive diagnosis is best obtained with endoscopy (Fig. 65-16); however, meticulous endoscopic technique is required in the very young, because any airway edema or trauma caused by instrumentation may lead to an obstructive airway emergency that cannot be managed by intubation and ventilation, which would require emergent extracorporeal membrane oxygenation or cardiopulmonary bypass. Recent advances in three-dimensional magnetic resonance and computed tomography[135] imaging provide an alternative for diagnosis and follow-up. Additionally, magnetic resonance imaging or contrast-enhanced computed tomography, coupled to echocardiography, is frequently needed to identify associated cardiovascular abnormalities.

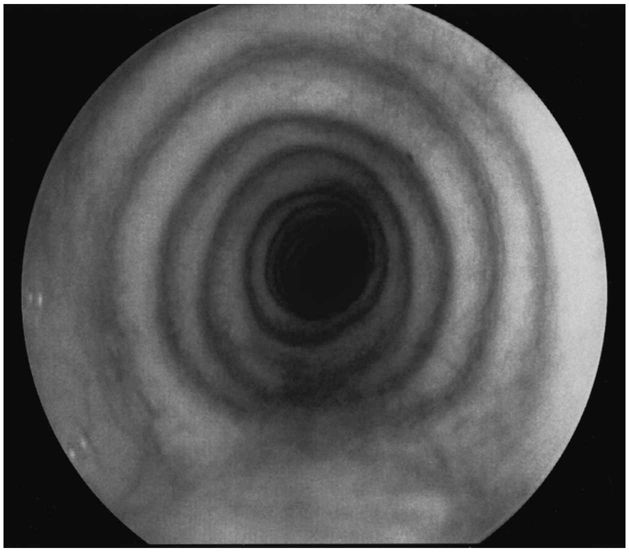


**FIGURE 65-16** Complete tracheal rings.

The management of congenital tracheal stenosis has evolved over the past 15 years with decreasing mortality rates. Segmental resection with primary anastomosis has been shown to be an excellent treatment option for stenosis, involving up to 50% of the trachea. However, there are a number of procedures used for long-segment stenosis, because historically none have been universally successful. In fact, Benjamin and colleagues, in 1981, recommended a nonsurgical approach because the 57% survival in this group of patients was higher than in their operated group.[136] Findings from the authors' institutions reiterate that nonoperative management of complete tracheal rings may be appropriate in selected patients.[137] We estimate that up to 10% of patients with complete tracheal rings will not require tracheoplasty. Selected patients must be asymptomatic or have minimal symptoms and demonstrate tracheal growth over serial examinations. However, the rate of growth remains to be determined. Surgery for long-segment tracheal stenosis has evolved over the past 25 years. Anterior tracheoplasty using pericardium was first described by Idriss and colleagues in 1984.[138] Since then, reported results of this technique reveal survival rates of 47% to 76% in the larger series.[139] Costal cartilage grafting for augmentation has had similar results[140] in a smaller number of patients. Other augmentation materials that have been tried include esophageal wall, rib, dura, and periosteum.

Slide tracheoplasty, as described by Tsang and colleagues[141] and modified by Rutter and colleagues,[142] involves a transverse division of the trachea in the middle of the stenosis and longitudinal incisions of the anterior portion on one end and the posterior portion on the other, sliding the two ends over each other, thus halving the length and doubling the diameter. In its original description, slide tracheoplasty was used for funnel-shaped stenosis. At the authors' institutions, this technique has evolved and has now become the preferred surgical approach for tracheal stenosis, regardless of the length of narrowing; furthermore, it is routinely applied successfully for the management of long-segment tracheal stenosis with less variable outcomes compared with previous techniques (Fig. 65-17).[142,143] Slide tracheoplasty using cardiopulmonary bypass support is a versatile and effective treatment for tracheal

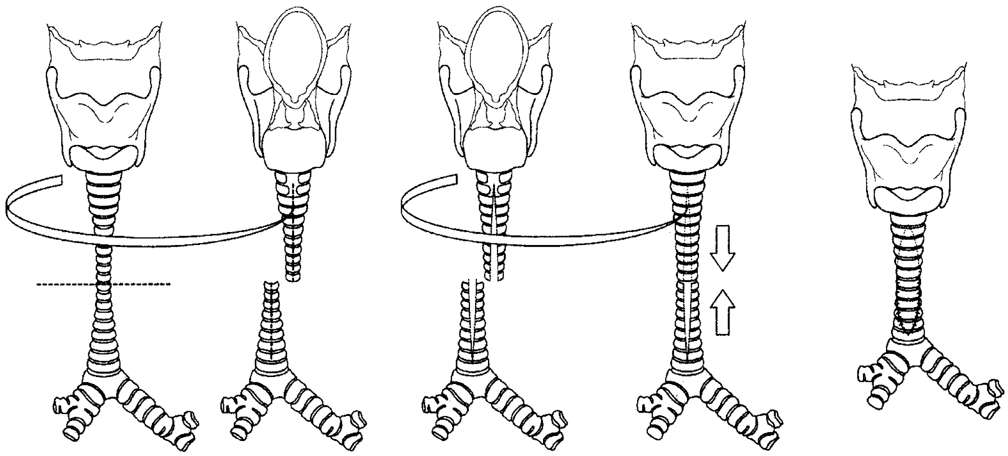


FIGURE 65-17 Slide tracheoplasty: transverse section of the trachea, with the proximal segment of the rings split posteriorly and the distal segment split anteriorly. Sliding of the two portions together doubles the circumference and halves the length.

stenosis in children even when combined with concurrent repair of congenital cardiac anomalies.[144] Slide tracheoplasty has also been described as a salvage procedure for failed patch tracheoplasty.[145] Another alternative is the use of tracheal homograft reconstruction in cases of severe long-segment and recurrent stenosis. An 83% survival rate is reported with this technique.[146,147] Long-term outcomes of homograft transplantation are currently not available. Use of this option is limited by the availability of cadaveric tracheal homografts and the potential for host rejection.

## Tracheobronchial Vascular Compression

Vascular compression of the tracheobronchial tree has been the subject of much discussion since 1945, when Gross described the first successful operation for a double aortic arch.[148] In 1963, Fearon and Shortreed[149] reviewed 104 cases and coined the term “reflex apnea” to describe the episodic apnea associated with airway vascular compression. In 1969, Mustard and colleagues[150] reviewed 285 cases and reported successful medical management in 86.3% of cases.

Indications for surgical management include reflex apnea and recurrent bronchopulmonary infections. In 1971, MacDonald and Fearon[151] divided the criteria for surgical intervention into absolute and relative criteria and added failure of medical management, greater than 50% compression of tracheal lumen, and associated airway and lung abnormalities to the existing criteria. In 1975, Moes and colleagues,[152] compared 60 children who were operated on for innominate artery compression of the trachea with 30 children who did not undergo surgery, noting that the appropriateness of surgical intervention was based not on the severity of compression seen at endoscopy or radiographically but on the severity of symptoms. In 1981, Strife and colleagues[153] concluded that the word “anomalous” should be omitted from innominate artery tracheal compression syndrome, because the origin of the innominate artery partially or totally to the left of the trachea was a normal finding in children as seen on aortogram in 96% of patients.

Vascular compression of the tracheobronchial tree has an overall incidence of 3%. The most common symptomatic true vascular ring is the double aortic arch, which occurs if the fourth aortic arches and the dorsal aortic root persist on both sides. In 1 in 2500 persons, the left arch has an atretic segment, but the right arch persists. A right-sided arch with a descending right aorta does not cause airway compromise. However, if there is an associated left ductus or an aberrant left subclavian artery, a loose vascular ring is formed that generally results in less airway compromise than a true double aortic arch. The pulmonary artery sling is the most symptomatic of the noncircumferential vascular anomalies and occurs when the left sixth arch resorbs and the left pulmonary artery arises as a large collateral artery from the right pulmonary artery, and passes between the esophagus and trachea to perfuse the left lung. This anomaly commonly results in significant compromise of the right mainstem bronchus and airway symptoms. In addition, 30% of patients with pulmonary artery slings have associated complete tracheal rings.[154] The aberrant right subclavian artery is the most common mediastinal vascular anomaly. However, because of its retroesophageal course, affected individuals may present with dysphagia but rarely with symptomatic airway compromise. Innominate artery compression of the trachea is not associated with a true vascular anomaly. The innominate artery normally passes from its origin on the aortic arch left of midline across the anterior trachea to the right side. It has been hypothesized that in patients who are symptomatic, the innominate artery is more taut than normal, and the tracheal cartilages are unusually compliant and more easily compressed, or that dilation of other structures, such as the heart, esophagus, or thymus, cause mediastinal crowding.

Respiratory compromise from tracheobronchial vascular compression is potentially life threatening but can present with subtle symptoms. A high index of suspicion is required to make the diagnosis. Patients with significant vascular compression usually present early with stridor, chronic cough, recurrent bronchitis and pneumonia, difficulty feeding and failure to thrive, and occasionally reflex apnea. Reflex apnea has been described as a reflexive respiratory arrest of variable duration that is secondary to stimulation of vagal afferent nerve fibers during swallowing and other forms of transient intrathoracic pressure changes.

Chest radiographs may provide some evidence of tracheal compression, and a barium esophagram can show relatively

characteristic filling defects that correspond to the various types of vascular compression. However, once vascular compression is suspected, the diagnostic modality of choice is magnetic resonance imaging, which will clearly demonstrate the mediastinal vascular anatomy as well as the size of the lower airway. Spiral computed tomography with intravenous contrast may be a useful adjunct or replacement to magnetic resonance.[155,156] Although today the diagnosis of vascular compression is usually known prior to undergoing endoscopy, bronchoscopy also reveals characteristic findings of compression, depending on the type of vascular ring or sling. Bronchoscopy provides an immediate visual assessment of the surgical results on relieving the compression and the degree of residual tracheomalacia present.

Nonsurgical management may be effective for the majority of innominate artery compression and loose vascular rings and slings that are mildly symptomatic. In contrast, moderately to severely symptomatic patients usually require surgical repair. Absolute indications for surgical treatment include reflex apnea, failure of medical management of severe respiratory distress after 48 hours, and prolonged intubation. Relative criteria include repeated episodes of lower respiratory tract infection, exercise intolerance, significant dysphagia with failure to thrive, or coexisting subglottic stenosis, asthma, cystic fibrosis, or symptomatic tracheomalacia after EATEF repair.

Innominate artery compression is relieved by aortopexy or reimplantation, with success rates of 93% to 100% and no reports of operative mortality or long-term morbidity.[157] Occasionally, aortopexy sutures can loosen, and the procedure needs to be revised.

Results of surgical treatment of vascular rings are also encouraging, with 70% to 92% obtaining complete resolution of symptoms.[158] Double aortic arch requires surgical division of the smaller of the two arches. The ductus arteriosus or aberrant subclavian artery is divided in the case of right aortic arch with left ductus arteriosus or aberrant left subclavian artery. In cases of severe tracheobronchial compression, residual tracheomalacia may persist for a variable period of time, and occasionally a tracheotomy is required to stent the malacic segment.

The pulmonary artery sling is corrected by dividing the aberrant left pulmonary artery at its origin and reimplanting it anterior to the trachea. There is a significantly increased morbidity and mortality rate in these cases, usually because of the associated complete tracheal rings.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 66

# Infections and Diseases of the Lungs, Pleura, and Mediastinum

Pramod S. Puligandla and Jean-Martin Laberge

## Lung Infections

Childhood pneumonia continues to be a significant global health problem affecting 150 million children around the world on an annual basis.[1] It is therefore not difficult to appreciate the burden pneumonia places on the health care system both from a medical and economic perspective. This chapter reviews the clinical presentation, diagnosis, etiologies, and management of pediatric pneumonia, with a special emphasis on the pediatric cancer patient and children infected with human immunodeficiency virus (HIV). We also focus on the management of complications that result from pneumonia, as well as additional specific disorders affecting the lungs, thorax, and mediastinum, including cystic fibrosis, pulmonary hemorrhage, spontaneous pneumothorax, chylothorax, and mediastinitis.

### EPIDEMIOLOGY

Acute respiratory infections represent a significant health burden for children across the globe. Indeed, these infections are the leading cause of hospitalization and outpatient visits in developed and developing countries alike.[2] The incidence of pneumonia varies between 0.03 episodes/child/year in developed countries to almost 10 times that rate in developing countries.[3–5] Pneumonia accounts for approximately 2 million deaths per year in children less than 5 years of age.[6,7] The vast majority of these deaths occur in developing countries, with greater than 50% located in sub-Saharan Africa,[8] where the rate of pneumonia parallels the rate of HIV infection.[1,9]

From an etiologic standpoint, studies have identified both *Streptococcus pneumoniae* and viral agents as the most common causes of respiratory infections.[3,10] In terms of age, respiratory syncytial virus (RSV) prevails in young children (<2 years), with a larger proportion of community-acquired pneumonia being attributable to *Streptococcus pneumoniae* in children older than 2 years of age.[3, 10,11] It is important to note that no causative agent may be identified in up to 25% of community-acquired pneumonia.[8]

### COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA

#### *Streptococcus pneumoniae*

*Streptococcus pneumoniae,* or pneumococcus, is a major cause of morbidity and mortality around the world. It is the most common pathogen in infants and children and is responsible for approximately 500,000 cases of pneumonia per year in the United States.[12] Worldwide, up to 1 million deaths per year occur as a result of pneumococcus infection, with the majority of these deaths occurring in developing countries.[13–15]

Pneumococcus is a gram-positive coccus that is a part of the normal respiratory flora in children and adults. Colonization rates, particularly of the nasopharyngeal mucosa, appear to decrease with age, and are an important factor in the development of infection.[12] The symptoms of infection include fever, productive cough, tachypnea, dyspnea, malaise, and occasional emesis. On physical examination, patients have hypoxia and decreased breath sounds with crackles over the affected area. Radiographically, pneumococcal infections can be lobar, multi-lobar, or sometimes segmental (Fig. 66-1), and up to 40% of these patients will also have pleural fluid. Treatment is most often performed on an outpatient basis. However, antibiotic resistance is quite prevalent with this species, and this has led to changes in empiric therapy that may not be quite as effective.[16–19] For patients infected with a strain demonstrating low to intermediate resistance, penicillin and other β-lactam antibiotics are still effective.[20] Third-generation cephalosporins may be used in cases of high resistance or if there is no clinical improvement with conventional therapy.[8]

The use of heptavalent conjugate vaccines since 2000 has dramatically affected the impact of invasive pneumococcal disease by those strains contained within the vaccine.[21–23] It has also led to a reduction in the overall incidence of pneumococcal pneumonia[24] as well as the admission rates for

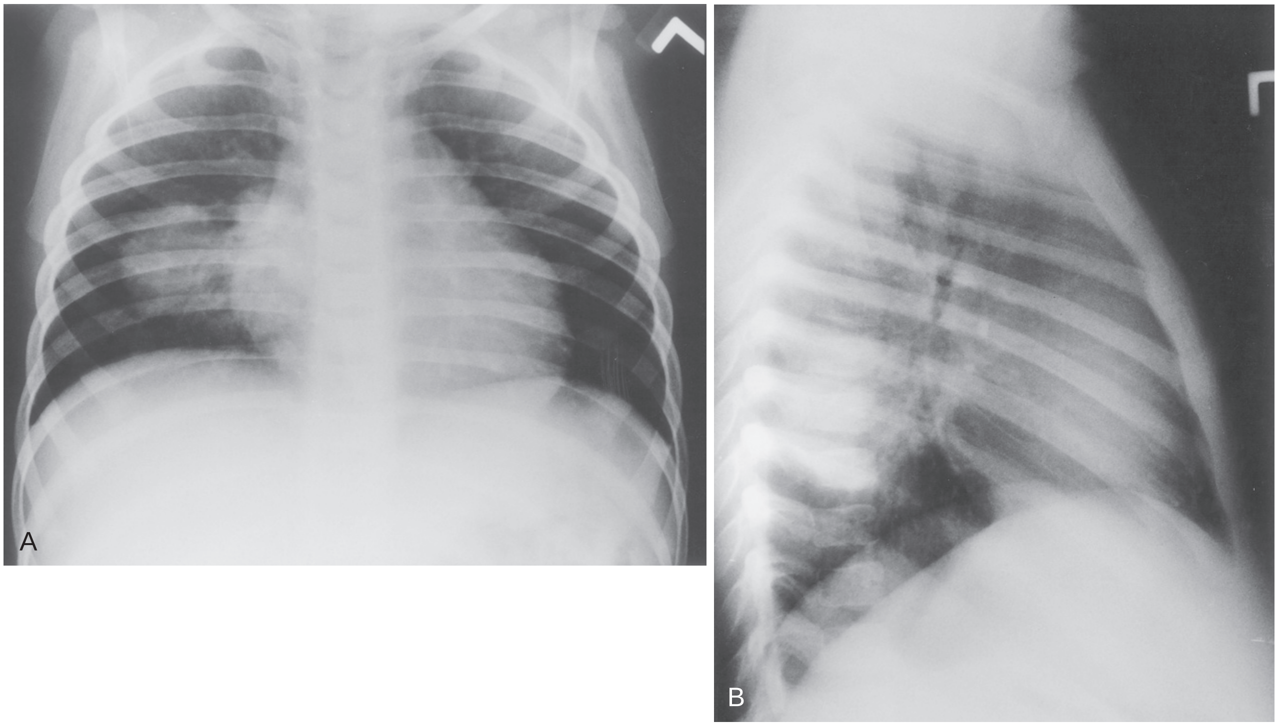


FIGURE 66-1 Chest radiograph of a 1.5-year-old boy with fever and dyspnea shows a typical round pneumonia of the superior segment of the lower lobe; an air bronchogram can be seen within the opacity. **A,** Anteroposterior view. **B,** Lateral view.

children less than 2 years of age.[25] However, invasive disease caused by nonvaccine serotypes has also increased, and these strains are now responsible for the majority of cases. To address this issue, a new 13-valent pneumococcal vaccine has been recently introduced that contains protection against an additional 6 serotypes that are currently responsible for 63% of invasive pneumococcal cases.[23]

### *Haemophilus influenzae*

More than 95% of invasive cases of *Haemophilus* are caused by the type B strain. Infections with *Haemophilus* usually occur in the winter and spring. The clinical presentation includes fever, tachypnea, elevated white cell count, and the presence of unilateral consolidation with pleural effusion on chest radiographs. Although extrapulmonary manifestations, such as meningitis and epiglottitis, may be more typical with this organism, *Haemophilus* can still cause pneumonia in infants and preschool-age children.[26] Treatment is based upon the susceptibility of these bacteria to β-lactam antibiotics because resistance has been reported to occur in more than 30% of isolates.[27] Third-generation cephalosporins can be used for those strains producing β-lactamase. The overall incidence of significant infections caused by this species has been dramatically reduced with the introduction of the *Haemophilus* vaccine. Global initiatives are currently underway to expand vaccine availability in developing countries where the burden and impact of *Haemophilus* infection is still unknown.[26]

### *Staphylococcus aureus*

These ubiquitous gram-positive cocci are commonly found on the skin and nasal mucosa, with 20% to 30% of the population being normal carriers of this bacterium. *Staphylococcus aureus* produces toxins and enzymes that form the basis of the lesions produced by this pathogen—a pyogenic exudate or an abscess. Staphylococcal infections are usually progressive, occurring in infancy and early childhood. Although community-acquired pneumonias with *Staphylococcus aureus* were generally thought to be uncommon, recent reports suggest an increasing incidence.[28] Patients generally present with fever and rapidly develop respiratory symptoms that may have been predated by flulike symptoms. Clinical and radiologic deterioration quickly ensues if left untreated. Radiographically, primary pneumonias display unilateral lobar consolidation. Secondary infection/pneumonia usually involves a prolonged febrile illness and is often accompanied by positive blood cultures. These infections commonly present as diffuse bilateral infiltrates on chest radiographs.

Staphylococcal pneumonias may be associated with pleural effusions, empyema, lung abscesses, or pneumatoceles. The latter lesions require follow-up until complete resolution (see later). More important, necrotizing pneumonia can occur when community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) strains produce Panton-Valentine-leukocidin (PVL).[29] PVL-producing MRSA strains are highly virulent, leading to rapidly progressive cardiorespiratory compromise and a mortality of greater than 50%.[28,30] Treatment involves the use of appropriate antistaphylococcal antibiotics, but widespread resistance to penicillin and methicillin is problematic. If resistance or penicillin allergy exists, other agents, including vancomycin, macrolides, and clindamycin may be used. The latter may be a useful toxin-neutralizing agent in cases of PVL.[30] The duration of treatment is usually 3 to 4 weeks with fevers persisting for up to 2 weeks after the institution of therapy.

### *Mycoplasma* and *Chlamydia*

*Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are unique pathogens that can cause respiratory infections in children of all ages, including preschool-age children.[31,32] These organisms represent clinically significant causes of atypical pneumonia and have similar sero-epidemiologic profiles. Infection is spread by person-to-person contact and usually involves a 1- to 2-week incubation period. The presentation of atypical pneumonias is very similar to that of viral respiratory infections. There is a gradual onset of symptoms, including sore throat, hoarseness, and rhinitis, with or without fever. These upper respiratory tract symptoms progress to the lower respiratory tract over several days and include cough, pleuritic chest pain, rales, and rhonchi. Although *Mycoplasma* can produce chills, headache, skin rashes, and myalgias, chlamydial pneumonia is generally indistinguishable from other causes. Interestingly, *Chlamydia* may be responsible for acute chest syndrome in up to 20% of children with sickle cell disease.[31] Classically, these infections display interstitial infiltrates with a unilateral subsegmental distribution, but *Mycoplasma* can also lead to lobar consolidation and effusion. The diagnosis is usually made on clinical grounds based upon the history and physical examination. Other adjunctive tests, including polymerase chain reaction (PCR), culture, and serology, can also be used to confirm the diagnosis.[33,34] Macrolides (erythromycin, clarithromycin) are the mainstay of therapy for these infections.[35]

### *Mycobacterium tuberculosis*

Childhood tuberculosis (TB) is a global health problem. Although the vast majority of cases occur in developing countries, especially sub-Saharan Africa, increasing rates have also been reported in developed countries.[8] TB causes significant morbidity and mortality in children, and their infection serves as a future reservoir of disease.[36] The development of latent infection or progressive disease after exposure is dependent on many factors, including age, immune status, inoculation size, and host factors (i.e., nutritional status, previous vaccination).[37] Children are much more likely to progress to active disease than adults, with the risk being highest in those less than 2 years of age. Pulmonary TB, the most common site of infection, often becomes symptomatic 4 to 12 months after exposure and is more common in infants and adolescents than in children between 5 and 10 years of age for unknown reasons.[38] However, only 5% to 10% of children with latent infection will progress to active disease after the age of 3 years.[36] Indeed, the aggressive treatment of infection during the early stages of disease can have a major impact on morbidity and disseminated infection in the future. In North America, surgical complications of tuberculosis have been dramatically reduced secondary to effective medical therapy and intensive follow-up. Recent reports on the epidemiology of tuberculosis in developed nations have common themes: (1) immigrants and their children have the highest incidence of tuberculosis, (2) more serious disease occurs in young children, and (3) skin testing and screening play an important role in identifying children with tuberculosis.[36] Antibiotic resistance continues to be a significant problem and arises almost exclusively from the inadequate treatment of adults with high bacterial loads. Nonetheless, children often suffer the consequences of contracting drug-resistant species.[39]

Childhood TB differs from the adult form because primary pulmonary tuberculosis is a disease of the lymphatic system, the "primary complex."[36] Primary TB results in secondary damage to the lungs through obstruction or damage to the large airways, leading to atelectasis, chronic infection, and bronchiectasis. Most primary infections heal without residual lesions in the lung other than the Ghon complex (calcium deposit in a mediastinal or hilar lymph node). The healing of the primary lesion is believed to be associated with a positive host–organism balance, which has been attributed to either a strong natural host resistance or to a small initial inoculating dose. If defense mechanisms are unable to control the primary infection, tuberculous pneumonia progresses with caseation, often accompanied by pleural effusion. The clinical manifestations include fever, cough, and occasionally hemoptysis. Suspicion of TB should be raised in any child with chronic cough, history of contact with an adult with tuberculosis, failure to thrive, or the inability to recover from infection despite adequate treatment.[40]

The diagnosis of TB is difficult due to the slow growth of organisms in culture. *Mycobacterium tuberculosis* may be obtained from sputum, bronchial washings, gastric aspirates, or other infected material.[41,42] In areas where TB is not endemic, a combination of known contact with a TB-exposed individual, positive tuberculin skin test, and radiographic findings often will suffice.[42] In endemic areas, this may be more difficult. Another novel diagnostic test is the blood interferon-γ–release assay.[36,43]

In children, a positive tuberculin skin test, defined as either greater than 15 mm in those without risk factors or greater than 5 to 10 mm in those with risk factors, indicates disease requiring antituberculous therapy. However, the skin test may be negative in immunosuppressed children, in those who are severely malnourished or in those with disseminated tuberculosis, as they are often anergic.[44] Antituberculous therapy may be indicated when the disease is suspected in such patients, because cultures may take several weeks to become positive. Antituberculosis therapy requires a multidrug regimen, and there is some evidence that drug levels may be affected by diet.[45] Furthermore, standard medications, such as rifampin, isoniazid, ethionamide, ethambutol, and pyrazinamide, can cause hepatotoxicity.

The main treatment for tuberculosis remains medical therapy, because these medications are often highly effective. However, surgery may be required for pulmonary tuberculosis in which significant damage to a localized area of the lung has occurred and in those for whom medical therapy is ineffective. In these cases, surgery aids to reduce the bacterial load. This is an important consideration for patients with multidrug-resistant TB.[46] The operation should be conservative, usually consisting of a wedge resection, segmental resection, or lobectomy. The indications for surgical intervention in childhood tuberculosis include (1) the need to confirm a diagnosis, (2) major airway obstruction by extraluminal lymph nodes, (3) chronic airway compromise or stenosis, (4) tuberculosis-induced bronchiectasis, (5) airway obstruction by intraluminal material, (6) hemoptysis, and (7) chronic cavitary lesions. Furthermore, pleural disease, in particular empyema, may be effectively treated by tube thoracostomy, thoracoscopy and debridement, video-assisted thoracic surgery (VATS), or thoracotomy.[46]

### Atypical Mycobacteria

Atypical mycobacterial species were first identified in the 1950s.[47] The incidence of infection with these organisms was relatively stable until the 1980s, when an increase in incidence concurred with the HIV epidemic.[48] Many more organisms are being identified because of more sophisticated culture techniques, as well as the increased number of immunocompromised patients.[49] The most common presentation of atypical mycobacterial infections is cervical lymphadenitis. The incidence of pulmonary infections with atypical mycobacteria in immunocompetent patients is low. However, it is frequently observed in patients with cystic fibrosis and in patients infected with HIV[50] (see next section). The most common subtypes responsible for pulmonary infection include the *Mycobacterium avium* complex. Other important species include *Mycobacterium kansasii, abscessus, xenopi,* and *malmoense*. The portal of entry is the oropharynx. Clinically, immunocompetent patients may have minimal symptoms or present with fatigue and chronic cough with wheezing. The diagnosis may be suspected on chest radiographs and high-resolution computed tomography. Although nodular interstitial lung disease may occur, pulmonary parenchymal involvement is usually rare. Rather, enlarged lymph nodes may compress bronchi leading to atelectatic changes and segmental collapse.[50] Chronic bronchial obstruction may also lead to bronchiectasis.[51] The laboratory diagnosis of atypical mycobacteria can be made with sputum samples using PCR techniques.[52,53] The relapse of infection after treatment used to be a common occurrence in the premacrolide era, because anti-tubercular medications are less potent against atypical mycobacteria than tuberculosis. Thus many patients required surgical excision of affected regions of the lung. However, with the development of macrolides (erythromycin, clarithromycin), azalides (azithromycin), and newer nonmacrolide antibiotics (ciprofloxacin), surgery is rarely indicated for pulmonary disease.[54] In contrast, atypical mycobacterial cervical lymphadenitis is best treated by surgical excision of the affected lymph nodes, with antibiotic treatment reserved for patients with unresectable lesions or disseminated disease.

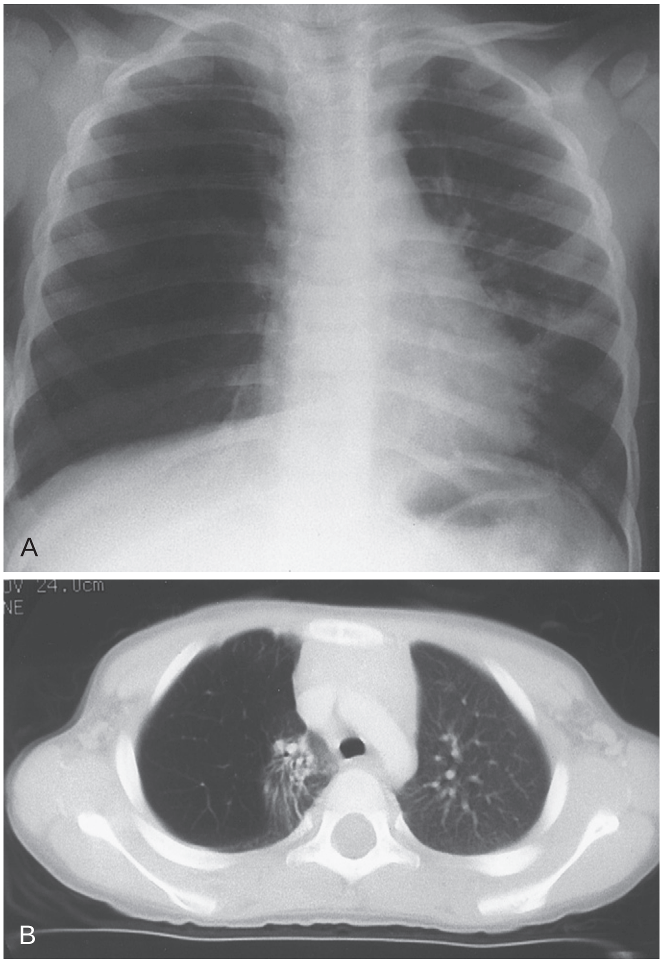


**FIGURE 66-2** **A,** Chest radiograph in a 3-year-old child with acquired lobar emphysema who developed pneumonia with respiratory syncytial virus. **B,** Computed tomographic scan of chest reveals collapsed upper lobe and emphysematous middle lobe.

## VIRAL INFECTIONS

### Bronchiolitis

Bronchiolitis is a major cause of respiratory infection in young children, and is responsible for 2% to 3% of all hospital admissions in children less than 1 year of age.[55] Pathogens that have been implicated include respiratory syncytial virus (RSV), parainfluenza, influenza, and adenoviruses. Peak times for infection occur during early winter through spring, with the mode of transmission being direct contact. Initially starting as an upper respiratory infection with rhinorrhea, cough, and low-grade fever, lower respiratory symptoms may subsequently progress rapidly over the ensuing 24 to 48 hours. At this time, patients may present with tachypnea, retractions, and wheezing. High fever is not uncommon, while young infants may also present with apnea. Radiographically, patients exhibit hyperinflation, interstitial pneumonitis, and occasionally pleural thickening. Acquired lobar emphysema also occasionally develops (Fig. 66-2). Rarely, lung resection may be indicated, but in most patients the hyperinflation resolves with time.

Several patient populations are at increased risk for RSV. These include premature infants, patients less than 6 weeks of age, and children with chronic lung or congenital heart disease.[56] Northern Aboriginal populations also have some of the highest rates of infection in the world,[57] whereas Hispanics are the group most affected in the United States.[58] Overall, the mortality from RSV has been estimated to be 2.9 per 100,000.[59] A presumptive diagnosis of bronchiolitis can often be made on the clinical presentation and is supported by radiographic impressions. Confirmation of infections requires a nasopharyngeal aspirate using a rapid immunosorbent assay.[55] The treatment for bronchiolitis is generally supportive with supplemental oxygen, maintenance of hydration, and close monitoring. In severe infection, particularly in at-risk populations, mechanical ventilation may be required. Interruption of transmission is paramount to prevent epidemics on the hospital wards; thus strict hand washing and the segregation of affected patients is also very important. Bronchodilators and inhaled steroid medications have a limited role in the overall treatment plan but have been

demonstrated to improve clinical scores.[60,61] Vaccinations against RSV should be provided to high-risk children.[62] Although most infections are self-limited, there is increasing evidence to support a link between previous RSV infections and the development of childhood asthma.[63]

### Human Metapneumovirus

Initially identified in 2001, human metapneumovirus (hMPV) has been demonstrated in most parts of the world.[64] Most children appear to be affected by 5 to 10 years of age.[65] Clinically, infection with this pathogen is indistinguishable from infection with RSV, although it tends to affect older infants.[66] However, coinfection with hMPV and RSV has been shown to cause a more severe bronchiolitis.[67] Recently, a reverse transcription PCR technique has become the method of choice for the diagnosis of hMPV infections.[68] Treatment is generally supportive. The effectiveness of antiviral medications against hMPV requires more investigation.[69] Monoclonal antibody vaccines are currently under development.

## PARASITIC INFECTIONS

### *Echinococcus*

*Echinococcus* (hydatid disease) is a parasitic tapeworm infection of sheep and dogs that is transmissible to humans. Infections are common in Egypt, the Middle East, and Australia. Once rare, hydatid disease in North America has increased because of immigration.[70] Cysts occur in the liver, spleen, and lungs. Most patients who present with pulmonary disease are children. These cysts should be removed, because 30% of these lesions may eventually rupture,[71] producing pleural effusions, bronchial seeding, and occasionally acute anaphylaxis.[70] Some children with hydatid lung disease are asymptomatic, while others experience a nonproductive cough. Chest radiographs typically demonstrate a single large pulmonary nodule or a large cyst(s) with an air-fluid level (Fig. 66-3). Computed tomography (CT) and magnetic resonance imaging (MRI) can also be used to provide more detail or to identify occasional lesions that are not apparent with conventional radiography despite the presence of symptoms.[72] Medical therapy with mebendazole has been recommended for patients with small cysts or asymptomatic disease.[8] Patients with secondarily infected or symptomatic/enlarging cysts will usually require pulmonary resection.[71,73,74] There is some evidence that primary surgical resection of large or complicated hydatid cysts without prior medical therapy may decrease postoperative complications and shorten hospital stay.[75] For the surgical management of hydatid cysts, gentle manipulation of lung tissue, careful control of cyst contents to avoid spillage, and a parenchyma-sparing approach is recommended. Thoracoscopic resection has also been described.[76] Percutaneous drainage of these cysts with injection of antiscolicidal agents has been described but with only partial success.[77]

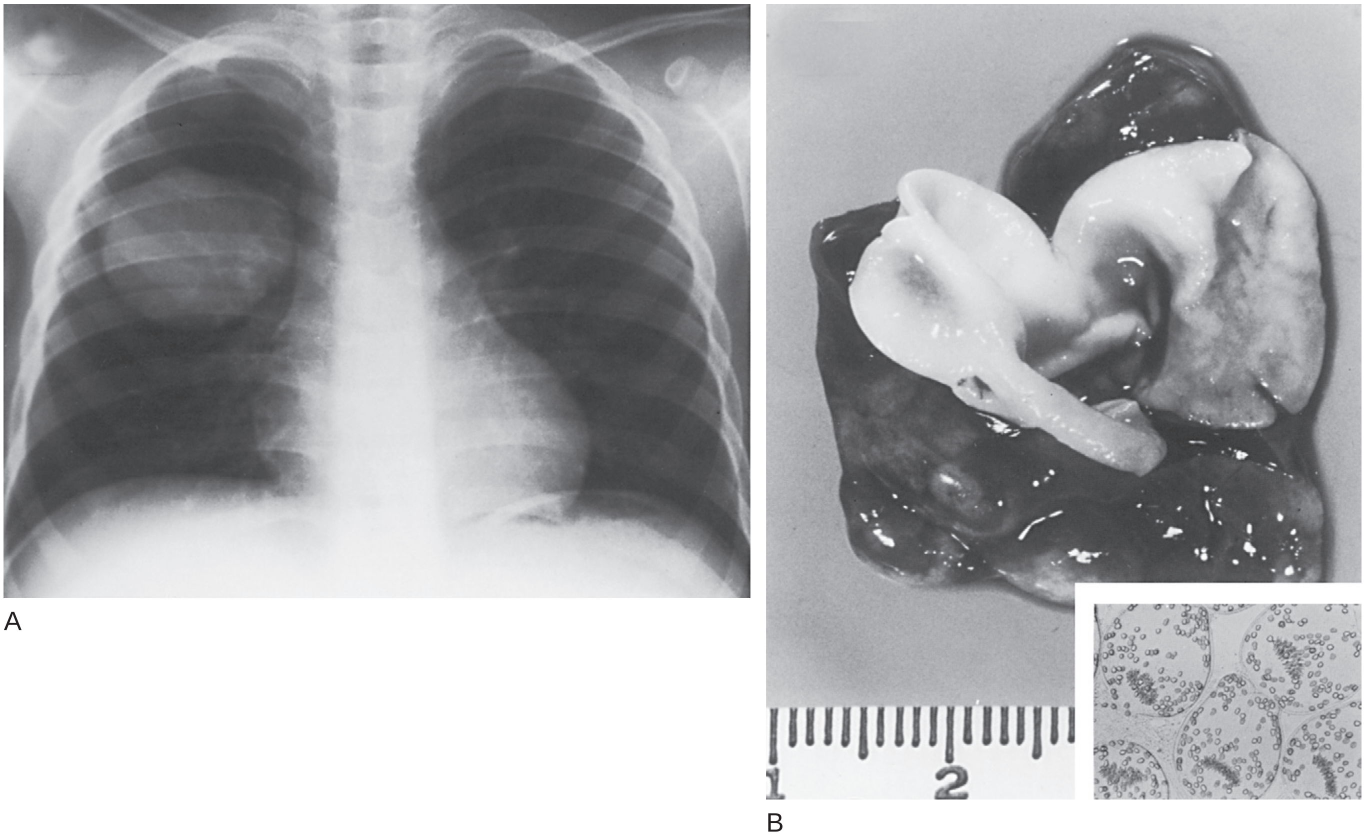



**FIGURE 66-3** Echinococcal cyst in a 4-year old Native American boy whose family lived in a sheep-herding area and owned several dogs. A large, homogeneous, spherical mass is visible in the right lung in (**A**) posteroanterior radiograph. At wedge resection (**B**), the opened cyst contained proglottids with scolices and hooklets. The boy recovered without complications. (*Inset*, 400×)

## THE IMMUNOCOMPROMISED PATIENT

### Pediatric Cancer Patient

Overall, cure rates for all types of childhood cancers have approached 80%.[78] This significant improvement has been the result of improved chemotherapy regimens, improved agents, and increased intensity of therapy. A persistent obstacle for these patients, however, is the threat of infectious complications. Indeed, the single most important factor contributing to the risk of infection is the degree of neutropenia. Neutrophil counts below $0.5 \times 10^9$/L place patients at a significantly increased risk of bacterial infection.[79] If the duration of neutropenia is prolonged, the incidence of fungal infections is also increased.[80]

The lung is the most common site of opportunistic infection in the immunocompromised cancer patient.[81] The incidence of pneumonia in this population ranges from 0.5% to 10%.[82] The mechanism of infection is either from the aspiration of pathogens from the upper airway into the tracheobronchial tree or by hematogenous spread. The immune system can be affected in many different ways depending upon the type, duration, or intensity of chemotherapy. Indeed, combination chemotherapy can impair multiple, different facets of the immune response as a result of the different mechanisms of action of these medications. Furthermore, many cancer patients have intrinsic immune defects related to their underlying malignancy, which further increases their risk of infection.[83]

***Bacterial Infections*** Bacterial infections represent the most common cause of pulmonary infection early in the course of chemotherapy. Several factors, including bacteremia, aspiration, ciliary dysfunction, decreased pulmonary toilet, impaired mucosal barriers, indwelling catheters, and endotracheal intubation may predispose pediatric cancer patients to pulmonary infections.[83,84] Deficiencies in immunoglobulins as a result of immunosuppression also place these patients at risk of infection by encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus,* because of improper opsonization.[83] *Legionella* infections are also more prevalent in those patients with T-cell defects such as lymphoma. The risk of infection in stem cell transplantation patients has been reported to be 15%, with one quarter of these infections occurring within the first 30 days after transplantation.[85]

Overall, gram-negative bacilli are the most common pathogens responsible for pulmonary infection in pediatric cancer patients.[85] The most common gram-negative species include *Pseudomonas*, *Klebsiella,* and *Enterobacter*. Patients with gram-negative infections present with early pulmonary infiltrates, which can be sufficiently treated with β-lactams, cephalosporins, and/or aminoglycosides. *Pseudomonas* infections generally require double antibiotic coverage. Infiltrates persisting longer than 7 days of treatment are usually caused by these same species that possess intrinsic antibiotic resistance, therefore necessitating a change to the treatment protocol. Gram-positive infections usually involve *Staphylococcus aureus*, *Streptococcus pneumoniae,* and group A *Streptococcal* spp. for which β-lactams, cephalosporins, and vancomycin are usually sufficient for treatment. Furthermore, empiric gram-negative antibiotic coverage for neutropenic patients has led to a rise in *Staphylococcus aureus* and *Streptococcus viridans* infections.[85] *Listeria* usually produces late and refractory infiltrates. Nocardial pulmonary infections are uncommon but very severe, leading to pulmonary necrosis and a predisposition for central nervous system spread.[83] Sulfonamides are the treatment of choice for this organism.

***Fungal Infections*** Fungal infections represent a common cause of morbidity and mortality in highly immunocompromised patients. The incidence is highest in those receiving chemotherapy for malignancy, those with chronic granulomatous disease, and those with hematopoietic stem cell transplants, and this appears to be increasing with advances in the care of these patients as well as improved diagnostic methods.[86,87] Two important fungal infections observed in pediatric cancer patients are *Aspergillus fumigatus* and *Candida* spp.

The lung is the most common site for an invasive infection with *Aspergillus fumigatus,*[85] and the most frequent portal of entry for this fungus is the upper airway. Its incidence has been estimated to be 5% in two pediatric series, but this may be an underestimate because of poor diagnostic yield.[88,89] However, case-mortality has been estimated to be between 50% to 60%, especially in hematopoietic stem cell transplantation patients.[90] Hospital epidemics have occurred secondary to the inhalation of shed spores from contaminated air-conditioning units and from nearby building construction or renovation sites.[91] However, the incidence of such infections can be reduced with the use of laminar flow and high-efficiency filters.[92]

*Aspergillus fumigatus* infections can be rapidly invasive. Necrosis and hemorrhage result from the invasion and thrombosis of pulmonary arteries and veins. This, in turn, leads to the development of cavitary lesions. Plain chest radiographs are not as sensitive for *Aspergillus* as CT scans because these infections may present with diffuse infiltrates, nodular disease, or cavitation (Fig. 66-4).[93] Voriconazole is considered

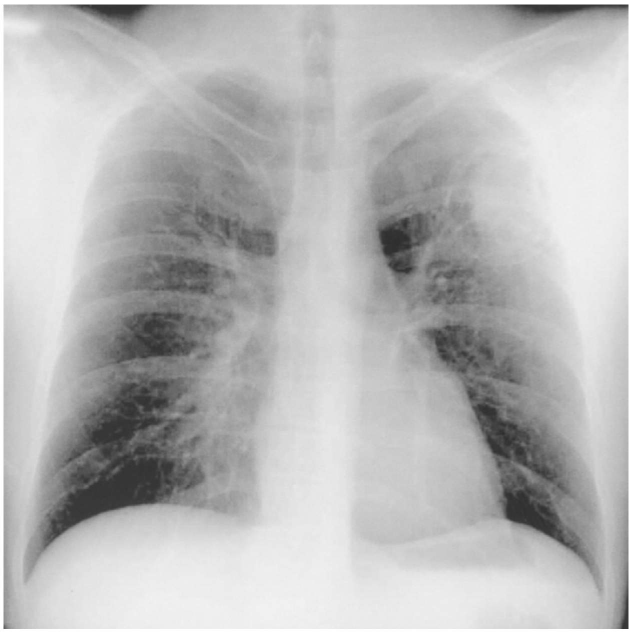


FIGURE 66-4 Left upper lobe aspergilloma with diffuse bilateral lung infiltrates in a 17-year-old patient with acute lymphoblastic leukemia undergoing intensive chemotherapy.

a first-line agent, and its effectiveness may be gauged by the recovery of white blood cells and granulocytes. Second-line agents include caspofungin and liposomal amphotericin B.[87] Surgical resection of disease may be required if no clinical improvement is observed.[94,95] In hematopoietic stem cell transplantation patients, the incidence of *Aspergillus* infection can be as high as 18.6%.[86] The diagnosis of aspergillosis may be difficult. Bronchoalveolar lavage (BAL) samples are positive in less than one third of patients.[96] Although polymerase chain reaction of these BAL samples may improve the yield, the gold standard for diagnosis is the identification of hyphae by histopathology or cytopathology. This may be possible with open or thoracoscopic lung biopsy, percutaneous needle biopsies, or transbronchial sampling.[83]

*Candida* spp. are the most common fungal organisms responsible for infection in immunocompromised patients,[97] with *Candida albicans* being the most common species causing invasive disease. Recent estimates place the rate of invasive infection at 47/100,000 admissions in the United States.[98] Risk factors for the development of candidemia include the presence of an indwelling central venous catheter, immunosuppression, parenteral nutrition, prolonged intensive care unit stay, and neutropenia.[93] Although the lung is not usually involved with *Candida*, it is the most common site of invasive infections.[87] Spread to the lung may occur hematogenously or from the aspiration of contaminated oropharyngeal secretions. Plain chest radiographs are usually nonspecific. Bronchoalveolar lavage can be useful in confirming the diagnosis but often a lung biopsy is required. First-line agents against *Candida albicans* include liposomal amphotericin B, fluconazole, and caspofungin.[87] However, certain strains of *Candida* have specific, intrinsic resistance to either the azoles and/or amphotericin (*Candida krusei* and *glabrata*). Caspofungin and other echinocandins, which affect fungal wall synthesis, are effective in cases of resistance or non–*Candida albicans* infection, previous azole use, if standard therapies are ineffective, or if the side effects of standard medications are limiting treatment.[87,93] However, it is clear that if left untreated, the prognosis of patients with candidal lung infections is uniformly poor.

***Viral Infections*** The susceptibility to viral infection depends on the extent to which host defense mechanisms have been affected. Indeed, pediatric cancer patients can be immunosuppressed because of their underlying disease process or the therapy they are receiving, and are thus generally unable to mount cellular and humoral responses against viral infection.[99] Difficulties in making a prompt diagnosis, especially with atypical clinical presentations, lead to delays in the initiation of appropriate management. Currently, reverse transcription PCR techniques allow for the rapid identification of offending viruses that are present in tissue, blood, sputum, stool, urine, nasopharyngeal aspirates, and cerebral spinal fluid. Immunocompromised children also shed virus for longer periods of time and may be the source of nosocomial infection, even if they no longer have symptoms.[100]

CMV infection is usually the result of the reactivation of a latent infection and occurs predominantly in patients receiving stem cell transplants.[101] The risk of CMV infection appears to be increased in patients who have concurrent graft-versus-host disease, receive frequent transfusions, or receive methotrexate or antithymocyte medications.[102] It presents with fever, headache, malaise, and myalgias that may precede the pneumonitis by 1 to 2 weeks. Radiographs are often nonspecific, demonstrating diffuse, nodular, or atelectatic changes within the lung. CMV can often be detected in the urine of patients with endogenous activation. Treatment includes the use of ganciclovir and immunoglobulins.[103]

Varicella pneumonia is rare in immunocompetent patients and may be difficult to diagnose because of the presence of few skin lesions and the predominant complaints of abdominal or back pain. Thirty percent of patients who have visceral involvement may develop pneumonia.[81] This can increase to 80% if they are receiving concurrent chemotherapy. Radiographically, these patients will present with diffuse bilateral fluffy infiltrates. If patients have been exposed to varicella, chemotherapy should be stopped for the period of incubation (up to 21 days). Passive immunization with varicella zoster immune globulin should be administered at this time. The treatment of active infection includes intravenous acyclovir.[100] Although herpesvirus infections are rare in the absence of concomitant gingivostomatitis, any signs of infection also require the prompt institution of acyclovir therapy. RSV infection can be very problematic in bone marrow transplantation patients because of their decreased T-cell–mediated immunity. Children with neutrophil counts less than $0.1 \times 10^9$/L or age less than 2 years are at increased risk of infection, with mortality rates up to 8.6%.[104] In general, supportive treatment is all that is offered, but severe infections may require ribavirin given by aerosolization in intubated patients or as an intravenous infusion for those who are not.[100] Preventive immunization with palivizumab has not been fully investigated in pediatric cancer patients, but new, more potent agents, such as motavizumab, may be considered as options for this population of patients.[105] Human metapneumovirus has also been shown, within 40 days post-transplant, to affect a small but significant number of patients receiving stem cell transplantation.[106]

***Pneumocystis jirovecii*** This unusual organism has properties of protozoa (susceptible to trimethoprim) as well as fungi (based on RNA studies) and is seen almost exclusively in patients who are immunocompromised. Infection with *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) is usually the result of the reactivation of latent disease, but routine prophylaxis has dramatically reduced its incidence.[83] However, the risk of infection is dependent upon the level of immunosuppression. Indeed, bone marrow/stem cell transplantation patients, and patients receiving steroids are at particular risk. Unlike HIV-infected patients, the other main population susceptible to *Pneumocystis* infection, the cancer and hematopoietic transplantation patient is more likely to present with acute respiratory disease within the first several days of infection.[107] Furthermore, CD4 counts cannot be used as a marker for the institution of prophylactic therapy in cancer patients. Thus clinical parameters, dose and duration of corticosteroid, time from transplantation, and the use of other immunosuppressives will determine the use of prophylactic therapy. Patients usually complain of a fever, dry cough, and dyspnea. Progressive disease may present with hypoxia and respiratory distress. Radiographically, fulminant disease presents with bilateral hilar infiltrates that extend to the periphery of the lung (Fig. 66-5). The diagnosis is confirmed by histology and cytology that identifies trophozoite

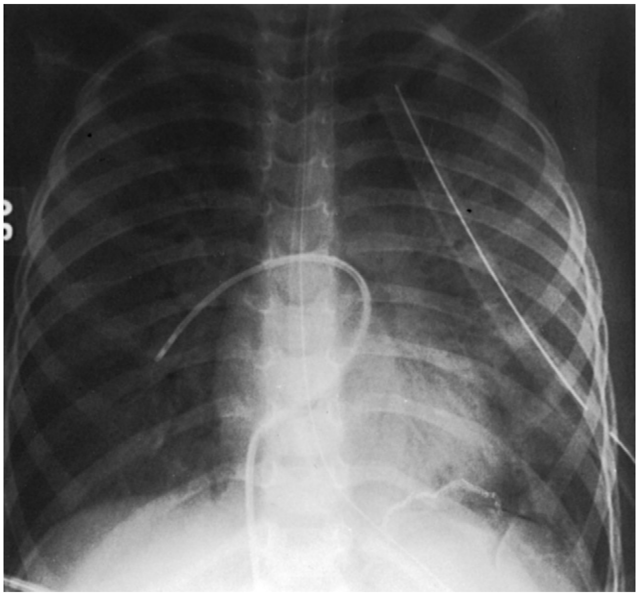


FIGURE 66-5 *Pneumocystis jirovecii (carinii)* pneumonia in a 5-year-old girl receiving chemotherapy for acute lymphocytic leukemia. Diffuse interstitial infiltrates are seen in both lungs. Biopsy of the lingula (note staples) demonstrated *P. jirovecii (carinii)*. A Swan-Ganz catheter is positioned in the right inferior pulmonary artery. Although her leukemia was in remission, the child died of respiratory failure from the pulmonary disease. (Currently with antibiotic prophylaxis, early institution of empiric therapy and diagnostic confirmation by bronchoalveolar lavage, such an outcome would be unusual).

cysts recovered by bronchoalveolar lavage. Trimethoprim/sulfamethoxazole (TMP/SMX) is the mainstay of treatment and prophylaxis.[107] Corticosteroids and supplemental oxygen are also useful for patients with severe infections. If no response occurs within 72 hours, a lung biopsy is indicated to confirm the diagnosis and to rule out concomitant infection with other pathogens. Mortality approaches 100% for untreated patients. If myelosuppression or rash develops secondary to TMP/SMX administration, pentamidine may also be used, but it has its own significant side effect profile, including nephrotoxicity and pancreatic insufficiency.[107]

## PEDIATRIC HIV PATIENT

Acute pneumonia is the most common severe infection in HIV-infected children in the United States. In developing countries, particularly in sub-Saharan Africa, respiratory infections are one of the most common causes of illness, hospitalization, and mortality in HIV-infected children.[108] The introduction of highly active antiretroviral therapy (HAART) in 1997 has dramatically improved the survival of HIV-infected adult patients in developed nations through the reconstitution of the immune system.[109] Indeed, HAART has dramatically reduced the incidence of opportunistic infections in HIV-infected children by more than 80%,[110] and its institution in infants has led to dramatic reductions in mortality.[111]

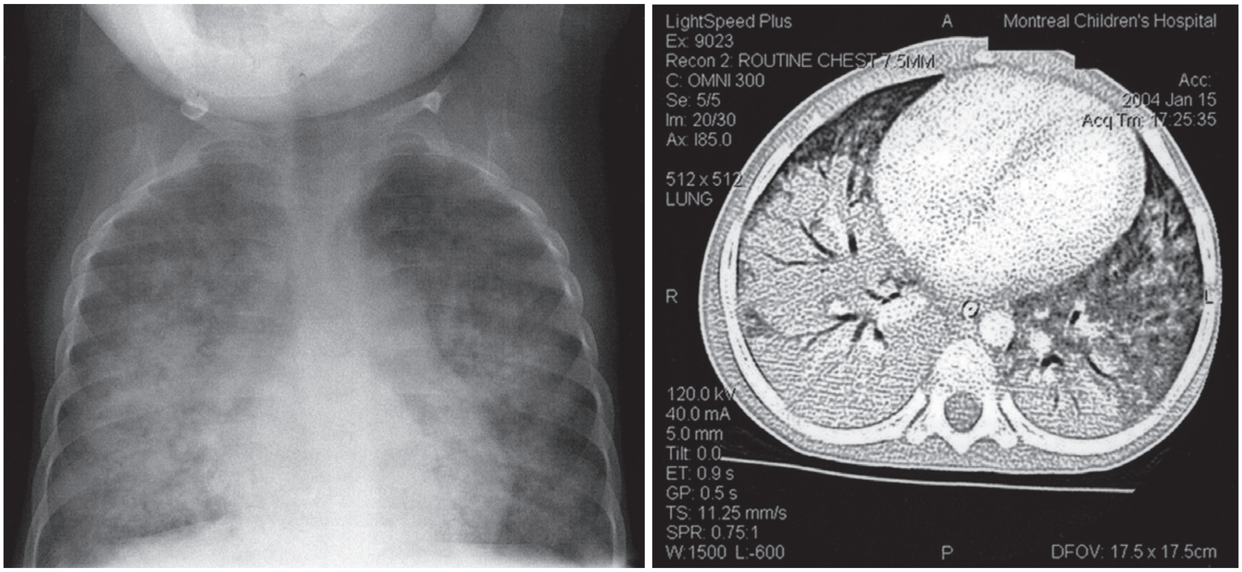
The most common organisms responsible for bacterial pneumonia in HIV-infected patients are *Streptococcus pneumoniae* (7.4%), *Staphylococcus aureus* (2.4%), *Haemophilus influenzae* type B (1.8%), *Escherichia coli* (0.8%), and *Salmonella* spp. (0.7%).[13,112] Antibiotic resistance is also more common in HIV-infected children, especially methicillin-resistant *Staphylococcus aureus* and extended-spectrum β-lactamase–producing enterobacteriaciae.[113] The clinical features of respiratory infections in children with HIV are similar to those with normal immune systems. However, patients with decreasing CD4 counts, severe immunosuppression, and previous acquired immune deficiency syndrome (AIDS)–defining respiratory infections are more likely to develop acute pneumonia.[114] Furthermore, these patients may be predisposed to recurrent infection and its sequelae, including bronchiectasis, abnormal lung parenchymal architecture, and bullous lung disease.[115] The diagnosis of pneumonia in HIV-infected children is based on clinical and radiographic findings. However, it is very important that opportunistic and mycobacterial infections be excluded in this population of patients. Furthermore, the differential diagnosis of pulmonary infiltrates for these patients also includes noninfectious causes such as lymphoid interstitial pneumonia and non-Hodgkin lymphoma. A lung biopsy may be required to confirm a diagnosis in these patients. The prevention of infection plays a key role in the management of these patients and includes the routine immunization against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B, as well as prophylactic TMP/SMX for *Pneumocystis jirovecii* if required. Treatment should be initiated against the specific pathogen as soon as possible, but empirical therapy (cefotaxime or ceftriaxone) may be instituted while waiting for culture results.

### *Pneumocystis jirovecii*

*Pneumocystis jirovecii* infection is the most common organism identified in HIV-infected children admitted to hospital for severe pneumonia. It is most common in infants and is associated with a mortality rate of 50%.[109] The incidence of *Pneumocystis jirovecii* pneumonia, however, has decreased with the introduction of TMP/SMX prophylaxis and HAART.[116] Although there is currently insufficient data for children, recent adult series have demonstrated minimal recurrence of pneumocystis pneumonia with the discontinuation of prophylaxis in patients experiencing a good response to HAART therapy.[117] Currently, *Pneumocystis jirovecii* prophylaxis is still recommended for (1) HIV-exposed infants, starting at 4 to 6 weeks of age until infection is disproven; (2) for all HIV-infected infants younger than 1 year of age, regardless of CD4+ count; and (3) all HIV-infected children if their CD4+ counts are below age-specific thresholds.[118] The clinical presentation of *Pneumocystis* pneumonia, imaging, diagnostic maneuvers, and treatment were discussed in the previous section.[109]

### Lymphoid Interstitial Pneumonitis

Lymphocytic or lymphoid interstitial pneumonitis (LIP) is a chronic lymphocytic infiltrative process seen in children with HIV who are greater than 2 years of age and represents another AIDS-defining illness. Epstein-Barr virus has been implicated in its pathogenesis. LIP has been estimated to occur in 20% to 30% of vertically transmitted cases of HIV in the United States and Europe.[119] Patients often present with an insidious onset of respiratory symptoms that may be confused with tuberculosis. Other clinical findings include fever, digital clubbing, asymptomatic parotid swelling, symmetric lymphadenopathy, and hepatomegaly. The clinical course is benign but may predispose patients to bacterial and viral pneumonias, bronchiectasis, and bullous lung disease.[115,120] Plain radiographs can




A B

**FIGURE 66-6** **A,** Three-year-old child recently immigrated from Africa presented with a history of weakness and coughing, having been treated for pulmonary tuberculosis 2 years previously. Respiratory distress worsened, and intubation was required. **A,** Plain radiograph demonstrates a lung infiltrate with an alveolar pattern. **B,** Diffuse consolidation with air bronchogram, especially in the right lower lobe, can be appreciated on computed tomography. Human immunodeficiency (HIV) was suspected and later confirmed. Bronchoscopy and bronchoalveolar lavage were not diagnostic. Lung biopsy revealed lymphoid interstitial pneumonitis. He was treated with steroids and triple antiretroviral therapy and rapidly recovered.

demonstrate persistent reticulonodular infiltrates and hilar adenopathy that can be better appreciated by CT scan (Fig. 66-6). Lung biopsy is usually necessary to confirm the diagnosis and demonstrates significantly altered pulmonary architecture with an infiltration of CD8+ cells.[121] Systemic steroid administration over 4 to 6 weeks usually leads to resolution of the infiltrates. HAART has been shown to improve the clinical course of LIP and may reduce the prevalence of chronic lung disease associated with it.[116]

### *Mycobacterium tuberculosis*

The increase in the incidence of tuberculosis (TB) in children in developed countries has paralleled the increase of the disease in HIV-infected adults, the primary source of transmission to children.[38] The clinical features of TB in HIV-infected children are similar to immunocompetent patients but with a predilection for rapid progression, extrapulmonary and/or disseminated disease resulting from the impairment of cell-mediated immunity.[38,122] Radiographs often demonstrate lobar or diffuse infiltrates and atelectasis from bronchi compressed by hilar adenopathy. If a child is found to have TB, HIV testing should be undertaken. The diagnosis of TB is based upon the clinical, epidemiologic, and radiographic data available. The early morning gastric aspirate of retained overnight secretions is the best noninvasive culture technique for tuberculosis and may provide a better yield than more invasive procedures such as bronchoalveolar lavage and bronchoscopy.[123] However, induced sputum, using nebulized hypertonic saline[124] (using proper infection control procedures) and the string method,[125] are viable alternatives. Although the tuberculin skin test is a poor indicator of tuberculosis infection in young children with HIV, and is unable to differentiate between latent and active disease,[38] it is still considered a valuable diagnostic aid in HIV-infected children.[44] Whole blood interferon-γ assays have recently helped differentiate tuberculosis from atypical mycobacterial infections.[43] Prevention is the key, and a clear determination of the TB status of all adults in the household is essential. Currently, vaccination of HIV-infected children with bacillus Calmette-Guérin is not recommended because of the risk of disseminated disease.[126,127] For patients with significant exposure, regardless of skin test result, isoniazid is indicated. If a repeat tuberculin skin test in 3 months is negative, the medication can be stopped. Treatment of active infections includes a multiagent regime, but care must be taken to watch for interactions between antiretroviral and antituberculous medications.[38] HAART should be instituted once antituberculous treatment has been established (usually 2 to 8 weeks). However, for those patients with mild infection and minimal immunosuppression, HAART therapy may be deferred for up to 6 months while TB is being treated.

### Atypical Mycobacterial Infections

Several species of atypical mycobacteria are clinically significant in patients with HIV. These include the *Mycobacterium avium* complex, *Mycobacterium intracellulare*, *Mycobacterium lepraemurium,* and *Mycobacterium scrofulaceum*. These bacteria represent a major source of morbidity for HIV-infected children and usually cause systemic infection later in the course of AIDS. Previously, HIV patients infected with atypical mycobacteria had a 9- to 11-month life expectancy,[128] but with the advent of more effective treatments for HIV (i.e., HAART), and atypical mycobacteria, the disease is less common and the prognosis better. Indeed, the incidence of atypical mycobacterial infections in children was reduced from 1.2 to 0.3 cases per 100 patient years in a study evaluating opportunistic infection rates in children in the pre-HAART and post-HAART era.[129]

The clinical presentation of these patients usually involves failure to thrive, abdominal pain, and fatigue, but can also involve respiratory symptoms. Patients may have leukopenia,

thrombocytopenia, and an increased serum lactate dehydrogenase. The diagnosis is made through blood culture or biopsy of a normally sterile site, including bone marrow and lymph nodes. These microbiologic investigations will also eliminate the possibility of TB infection. In addition, a skin test or whole blood interferon-γ assay may be helpful initially to distinguish atypical mycobacterial infections from that of TB.[43] Prevention of infection is accomplished through protection of the immune system with effective antiretroviral therapy. Treatment of active infections can be accomplished with clarithromycin, azithromycin, rifabutin, rifampin, ethambutol, ciprofloxacin, or amikacin. It is important to remember that the rifamycins (i.e., rifampin and rifabutin) inhibit the metabolism of many antiretroviral medications.

### Viral Infections

CMV infection can present as chronic interstitial pneumonitis and is usually accompanied by retinitis, hepatitis, or colitis. It often occurs in severely immunosuppressed patients. Respiratory symptoms include nonproductive cough, dyspnea, and hypoxemia. Pneumonitis may be associated with concurrent *Pneumocystis jirovecii* infection. Radiographic findings include diffuse interstitial infiltrates. The diagnosis of CMV is made through PCR of the blood, identifying viral inclusions in bronchoalveolar lavage or biopsy specimens, or viral culture. However, the differentiation between active infection and asymptomatic viral shedding in HIV-infected patients is difficult and may complicate management regimes.[109] The preferred treatment is gangiclovir, particularly if gastrointestinal or retinal involvement is also identified.

### Fungal Infections

Systemic fungal infections are infrequent in HIV, because more commonly, fungal infections involve the skin or mucosa. Pulmonary mycoses are occasionally identified in children with HIV resulting from impaired T-cell immunity. Histoplasmosis is uncommonly reported in this group of patients. A primary pulmonary focus may progress rapidly to disseminated disease and become fatal if left untreated. Severe disease presents with fever, hepatosplenomegaly, pancytopenia, reticulonodular lobar infiltrates, and the occasional progression to septic shock. The diagnosis is based upon cultures of bronchoalveolar lavage samples or lung biopsy. Treatment involves the use of intravenous liposomal amphotericin B with or without itraconazole. Children with primary pulmonary disease should receive itraconazole for prophylaxis in the hope of preventing disseminated disease.

*Cryptococcus neoformans* and *Coccidioidomycosis* spp. infections are usually associated with disseminated infection, and 50% of these patients have concurrent pulmonary infection. Disseminated cryptococcal infections present with fever, headache, meningitis, pulmonary infiltrates, and confusion. The diagnosis is made through sputum, blood, or cerebrospinal fluid cultures and the direct examination of cerebrospinal fluid with India ink or latex agglutination. Treatment includes amphotericin B and fluconazole for several weeks followed by lifelong fluconazole prophylaxis. *Coccidioidomycosis* usually presents as disseminated disease affecting the lungs, brain, and skin. Fever, weight loss, cough, and an altered level of consciousness are often present. The diagnosis is made from sputum, bronchoalveolar lavage, or lung biopsy specimens. Acute infections are managed with amphotericin B, but recurrence is common, thus mandating secondary prophylactic therapy with fluconazole. *Aspergillosis* is another uncommon infection that usually presents with pulmonary disease and sinusitis. These patients experience fever, cough, dyspnea, and pleuritic chest pain. Sputum analysis, bronchoalveolar lavage, and, occasionally, lung biopsy are required to confirm the diagnosis. Voriconazole is the treatment of choice, although the echinocandins (i.e., caspofungin) have also been shown to be effective.

The immunocompromised pediatric patient is under the constant threat of infection. These patients require constant surveillance and aggressive management strategies. For patients with pulmonary infiltrates, broad-spectrum antibiotics should be started promptly, and depending on the presentation of the patient, an emergent bronchoalveolar lavage may be required to rule out *Pneumocystis jirovecii*. For persistent lung infiltrates, lung biopsy should be strongly considered. Indeed, the results of lung biopsy for patients with persistent lung infiltrates have been shown to impact on the management of these patients up to 90% of the time.[130]

## CYSTIC FIBROSIS

Cystic fibrosis (CF) is the most common autosomal recessive disease affecting whites and occurs in approximately 1 in 3,400 live births.[131] The prognosis for this disease has improved considerably over the last 30 years but has plateaued since the mid-1990s. The current life expectancy for patients with CF is more than 30 years of age. CF is characterized by thick, inspissated mucus, chronic infection, and neutrophil-dominated inflammation of the airways.[132] The cystic fibrosis transmembrane conductance regulator (CFTR) is a cyclic adenosine monophosphate–dependent chloride channel located on chromosome 7q21-31.[133] CFTR mutations lead to abnormal ion transport (increased sodium transport and failure to secrete chloride) and altered airway-surface liquid, resulting in viscous mucus and reduced mucociliary clearance, respectively. Bacterial penetration and proliferation within the thick and adherent secretions subsequently allows persistent infection and inflammation of the airways.[132] Furthermore, chronic inflammation, stasis of mucus, and airway obstruction ultimately lead to the pulmonary sequelae observed with long-standing cystic fibrosis.

The clinical signs and symptoms of CF can vary widely. Patients may be relatively asymptomatic, present with chronic illness, and fail to thrive, or complain of acute, recurrent exacerbations of pulmonary disease. However, the usual presentation is with the progression of a nonproductive cough to a loose productive cough with copious, purulent secretions. Classical physical findings include a barrel chest, rales, rhonchi, and digital clubbing with occasional cyanosis. Although initial pulmonary function tests demonstrate obstructive patterns, disease progression leads to the development of restrictive lung disease. The gold standard for the diagnosis of CF is the sweat test (elevated chloride $> 60$ mEq/L) or the identification of mutations in CFTR, the most common being $\Delta$F508. However, a negative result may not be as meaningful because of the limited number of commercially available analyses. However, DNA restriction fragment length polymorphism analysis from fetal DNA obtained by amniocentesis can help predict CF status in the fetus if the mutation within the family is known.

In the first decade of life, the most common organism isolated from cystic fibrosis patients is *Staphylococcus aureus* (40%), followed by *Haemophilus influenzae* (15%).[134] *Pseudomonas* is usually the first pathogen isolated in children less than 1 year of age, and greater than 80% are infected with this organism by 18 years of age.[135] Clinically, *Pseudomonas* is the most important pathogen in CF because it is able to form biofilms that enable bacteria to avoid normal clearance mechanisms and the penetration of antibiotics. *Pseudomonas* has also been associated with increased airway inflammation, a more rapid decline in lung function, and increased mortality.[136] *Burkholderia cepacia* is an organism with intrinsic antibiotic resistance. Patients infected with this organism present with high fevers, rapid pulmonary deterioration, and sometimes death. Viral infections may pose a special problem, particularly in young children, where they may predispose to secondary infection, the need for mechanical ventilation, and oxygen dependence. RSV prophylaxis has been recommended for these infants.[137]

The cornerstone of medical therapy for pulmonary disease in CF patients is the aggressive use of intravenous, oral, and nebulized antibiotics. Indeed, the increased life span of CF patients can be attributed directly to the development of effective antipseudomonal medications. Maintenance therapy is designed to prolong the period between pulmonary exacerbations with *Pseudomonas*. Nebulized tobramycin has been shown to be effective in eradicating *Pseudomonas* in early infection, as well as decreasing bacterial load, improving lung function, and decreasing hospital admissions.[138] Azithromycin has also been effective as an immunomodulator to reduce airway inflammation, thereby improving lung function in those with *Pseudomonas*. The clearance of abnormal secretions is of paramount importance and includes regular chest physiotherapy and postural drainage.[139] Mucolytic agents, such as dornase alpha, can help mobilize thick inspissated secretions in CF patients.[140] Attempts to reduce the inflammatory response with antiinflammatory medications, such as ibuprofen, may help to slow the progression of lung disease.[141] However, similar effects have not been demonstrated with inhaled corticosteroids.[142]

Adequate nutritional support and the early treatment of pancreatic insufficiency is another critical area for the medical therapy of patients with CF. Significant malnutrition may already be evident at the time of diagnosis in neonates and young children, even if they are asymptomatic. The imbalance between the increased energy needs of infants for growth and their impaired ability to achieve adequate nutritional intake can predispose to pulmonary complications. Recommendations are in place to help guide clinicians with regard to nutritional requirements and surveillance for children with cystic fibrosis.[143,144]

Pediatric surgeons may be involved in the care of these patients in several ways as they get older. Implantable intravenous access devices are useful for patients who frequently require antibiotics for pulmonary exacerbations. Nutritional management may require the use of a gastrostomy.[145] Pulmonary complications of CF, such as bronchiectasis, massive hemoptysis, and pneumothorax are discussed later, while gastrointestinal and hepatic complications are discussed in other chapters.

Lung disease is the main cause of premature death in cystic fibrosis, and lung transplantation remains the ultimate resort for patients with end-stage pulmonary disease. However, with the improved medical care of these patients, the need for lung transplantation has been delayed. Bilateral, sequential lung transplantation is the preferred approach for children with CF. Current data report overall survival rates of 77% to 89% and 55% to 80% at 1 and 5 years, respectively, and are much better than the survival rates of nontransplanted patients on the waiting list.[146] Furthermore, a comparison of children with and without cystic fibrosis who underwent lung transplantation had similar overall rates of survival at 1, 3, and 5 years.[147]

## BRONCHIECTASIS

First described by Laënnec in 1819,[148] bronchiectasis is the irreversible dilatation of the airways secondary to the inflammatory destruction of bronchial and peribronchial tissue. Currently, it has become an uncommon disease in developed countries and predominantly limited to the pediatric population.[149] However, the incidence of and morbidity secondary to bronchiectasis is still a problem in developing countries and certain indigenous populations in developed nations, such as the aboriginal peoples of Alaska and Australia.[150,151]

### Pathogenesis and Etiology

The pathogenesis of bronchiectasis follows three progressive stages. Initially, there is destruction of the ciliary epithelium, which is replaced with cuboidal squamous epithelium. In the early stages of disease (cylindrical bronchiectasis), there is localized damage to the elastic tissue of the airway in addition to edema and inflammation. Later in the disease (saccular bronchiectasis), the damage involves the muscle layers and cartilage of the airways, with anastomoses forming between pulmonary and bronchial arteries in the areas of saccular dilation. There is also evidence to support a host-mediated component to local tissue damage.

Numerous different hypotheses regarding the development of bronchiectasis have been proposed. It is clear that infection is the most common cause of bronchiectasis (Fig. 66-7). Bronchiectasis may not result from the index infection but is usually the result of concomitant or subsequent infection with many agents, such as TB and histoplasmosis, viruses, certain fungi, and occasionally *Mycoplasma*.[152] Cystic fibrosis is the most common genetic cause of bronchiectasis; here it occurs secondary to infection and bronchial obstruction with inspissated mucus. Other causes include the congenital absence of supportive airway cartilage (Williams-Campbell syndrome), tracheomegaly, Marfan syndrome, alpha-1 antitrypsin deficiency, foreign body aspiration, ciliary abnormalities (Kartagener syndrome), immunodeficiencies (IgA), asthma, and right middle lobe syndrome.[148,153] The distribution of bronchiectasis may give insight into the underlying cause. Patients with tuberculosis generally have unilateral involvement, while patients with CF and viral-induced disease have involvement of the upper lobes and lower lobes, respectively.

### Clinical Manifestations and Investigation

Most patients present during the preschool years with cough, profuse sputum, wheezing, and chest pain. Up to 50% may have digital clubbing, which is reversible. Bronchiectasis, demonstrated by bronchial dilation, bronchial thickening,

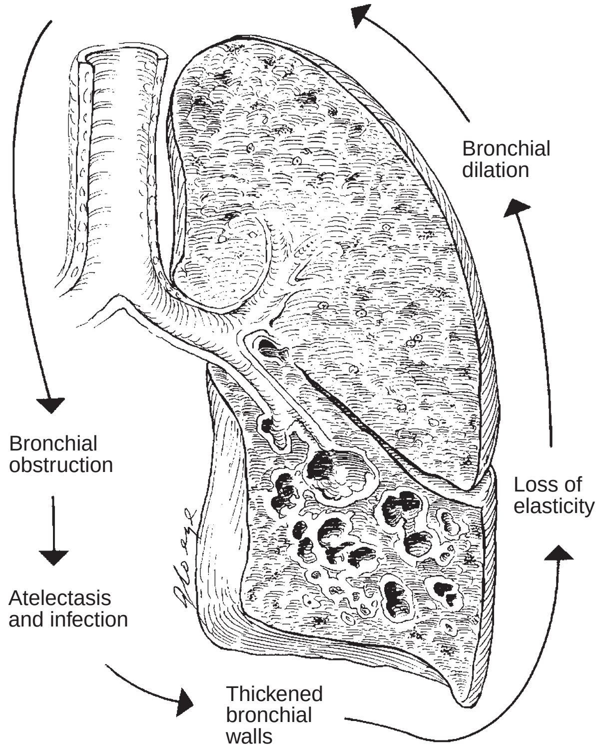



FIGURE 66-7 Diagrammatic representation of factors influencing the pathogenesis of bronchiectasis.

or a signet ring sign, may be apparent on chest radiographs. High-resolution computed tomography of the chest has replaced bronchography to document the pattern and severity of disease.[154,155] Findings include cylindrical or saccular dilatation of bronchi, pooling of secretions, and bronchial thickening (Fig. 66-8). Increased awareness and the wide availability of CT have also resulted in the earlier identification of bronchiectasis, and have brought into question the irreversibility of the process. Indeed, acute suppurative infections of the lung may cause *reversible* dilatation of the bronchi that may be confused with bronchiectasis.[156] A new classification system has been developed to describe the different stages of disease, including prebronchiectasis (reversible), high-resolution CT bronchiectasis (may reverse or progress), and established bronchiectasis (irreversible).[157]

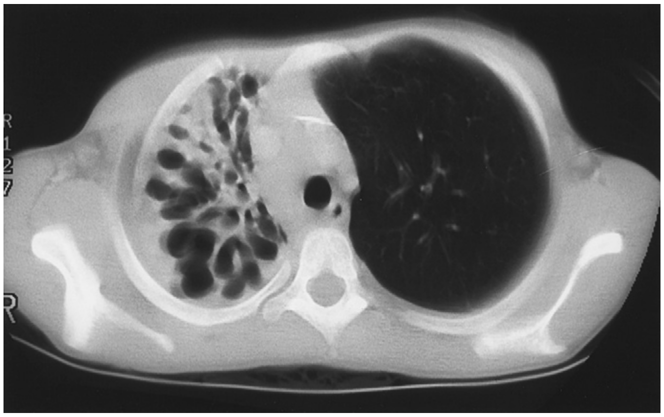


FIGURE 66-8 Computed tomographic scan of the chest of a 10-year-old girl with cystic fibrosis. Preoperative ventilation-perfusion scanning revealed no function of this bronchiectatic lobe. The patient underwent an upper lobectomy.

## Therapy

The treatment of bronchiectasis focuses on identifying and treating the underlying causes. Regular microbiologic surveillance, prolonged antibiotic therapy, and adequate nutritional support, with pancreatic enzyme replacement for patients with cystic fibrosis, are needed to prevent failure to thrive from recurrent infections and pulmonary exacerbations. Vaccination against *Streptococcus pneumonia* and *Haemophilus influenzae*,[158,159] postural drainage techniques with chest physiotherapy,[160] and mucolytics[161,162] are part of the armamentarium against disease progression. Bronchoscopy has also been used to temporarily help alleviate bronchial obstruction resulting from foreign bodies and inspissated secretions, or to aid in the preoperative or diagnostic evaluation of chronic lung infection.

Although the frequency of surgical therapy for bronchiectasis has declined over the last several years, there are still those patients who do not respond to medical therapy and would benefit from surgical resection. The main indications for surgery include (1) localized disease with severe and debilitating symptoms, such as profuse sputum, fetid breath, and severe cough, that significantly impacts quality of life; (2) life-threatening hemorrhage from localized disease; (3) resectable disease in the context of failure to thrive; and (4) resectable disease in an area of recurrent lower respiratory tract infections. Lesser indications for surgery include bilateral or nonlocalized disease or patients with only mild-to-moderate symptoms.[163]

The outcome of pediatric patients undergoing surgical resection has generally resulted in the cessation or improvement of clinical symptoms in the majority of patients. Indeed, several studies have demonstrated that 70% of patients are asymptomatic or improved after surgical resection for localized disease.[164–169] The morbidity in these series ranged from 10% to 24%. However, many patients present with more diffuse disease. Schneiter[163] and Otgun[170] both demonstrated the safety and improvement in symptoms with more extensive pulmonary resections for bronchiectasis. Most recently, Rothenberg described thoracoscopic resection for patients with severe, localized bronchiectasis.[171] In this series, nineteen patients, ranging from 14 months to 15 years of age, underwent successful thoracoscopic lung resection. The average length of stay was 3.6 days, and only 2 patients incurred complications (air leak and hydropneumothorax) that extended the length of stay. The main advantages of this approach, despite the technical challenges, were the avoidance of thoracotomy, and thus a faster progression to mobilization, reduced postoperative pain and the resumption of chest physiotherapy for a population with existing pulmonary morbidity. The common themes for the successful operative management of bronchiectasis are careful patient selection, preoperative evaluation and surgical technique, as well as an attempt to completely resect all diseased lung tissue.

## PULMONARY HEMORRHAGE AND HEMOPTYSIS

The etiologies of pulmonary hemorrhage and hemoptysis are wide ranging and may be classified according to the age of the patient or on the basis of underlying lung disease. In neonates, prematurity, pulmonary edema, respiratory distress syndrome, intracerebral bleeding, coagulopathy, and metabolic disorders can lead to pulmonary hemorrhage. For patients with chronic lung disease, bronchiectasis secondary to cystic fibrosis is the most common cause in the pediatric population. However, cavitary lung lesions, TB, neoplasms, retained foreign bodies, and frequent airway manipulation can lead to symptomatic hemorrhage. In otherwise normal patients, massive hemoptysis may be secondary to hemangiomas, congenital arteriovenous malformations, intralobar pulmonary sequestration, bronchopulmonary foregut malformations, unilateral pulmonary artery agenesis (resulting from the development of collaterals), and Ehlers-Danlos syndrome.

Hemoptysis in children can be classified as mild ($<$100 mL/day) or massive, if the amount is greater than 250 mL/day, or if recurrent episodes involve substantial amounts of blood ($>$100 mL/day) over days to weeks.[172] Although minor hemoptysis occurs relatively frequently, approximately 5% of patients with cystic fibrosis will have an episode that is massive. Indeed, massive hemoptysis is seen in older patients with more severe lung disease and portends a poorer outcome, with a 5-year survival rate of 35%.[173] The pathogenesis is related to the enlargement and tortuosity of the bronchial arteries and the multiple anastamoses that form between these vessels and the pulmonary arteries (Fig. 66-9).[157] Nonbronchial arteries may also form collaterals with the bronchial circulation or enter the lung through granulation tissue. Most episodes of major hemoptysis resolve spontaneously but sedation and the discontinuation of medications that impair coagulation should be initiated. Hemoptysis usually indicates deteriorating lung function and thus antibiotics may be used at this time to treat underlying infection.

Bronchial artery embolization has emerged as a highly successful nonsurgical intervention for the short-term control of hemoptysis. Several series have demonstrated that this technique is safe and effective for the control of massive hemoptysis[174,175] with success rates, defined as no repeat bleeding within 24 hours, approaching 95%. However, almost 50% of these patients require repeated embolization within 19 months.[174] Failure of embolization is mainly attributable to nonbronchial collaterals.[176] Bronchoscopy can be used to help with the preoperative localization of bleeding. Surgery with lobectomy may be life-saving for patients who fail embolization or for those patients with fulminant, massive hemoptysis. In this scenario, mortality is high, ranging up to 36%.[146]

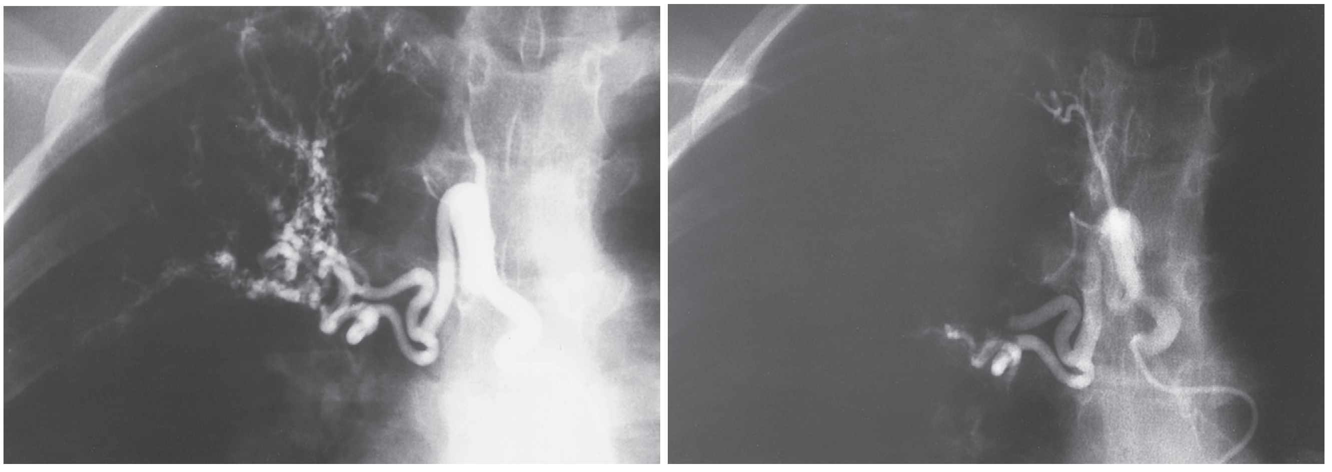
## COMPLICATIONS OF PNEUMONIA

### Pneumatocele

Pneumatoceles are small, thin-walled structures consisting of single or multiple air-filled cysts secondary to alveolar and bronchiolar necrosis. These abnormalities are seen frequently as a consequence of infection by *Staphylococcus aureus*, group A *Streptococcus*, and occasionally *Haemophilus influenzae*. Pneumatoceles secondary to *Staphylococcus aureus* infections may be identified early in the disease process and occur in up to 80% of patients.[177] Pneumothorax and pyopneumothorax are complications resulting from the rupture of pneumatoceles, with or without infection. These lesions can be difficult to distinguish from congenital cysts of the lung. However, pneumatoceles are prone to spontaneous resolution, whereas congenital abnormalities should not involute. Follow-up chest radiographs are required until the resolution of the pneumatocele. A CT scan may be useful in suspicious instances (Fig. 66-10).

### Lung Abscess

A pulmonary abscess develops when a localized infection in the lung parenchyma leads to necrosis and cavitation. It occurs much less frequently than pneumonia or empyema, with an estimated incidence of 0.7 per 100,000 admissions per year.[178] Classically, pulmonary abscesses were classified into primary (occurring in healthy children) or secondary



A B

**FIGURE 66-9** **A,** Arteriogram obtained to identify the cause of hemoptysis in a 10-year-old girl with cystic fibrosis. Note the tortuous bronchial artery. **B,** After successful Gelfoam embolization, the peripheral branches of the artery are not visualized.

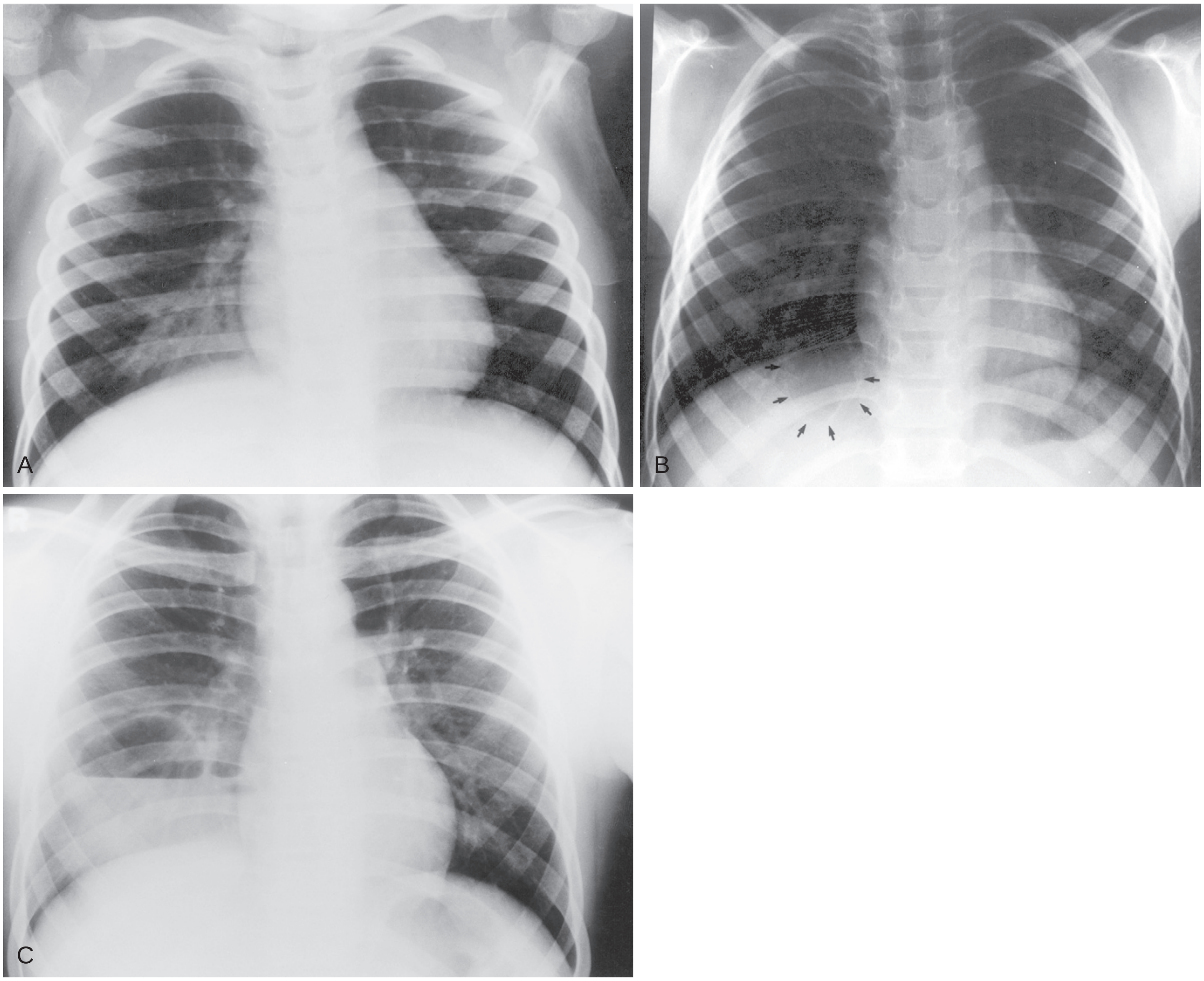



**FIGURE 66-10** **A,** A five-year-old child presented with a right lower lobe pneumonia that responded to intravenous antibiotics. **B,** During outpatient monitoring, small cysts were noted 6 weeks later and appeared to coalesce in a larger pneumatocele on this radiograph, taken 11 weeks after the initial study. Follow-up was recommended. **C,** At 14 years of age, the patient presented with a new episode of infection with a large air-fluid level and some smaller ones. Intravenous antibiotics were required for more than 2 weeks. Computed tomography (CT) confirmed the presence of three cysts. Six weeks later, a right lower lobectomy was performed, and microscopic examination confirmed a type I congenital cystic adenomatoid malformation.

(occurring in otherwise compromised children).[179] However, it is now clear that lung abscesses occur almost exclusively in areas of pneumonia.[180] When appropriate antibiotic therapy is administered early, the frequency of lung abscesses decreases considerably. Abscesses developing in immunocompromised, severely ill, or occasionally very young patients have recently become a more frequent problem. Occasionally, congenital bronchogenic or pulmonary cysts may become secondarily infected. These lesions may be indistinguishable from lung abscess on chest radiographs (Fig. 66-11, see Fig. 66-10, *C* ).

***History*** In the 17th century, Bonet described two patients whom he cured of lung abscess by external drainage.[181] In the 1930s, Neuhoff and Touroff[182] reported good results with one-stage surgical drainage of an acute putrid abscess of the lung. A two-stage procedure, the first step to induce pleural symphysis, was used by Welch[183] with a mortality rate of 40%. The treatment of lung abscess by resection in the early 1940s gave way to almost total reliance on antibiotics, which is still the approach now.[184]

***Pathogenesis*** The aspiration of gastric contents is a leading cause of chronic pneumonia and lung abscess in children, particularly in those with neurologic deficits.[178] Aspiration may occur acutely during trauma, anesthesia, epileptic seizures, or in those children with severe gastroesophageal reflux. Patients with repaired esophageal atresia or esophageal dysmotility are also at risk of aspiration.[184] Previously, common antecedents of lung abscess were the aspiration of foreign bodies, including blood or tissue following tonsillectomy.[184] Such abscesses are now infrequent, because they are prevented by prompt bronchoscopic removal[185] and by endotracheal intubation and pharyngeal packing, which protects against aspiration during operations on the oropharynx.

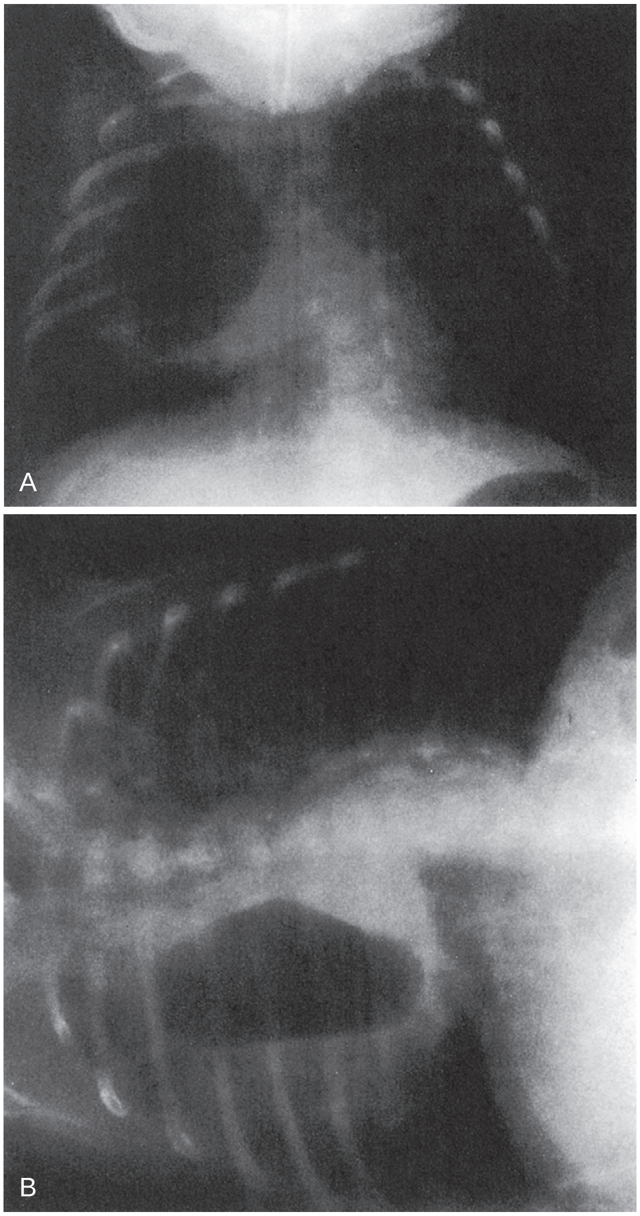



**FIGURE 66-11** Lung abscess following aspiration in an infant. **A,** A thick-walled cavity is present on the anteroposterior supine view. **B,** An air-fluid level is visible on the lateral decubitus view.

Lung abscess is an occasional complication of bacterial pneumonia and is much less frequent in the pediatric population than in adults. The most common causative organisms are anaerobes, followed by *Staphylococcus aureus*, *Pseudomonas*, *Streptococcus pneumoniae,* and occasionally *Haemophilus influenzae*. Other bacteria implicated in lung abscess include *Klebsiella*, *Escherichia coli*, *Peptostreptococci,* and *Peptococcus*.[186,187] Children with cellular or humoral immune deficiencies, either congenital or acquired, are occasionally unable to eradicate a pulmonary infection despite appropriate antibiotics, leading to inflammation, the breakdown of pulmonary parenchyma, and eventual abscess formation. Histologically, a lung abscess may be identified 18 to 36 hours after the inciting event but may only be apparent on chest radiographs after 7 days. When a lung abscess occurs in infants, an underlying congenital anomaly, such as a bronchogenic cyst or congenital cystic adenomatoid malformation, should be suspected (see Fig. 66-10).[188] These lesions require resection, but initial treatment with antibiotics with or without drainage is usually indicated.

The position of the child at the moment of aspiration determines the location of the lung abscess.[184] In supine patients, the superior segments of the lower lobes are most often involved. If the child is on the right side, the right upper lobe is at risk; if on the left side, the apical posterior segment of the left upper lobe may be the site. The upright child aspirates into basilar segments of the lower lobes. The distribution of lung abscesses in various lobes and segments in children is similar to that in adults. Lung abscesses often occur at the periphery of a segment or lobe, making them amenable to external drainage procedures (see later).

***Diagnosis*** The most common symptoms caused by lung abscess include fever, cough, chest pain, anorexia, productive sputum, weight loss, malaise, hemoptysis, and chills.[189] Purulent sputum may be easily obtained from older children to help with a bacteriologic diagnosis; younger patients usually swallow their secretions. Putrid sputum is characteristic of an anaerobic abscess. The affected area of the chest may be dull to percussion and have decreased breath sounds. Leukocytosis is common. Patients may also present with restrictive lung disease patterns resulting from the enlarging abscess or secondary to pleuritic chest pain.

The diagnosis of lung abscess may be established by chest radiographs, which show a cavity, commonly with an air-fluid level (see Fig. 66-11). An abscess should be distinguished from pneumatocele, a localized collection of intrapulmonary air that usually does not have an air-fluid level, and from empyema with an air-fluid level. However, computed tomography scans have become the most valuable radiologic investigation in the diagnosis and characterization of lung disease in complicated pneumonia, revealing pathology that may not be apparent on plain chest radiographs.[189]

***Treatment*** A specific bacteriologic diagnosis should be established before treatment whenever possible. Diagnostic bronchoscopy with direct aspiration of purulent fluid from the parent bronchus should be performed, except in those older children who are able to induce a satisfactory sputum sample. The needle aspiration of a peripheral abscess cavity under imaging guidance to isolate bacterial species and drain collections has been used with success.[190] Furthermore, isolation of the causative organism is possible with this technique even if patients are concurrently receiving antibiotic therapy.

The vast majority of lung abscesses may be treated effectively with appropriate intravenous antibiotic therapy. Penicillin is the antibiotic of choice because of its efficacy against streptococcal and anaerobic species. However, β-lactam resistance may be a problem, and thus clindamycin may be added to address this issue, as well as to cover against *Staphylococcus aureus* in children who are very ill.[191] Third-generation cephalosporins are also very effective. Intravenous antibiotics are recommended for 2 to 4 weeks, followed by oral antibiotics for a total treatment period of 6 to 8 weeks.[178]

Percutaneous catheter drainage of the abscess has become a standard part of the management scheme for children with lung abscesses over the last 20 years. It may be helpful in acutely ill children, particularly for those who experience rapid progression of the disease despite maximal antibiotic therapy.[178,192] Percutaneous drainage provides an opportunity to culture responsible organisms, effect ongoing drainage, and thus hasten recovery.[189] Complications related to percutaneous techniques occur occasionally and include pneumothorax, hemothorax, incomplete drainage, and bronchopleural fistulae.[193] Surgical resection of the lung abscess by segmental resection or lobectomy is recommended for the chronic, large, and thick-walled abscesses or for those few patients who do not respond to intensive antibiotic therapy or percutaneous drainage.[188,194] Other indications for resection include chronic abscesses lasting longer than 3 months, persistent significant hemoptysis, bronchial stenosis, significant bronchiectasis, and massive pulmonary necrosis. The overall outcome of children with lung abscess is very good. Mortality rates are low (approximately 5%) and usually occur in those with secondary abscesses.

## Empyema

***History*** Even during the ancient times of Hippocrates, Paul of Aegina, and Fabricus, empyema was a known complication that followed pulmonary infections and required external drainage for cure. In the 16th century, Paré manually evacuated a putrid hematoma from the pleural cavity of a French soldier.[181] Formal decortications were performed by Kuster in 1889 and Fowler in 1891.[195] Until the antibiotic era, discussions of therapy for empyema largely centered on the relative advantages of open drainage, various types of closed drainage, and the optimal time for the use of these measures.[196]

***Definition and Pathogenesis*** An empyema is the accumulation of purulent fluid in the pleural cavity and complicates pneumonia in 1 of 150 affected children.[197] It may also occur following trauma, neoplastic processes, intrathoracic esophageal perforation, or as a complication of intrathoracic surgery. Normally, the pleural membranes are permeable to liquid, and a small amount of fluid exists between the visceral and parietal pleura to minimize friction during respiration. When the adjacent lung is healthy, the pleural cavity is generally resistant to infection. Empyema, once established, exhibits three characteristic stages[198,199]: (1) an exudative or early stage when the fluid is thin and of low cellular content; (2) an intermediate or fibrinopurulent stage during which large numbers of polymorphonuclear cells and fibrin are deposited in the pleural space, progressively impairing lung expansion and leading to the formation of fluid loculations, and (3) a final stage or organizing empyema during which a thick exudate forms and fibroblasts invade the fibrinous peel. The empyema may be diffuse and involve the entire pleural space or it may be localized and encapsulated in an interlobar, diaphragmatic, or paramediastinal location.

Currently, the most common organisms in childhood empyema are *Streptococcus pneumoniae*, *Staphylococcus aureus,* and *Haemophilus influenzae*.[200] Other streptococci, mixed oral flora, and anaerobes have also been classically associated with the development of empyema. The changes in bacteriology are likely due to changing antibiotic resistance patterns. However, the incidence of empyema may be increasing,[197] and the virulence of the causative organisms appears to impact the natural course and, ultimately, the management of these patients.[201] Tuberculous empyema is much more rare than effusion and is associated with a high bacterial load within the pleural space. Mycobacterial resistance is a problem in this situation because of the poor pleural penetration of standard antitubercular agents.[202]

***Clinical Manifestations and Diagnosis*** The symptoms of empyema in a child include a short history of pulmonary infection, followed by respiratory distress, fever, and cough. Chest or shoulder pain coupled with abdominal pain, distension, and ileus may intensify the respiratory difficulty. The radiographic appearance often includes bilateral pulmonary involvement, with pneumatoceles occasionally identified within the lung. Haziness of a hemithorax may represent either pulmonary consolidation or pleural fluid. In the early exudative phase, the pleural fluid flows freely along the lateral chest wall on decubitus views (Fig. 66-12). In advanced empyema, the exudate is a solid mass of fibrin and does not move with changes in position. In the intermediate fibrinopurulent stage, loculations typically develop (see Fig. 66-12, *C*). Air-fluid levels within the loculations suggest the presence of anaerobes in the pleural contents. Thoracentesis may provide valuable information on the quality of pleural fluid. The progression to advanced-stage empyema may be suspected if the fluid demonstrates any of the following characteristics after diagnostic thoracentesis: (1) gross pus, (2) pH less than 7.0, (3) lactate dehydrogenase greater than 1000 U/mL, (4) glucose less than 40 mg/dL, and (5) bacteria visible on Gram stain.

***Treatment*** Primary therapy for empyema is the administration of high-dose intravenous antibiotics. Effective drainage of the pleural space will accelerate its resolution. Indeed, fluid that layers in the decubitus position on chest radiographs may be amenable to chest tube drainage alone. However, loculated fluid collections may not be sufficiently drained in such a manner, and the optimal management of these patients is still debated. The options for therapy include chest tube drainage alone, fibrinolytic therapy, and VATS.

There appears to be ample evidence demonstrating that both fibrinolytic therapy[203–205] and VATS[206–210] are superior to chest tube drainage alone for loculated empyema. Furthermore, there has been broad acceptance of the use of VATS as the first line of treatment.[197,206] In 2006, Sonnappa and colleagues[211] performed the first prospective randomized control trial, involving 60 children, that compared intrapleural urokinase with VATS. The authors found that the post-intervention length of stay for patients receiving urokinase (6 days, range 4 to 25 days) was similar to the length of stay for VATS patients (6 days, range 3 to 16 days). The failure rates were also similar between groups, with five in the urokinase group and four in the VATS group who were "rescued" by VATS or mini-thoracotomy, respectively. An important conclusion in favor of fibrinolytic therapy was that it was 25% less expensive than VATS. In 2009, St. Peter and colleagues[212] published a similar prospective trial involving 36 patients who were randomized to receive either recombinant tissue plasminogen activator or VATS as primary therapy for empyema. In this study, equivalent lengths of stay, post-therapy oxygen support, days until afebrile after intervention, and analgesia doses were noted

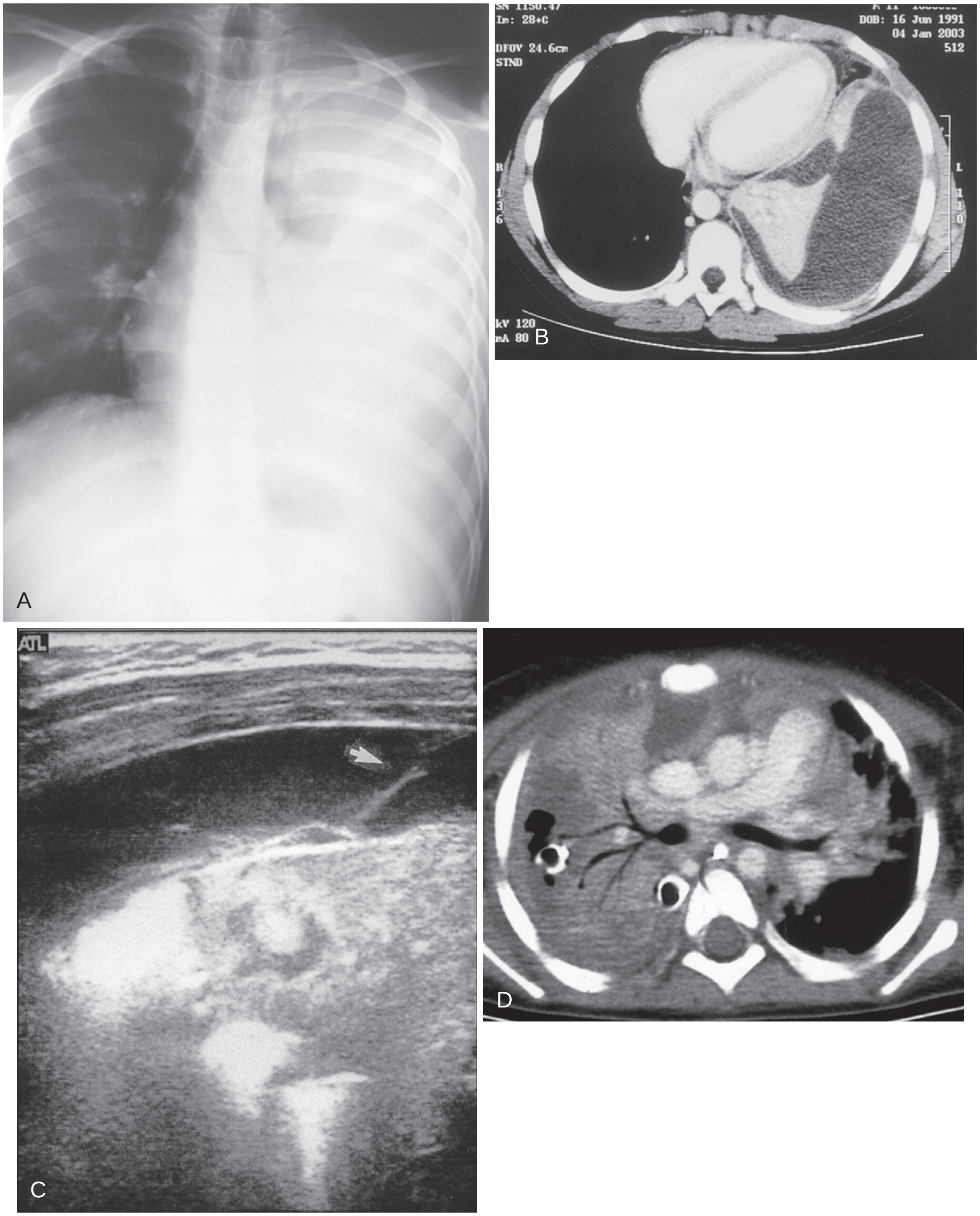



**FIGURE 66-12** **A** and **B,** An 11-year-old boy presented with left-sided pleuritic pain and fever. **A,** Chest radiograph shows a large left-sided effusion with mediastinal shift. **B,** Because of concern about an underlying malignancy, a computed tomography (CT) scan was obtained. This shows a large nonloculated fluid collection with a collapsed lower lobe; fluid can be seen in the fissure. A chest tube was inserted and drained 400 mL of serous fluid, with a lactate dehydrogenase level of 4,000 U/L, thus qualifying it as a fibrinopurulent empyema. There were no bacteria on Gram stain, but cultures grew *Streptococcus pneumoniae*. The patient improved with intravenous antibiotics, and the chest tube was removed 8 days later. **C** and **D,** A 3-year-old girl had a more fulminant course. Loculations *(arrow)* and debris in the pleural fluid were evident on ultrasonography in **C,** Despite early thoracoscopic drainage, she developed lung necrosis—seen on computed tomography with intravenous contrast in (**D**) with a persistent air leak, requiring 10 days in the intensive care unit and 1 month in hospital.

between the groups. The only significant difference was the 35% reduction in hospital charges in those receiving fibrinolysis. Interestingly, these two trials had almost identical study designs and produced results that were strikingly similar, especially with regard to the length of stay postintervention (6 days) and failure rates (16.6% in each trial) of fibrinolysis. Although some criticism has been voiced about the broad applicability of the results of these single-center trials to individual centers (i.e., placement of chest tubes at the bedside), and the rather long period of symptoms (10 days) before intervention,[213] which may have mitigated the benefit of early VATS, the current recommendations for primary therapy in loculated empyema appear to favor fibrinolysis. Importantly, however, the overall excellent outcomes of children with empyema, irrespective of the treatment modality, still complicate the debate regarding the “best” strategy to treat intermediate/advanced empyema and loculated parapneumonic effusions.

Treatment algorithms for pediatric patients with empyema are often institution specific and vary with local expertise and experience. Presently, based on the results of the two prospective randomized trials, St. Peter[212] has suggested an algorithm in which patients with empyema, diagnosed either by the presence of loculations on ultrasonography or greater than 10,000 white blood cells/μl in pleural fluid, should receive three daily doses of recombinant tissue plasminogen activator (4 mg in 40 mL saline) after the insertion of a small chest tube. Should drainage decrease in the absence of clinical improvement, imaging with ultrasonography or CT scan is indicated. In this context, the absence of pleural disease would require the continuation of antibiotics only, while persistent pleural disease would require rescue VATS. A slightly varied approach based on the interval of time from the onset of symptoms has been suggested by the American Pediatric Surgical Association (APSA) New Technology Committee.[213] This algorithm recommends chest tube drainage for simple effusions of less than 5 days duration. For patients with more than 5 days of symptoms, either fibrinolysis or VATS may be used. If symptoms persist more than 7 days after intervention, CT scans are recommended to determine the presence of pleural disease. As with the St. Peter algorithm, antibiotics are only required in the absence of pleural diseases, while persistent loculations are treated with VATS. If VATS is unsuccessful at any point, decortication by thoracotomy is recommended.

# Pediatric Spontaneous Pneumothorax

Primary spontaneous pneumothorax is defined as a pneumothorax occurring secondary to apical blebs (<2 cm) or bullae (>2 cm) without evidence of other lung pathology.[214,215] It can also occur in term neonates without any risk factors. In contrast, secondary spontaneous pneumothoraces occur in the context of underlying lung disease, such as cystic fibrosis or *Pneumocystis jirovecii* pneumonia. Other lung infections, bronchiolitis, asthma (even mild), connective tissue disorders, congenital cystic adenomatoid malformations, and traumatic lung contusions are other risk factors.[215–217] The incidence of primary spontaneous pneumothorax is estimated to be 7.4 to 18 per 100,000 boys and 1.2 to 6 per 100,000 girls in the United States.[218,219] Typically, the patient is a thin, lean adolescent who presents with an acute onset of ipsilateral pleuritic chest pain and nonproductive cough. Most patients are clinically stable upon initial assessment. However, a small number may present in fulminant distress, including hypotension and respiratory failure, secondary to a tension pneumothorax. Other clinical findings in patients with pneumothorax include tachypnea and tachycardia. Chest radiographs confirm the diagnosis and may identify underlying pathology within the lung. Expiratory films may be helpful to identify small pneumothoraces. Different methods are available to quantitate the size of the pneumothorax, because this factor is most likely to influence subsequent management. These include the Light,[220] the Rhea[221] and the Collins methods.[222] The Light method, using only a posteroanterior (PA) radiograph, has been endorsed by the British Thoracic Society,[223] but it is unclear exactly where the measurements should be taken. The Rhea method does possess standardized measurement points, but it requires both PA and lateral radiographs for calculation. The Collins method has been developed using helical CT scans of the chest, and like the Light method, can be calculated based on a single PA chest radiograph. However, like the Rhea method, it has not been validated for digital images. Furthermore, although the Collins method appears to be the most accurate, it needs further validation.[224] There are also differing definitions of “large” pneumothoraces. The British Thoracic Society describes these as greater than 2 cm of separation between the lung and the entire lateral chest wall, but this does not account for those located at the apex.[223] The American College of Chest Physicians,[225] however, describes large pneumothoraces as greater than 3 cm of apical distance but does not account for those pneumothoraces that are more equivalently distributed. A combination of both definitions likely seems appropriate.[224]

Patients who present with an acute pneumothorax require supplemental oxygen and intravenous access. For those few patients presenting with a tension pneumothorax, immediate needle decompression in the second intercostal space (midclavicular line) is necessary even before chest radiograph confirmation, followed by the prompt placement of a chest tube. A pneumothorax of less than 15% can often be managed by observation with or without supplemental oxygen, especially if the initial symptoms occurred more than 24 hours before presentation. Needle aspiration is emerging as a first-line therapy in adults with large, asymptomatic pneumothoraces or small symptomatic ones[224] and this strategy has been endorsed by the British Thoracic Society.[223] However, pediatric data are sparse,[224] and the Delphi Consensus Statement from the American College of Chest Physicians (2001) does not support the routine use of needle decompression in this instance.[225] Heimlich valves connected to the pleural drain allow for outpatient management of small pneumothoraces in compliant patients. Large pneumothoraces require the placement of a chest tube with underwater seal and drainage. An air leak that persists for more than 5 to 7 days may require further intervention, or at least confirmation that the chest tube in place is functioning properly.[226] For most young children (<8 years of age), and those with asthma as a predisposing factor, chest tube drainage is sufficient for treatment. However, adolescents with spontaneous pneumothorax have been reported to have a recurrence rate of up to 40% to 60%.[214,227] Interestingly, in one adult series, large drains were associated with a higher recurrence rate of pneumothorax

(33%) than either observation alone (17%) or small-bore chest tubes (6%).[228] In the end, symptomatology should direct further investigation and treatment. Computed tomography scans are more sensitive at detecting blebs and bullae than normal radiographs, but it is unclear if their routine use for spontaneous pneumothorax ultimately changes management. Some adult series have identified blebs and bullae in up to 56% to 88% of adults with spontaneous pneumothorax.[229,230] However, a recent series identified a much lower rate of blebs (28%), with none identified in the control group, in a series of 43 adolescents from 13 to 19 years of age.[231] These lesions were always located at the lung apices. This series also identified *contralateral* blebs and bullae in 78% of patients with pneumothorax. Furthermore, blebs and bullae are not to be confused with "apical lines," which occur in 56% of patients with pneumothorax and 28% of controls, and could represent normal variants in the apices of the lung.[231] Some authors advocate the use of computed tomography after the index presentation, while others wait for a recurrence before further investigation.[215,224] Ouanes-Berbes and colleagues[232] reported a 19% recurrence rate over 7 years in young adults (17 to 27 years of age) who had an incidence of blebs/bullae of 72%. However, there is still equipoise regarding the role of imaging, especially the indications for and timing of CT scans, in spontaneous pneumothorax.

The indications for surgical management include recurrence, persistent air leak, bilateral disease, and possibly the presence of large bullae. Video-assisted thoracoscopic surgery appears to be superior to standard thoracotomy with respect to postoperative pain and complications.[227,233] Transaxillary mini-thoracotomy is a viable alternative to VATS and has certain advantages, particularly in the context of poor visualization and the presence of dense adhesions.[215,234] For pleurodesis, thoracoscopic pleural abrasion is effective.[227,233] Talc poudrage has also been used with success, but some caution against it because of the small but clinically significant risk of respiratory distress associated with its use.[235] Apical pleurectomy can be easily performed through a transaxillary incision and is another effective method for pleurodesis, especially in the context of recurrence. For bilateral disease, both VATS and transaxillary mini-thoracotomy are effective and can be used as a single-stage operation.[215] Despite similar results in outcome, VATS has become more popular among surgeons for the treatment of spontaneous pneumothorax, even though some controversy persists. Recurrence rates in VATS have been linked to experience with this technique.[236] The overall recurrence rate of pediatric spontaneous pneumothorax treated nonoperatively approaches 50% to 60%,[224,237] but those managed operatively have recurrence rates between 6% to 9%.[214,238] For transaxillary mini-thoracotomy, the recurrence rate has been reported to be equivalent.[224] All in all, both VATS and transaxillary thoracotomy are effective in the treatment of spontaneous pneumothorax. Furthermore, the guidelines for the treatment of spontaneous pneumothorax are often extrapolated from adult series and randomized trials in the pediatric population are clearly warranted.

Pneumothoraces in patients with cystic fibrosis are more difficult to treat, because the air leak frequently persists. The use of a higher negative pressure (20 to 25 cm $H_2O$) may be helpful. If this fails, thoracoscopic talc poudrage[239] or other sclerosing agents[240] are required to achieve pleurodesis and prevent recurrence. Pleurectomy is usually avoided to facilitate pneumonectomy should lung transplantation become necessary.

# Intrathoracic Access and Procedures

## CHEST TUBE INSERTION IN THE NEWBORN FOR PNEUMOTHORAX

In preparation of chest tube insertion, the infant is placed in an oxygen hood or, if intubated, maintained on ventilator support, restrained, and monitored by pulse oximetry and electrocardiogram. A surgical headlight or an overhead light source of similar quality should be available. The procedure is performed with sterile technique (mask, cap, gown, and gloves). In addition to sterile instruments (scalpel, mosquito clamps, Adson forceps, needle holder, fine scissors) and drapes, 8- and 10-Fr catheters, a sterile connector, 3-0 and 4-0 nonabsorbable suture on curved swaged-on needles, and an infant-sized underwater seal drainage system should be readily available. The chest wall is prepared with chlorhexidine or an iodophor solution and draped with sterile towels. The skin is infiltrated with lidocaine through a 25-gauge needle placed lateral to the nipple in the anterior axillary line over the fourth rib. Injury to the nipple and underlying breast tissue should be avoided. A 3- to 4-mm incision is made with a No. 11 scalpel blade. A mosquito clamp is placed through the incision and used to spread the subcutaneous tissues. It is advanced upward over the rib and used to spread the intercostal muscles above the incision, which requires firm pressure, and then passed into the pleural cavity. This method produces a "tunnel" so that the entrance into the pleural cavity is superior to the level of the skin incision. Entry into the pleural space is heralded by reduced resistance and is usually followed by the sound of escaping air. The tip of the 8-Fr chest tube is placed in the end of the curved mosquito clamp, and the tube is advanced into the pleural cavity (Fig. 66-13). An alternative is to use a trocar inside the chest tube to guide the latter through the tunnel. With this technique, it is safer to withdraw the tip of the trocar by a few millimeters and to place a large clamp on the tube 5 cm proximal to the tip to avoid uncontrolled penetration and injury to the mediastinal structures. The tube is advanced superiorly and anteriorly 3 to 4 cm, being certain that all of the holes in the tube are intrapleural, yet avoiding a tube that is too far and kinks after reaching the mediastinum. The tube is then sutured in place with a 3-0 nonabsorbable purse-string suture. Povidone (Betadine) ointment is placed at the tube–skin interface, and the tube is secured. The connecting tube is attached to an underwater seal, and the water level is observed to ensure fluctuation with respiration. The system may be set at 10 cm of water of negative pressure if necessary, remembering that a high negative pressure will add to the positive pressure applied by a ventilator, and may lead to barotrauma. A disposable infant Pleur-evac system (Teleflex, Research Triangle Park, NC) is highly effective and easily managed in the neonatal intensive care unit (NICU).

A chest radiograph is obtained to determine the location of the tube, to ensure that all the holes are intrapleural, and to check that tube placement was effective in expanding the

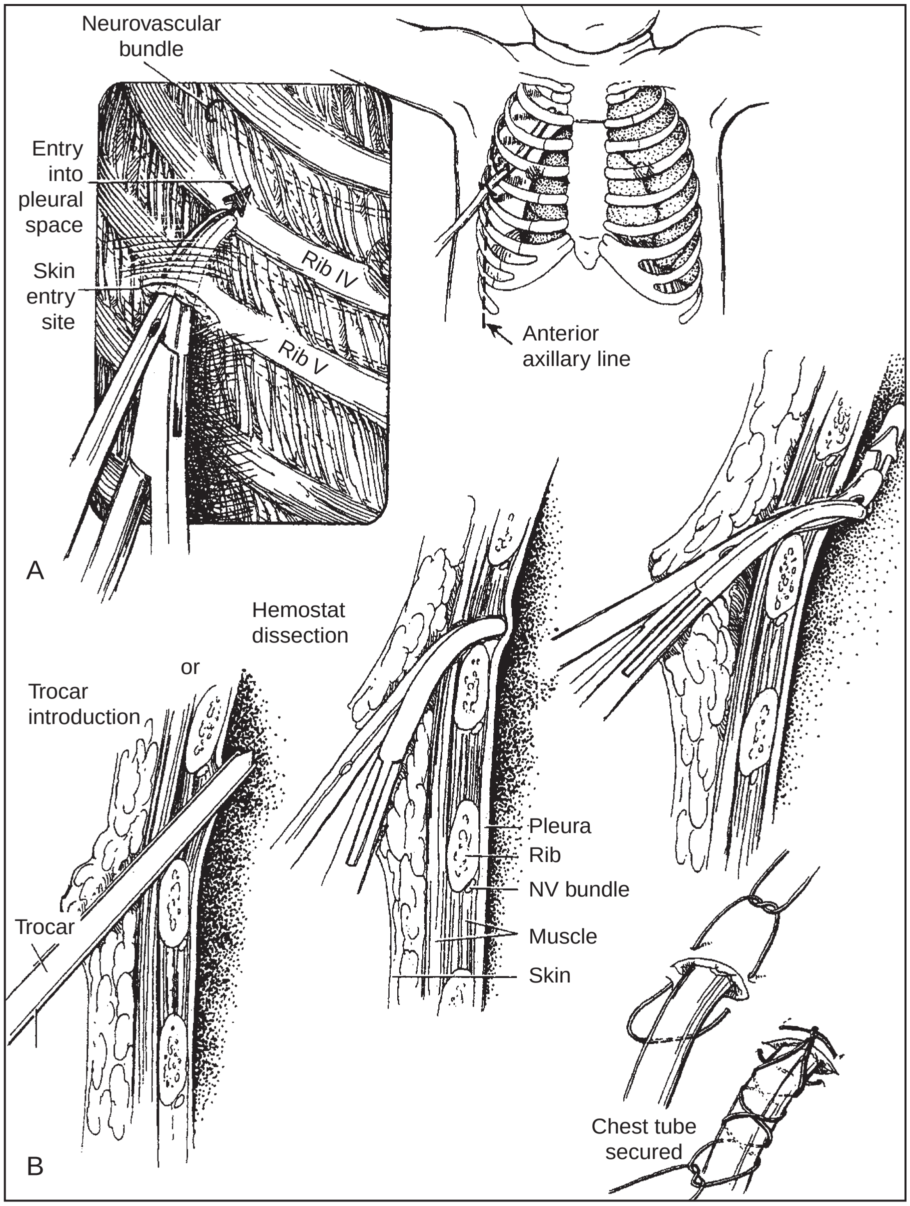



**FIGURE 66-13** Chest tube insertion in the newborn for pneumothorax. **A,** Preferably, a small hemostat is inserted through a small incision in the anterior or midaxillary line and is tunneled upward, entering the chest above the next rib. The chest tube is tunneled upward, entering the chest above the next rib. The chest tube is inserted and secured with a suture ligature. Several knots should be placed after each circumferential pass of the thread to avoid any slippage. **B,** A trocar can be used as an alternative method of tube insertion, as long as the trocar is withdrawn by a few millimeters within the tube; this technique allows easier guidance of the tube, for example, if it has to be placed posteriorly and inferiorly to drain an effusion.

collapsed lung. A lateral chest radiograph may be obtained to determine whether the tube is in an anterior or a posterior location. A superior and anteriorly placed tube most effectively evacuates pneumothorax. Excessive bubbling indicates a continued source of air leak from the injured lung, a bronchopulmonary fistula, or a leak in the system.

The most frequent complications related to chest tube insertion are (1) injury to the intercostal vessels during insertion and (2) lung perforation caused by the clamp or tube. If there is excessive bleeding and continued significant air leak, surgical correction is required. Injury to mediastinal lymphatic, venous, and nervous structures have also been described.

Kits are available that allow the Seldinger technique to be used to rapidly and safely place a small chest tube in infants. A needle is inserted in the pleural cavity and a guidewire passed. The needle is removed and a dilator passed over the wire, followed by a pigtail catheter.

## CHEST TUBE CARE AND REMOVAL

Following insertion for pneumothorax a chest tube usually drains little fluid after the air is evacuated. In babies who do not require mechanical ventilation, when there is no further bubbling in the water seal chamber and the lung is fully expanded for 24 to 48 hours, the suction, if used, is removed and the tube left only on an underwater seal. If the pneumothorax does not reaccumulate in 12 to 24 hours, it is probably safe to remove the tube. The tube should be removed rapidly and the tube site sealed with petroleum gauze dressing to prevent air from entering the chest. An additional chest radiograph is usually obtained to be sure that there is no recurrence of the pneumothorax. It is probably safer to leave the chest tube in place for longer periods if the infant requires mechanical ventilation, especially if high peak-inspiratory pressure and/or positive end-expiratory pressure are necessary.

## CHEST TUBE INSERTION IN OLDER CHILDREN

Pneumothorax in older children is usually encountered in patients with spontaneous rupture of a bleb, asthma, cystic fibrosis, and following blunt, or, occasionally, penetrating chest wall trauma. A tube thoracostomy is required in symptomatic patients. Chest tube insertion in older infants and children may also be required for pleural effusions from a variety of causes, including chylothorax, traumatic hemothorax, lymphoma, inflammation as a result of bacterial, fungal, and viral pneumonia, empyema, and other causes.

Insertion of a chest tube in these patients follows the same pattern of sterile techniques and preparation described in the management of neonates. Infants and toddlers can be premedicated with intravenous fentanyl (1 μg/kg) and midazolam (0.1 mg/kg) as part of a conscious sedation protocol. Alternatively, ketamine (1 mg/kg) with or without midazolam provides excellent analgesia and sedation while preserving respiration reflexes and cardiac parameters throughout the duration of the procedure. Children are kept in the supine position with a small roll under the affected hemithorax to elevate the area. The ipsilateral arm is positioned superiorly and laterally. The chest tube size is determined by the child's weight and whether the problem is a pneumothorax, a transudate, or an exudate (Table 66-1), although the recent trend has been to use smaller-caliber tubes, even for empyema drainage. After sterile preparation, a local anesthetic, and placement of a small skin incision, the appropriate-sized tube is inserted in the third or fourth interspace in the anterior to midaxillary line and positioned upward and anteriorly for pneumothorax. If the patient has an effusion, the location should be determined by correlating the physical examination (e.g., dullness to percussion and diminished tactile fremitus) with the findings on chest radiograph, ultrasonography, and/or chest computed tomography. A 20-gauge needle or angiocatheter may be inserted just at the level of transition of percussion sounds (from tympanic to dull) to locate the effusion. The chest tube can then be inserted as noted earlier and positioned inferiorly and posteriorly. The chest tube should not be placed below the level of the seventh rib to avoid injury to the spleen, liver, or diaphragm.

**TABLE 66-1**
**Guide for Chest Tube Selection**

| | Size (French) | | |
|---|---|---|---|
| *Patient Weight (kg)* | *Pneumothorax* | *Transudate* | *Exudate* |
| <3 | 8-10 | 8-10 | 10-12 |
| 3-8 | 10-12 | 10-12 | 12-16 |
| 8-15 | 12-16 | 12-16 | 16-20 |
| 16-40 | 16-20 | 16-20 | 20-28 |
| >40 | 20-24 | 24-28 | 28-36 |

## LUNG BIOPSY

Open lung biopsy is usually obtained early in the diagnostic evaluation of diffuse pulmonary disorders in children and is generally preferred to a percutaneous transthoracic needle biopsy for establishing the diagnosis. Needle lung biopsies are fairly reliable and accurate; however, pneumothorax or hemothorax occur in approximately one third of patients. Larger specimens are obtained by open lung biopsy for cultures and histologic study as well as special staining, and occasionally for electron microscopy. It is easier to avoid air leaks and to secure complete hemostasis with a wedge biopsy. Pneumothorax is prevented by the routine use of a chest tube. The mortality after surgery is rarely a result of the procedure; death, when it occurs, is almost always caused by the patient's underlying disease. A tissue diagnosis is established in almost all patients after open or thoracoscopic lung biopsy and influences subsequent therapy in greater than 90%.[130] The preoperative diagnosis is confirmed in approximately 60% of patients and corrected in greater than 35%. Moreover, the differential diagnosis is often between infectious, neoplastic, or inflammatory processes, such as bronchiolitis obliterans with organizing pneumonia (BOOP) or lymphoid interstitial pneumonitis. Because the latter require tissue for diagnosis and are treated with steroids, a lung biopsy is essential to confirm diagnosis (Fig. 66-14, see Fig. 66-6).

Children who must undergo lung biopsy may be poor risks for surgery and anesthesia. They are often immunosuppressed with spreading pulmonary infiltrates and impending respiratory

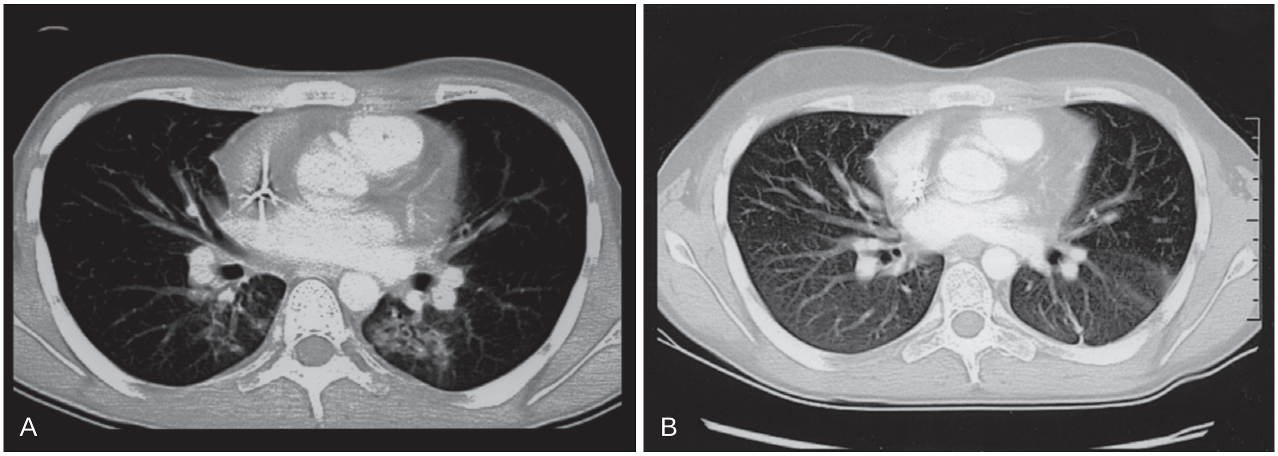



**FIGURE 66-14** A 17-year-old child with stage IV Hodgkin disease underwent radiotherapy and autologous bone marrow transplantation. **A,** On routine surveillance computed tomography, bilateral focal airspace disease was seen, mostly in the superior segments of the lower lobes. Lung biopsy revealed bronchiolitis obliterans. He was treated with steroids, and a repeat scan 3 months later (**B**) showed a near-complete resolution.

failure. Biopsy should be performed early, when indicated, rather than after respiratory failure has supervened and the child is dependent on a ventilator. However, even for patients with persisting or undiagnosed respiratory failure, lung biopsy still leads to significant changes in management despite a higher incidence of complications, mainly as air leak (45%). Careful preoperative review of chest roentgenograms is essential to identify the optimum site for biopsy; sometimes two different areas should be biopsied, one heavily infiltrated and the other less involved. Preoperative discussion with the pathologist is invaluable. A small anterior thoracotomy incision with the biopsy performed using a stapler device is safe and expeditious; in smaller children, a Lahey clamp allows an adequate biopsy specimen through a smaller incision, especially if the lung parenchyma is stiff and cannot be brought out through the incision (Fig. 66-15). Alternatively, a transaxillary incision may provide adequate access to lung tissue desired for lung biopsy. In experienced hands, there is minimal mortality or morbidity from open lung biopsy, in spite of the patient population. In patients large enough to allow the use of endoscopic stapling devices, lung biopsy can also be performed by thoracoscopy, with similar risks and complications to the open procedures.

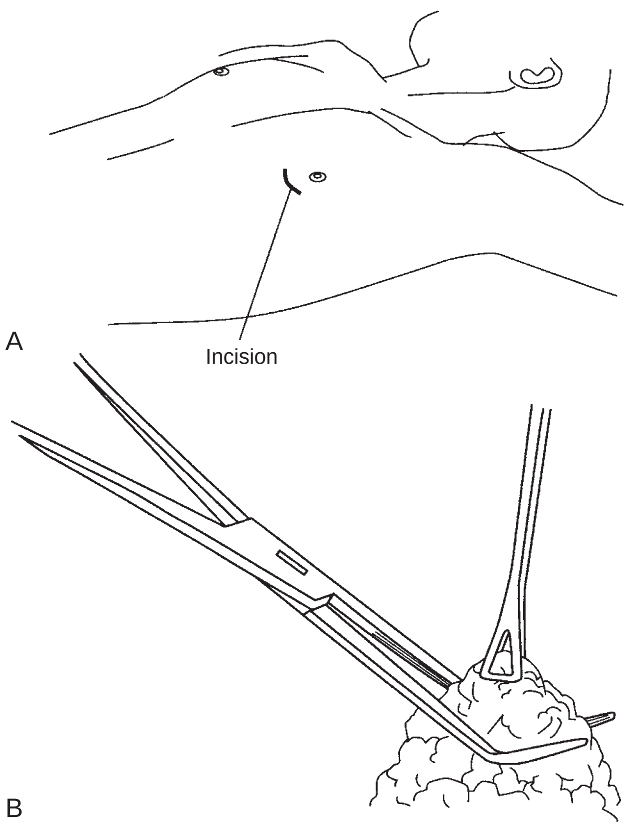



FIGURE 66-15 **A,** An open lung biopsy can be done with minimal morbidity using a small anterior thoracotomy. **B,** The lingula can be grasped easily and provides an adequate specimen in patients with diffuse lung infiltrate; in small children (or when a stiff lung cannot be brought outside the chest wall) a Lahey clamp is used to obtain the biopsy specimen instead of a linear stapler. After the lung tissue above the Lahey clamp is cut sharply with a scalpel, a continuous U suture is passed underneath the clamp, the clamp is released, and the suture is tightened and brought back as a simple continuous stitch. This provides excellent hemostasis and prevents air leaks.

# Chylothorax

The escape of chyle into the mediastinum from a defective thoracic duct, and thence into one or both pleural spaces, is a well-described entity. Historical perspectives on chylothorax and its management include the evolution of the knowledge of anatomy and physiology of the thoracic duct, the development of the science of nutrition, and progress in thoracic surgery. Of note, in 1937, Blalock reported that the experimental occlusion of the superior vena cava could produce chylothorax, which was prevented by prior ligation of the thoracic duct.[241] A decade later, Lampson was the first to use this treatment clinically.[242] Considerations of therapy focus on causative factors and include dietary modification and octreotide to decrease thoracic duct flow; thoracentesis and/or thoracostomy drainage to relieve respiratory embarrassment and promote pleural sealing; and surgical ligation of the disrupted duct, pleurodesis, or pleuroperitoneal shunting when conservative measures fail.

## ETIOLOGY

Effusion of chylous fluid into the thorax may occur spontaneously in newborns and has usually been attributed to congenital abnormalities of the thoracic duct or trauma from delivery.[243] However, the occurrence of chylothorax in most cases cannot be related to the type of labor or delivery, and lymphatic effusions may be discovered prenatally.[244,245] Chylothorax is the leading cause of pleural effusions in neonates.[246]

Chylothorax in older children is rarely spontaneous and occurs almost invariably after trauma or cardiothoracic surgery, with the latter having an incidence of 0.85% to 6.6%.[247–249] Some patients with thoracic lymphangioma may also present in this older age group (Fig. 66-16).[250] Operative injury may be in part a result of anatomic variations of the thoracic duct. Trauma leading to hyperextension of the spine with rupture of the duct from stretching has been reported with high diving, wrestling, and other such

FIGURE 66-16 Chest radiograph of 4-year-old girl with bilateral extensive lymphangioma and chylothorax. Note hazy appearance of fluid and major compression of the left lung.

activities.[247] Chylothorax has also been observed in "nonaccidental trauma" and mistaken for spontaneous chylothorax.[251] Extensive bouts of coughing may also lead to thoracic duct rupture, which is particularly vulnerable when full following a fatty meal. Neoplasms, particularly lymphomas and neuroblastomas, have occasionally been noted to cause obstruction of the thoracic duct. Lymphangiomatosis or diffuse lymphangiectasia (such as seen in Gorham disease and other syndromes) may produce chylous effusion in the pleural space and peritoneal cavity. Other causes include mediastinal inflammation, increased central venous pressure, subclavian vein or superior vena caval thrombosis, and misplaced central venous catheters.[247]

## ANATOMY AND PATHOPHYSIOLOGY

The thoracic duct develops from outgrowths of the jugular lymphatic sacs and the cisterna chyli. During embryonic life, bilateral thoracic lymphatic channels are present, each attached in the neck to the corresponding jugular sac. As development progresses, the upper third of the right duct and the lower two thirds of the left duct involute and close. The wide variation in the final anatomic structure of the main ductal system attests to the multiple communications of the small vessels comprising the lymphatic system. The thoracic duct originates in the abdomen at the cisterna chyli located over the second lumbar vertebra (Fig. 66-17). The duct extends into the thorax through the aortic hiatus and then passes upward into the posterior mediastinum on the right before shifting toward the left at the level of the fifth thoracic vertebra. It then ascends posterior to the aortic arch and into the posterior neck to the junction of the subclavian and internal jugular veins.

Many variations are present in the entire ductal system, and the typical course of the thoracic duct is present in only approximately 35% to 50% of individuals.[252,253] The most common variations are a double system originating from the cisterna or a multiple ductal pattern at the level of the diaphragm. In the chest, a rich collateral system originates from intercostal spaces, the posterior mediastinum, and visceral lymphatics, which communicate freely with the main duct through collecting trunks.

The thoracic duct contains smooth muscle in the wall that is capable of contracting with sufficient force to propel lymph upward toward the jugular venous junction at a rate of 50 to 200 mL/hour.[254] The rate of lymph flow in the thoracic duct varies widely and relates to the volume of fat ingestion, scar tissue in the mediastinum, presence of portal hypertension, and other factors. The flow of chyle superiorly into the subclavian vein is enhanced by the presence of valves in the thoracic duct, portal pressure, and the differential gradient between the negative intrapleural pressure and the positive intra-abdominal pressure.[241,255] Conversely, increasing the intrathoracic pressure through the use of positive end-expiratory pressure has been shown to decrease the flow of chyle by half in the thoracic duct.

The chyle contained in the thoracic duct conveys approximately three fourths of the ingested fat from the intestine to the systemic circulation. The fat content of chyle varies from 0.4 to 6.0 g/dL.[247] The large fat molecules absorbed from the intestinal lacteals flow through the cisterna chyli and superiorly through the thoracic duct.[256] Total protein content of thoracic duct lymph is also high. Nutritional complications were a major source of mortality from chylothorax in the era preceding parental nutrition. Other than nutrients, the thoracic duct carries white blood cells, primarily lymphocytes (T cells)—approximately 2,000 to 20,000 cells/mL. Eosinophils are also present in higher proportion than in circulating blood. Loss of lymphocytes through a thoracic duct fistula may lead to an immunocompromised state[255]; in fact, external drainage of the thoracic duct was used as an adjunct to immunosuppression in the early era of organ transplantation. Chyle appears to have a bacteriostatic property, which accounts for the rare occurrence of infection complicating chylothorax.

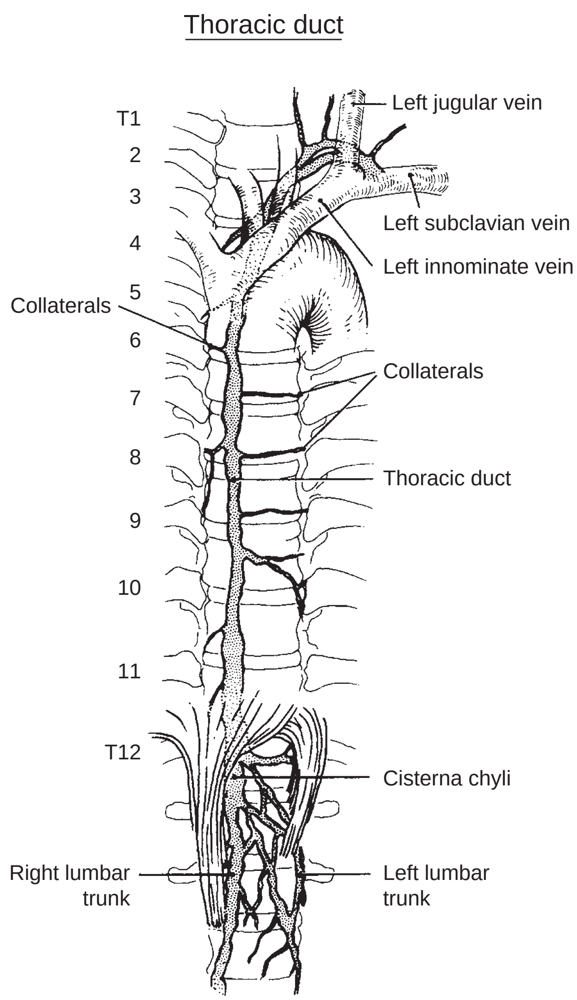



**FIGURE 66-17** Schematic representation of most common anatomic arrangement of the thoracic duct. (From DeMeester R, Lafontaine E: The pleura. In Sabiston DC, Spencer FC (eds): Gibbon's Surgery of the Chest, ed 4. Philadelphia, WB Saunders, 1983. Reprinted with permission.)

## CLINICAL MANIFESTATIONS

Birth trauma was formerly thought to be the cause of many neonatal chylothoraces, but the increasing use of prenatal ultrasonography has changed this perspective. Noniatrogenic chylothorax occurring in young children is usually related to congenital anomalies of the chyliferous vessels, cisterna chyli, or the thoracic duct itself. Most of these chylothoraces result from intrapleural leakage from dilated and thin-walled intercostal, diaphragmatic, or accessory mediastinal lymphatics. When there is lymphatic

overload, these alternate lymphatics may dilate considerably to eventually become transudative lymphatic varices. In other cases, subpleural lymphatics may rupture into the pleural cavity, as in certain cardiac anomalies (e.g., total anomalous pulmonary venous return).

The accumulation of chyle in the pleural space from a thoracic duct leak may occur rapidly and produce pressure on other structures in the chest, causing acute respiratory distress, dyspnea, and cyanosis with tachypnea. In the fetus, a pleural effusion may be secondary to generalized hydrops but a primary lymphatic effusion (idiopathic, secondary to subpleural lymphangiectasia, pulmonary sequestration or associated with syndromes, such as Down, Turner, and Noonan) can cause mediastinal shift and result in hydrops or lead to pulmonary hypoplasia.[244,245] Postnatally, the effects of chylothorax and the prolonged loss of chyle may include malnutrition, hypoproteinemia, fluid and electrolyte imbalance, metabolic acidosis, and immunodeficiency.[257]

In a neonate, symptoms of respiratory embarrassment observed in combination with a pleural effusion strongly suggest chylothorax. The involved side presents characteristic findings of intrapleural fluid with respiratory lag, dullness on percussion, diminished breath sounds, and shift of the mediastinum. Fever is not common. Chest roentgenograms typically show massive fluid effusion in the ipsilateral chest with pulmonary compression and mediastinal shift. Bilateral effusions may also occur. Aspiration of the pleural effusion reveals a clear straw-colored fluid in the fasting patient, which becomes milky after feedings. Analysis of the chyle generally reveals a total fat content of more than 400 mg/dL (or triglyceride level greater than 110 mg/dL) and a protein content of more than 5 g/dL. In a fetus or a fasting neonate, the most useful and simple test is to perform a complete cell count and differential on the fluid; when lymphocytes exceed 80% or 90% of the white blood cells, a lymphatic effusion is confirmed; the differential can be compared with that obtained from the blood count, where lymphocytes rarely represent more than 70% of white blood cells.

Most cases of traumatic chylothorax develop after thoracic operations, in particular, surgery for congenital heart disease.[247] Injury to the thoracic duct in the left chest is also common during secondary thoracotomies for correction of lesions in the descending aorta or esophagus just inferior to the arch. If lymphatic drainage is noted at operation, the proximal and distal ends of the thoracic duct should be ligated.[258] A period of days or weeks may elapse between trauma or surgery and the development of a symptomatic chylothorax.

As chyle accumulates in the pleural space from a thoracic duct leak, progressively more pronounced respiratory symptoms develop as pulmonary compression becomes more severe. Dyspnea, tachypnea, and, eventually, arterial desaturation with cyanosis can develop. Nutritional deficiency is a late manifestation of chyle depletion and occurs when dietary intake is insufficient to replace the thoracic duct fluid loss.

## THERAPY

Whereas small quantities of short-chain fatty acids are absorbed through the portal venous circulation, 80% to 90% of all fat absorbed from the gut is transported by way of the thoracic duct in the form of chylomicrons. Thus feedings restricted to medium- or short-chain triglycerides theoretically result in reduced lymph flow in the thoracic duct and may enhance spontaneous healing of a thoracic duct fistula.[247] However, it has been shown that any enteral feeding, even with clear fluids, significantly increases thoracic duct flow.[259] Therefore for patients who experience large chylous fluid losses, withholding oral feedings and providing total parenteral nutrition (TPN) is preferred as the initial treatment.[249] For patients who are already on mechanical ventilation, the addition of positive end-expiratory pressure can further decrease the lymphatic flow. First described by Ulibarri and colleagues in 1991,[260] somatostatin, or its analog octreotide, has been found useful in treatment of pediatric chylothorax in several reports.[261–264] These agents decrease gastric, pancreatic, and intestinal secretions and have become an important tool in the management of pancreatic and intestinal fistulae. Because of its short half-life, somatostatin requires a continuous intravenous infusion,[265] while the synthetic analog octreotide can be given subcutaneously every 8 hours, starting at a dose of 10 to 20 μg/kg/day.[262] Octreotide infusions may also be used, with dose ranges between 0.5 μg/kg/hour to 50 μg/kg/hour.[266] It has also been used as a rescue after failed surgery,[261] and even as the first-line treatment without diet modification.[266] The response to octreotide has been observed as early as 2 days after the initiation of therapy. In a recent systematic review by Roehr and colleagues,[266] patients given a continuous infusion of octreotide had a median time of treatment of 7 days compared with 17 days for those patients receiving it subcutaneously. If nonoperative management is effective, enteral intake should be reinstituted first with medium-chain triglycerides, followed by a normal diet for age after 2 weeks. Cultures of chylous fluid are rarely positive and providing long-term antibiotics during the full course of chest tube drainage is not considered necessary.

Thoracentesis is used for diagnosis and may be sufficient to relieve spontaneous chylothorax in occasional infants with the dietary measures described. However, chest tube drainage will be necessary for the majority. Further, drainage allows for daily quantification of the chyle leak and promotes pulmonary reexpansion, which may enhance healing. Chylothorax in newborns usually ceases spontaneously,[244] but octreotide has also been shown to be effective.[267] Because identifying the actual site of the fluid leak is difficult, surgery is often deferred for several weeks. Similarly, most cases of traumatic injury to the thoracic duct can be managed successfully by chest tube drainage and replacement of the protein and fat loss.[258] If drainage persists in quantities beyond the tolerance of the infant or child and shows no evidence of diminishing, or if it persists after 2 to 3 weeks without decreasing, ligation of the thoracic duct on the side of the effusion may be necessary. Standard contrast lymphangiography has been abandoned, but lymphoscintigraphy using technetium-99m colloid or other markers may be helpful in identifying the site of the fistula, because it is more technically feasible in children and does not expose them to radiation.[268,269]

Occasionally, the chylous fluid may enter the pericardial sac and cause chylopericardial tamponade, in which case pericardiocentesis should provide immediate relief.[258] Although bilateral spontaneous chylothorax in newborns is uncommon, it can produce fatal respiratory distress unless recognized and drained promptly.

When chylothorax remains resistant despite prolonged chest tube drainage and TPN, thoracotomy or thoracoscopy

on the ipsilateral side may be necessary. The decision whether to continue with conservative management or to undertake surgical intervention should be based on the nature of the underlying disorder, the duration of the leak, the daily volume of fluid drainage, and the severity of nutritional and/or immunologic depletion. Several authors have suggested that patients in whom the chest tube drains more than 100 mL/year of age/day or 10 mL/kg/day, without slowing down after 10 to 20 days, should undergo surgery.[258,259,269a] Although this is not an absolute indication, one should remember that the loss of lymphocytes can lead to overwhelming bacterial or fungal infections, and explains the majority of deaths from chylothorax in the current era.[270] Others suggest that persistent drainage for more than 3 weeks despite maximal medical therapy is another indication for surgical intervention. The identification of the thoracic duct and the fistula may be facilitated by the ingestion of 60 mL of table cream 30 minutes before surgery. When identified, the draining lymphatic vessel should be suture ligated above and below the leak with reinforcement by a pleural or intercostal muscle flap. Meticulous dissection of the thoracic duct with isolation of the fistula is often not feasible. When a leak cannot be identified with certainty, or when multiple leaks originate from the mediastinum, ligation of all the tissues surrounding the aorta at the level of the hiatus provides the best results. Pleurectomy is another option. Fibrin glue and argon-beam coagulation have also been used as an adjunct for ill-defined areas of leakage or incompletely resected lymphangiomas.[271]

Thoracoscopy has been used in larger patients to avoid thoracotomy.[272,273] The leak, if visualized, can be ligated, clipped, or sealed with fibrin glue. If the leak cannot be identified, pleurodesis can be accomplished with talc or other sclerotic agents under direct vision through the thoracoscope, but this technique should be used cautiously in infancy because of the potential consequences on lung and chest wall growth. If there is concomitant chylopericardium, a pericardial window can be fashioned. Because thoracoscopy is less invasive, some surgeons advocate early intervention, as early as 5 to 10 days. This approach may be indicated in conditions where the failure rate of conservative management is higher, such as superior vena cava thrombosis or problems associated with increased central venous pressures.

Pleuroperitoneal shunts have been used for refractory chylothorax in which a leak has not been identified and in those patients who do not respond to initial nonoperative management, especially if they have a higher operative risk.[274–276] This approach has been used with occasional success both in patients with congenital anomalies of the thoracic duct or lymphangiomas, or in patients who have persistent drainage after cardiac surgery.[277] A Denver double-valve shunt system is the type most commonly used; it may be implanted under local anesthesia and allows the patient or parent to pump the valve to achieve decompression of the pleural fluid into the abdominal cavity, where it is reabsorbed. An externalized pumping chamber was found to be superior in smaller babies.[275] It may offer the least invasive treatment for neonates or infants who develop a refractory chylothorax after surgery for complex cardiac malformations, as long as right heart pressures are less than 25 cm $H_2O$.

Overall, most patients with chylothorax can be cured with conservative measures, nutritional support, and occasional operative intervention. Patients with diffuse lymphatic malformations remain a challenge.

# Mediastinal Infections

## ACUTE MEDIASTINITIS

Acute mediastinitis occurs as a result of contamination and/or soilage of the mediastinal space secondary to the trauma or perforation of either the trachea or esophagus. Furthermore, mediastinitis can develop from a descending retropharyngeal or cervical abscess[278] or the rupture of suppurative mediastinal lymph nodes. Infection within the mediastinum can disseminate quickly, because this space contains no anatomic barriers to the spread of infection. Clinically, acute mediastinitis is heralded by high fever, chest pain, dyspnea, cyanosis, marked tachycardia as well as a significant leukocytosis. In neonates, the signs and symptoms may be subtle, including lethargy, fever, apnea, temperature instability, and leukopenia. The management of mediastinitis includes hemodynamic support, the prompt administration of intravenous antibiotics, and mediastinal drainage. Drainage may be particularly important in the context of a mediastinal abscess or continued leak/contamination from a perforated esophagus. Cervical, transthoracic, retropleural, or anterior approaches may be used to facilitate drainage, depending upon the location of abscess or leakage.

## INFECTIONS AFTER MEDIAN STERNOTOMY

Although the incidence of sternal wound and mediastinal infections after median sternotomy is low, these infections can have devastating implications on the postoperative course of these patients. In adult series, sternal wound infections have been shown to occur in up to 20% of patients, while the incidence of mediastinitis ranges from 1% to 3%.[279] Barker and colleagues noted an incidence of mediastinitis of 0.3% when reviewing 30,078 pediatric cardiac cases from 48 centers.[280] The most common infective organisms included *Staphylococcus* species, including methicillin-resistant organisms.[281] Other organisms included *Pseudomonas* and *Candida*. Deep sternal infections may also be caused by gram-negative enteric flora and anaerobes. Several risk factors for the development of poststernotomy mediastinitis in children have been identified and include young age, perioperative interventions, the use of parenteral nutrition, preoperative admission greater than 1 day, and long aortic cross-clamp and cardiopulmonary bypass times.[280,282,283]

The early identification and aggressive treatment of mediastinal infections is required. Clinically, patients present with local erythema, fluctuance, purulent drainage, sternal instability, fever, and leukocytosis. These features may only be apparent after the first postoperative week and even after discharge. CT and gallium scanning has been useful in identifying deep sternal infections as well as sternal osteomyelitis. Controversy still exists regarding the optimal modalities that may be used to treat mediastinitis in sternotomy patients. Classic management strategies, including local debridement, wound packing, and antibiotic irrigation have evolved to the liberal use of omental and rotational muscle flaps.[284] More recently, vacuum-assisted closure has been used with success in the pediatric population.[285,286] The results with all techniques have generally been good, but the early identification of infection and an aggressive approach to the management of sternal

wound complications is strongly recommended to prevent morbidity and mortality.[280]

## GRANULOMATOUS AND SCLEROSING MEDIASTINITIS

This invasive and compressive process results from the enlargement of mediastinal and hilar lymph nodes secondary to tuberculosis or fungal diseases such as histoplasmosis.[287] These lesions may mimic anterior mediastinal masses, and thus malignancy must also be included as part of the differential diagnosis.[288] In a classical review of 180 cases, Schowengerdt demonstrated that ongoing enlargement or suppuration of these lymph nodes would lead to the compression, invasion, and fibrosis of mediastinal structures.[289] The superior vena cava syndrome and pulmonary vascular and bronchial obstruction have also been ascribed to this process. CT and MRI are often used to fully delineate the extent of disease, but biopsy is often required to confirm the diagnosis.[290,291] The course of this disease is generally mild and may be treated medically. Symptoms related to the compression of mediastinal structures usually subside with control of the underlying tubercular or fungal infection.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 67

# Esophagoscopy and Diagnostic Techniques

Harry Lindahl

## History

The first person to perform esophagoscopy was Kussmaul in 1870, who used a hollow rigid tube with a reflected light for illumination. Mikulicz introduced the gastroscope in 1881. His instrument consisted of several small optical units coupled with articulated joints. In 1897 Kelling invented a flexible metal esophagoscope, and in 1898 he invented a gastroscope, the lower third of which could be flexed to 45 degrees. In 1936 Schindler worked with Wolf, an optical physicist and manufacturer, to design a semiflexible gastroscope that incorporated a rubber finger at the working end.[1]

Hirschowirz and colleagues developed flexible fiberglass gastroscopes in 1958 for endoscopy of the upper gastrointestinal tract. For more than 15 years flexible video endoscopes have surpassed the use of fiber endoscopes. Video endoscopes are at present available from major manufacturers in sizes enabling upper gastrointestinal endoscopy even in small premature infants.[1]

## Evaluation of Esophageal Anatomy and Function

### RADIOGRAPHIC IMAGING

Esophageal length, diameter, and contour are best evaluated by radiographic imaging with intraluminal barium. Whenever esophageal perforation is suspected, however, a water-soluble iso-osmotic contrast medium such as Omnipaque (Amersham Health, Buckinghamshire, UK) is preferred over barium. The possibility of leaking barium into the mediastinum through an esophageal perforation should be avoided.

### ESOPHAGOSCOPY

Direct visualization and mucosal biopsy through an esophagoscope are the only accurate means of evaluating mucosal changes in the esophagus. The normal esophageal mucosa has a flat, shiny surface with a pattern of fine vessels.

With slight air insufflation, the point of diaphragmatic closure is easily identified at the lower end, and the junction between the flat esophageal and the more reddish and velvety gastric mucosa is normally below the level of diaphragmatic closure. This gastroesophageal junction forms an undulating circle that is usually easy to identify.

Mucosal biopsy is necessary to evaluate submucosal and subtle surface changes. Advanced degrees of inflammation are obvious by visual inspection, and the deeper changes can often be inferred.

### PRESSURE MONITORING

Intraluminal recording of esophageal pressure dynamics is currently the most accurate way to evaluate esophageal motility. Observation of peristalsis during radiographic contrast study is less reproducible and certainly less quantifiable, although information about coordination of peristalsis, esophageal spasm, and completely uncoordinated esophageal contractions is easily seen radiographically. Early pressure recording techniques used intraesophageal balloons. Water-perfused catheters with multiple pressure recording ports that are pulled back through the length of the esophagus during the recording have supplanted this technique. More sophisticated techniques incorporate circular ports to calculate radial pressure vectors during the pullback.[2]

Manometry has been applied much less widely in infants and children. Patient cooperation is required for a good study. Infants and children seldom tolerate esophageal-pressure recording probes without sedation, and the sedation itself may alter interpretation of the study results. Moreover, the motility disorders identified by manometry in adults are much less common in children. Finally, data from motility studies in children, with the exception of the few with achalasia, have seldom produced significant changes in surgical management.[3]

### EIGHTEEN TO 24-HOUR pH MONITORING

Reflux of gastric acid into the esophagus is thought to be the most common cause of esophageal inflammation, and evaluation of the presence and severity of reflux esophagitis is the

most common reason for esophagoscopy in children. In situations in which some quantification of reflux is important, the 24-hour esophageal pH study is suggested.[4] Several authors have described the technical aspects of performing esophageal pH studies in children.[5,6] Normal values for infants and children have also been documented.[7,8] However, pH monitoring only measures acid reflux, and one study has demonstrated a 30% discordance between two consecutive 24-hour pH measurements.[9]

### MULTICHANNEL ESOPHAGEAL IMPEDANCE MONITORING

Multichannel esophageal impedance monitoring is able to detect nonacid reflux. It increases diagnostic accuracy when combined with pH monitoring, compared with pH monitoring alone. In modern equipment, the impedance transducers are built into the same catheter as the pH transducers, and both measurements can be performed simultaneously.[10]

### BILE REFLUX DETECTION

Reflux of bile into the esophagus has been implicated as a synergistic factor in the development of reflux esophagitis,[11] and convincing data suggest that bile, combined with acid reflux, is the critical factor in the development of Barrett mucosal dysplasia in the lower esophagus.[12]

Esophageal bile detection is difficult and uncertain with pH monitoring because the mixture of acid with alkaline bile is often recorded in the neutral range by pH monitoring. The presence of bile and acid reflux is thus masked unless bile acids are measured directly from gastric aspirates. Technical improvements have allowed the direct and continuous measurement of bile in the esophagus independent of pH.[13]

## Indications and Applications of Esophagoscopy

Esophagoscopy is performed for either diagnostic or therapeutic indications. For diagnostic endoscopy the flexible adequate-size video endoscope is superior. For some therapeutic procedures the open-tube rigid esophagoscope still has its advantages. Esophagoscopy is an unpleasant procedure and should preferably be performed in children under general anesthesia with endotracheal intubation. Therapeutic esophagoscopy should always be performed under general anesthesia with endotracheal intubation. In units where safe anesthesia cannot be guaranteed, therapeutic esophagoscopy should not be done.

### DIAGNOSTIC EVALUATION

#### Suspicion of Gastroesophageal Reflux

The suspicion of gastroesophageal reflux is probably the most common cause of diagnostic esophagoscopy in children. The examination is performed to evaluate the presence or severity of reflux esophagitis. However, inflammation of the esophageal mucosa and submucosa is not reliably diagnosed endoscopically in the absence of mucosal ulcerations or erosions. The macroscopic appearance of the esophageal mucosa is difficult to interpret, and therefore the diagnosis and grading of esophagitis depend on mucosal biopsy.[14]

The more advanced degrees of esophagitis are easily recognized. Normally, a fine vascular pattern can be seen just below the mucosal surface (Fig. 67-1). Loss of this superficial vascular pattern, along with erythema, erosions, ulcerations, or nodularity, is associated with varying degrees of biopsy-proven esophagitis. Additional signs of esophagitis include mucosal bleeding on contact, white plaques of various configurations surrounded by an erythematous border, and a cobblestone appearance of the mucosa. Narrowing of the lumen caused by stricture is a complication of long-standing untreated severe esophagitis.

Esophagoscopy for suspicion of gastroesophageal reflux must include gastroduodenoscopy to evaluate possible gastric mucosal lesions and to rule out pyloric or duodenal obstruction. Retrograde view of the cardia gives information of hiatal hernia and the angle of His, which are factors affecting gastroesophageal reflux (Fig. 67-2).

#### Dysphagia

Dysphagia may be associated with esophagitis, esophageal foreign body, congenital or acquired stricture, congenital malformations, benign tumors, structural disease of the esophageal wall, or functional disorders. Endoscopic evaluation gives information of anatomic defects (e.g., stricture) but nothing of functional disorders.

#### Corrosive Injury

Indications for esophagoscopy after caustic ingestion are controversial in children. Also, the preferred timing of endoscopy varies. I prefer to perform esophagoscopy within 24 hours of ingestion of caustic liquid in symptomatic patients. Patients without symptoms, that is, those who can swallow without difficulties and pain, do not need endoscopy.

Flexible endoscopes instead of rigid instruments should be used to assess the severity of mucosal injury. In severe cases,

FIGURE 67-1 Normal cardia of a 7-month-old boy as seen from above. Normal esophageal mucosa: A pattern of fine vessels can be seen under the mucosa.

FIGURE 67-2 Cardia of a 10-year-old boy with portal vein thrombosis 3 months after a successful Rex shunt. The His angle is normal. Submucous veins are still prominent after 10 years of portal vein hypertension.

even in older children, the use of a neonatal video endoscope of 5 to 6 mm in diameter can be useful because it causes less trauma than a larger instrument. Endoscopy should always be performed with complete visual control. The instrument must never be pushed blindly forward because this may cause esophageal perforation, especially in cases with full-thickness injury. Circumferential damage is not a contraindication of passing the endoscope, provided it can be done in full visual control. In circular damage it is advisable to pass a silicone tube to the stomach because this enables enteral feeding and also assists dilatation of the following stricture.

The diagnosis of full-thickness injury cannot be made with endoscopy. It is a clinical diagnosis, in which the knowledge of the nature and amount of ingested material, the patient's clinical condition, and the laboratory parameters are more important than endoscopic findings.

### Upper Gastrointestinal Bleeding

Upper gastrointestinal bleeding is rare in children. Severe esophagitis, variceal bleeding, Mallory-Weiss lesion, and bleeding from mucosal lesions of the stomach or duodenum are the causes. The best way to diagnose these is with upper gastrointestinal endoscopy.

Endoscopy for acute upper gastrointestinal hemorrhage is technically demanding and should only be performed by an experienced endoscopist. Bleeding from esophageal varices can be anticipated from a palpable large spleen. The cause can be either portal vein thrombosis or liver cirrhosis, which in children is usually caused by biliary atresia. If variceal bleeding is suspected, preparation for acute sclerotherapy or ligation of the varices should be made.

Severe esophagitis causing significant blood loss is rare but easily detected in endoscopy. Mallory-Weiss tear occurs even in neonates and is best seen in inversion endoscopy from the stomach side of the cardia. Often Mallory-Weiss tear appears as a local hematoma in the cardia, which hides the actual tear.

### Trauma

The most common cause of esophageal disruption is iatrogenic. Most often it results from esophageal dilatation or other therapeutic instrumentation.[15] If the dilatation is performed under endoscopic control, the perforation is usually easily diagnosed in the same endoscopy.

Compression injuries to the chest more commonly disrupt the airway, but an air-filled esophagus may also be disrupted. In these cases esophagography with water-soluble contrast medium provides the best approach to diagnosis of esophageal perforation if the patient is conscious and a swallowing study can be performed. Flexible esophagoscopy can identify major tears or complete disruption, but a small crack in the wall after stricture dilatation may not be apparent without contrast radiographic imaging.

### Anatomic Abnormalities

Anatomic abnormalities of the esophagus such as congenital stenoses, cartilaginous rings in the esophageal wall, leiomyomas, and cystic duplications are usually first identified radiographically and then confirmed endoscopically. The unyielding, ribbed esophageal wall associated with cartilaginous rings is striking to view with a flexible scope. Tracheoesophageal fistulas are best seen with tracheoscopy and are usually invisible from the esophageal side. Figure 67-3, *A* shows the anastomotic stricture of a patient after esophageal atresia repair.

### Follow-up of Congenital Upper Gastrointestinal Anomalies

Operated congenital upper gastrointestinal anomalies such as esophageal atresia carry a significant risk of late esophageal pathology. Complications of gastroesophageal reflux, esophagitis, gastric metaplasia, and even adenocarcinoma have been reported. Many of the patients are asymptomatic, even when harboring gastric metaplasia. To prevent irreversible premalignant mucosal changes, routine follow-up esophagoscopy of corrected upper gastrointestinal anomalies should be considered.[16–19]

## THERAPEUTIC APPLICATIONS

### Stricture Dilatation

Balloon dilatation with or without a guidewire and with either fluoroscopic or endoscopic control is the treatment of choice for strictures. Localized anastomotic strictures are commonly managed with balloon dilatation either under fluoroscopic control or using direct endoscopic visualization. Long or tight and tortuous strictures require the passage of a guidewire either endoscopically or under fluoroscopic control.

### Balloon Dilatation with Fluoroscopic Control

The dilating balloon is passed over a small slippery wire, which is positioned through the esophagus and into the stomach by fluoroscopy. In simple, not too tight strictures a soft-tipped balloon without a guidewire can also be used. The balloon is then filled with water-soluble contrast agent so that the waistlike indentation on the balloon can be visualized under fluoroscopy as the stricture is stretched.

This technique offers the advantage of direct visualization during dilatation, and the radial forces generated during

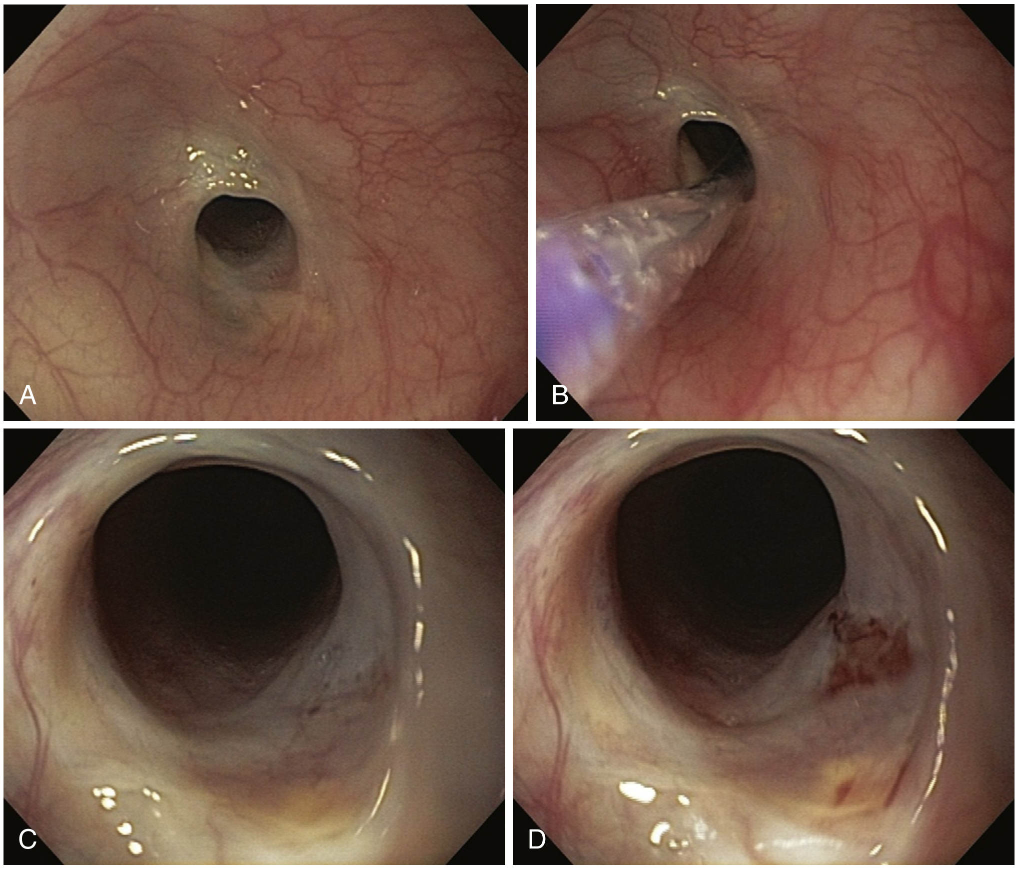



**FIGURE 67-3** Anastomotic stricture of a 5-month-old infant with esophageal atresia undergoing a fourth session of endoscopic balloon dilatation. **A,** The 5.6-mm flexible gastroscope could not pass beyond the stricture. **B,** The balloon dilator is passed over a guidewire through the instrument channel. **C,** Minimal petechiae after 8-mm dilatation. **D,** Superficial mucosal tear after 9-mm balloon dilation; the 5.6-mm endoscope could now pass. Note the yellowish plaque at 5 o'clock, caused by residual triamcinolone injected at the previous dilatation session. (Courtesy Dominique Lévesque, MD, pediatric gastroenterologist, McGill University Health Center.) *(See Expert Consult site for color version.)*

dilatation are thought to be safer and more localized than the shearing forces generated by longitudinal tapered dilators.[20]

### Balloon Dilatation with Direct Endoscopic Visualization

The balloon dilatator can also be introduced with endoscopic control. Small-caliber dilatators fit the endoscope working channel and can be directly pushed into the stricture. Larger caliber balloons usually require separate passing of the guidewire through the working channel of the scope into the stricture. After that, the endoscope is removed and the dilator is passed over the wire as in fluoroscopic-assisted dilatation. In simple strictures a soft-tipped dilatator without a guidewire can be passed blindly through the stricture. The dilatation procedure can be inspected if the endoscope is passed beside the dilator to have a direct view of the stricture. The advantage of this method is that the extent of inflammation can be assessed and biopsy can be done, balloon dilatation can be monitored through the flexible esophagoscope, and any cracking or mucosal damage can be evaluated after the balloon is withdrawn (Fig. 67-3).

### Dilatation with a Guidewire Left in Situ

In difficult strictures requiring multiple dilatations this technique is helpful. A gastrostomy is required. A guidewire is passed from the upper esophagus through the flexible scope into the stomach. Through the gastrostomy opening, the intragastric portion is then recovered with an endoscope or blindly using a nerve hook. With the use of this guidewire, balloon dilators can be pushed to the stricture either from below or from above. After dilatation the guidewire can be replaced with a nasogastric tube, which is tied to the gastrostomy tube. In the next session the nasogastric tube can be used to lead the guidewire from the nose through the gastrostomy, making repeated dilatations easy and safe. An alternative method is to leave a long No. 2 silk in situ between dilatations. The silk is initially tied to the guidewire at the gastrostomy site and withdrawn out through the mouth. A feeding tube is placed through the nose, and its tip is retrieved from the mouth using a laryngoscope and Magill forceps. The silk is tied to the feeding tube, which is used to guide it out of a nostril. The long silk is then taped loosely behind the ear, down the neck and chest, and tied to its gastric end, thereby making a long continuous loop. The gastrostomy tube is replaced, and the silk remains in situ with minimal discomfort and cannot be dislodged accidentally. At the next session, the silk is cut, the gastric end can be tied into a loop to assist retrograde dilatations with Tucker bougies or used to pull a guidewire through the stricture to allow balloon dilatation.

### Gastrostomy Tube or Button Insertion

Flexible gastroscopy is an essential component of the retrograde "pull" technique for percutaneous placement of gastrostomy tubes or gastrostomy buttons.[21] Details of the technique

are well described in the supply kits for these devices. The final position of the flared end in the stomach should be monitored by direct inspection through the gastroscope to make certain the gastric wall is pulled up snugly against the parietal peritoneum. Previous upper-abdominal surgery is a relative contraindication to endoscopic placement of gastrostomy devices because adhesions may prevent apposition of the stomach with the anterior abdominal wall when it is filled with air through the gastroscope. Tubes have actually traversed the colon or small bowel en route to the stomach because of adhesions limiting direct contact between the stomach and parietal peritoneum.[22]

I prefer to make the first tube or button change with endoscopic control to ensure that the end of the tube or button is inside the stomach. Separation of the stomach and anterior peritoneum has happened, resulting in feeding into the peritoneal cavity, which is a potentially lethal complication.[23] Because endoscopy requires general anesthesia in infants and toddlers, others prefer to delay the first tube change for at least 4 months and ensure correct placement at the time of tube change by confirming return of gastric contents before feedings are resumed.

### Foreign-Body Removal

Effective management of esophageal foreign bodies requires familiarity and skill in the use of several different extraction techniques.

Many esophageal foreign bodies that are not sharp and not embedded in the mucosa as a result of long-term residence can be removed with a contrast medium-filled balloon catheter under fluoroscopic control. Coins account for most of these problems. In a series of 415 cases, 76% were caused by coins; the catheter removal technique was successful in 91%.[24] Foreign bodies that are stuck at the cricopharyngeus sphincter can often be removed using a long-bladed laryngoscope and Magill forceps.[25] There are also other minimally invasive techniques for removing coins.[26] Esophagoscopic removal is considered necessary when the foreign body seems embedded, has sharp points or corners, or is soft and fragmented and may present a risk for aspiration during balloon extraction. However, depending on the experience of the unit, esophagoscopic removal using an open channeled esophagoscope can also be used in simple coin removals.

Impacted organic matter is best removed using the rigid open-channel esophagoscope. Large extraction forceps can be introduced through the rigid scope, allowing several passes of the instrument without removal of the scope sheath with each fragment. Large, sharp objects are also more safely manipulated into the protecting sheath of the open-channel scope. This prevents contact with the esophageal wall during extraction of the foreign body and scope as a unit. In all extractions with the open-channel esophagoscope, the use of optical forceps from a rigid pediatric bronchoscope can be helpful because it provides a magnified view.

Small, embedded objects can sometimes be handled with the flexible scope and the appropriate alligator, cup, or tack forceps or various grasping wires or baskets. Open safety pins pointing upward are easily extracted by grasping the spring loop with a tack forceps, passing the entire pin into the stomach for a turnaround, and then extracting the pin with the open point downward as it is removed as a unit with the scope.

### Injection Sclerotherapy

Injection sclerotherapy for esophageal varices is done with the flexible esophagoscope and the flexible needle injector. We have used intravariceal injection with 3% sodium tetradecyl sulfate. The injection volume has been 0.5 to 1 mL per varicose vein, with a total volume of 2 to 3 mL per session. In about 30 years of experience I have seen one complication associated with the sclerosant. There has been no need for blood transfusions because of the injection. There are few randomized controlled trials of the effect of injection sclerotherapy. In a series of 100 children with varices, randomized for prophylactic sclerotherapy, good elimination of varices was achieved in the sclerotherapy group, but this did not improve survival.[27]

Endoscopic variceal ligation with small rubber bands has been developed as an alternative to endoscopic variceal sclerosis, and the effectiveness and complication rates for the two techniques were similar in a randomized trial in adults.[28] Ligation of varices is gaining popularity also in the pediatric age group.[29,30]

### Intraluminal Laser Therapy

Intraluminal laser ablation of esophageal lesions is used in adults.[31] Flexible optical fibers for cutting, sclerosing, or ablating lesions are available for passage through the instrument channel of a fiberscope, but clinical applications in infants and children are currently so rare that most pediatric surgical units do not maintain the necessary equipment or expertise. Endoscopic laser applications can be a possibility for future development.

# Instrumentation

## FLEXIBLE ENDOSCOPY

The flexible video end-viewing gastroscope is the instrument of choice for esophagoscopy in infants and children. Excellent videoscopes in pediatric sizes are now available from several major manufacturers of endoscopic equipment. For routine diagnostic and therapeutic applications, the endoscopes are equipped with at least one channel for suction and instrumentation. The gastroscopes also include positive-pressure insufflation and the capability to flush and clear the lens without withdrawal of the scope. Four-way directional controls for the viewing tip are standard. The video picture can be recorded, and both paper and digital pictures can be obtained with modern equipment. The external diameter of most pediatric videoscopes with these features ranges from 6 to 9 mm.

Guidelines for sterilization of fiberscopes are now fairly rigid. Automatic sterilizers are available from the manufacturers to assist cleaning and decontamination. Accessory instrumentation for passage through the long working channel of the scopes includes various biopsy and foreign-body forceps, graspers, baskets, flexible injectors, magnets, diathermy loops, and laser optical fibers.

## RIGID, OPEN-CHANNEL ENDOSCOPY

The use of a rigid, open-channel instrument in the esophagus still has a few specific indications. The large working channel of the open, rigid scope allows safe removal of large, sharp,

pointed foreign bodies because the sharp edges of the foreign body can be partially drawn into the scope for protection during withdrawal. Large organic foreign bodies are also more easily removed.

## Patient Preparation, Sedation, and Pain Control

Even flexible esophagoscopy is an unpleasant procedure in children. Therefore I prefer general anesthesia with airway intubation. It provides a more controlled and, in many cases, a safer environment for esophagoscopy than sedation. General anesthesia is mandatory in children for the management of foreign-body extraction, stricture dilatation, injection sclerotherapy, or variceal ligation. It might seem that general anesthesia would involve increased risk, but the reverse is usually the case. Intravenous sedation and a forceful endoscopy in an agitated or uncooperative child without airway control can invite disaster from respiratory depression and cardiovascular collapse. Aspiration is also an increased risk in procedures such as injection sclerotherapy or evaluation of acute bleeding, in which irrigation fluid or blood may reflux back into an unprotected airway. General anesthesia minimizes psychic trauma, increases the safety of the manipulation, and makes endoscopy much easier for the surgeon.

I have no personal experience with esophagoscopy under conscious sedation without general anesthesia. However, some clinicians still use this approach. The usual agents for intravenous sedation include a short-acting central nervous system depressant of the benzodiazepine class combined with a narcotic. Dosages are titrated to effect, within predetermined limits. A topical anesthetic spray of the hypopharynx is helpful before introduction of the endoscope. Continuous monitoring of heart rate and oxygen saturation and intermittent monitoring of blood pressure during the procedure and for an appropriate interval afterward are mandatory. Oxygen, bag, mask, and an intravenous narcotic antagonist should be available at the bedside during the procedure. Esophagoscopy under sedation should only be performed in facilities that are equipped for resuscitation and cardiorespiratory support.

Some cooperative teenagers can undergo endoscopy without sedation, using only topical anesthetic spray of the pharynx. In selected patients this provides better cooperation than endoscopy under sedation.

## Technical Considerations

Before use, all equipment must be checked to ensure that it is in working order. The lens focus on the flexible endoscope must also be adjusted before insertion, and the video endoscope must be white balanced. The control element of the flexible scope is held in the notch between thumb and fingers of the left hand. The upward-pointing second and third fingers operate the suction and insufflation controls, and the fourth and fifth fingers stabilize the endoscope. The left thumb is used to control the north and south movement, and the right hand stabilizes the distal scope at the mouth, controls insertion, and provides lateral movement by rotational changes. Fine adjustments in east and west orientation of the tip can be made with the lateral adjustment control wheel. To protect the flexible scope, a mouthpiece is inserted between the anterior teeth.

### FLEXIBLE ENDOSCOPY WITH GENERAL ANESTHESIA

Flexible videoendoscopy under general anesthesia is simpler in every respect except for insertion of the scope through the cricopharyngeus. The anesthetized patient does not swallow, either voluntarily or involuntarily. The patient is placed supine, and the endoscopist stands at the head of the patient on the right side of the table. Alternatively, the patient may be placed in lateral decubitus. The endoscope is passed under visual control behind the larynx to the esophagus. If the larynx lies tightly against the back wall of the hypopharynx, the anesthetist can be asked to gently lift the angle of the jaw. A small jet of air can be introduced from the level of the pyriform sinus to open the cricopharyngeus. The tip of the endoscope is then advanced under vision into the orifice that comes into view. Once through the cricopharyngeus, the endoscope is adjusted so that the lumen of the esophagus is straight ahead. Observations are made during advancement and withdrawal of the endoscope. In evaluation of esophagitis or caustic injury, it is important to record the condition of the mucosa before the endoscope has passed over it.

### FLEXIBLE ENDOSCOPY WITH INTRAVENOUS SEDATION OR WITHOUT SEDATION

Intravenous sedation rarely provides total cooperation of the child undergoing endoscopy. The examination must be comprehensive but brief. This requires gentleness, precise manipulation, no unnecessary or false maneuvers, and considerable experience on the part of the endoscopist.

In larger patients without sedation and those only lightly sedated, the introduction of the endoscope is best performed when the patient is sitting. After the introduction of the endoscope through the cricopharyngeus sphincter, the patient is usually placed in the left lateral position with the head slightly extended. A smooth introduction greatly reduces fear of and resistance to the procedure. Many endoscopists prefer blind intubation of the cricopharyngeus, accomplished by pressing the tongue forward with the index and middle fingers of the left hand while the right hand advances the scope during a swallow. However, introduction under direct vision through the scope offers more precise placement. A swallow can sometimes be initiated in a child by squirting water into the pharynx through the lens-washing system.

### RIGID ENDOSCOPY WITH OPEN-CHANNEL VIEWING

Rigid endoscopy in a child should always involve general intubation anesthesia to minimize trauma and the risk for perforation. The supine position, with the neck forward and the head extended, is satisfactory for most examinations.

The open-channel rigid esophagoscope is introduced under direct vision into the back of the pharynx with the lip of the beveled portion anterior. This lip is then used to elevate the larynx gently and to open the cricopharyngeus.

The patient's mandible and maxilla are supported with the endoscopist's left hand; the thumb and index finger hold the esophagoscope as if holding a billiard cue. The right hand manipulates the scope as it would a cue. The scope should not be advanced unless the lumen of the pharynx or esophagus is clearly visualized straight ahead. If the cricopharyngeus does not open up with elevation by the lip of the scope against the posterior portion of the larynx, the esophageal lumen should be identified by passage of a soft suction catheter through the scope as a lumen finder. The scope is then passed over this catheter into the upper esophagus under direct vision. A view of the esophageal lumen should be maintained as the scope is advanced through the gastroesophageal junction into the stomach. More detailed inspection can then be obtained as the scope is withdrawn.

## Complications

Esophagoscopy involves risks associated with sedation or anesthesia in addition to the risk for direct instrumental perforation of the pharynx, esophagus, or stomach. Drug reactions, tracheobronchial aspiration, and hypoxic brain damage are all potential and almost entirely preventable complications associated with upper gastrointestinal endoscopy. Instrumental perforation should be entirely preventable; unfortunately, this complication still occurs.

Before flexible endoscopy, the more common sites for perforation involved the posterior pharynx in children who were restrained and were examined while awake. Esophagoscopy associated with the dilatation of tight strictures still carries a greater risk for perforation than does a purely diagnostic procedure, but reliable figures on the incidence of instrumental perforation are not available for children. Even for simple diagnosis, the risk for perforation in the presence of severe esophagitis, whether from reflux or from caustic ingestion, must be greater than that in a patient with an esophagus that is not inflamed. The predominant use of flexible instruments in recent years is a major factor in reducing and almost eliminating instrumental perforation in children. As long as a magnified view of the esophageal lumen is maintained throughout the procedure, perforation remains unlikely.

During the 16-year period 1994-2009 there were 9155 esophagoscopies or upper gastrointestinal endoscopies performed by pediatric surgeons in Helsinki University Children's Hospital. Esophageal dilatation was performed in 539 sessions. There were two perforations, both related to dilatation of anastomotic stricture after esophageal atresia repair. Both required surgical correction. There was no mortality associated with the perforations, but in one patient several operations were required to preserve the patient's esophagus. During the same period, esophagoscopy and extraction of esophageal foreign body were performed on 174 patients and sclerotherapy of esophageal varices was performed in 197 sessions. There was one esophageal perforation after injection sclerotherapy. There were no esophageal perforations or other complications needing treatment associated with diagnostic esophagoscopies.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 68

# Esophageal Rupture and Perforation

Thomas R. Weber

Boerhaave's classic postmortem description of a patient, Baron Wassenaer, is recognized to be the first report of a case of spontaneous, postemetic esophageal rupture. In 1952 Fryfogle[1] reported spontaneous rupture of the esophagus in a neonate that was successfully repaired surgically. In 1968 Eklof and colleagues[2] first emphasized iatrogenic perforation of the cervical esophagus by catheters in the newborn. These authors suggested that nonsurgical therapy might be appropriate in many cases.

## Classification and Incidence

Abnormal communications of the esophagus into the pleural cavity, mediastinum, or peritoneal cavity are classified as either esophageal rupture or esophageal perforation. Esophageal rupture is also labeled spontaneous perforation, Boerhaave syndrome, effort perforation, and esophageal apoplexy. In these conditions, no instrumentation or intubation of the esophagus has occurred, thus implying that an intrinsic anatomic abnormality or dysfunction is present within the esophageal wall.[3–8] A recently recognized clinical entity, eosinophilic esophagitis has been the cause of spontaneous esophageal rupture in several studies.[9,10] Esophageal perforation, on the other hand, is produced by the introduction of an object into esophageal lumen. These lesions are traumatic and, in many cases, result from diagnostic or therapeutic manipulation.[11–17] Esophageal perforation can also be caused by the ingestion of foreign bodies[18,19] and caustic substances or by blunt and penetrating trauma.[20,21] Spontaneous rupture of the esophagus in neonates and infants is rare and accounts for 4% of all reported cases.[14] In contrast, iatrogenic perforation of the upper part of the esophagus by attempted passage of a nasogastric or endotracheal tube is not uncommon and probably occurs more frequently than reported in the literature.[15,22] In addition, esophageal perforation complicates 0.4% to 1.2% of esophagoscopy and esophageal dilatation procedures,[16] thus making this an important risk factor in the use of these procedures.

## Clinical Findings

Neonatal spontaneous esophageal rupture occurs most frequently in full-term babies after uncomplicated pregnancies. Respiratory distress with cyanosis may be present immediately or may be delayed for several hours.[6] Respiratory distress is caused by a pneumothorax that is usually located on the right side and in which tension may rapidly develop. The predilection for neonatal Boerhaave syndrome to be manifested as a right-sided pneumothorax, as opposed to the left pleural cavity (most commonly found in adults), is explained by the close adherence of the aorta to the left side of the esophagus in infants. This adherence provides additional support to that side of the esophagus.[23] If the perforation remains undiagnosed, respiratory distress usually worsens with the first feeding. Vomiting, coughing, choking episodes, and mild hematemesis have been observed in several cases. Thoracentesis or tube thoracostomy may reveal serosanguineous or grossly bloody pleural fluid or the contents of previous feedings.[24] Formula promptly appears if feeding is again attempted.[25]

In contrast, esophageal perforation is most frequently associated with difficulty passing a nasogastric tube in premature infants (63% of cases).[15,22] At least 75% of patients with perforation have difficulty swallowing, characterized by drooling, increased oral secretions, and feeding problems. In older children, severe pleuritic or substernal pain is the hallmark of perforation as a result of esophagoscopy or dilatation procedures. Fever, often high, and rapid, toxic progression to shock may occur in any age group but seems to be more prevalent in older children after mediastinal or free pleural perforation. Subcutaneous emphysema, often present in adults with esophageal perforation, is rare in infants unless massive pneumomediastinum occurs.

## Diagnosis

The early diagnosis of esophageal rupture or perforation is indicated by clinical findings and confirmed by radiographic procedures. The typical appearance of spontaneous rupture or extensive traumatic injury of the esophagus includes

right-sided tension pneumothorax or hydropneumothorax on an upright radiograph or pneumomediastinum (Fig. 68-1). Plain chest radiographs in children with iatrogenic catheter perforation frequently show malpositioning of a nasogastric tube, usually into the right pleural cavity (Fig. 68-2). In other cases the perforating tube may be located in a submucosal or mediastinal position and cause the formation of a "pseudodiverticulum" of the esophagus. In cases of perforation caused by esophageal dilatation, pneumomediastinum or left chest pneumothorax is frequently present (Fig. 68-3). A lateral chest radiograph may be necessary to demonstrate mediastinal air early. Premature infants with iatrogenic perforation are often initially suspected of having esophageal atresia, but the nasogastric or orogastric tube returns blood-tinged secretions and the tube is displaced away from the midline on chest radiograph.[15,26]

In all cases of esophageal perforation, esophagography is necessary to establish the diagnosis, localize the perforation, and direct therapy.[13] If perforation of the upper part of the esophagus by a nasogastric tube is suspected, the tube can be left in place and a small amount of water-soluble contrast injected through it. If the tube has been removed or if the perforation was suspected after other procedures such as laryngoscopy or endotracheal intubation, esophagography may be performed by carefully injecting soluble contrast material into the upper part of the esophagus through a small tube. Patients with suspected lower esophageal perforation secondary to instrumentation frequently show extravasation of contrast into the pleural space or mediastinum during esophagography. If questions remain after water-soluble contrast esophagography or if anatomic definition is inadequate, the study may be repeated with barium. However, most surgeons consider extravasation of barium into the thorax undesirable. Computed tomography with oral contrast offers another option.[13] Esophagoscopy offers no diagnostic advantages and may actually enlarge the perforation, thus making subsequent repair more difficult.

Patients with swallowed foreign bodies stuck in the esophagus present with drooling, dysphagia, and occasionally chest pain. If the foreign body is not visible on plain radiographs, contrast esophagography is indicated. Prompt removal of all esophageal foreign bodies, especially button batteries, is essential before perforation occurs; these patients are at risk for mediastinitis, but most importantly, aorto-esophageal fistula formation.[32]

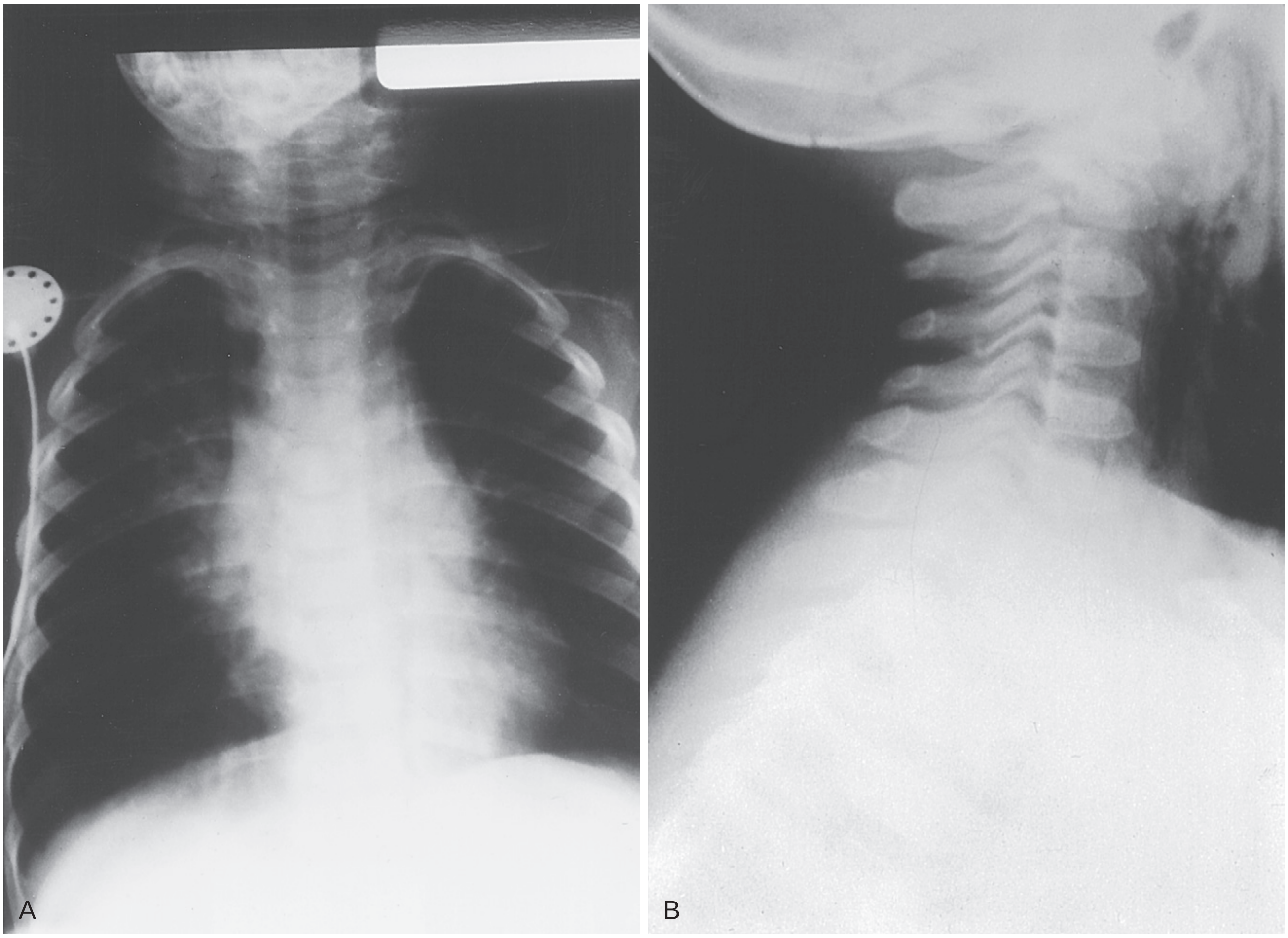



**FIGURE 68-1** **A,** The esophagus was injured when the patient fell while holding a pencil in his mouth. Note the large amount of mediastinal air on each side of the mediastinum. **B,** Air is also seen in the soft tissues of the neck, indicative of injury to the cervical esophagus. Lateral views are particularly helpful for demonstration of air in the neck or chest.

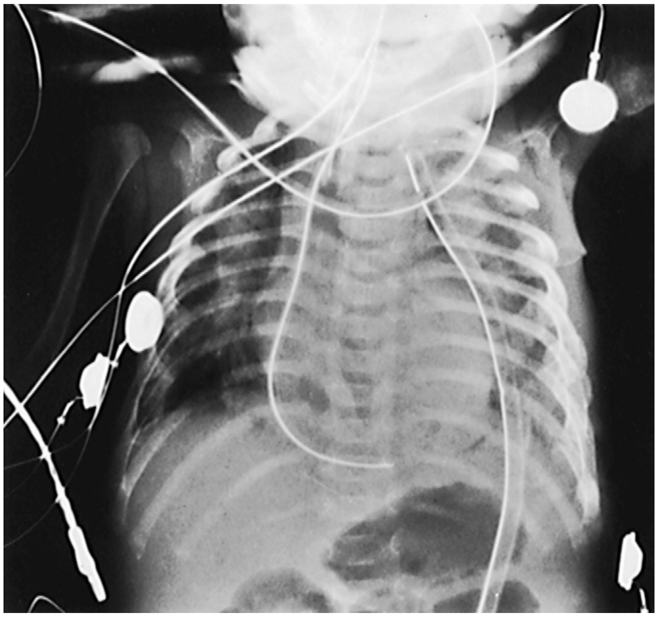


**FIGURE 68-2** Upper esophageal perforation in a premature infant. Note the position of the presumed nasogastric tube in the right side of the chest. The tube was withdrawn, and nonsurgical therapy resulted in complete recovery.

**FIGURE 68-3** This collection of gas in the mediastinum behind the heart occurred 1 hour after an esophageal dilatation procedure. Subsequent esophagography demonstrated distal esophageal perforation.

## Treatment

The decision about the most appropriate therapy after the diagnosis of esophageal rupture and perforation depends on the site of perforation, whether the perforation is free or contained, the interval from injury to diagnosis, and the systemic response to injury.[27,28] Spontaneous rupture not related to instrumentation usually results in substantial contamination of the mediastinum or pleural space and elicits a severe systemic response of fever, sepsis, pleuritic pain, and occasionally shock. This group of patients needs rapid preoperative preparation including intravenous fluids, antibiotics, thoracentesis, tube thoracostomy (if pneumothorax or hydrothorax is present), and cessation of oral intake. Esophagography should be performed to define the location of the perforation, followed immediately by thoracotomy, irrigation of the pleural space, and suture or patch of the laceration if it can be found. Flexible esophagoscopy during the exploration may help localize the perforation. A flap of pleura or pericardium can also be used to reinforce the esophageal closure.[29] Placement of several large chest tubes completes the procedure.

Free pleural perforation secondary to instrumentation should be managed in an identical manner. Because most of these latter perforations are diagnosed early, little reaction is generally present and primary repair of the perforation or esophageal resection with primary anastomosis is usually possible. The pleural cavity should be generously irrigated and drained with one or two chest tubes. Ancillary procedures such as diverting or tube cervical esophagostomy, esophageal division without anastomosis, gastrostomy, and feeding jejunostomy also have a role in selected cases. These techniques, however, have not been used extensively in children. In addition, stenting techniques have been used in a few cases[30] and may be useful in highly selected children. A more conservative approach, without chest tube drainage or surgical repair, has been advocated,[31] but most authors would not recommend such an approach.

In general, upper esophageal perforation caused by attempted placement of a nasogastric or endotracheal tube can be managed nonsurgically.[15,31] These perforations may affect the mediastinum only or may extend into the pleural space (usually the right side). The perforating tube should be withdrawn, a new nasogastric tube should be inserted under fluoroscopic guidance, and contrast should be injected to confirm placement of the tube in the stomach. A chest tube is placed if a pneumothorax is present. The infant is given broad-spectrum antibiotics and intravenous nutrition, and oral feedings are withheld. After several days, feedings through the nasogastric tube may be started. If gastroesophageal reflux occurs, the nasogastric tube can be advanced through the pylorus so that duodenal feedings can be initiated. If sepsis occurs at any time during nonsurgical therapy, formation of a mediastinal abscess must be suspected. Computed tomography of the chest should be done and surgical drainage performed.

Regardless of the therapy used, contrast esophagography is performed 7 to 10 days after injury or repair. If the perforation has completely healed, the chest or mediastinal tubes are removed and oral feeding is resumed. If extravasation is observed, continued conservative therapy generally results in healing within another 7 to 10 days. Persistent esophageal fistula is unusual and suggests distal esophageal or gastric outlet obstruction.

## Results of Therapy

Because of the rarity of spontaneous esophageal rupture in childhood, it is difficult to assess the success of surgical repair. In a review of 13 patients, Aaronson and colleagues[3] noted that 3 patients treated by chest tube drainage alone

died, whereas 7 of 8 infants treated by thoracotomy and suture repair survived. Late stricture was occasionally encountered at the site of the repair; this complication responded well to dilatation. Other case reports have emphasized the uniform mortality with nonsurgical therapy[12] and the satisfying results obtained with thoracotomy and repair.[4] Similar results can be expected with aggressive surgical repair of esophageal perforation secondary to instrumentation and foreign bodies in which the perforation has entered the pleural space.

Many authors advocate the use of nonsurgical therapy for upper esophageal perforations.[2,7,14,15,17,28,31] When selectively applied to infants with no systemic symptoms of perforation, the survival rate approaches 100%. This is usually the case when the perforation is submucosal or well contained in the mediastinum, the so-called pseudodiverticulum of the esophagus. When free perforation into a pleural space has occurred, conservative therapy can still be used if the baby does not appear ill; however, vital signs must be monitored closely and thoracotomy performed if signs of sepsis appear.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 69

# Congenital Anomalies of the Esophagus

Carroll M. Harmon and Arnold G. Coran

## Historical Background

The documented history of esophageal atresia (EA) began in the year 1670 with William Durston's published description of "A Narrative of a Monstrous Birth in Plymouth . . ." in which he described a blind-ending upper esophageal pouch in the right infant of a set of female thoracopagus-conjoined twins.[1] The first description of EA with the typical form of tracheoesophageal fistula (EA-TEF) appeared in 1697 in the fifth edition of Thomas Gibson's *The Anatomy of Humane Bodies Epitomized*.[2] Isolated case reports of EA-TEF surfaced in the nineteenth century including one by Thomas Hill in 1840. Published in the *Boston Medical and Surgical Journal*, this report described an infant with EA-TEF and associated rectal agenesis with a rectourinary fistula.[3] In 1861 Harald Hirschsprung of Copenhagen reported 4 cases of his own and collected 10 cases of EA and distal TEF from the literature.[4] In 1880 Morell Mackenzie,[5] another prominent medical figure of the nineteenth century, reported 57 cases of congenital esophageal malformation with 37 examples of tracheal or bronchial esophageal fistula. He also discussed at length the embryology, pathology, and clinical diagnosis of these anomalies including a description of associated anomalies such as spina bifida, horseshoe kidney, and imperforate anus. E. D. Plass, an instructor in obstetrics at Johns Hopkins University, surveyed the literature in 1919 and reported 136 verifiable cases of EA including 92 with an associated TEF.[6] By 1931, Rosenthal had collected data on 255 patients[7] and indicated, as Ladd emphasized in 1944,[8] "that atresia of the esophagus is a much more frequent anomaly than it has usually been considered to be."

The history of the surgical treatment of EA-TEF is remarkable and covers 270 years linking the first description and the first survivor. In 1869 Timothy Holmes of London, the author of *Surgical Management of Children's Diseases,* was the first to suggest the possibility of a surgical esophageal anastomosis in infants who had EA without TEF; however, he added that "the attempt ought not, I think, be made."[9] The first operative attempt to correct EA without TEF was undertaken in 1888 by Charles Steele of London, and his report titled "Case of Deficient Oesophagus" was published in the journal *Lancet.*[10] Using chloroform anesthesia, Steele performed a gastrotomy and attempted to perforate through what he suspected was an esophageal membrane by pushing a long, slender steel probe through the gastrotomy site and up the lower esophageal pouch into the upper pouch, which was simultaneously pushed down with a bougie.[10] The attempt was unsuccessful, and at autopsy, the esophagus was found "to terminate above and below in blind rounded ends an inch and a half apart and there was no cord or connection between the parts."[10] In 1899 Hoffman performed the first permanent gastrostomy in an infant with EA.[11] In 1913 H. M. Richter of Chicago described two infants with EA-TEF, on whom he operated without success. Despite his results, Richter was optimistic about the eventual success of primary esophageal repair and stated, "I do not wish to dismiss the idea of immediate union of the two ends of the esophagus."[12] In the same year, however, J. Brennemann, a prominent pediatrician working in Chicago with Richter, referred to the fatal outcome of the two infants who underwent attempted surgical repair by stating that "the physician who, after making his diagnosis of congenital atresia of the esophagus, decides to let his little patient die undisturbed can amply justify his course."[13] Despite Richter's optimism, primary esophageal anastomosis and a myriad of other operations continued to fail; the mortality rate for EA remained 100%. In a 1925 textbook of thoracic surgery, Lilienthal proposed that operative treatment might include "division of the tracheoesophageal fistula and 'anastomosis' of the atretic esophagus by tying each pouch over a rubber tube stent."[14] In 1936 Mims Gage and Alton Oschner of New Orleans, Louisiana, proposed early transabdominal ligation of the cardiac end of the esophagus and gastrostomy with early secondary cervical esophagostomy.[15] Like Richter, they noted that "the ideal operation would be the separation of the esophagus from the trachea and an end-to-end anastomosis of the upper to the lower segment."[15] They added that "such an extensive intrathoracic procedure is not justified in a newborn infant, however, and the operation would always be finished as a postmortem procedure."

The first published report of a case of EA-TEF treated by fistula ligation and primary esophageal anastomosis was presented by Robert Shaw of Dallas, Texas. Shaw performed the operation on September 25, 1938, and reported it in

December 1939.[16] In his report, Shaw referred to a personal communication from Paul C. Samson, who had also performed "an operation very similar" to the one Shaw described. Samson's patient died 12 hours after the operation. Shaw's patient died on the twelfth day after the operation, apparently as the result of a transfusion reaction. Shaw performed the operation without knowing that Thomas Lanman in Boston had performed four primary esophageal repairs for EA-TEF between January 2, 1936, and July 27, 1937, with the use of an extrapleural approach.[17] In November 1940, Lanman reported these 4 cases, 1 other case of primary esophageal repair, and 27 other cases of EA seen at Boston Children's Hospital between September 1929 and February 1940. All 32 patients in the series died. However, Lanman's fourth patient treated by fistula ligation and primary esophageal repair lived 9 days and at autopsy was found to have died of overhydration, not of mediastinitis or pneumonia. Remarkably, Lanman summarized: "In spite of the fatal outcome in all the 30 operative cases, it is felt that considerable progress along rational lines is being made. The successful operative treatment of a patient with this anomaly is only a question of time."

According to Humphreys and Ferrer,[18] the first survivor of congenital atresia of the esophagus without TEF was a boy born in New York on February 16, 1935. The patient was initially treated by gastrostomy alone, with his "first thoracic operation performed in 1946."[18] The first survivors of EA-TEF were a boy born in Minnesota on November 26, 1939, and a girl born in Massachusetts on the next day. After many failures in caring for infants with EA, N. Logan Leven of the University of Minnesota performed a gastrostomy on a 2500-g male infant with EA-TEF on November 29, 1939. After a failed attempt to close the TEF bronchoscopically with a coagulation electrode, extrapleural ligation of the fistula was accomplished on January 5, 1940. When the infant's weight increased to 4630 g, a cervical esophagostomy was performed on March 27, 1940. The child thrived, and Leven proposed that a subsequent antethoracic esophagoplasty be performed to reestablish continuity of the gastrointestinal tract. In Boston, William Ladd performed a gastrostomy on a female infant on November 28, 1939; on March 15, 1940, he closed the TEF and created a cervical esophagostomy. Although both these patients survived, esophagogastric continuity was achieved only after multiple operations to create an anterior skin-lined thoracic neoesophagus.

In 1935 Cameron Haight began caring for infants with EA at the University of Michigan (Fig. 69-1). His first patient was managed unsuccessfully by a gastrostomy alone. In 1939 Haight attempted his first primary repair of EA, which was unsuccessful. Four subsequent attempts at primary repair also failed; however, on March 15, 1941, the first successful primary repair of EA was performed. The infant girl was an "unusually robust" 12-day-old child who weighed 8 lb, 4 oz and had been transferred from Marquette, Mich., to the care of the Chief of Pediatrics, Harry A. Towsley. Dr. Towsley, in turn, consulted Dr. Haight.

The first successful primary repair of EA-TEF was accomplished by using a left extrapleural approach with fistula ligation and a single-layered esophageal anastomosis. An anastomotic leak developed on postoperative day 6 but was managed without surgical intervention. A stricture later developed at the anastomosis and responded to a single dilation. Drs. Haight and Towsley presented this case in February 1942 at the Central Surgical Association meeting in Chicago and published the report in 1943.[19] In 1943 Haight revised his procedure to a right extrapleural approach because he believed that better exposure of the distal segment was obtained from this side. He also moved to a modified two-layer, "telescoping" anastomosis in the hope of decreasing the risk for leak. Between 1939 and 1969, Dr. Haight cared for more than 284 infants with EA and reported a 52% overall survival rate.[20] After Haight's first success in 1941, reports of survival after direct esophageal anastomosis were sporadic; however, many centers soon began reporting series of successes. One interesting report by Longmire in 1947 describes four consecutive successful primary esophageal anastomoses including success in a baby who weighed only 1.4 kg.[21]

**FIGURE 69-1** Cameron Haight, MD, performed the first successful primary repair of esophageal atresia with a tracheoesophageal fistula on March 15, 1941.

The history of attempts to classify EA reflects differences in the terminology, but not in the types of anomalies encountered. In 1929 E. C. Vogt, a radiologist, recognized and classified the types of anomalies.[22] With the success of operative repair, many other anatomic classifications were proposed. In 1944 Ladd introduced a numeric form of classification that consisted of five types with Roman numerals.[8] Gross altered the numeric system in 1953 to an alphabetic system that is still frequently used (Fig. 69-2).[23] In 1962 Swenson returned to a numeric classification and used Arabic numbers instead of Roman numerals.[24] In a 1976 report, Kluth published a complete listing of all described variations of EA including 10 separate classes and additional subclasses.[25]

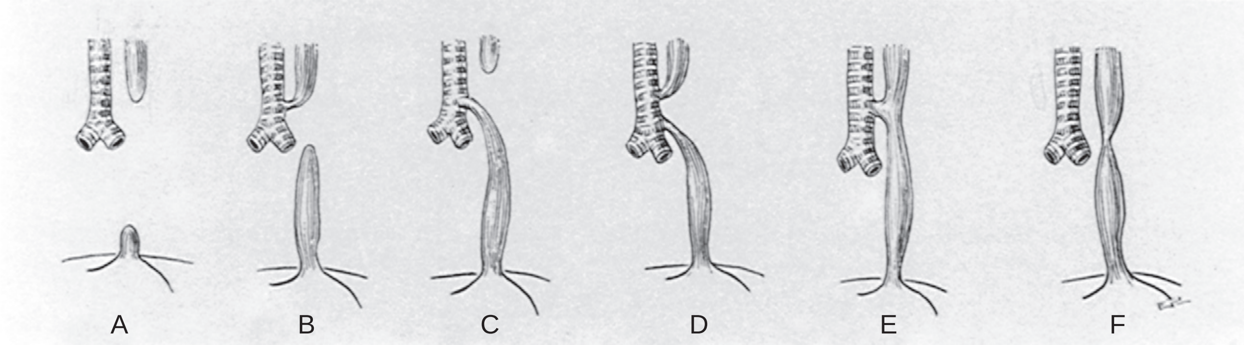



**FIGURE 69-2** Gross classification of anatomic patterns of esophageal atresia. **A,** Esophageal atresia without a tracheoesophageal fistula. This malformation is almost invariably associated with a "long gap." **B,** Atresia with a proximal tracheoesophageal fistula. It is an uncommon anomaly; the abdomen is airless, and the diagnosis may be missed unless contrast studies or endoscopy is performed. **C,** Esophageal atresia with a distal tracheoesophageal fistula, the most frequently encountered form of esophageal anomaly. **D,** Atresia with a double (proximal and distal) fistula. Though rare, this form is found more often than originally thought. **E,** Tracheoesophageal fistula without atresia (H-type fistula). This anomaly may be missed in the newborn period because swallowing is possible. It is associated with recurrent cough, pneumonia, and abdominal distention. **F,** Esophageal stenosis. (From Gross RE: Surgery of Infancy and Childhood. Philadelphia, WB Saunders, 1953.)

**TABLE 69-1**
**Waterston Risk Groups and Current Survival Figures**

| *Group* | *Survival (%)* | *Waterston Classification* |
|---|---|---|
| A | 100 | Birth weight > 2500 g and otherwise healthy |
| B | 85 | Birth weight 2000-2500 g and well or higher weight with moderate associated anomalies (noncardiac anomalies plus patent ductus arteriosus, ventricular septal defect, and atrial septal defect) |
| C | 65 | Birth weight < 2000 g or higher with severe associated cardiac anomalies |

In addition to anatomic classifications, in 1962 D. J. Waterston, R. E. Bonham Carter, and Eoin Aberdeen of the Hospital for Sick Children in London developed a classification system related to risk factors in infants with EA.[26] This risk stratification allowed comparison of case outcomes over time and between hospitals. The use of this classification scheme—which was based on birth weight, the presence of pneumonia, and associated congenital anomalies—allowed the identification of factors that predicted survival and guided operative treatment. This approach to the classification of EA anomalies has been an important contribution to the care of these infants (Table 69-1).

# Embryology

The pathogenesis of congenital EA malformations remains unknown. Although many theories have been offered to explain the etiology of EA, EA-TEF, and TEF, no single unifying theory has been proposed that addresses all the variations seen with this group of anomalies. The pathogenesis is heterogeneous and multifactorial and involves multiple genes and complex gene-environment interactions. In addition, about half of the cases of EA are isolated and the other half are associated with other malformations.

A clear understanding of the pathogenesis of the EA malformation is hindered by the fact that normal foregut embryology is still obscure. Wilhelm His, Sr., the founder of human embryology, was the first to describe normal development of the respiratory system.[27] He believed that division of the foregut was the result of fusion of invaginating lateral longitudinal ridges that created a septum dividing the foregut into a dorsal digestive tract and a ventral respiratory system. Formation of the so-called tracheoesophageal septum is believed to begin caudally and end cranially.[7] Many of the theories concerning the pathogenesis of EA malformations have been based on this description.[7,28–31] However, several investigators have more recently found little evidence to support this theory of normal foregut separation and development. Reinvestigation of human specimens from the Collection of Embryos at the Carnegie Institute suggests that ingrowth of lateral foregut wall ridges and cranial development of a tracheoesophageal septum do not occur in the human embryo.[32,33] In addition, Kluth and colleagues[34] studied staged chicken embryos via scanning electron microscopy in an attempt to clarify normal foregut development. In this model they also found no evidence of lateral ridges or an epithelial tracheoesophageal septum.

A summary of the major theories to explain the embryopathology of the foregut has recently been presented by Kluth and Fiegel.[35] Theories of foregut occlusion and failure of recanalization of the intestinal lumen have been historically prominent in discussions regarding the pathogenesis of intestinal atresias including EA.[36,37]

Overwhelming proliferation of esophageal epithelium may play a role in the development of rare membranous EA, but it falls short as a comprehensive theory of typical EA malformations.[25] Another theory has been put forth by Cozzi and colleagues[38,39] and others[40] in which it is suggested that EA is a component of cephalic neurocristopathy. The observation that there is a clear association of neural crest-implicated cardiovascular anomalies (aortic arch, conotruncal and membranous ventricular septal defects), as well as thymic, thyroid, parathyroid, and facial malformations with EA, as seen with the DiGeorge syndrome, suggests that the pathogenesis of EA may be related to defective pharyngeal arch development.

An animal model in which Adriamycin is used as a teratogen and results in embryos with a variety of malformations, including EA and TEF, has been described and promises to provide new insight into EA pathogenesis.[41,42] Merei and Hutson have used this model to develop a theory suggesting that the primitive foregut develops into the trachea, with

subsequent EA-TEF anomalies.[43] Gittes has recently used this model, as well as human TEF tissue samples, to investigate the molecular mechanisms that may play a role in the pathogenesis of EA-TEF. He has proposed that the distal fistula tract and esophagus are of respiratory origin and that defects in lung morphogenesis account for this aspect of the EA-TEF anomaly.[44,45] Insight into the pathogenesis of EA-TEF will also come from a clearer understanding of the genetics of this and associated conditions. More than 50% of cases of EA-TEF are associated with other anomalies, and up to 10% of cases are found in specific chromosomal or single-gene disorders. Chromosomal abnormalities associated with EA-TEF include DiGeorge syndrome; full trisomies (21, 13, and 18); Opitz syndrome; and 13q, 17q, and 16q24 deletions.[46] Single-gene mutation examples include MYCN (Feingold syndrome), CHD7 (CHARGE syndrome), SOX2 (AEG syndrome), GL13 (Pallister-Hall syndrome), MID1 (Opitz G syndrome), and FANCA (Fanconia anemia).[46]

Recent insights into the genetics involved in VACTERL association will also provide new information into the etiology of EA-TEF. For example, the VACTERL-hydrocephalus association is related to mutations in the following genes: FANCC, FANCD1 and 2, FACCG, FANCB, and PTEN. In addition to VACTERL associations, EA-TEF is also increased in several other conditions such as Goldenhar syndrome and Martinez-Frias syndrome.[47] The development of rat and mouse models of EA has recently allowed the parallel study of both normal and abnormal embryogenesis. As discussed earlier, controversies persist, but the fundamental morphogenetic process appears to be a rearrangement of the proximal foregut into separate respiratory (ventral) and gastrointestinal (dorsal) tubes. This process depends on the precise temporal and spatial pattern of expression of a number of foregut patterning genes. Disturbance of this pattern disrupts foregut separation and underlies the development of tracheoesophageal malformations.[48] Specific murine models of EA-TEF have suggested a number of important genes related to pathogenesis that are mostly in developmental pathways including vitamin A effectors, retinoic acid receptors α and β (Rarα and Rarβ), sonic hedgehog pathway effectors (Shh, Gli2, Gli3, Foxf1), and other homeobox containing transcription factors (Hoxc4, Ttf-1, Pcsk5).[46] As suggested by the Adriamycin rat model for EA-TEF, environmental teratogens have also been implicated in the pathogenesis of EA ± TEF. EA has occurred in infants born to mothers with prolonged exposure to contraceptive pills[49] and exposure to progesterone and estrogen during a pregnancy.[50] In addition, EA has been reported in some infants of hyperthyroid[51] and diabetic mothers and after intrauterine exposure to thalidomide and diethylstibestrol.[46,52]

Many studies have described transverse and vertical familial cases of all varieties of EA. Empirical risk figures based on the literature to date give a 0.5% to 2% recurrent risk in siblings of one affected child; the risk increases to 20% if more than one sibling is affected.[53] The empiric risk for a child born to an affected parent is 3% to 4%.[53]

## Epidemiology

The reported incidence of EA, with or without TEF (EA ± TEF), is 1:3500 live-born infants; however, it varies geographically from 1 in 2440 births in Finland[54] to 1 in 4500 births in the United States[55] and Australia.[56] According to data from the California Birth Defects Monitoring Program database, from 1983 to 1988 the total prevalence of EA, EA-TEF, and TEF alone was reported to be 2.82 per 10,000 live births and stillbirths.[57] In Europe, the prevalence rate of EA-TEF during 1980 to 1988 was 2.86 per 10,000 births, although this rate appeared to be decreasing over time.[58] In this European study, 62% of infants with EA-TEF were male, whereas the California database found that male-to-female ratios varied considerably between types of EA-TEF defects, with ratios of 2.29 for TEF alone, 1.44 for EA-TEF, and 1.33 for EA alone.[57] Mothers of white ethnicity have a higher (>60%) prevalence of EA-TEF and TEF than nonwhite populations do.[59,60] An increased risk for EA-TEF with a first pregnancy,[59] as well as increasing maternal age,[57] have been reported (twofold increased risk for women 35 to 40 years old and threefold increase for those older than age 40).[60]

The rate of multiple births is high for each type of EA-TEF anomaly (TEF, 3.7%; EA-TEF, 4.9%; and EA alone, 8.8% in a control population).[57] In addition, EA, along with other congenital anomalies, is significantly increased in the offspring of in vitro fertilization patients (OR 3.65:CI 2/53-5/26).[61]

## Associated Anomalies

The early disturbance in organogenesis that results in EA deformities, whatever the exact cause, also affects other organ systems. Other congenital anomalies are frequently associated with EA, and the associated anomaly often significantly alters treatment and affects survival. Numerous reports have suggested that between 50% and 70% of infants with EA have at least one associated congenital malformation. The anomalies are most common in cases of EA without TEF and are least common in cases of H-type TEF.[62] About half of all EA-TEF-associated malformations can be classified as part of a recognizable malformation syndrome such as chromosomal, VACTERL, CHARGE, Fanconi anemia, Opitz G, and Goldenhar. The other 50% of patients with associated malformations are considered as “nonsyndromic” with multiple congenital anomalies. In a recent study from France, these malformations included cardiovascular system (24%), urogenital (21%), digestive (21%), musculoskeletal (14%), and central nervous system (7%).[63]

Considering reports over recent decades, cardiovascular anomalies occur most frequently (11% to 49%),[39,64–66] followed by genitourinary (24%),[67] gastrointestinal (24%),[68] and musculoskeletal (13% to 22%)[69,70] anomalies (Table 69-2). Associated neurologic anomalies include neural tube defects (2.3%), hydrocephalus (5.2%), holoprosencephaly (2.3%), and anophthalmia or microphthalmos (3.7%).[59] Other reported associated anomalies include choanal atresia (5.2%), facial cleft (7.2%), abdominal wall defects (4.3%), and diaphragmatic hernia (2.9%).[59] One report suggests that the incidence of certain associated anomalies may vary by world region in that genitourinary anomalies were found in 26% of a European cohort of patients versus only 4% of an Asian cohort.[70]

Complex cardiac deformities may account for most of the deaths associated with EA malformations. The relative risk for death in infants with EA malformations associated with a major cardiac anomaly is reported to be 3.47 (95% confidence interval [CI], 1.51 to 7.96).[65,71] In a series of 153 patients

**TABLE 69-2**

**Incidence of Associated Anomalies**

| | |
|---|---|
| Cardiovascular | ≈24% |
| Genitourinary | ≈21% |
| Gastrointestinal | ≈21% |
| Musculoskeletal | ≈14% |
| Central nervous system | ≈7% |
| VACTERL association | ≈20% |
| Overall incidence | 50%-70% |

VACTERL, vertebral, anorectal, cardiac, tracheoesophageal, renal, and limb abnormalities.

with EA, Leonard and colleagues reported that the 1-year survival rate of infants with congenital heart disease (CHD) was 67% versus 95% in those without CHD.[66] Interestingly, these authors concluded that although CHD is associated with higher mortality in EA patients, it is not the direct cause of it.[66] The most common single defects identified are ventricular septal defects (19%), which have reportedly been associated with a mortality rate of 16%[72] and atrial septal defects (20%).[64] Other common cardiac anomalies include the tetralogy of Fallot (5%) and patent ductus arteriosus (13%).[64] Coarctation of the aorta is found in 1% to 4% of infants with EA malformations.[64,73] A descending aorta on the right side has been reported in 4% of infants with EA.[64]

Some gastrointestinal anomalies associated with EA ± TEF are anorectal malformations (14%),[64] duodenal atresia (2%),[64] intestinal malrotation (4%),[74] ileal atresia, annular pancreas, and pyloric stenosis. Genitourinary defects are varied and include renal agenesis or hypoplasia (1%), hypospadias, undescended testes, cystic renal disease, hydronephrosis, vesicoureteral reflux, ureteric duplication, ureteropelvic and vesicoureteral obstruction, urachal anomalies, ambiguous genitalia, and cloacal or bladder exstrophy.[59,75,76] Typical musculoskeletal malformations include limb (15%) and vertebral (17%) anomalies.[64]

In 1973 Quan and Smith,[77] suggested a broad spectrum of associated malformations that are associated with EA malformations. They arranged this association into the acronym VATER: vertebral defects, anal atresia, tracheoesophageal fistula, esophageal atresia, and renal defects. Opitz defined the term "association" as the idiopathic occurrence of multiple congenital anomalies during blastogenesis.[47,77] Affected patients have no family history of malformations, no recognizable teratogen is involved, and no chromosomal abnormality is observed. As the phenotype expanded, the acronym was changed to the VACTERL association, which includes vertebral, anorectal, cardiac, tracheoesophageal, renal, and limb abnormalities.[78] The incidence of the VACTERL association in the EA population is approximately 20%.[65] Infants specifically with EA-TEF frequently have VACTERL anomalies (vertebral, 17%; anal, 12%; cardiac, 20%; renal, 16%; limb, 10%), as well as other midline defects (cleft lip and palate, 2%; sacral dysgenesis, 2%; urogenital anomalies, 5%).[79] The "renal" category should include urinary tract anomalies such as megalourethra, urethral duplication, urethral valves, stricture, and hypospadias. It generally requires a minimum of three of the components to qualify as a "VACTERL patient." Recently, the VACTERL-H association has been described and includes congenital hydrocephalus.[77,80] Infants with EA malformations in association with the VACTERL association have a high mortality rate. Iuchtman and colleagues[81] analyzed the results of 46 infants born with EA and features of the VACTERL association among 313 patients with EA, TEF, or both. In this series, the mortality rate was 24%. Cardiovascular anomalies were present in 78% of the patients and were the principal cause of death. More recently, Driver and colleagues reported that the relative risk for mortality in patients with VACTERL associations was 2.54 (95% CI, 1.14 to 4.86).[65]

EA malformations are increasingly being described in association with other polytopic defects, sequences, syndromes, and associations. Some of these include Down syndrome[82]; the DiGeorge sequence[83]; the polysplenia sequence; Holt-Oram syndrome; the Pierre Robin sequence[53]; Feingold syndrome[84]; Fanconi syndrome; Townes-Brock syndrome; Bartsocas-Papas syndrome; McKusick-Kaufman syndrome[53,85–88]; the CHARGE association (coloboma, heart defects, atresia choanae, developmental retardation, genital hypoplasia, and ear deformities)[89]; and the schisis association (omphalocele, neural tube defects, cleft lip and palate, and genital hypoplasia).[90,91] Other serious or lethal associations are trisomy 18, cerebral hypoplasia, and Potter syndrome (bilateral renal agenesis).[92,93] In addition to the well-described anomalies associated with EA just discussed, many recent reports describe significant malformations and associated conditions that may become more frequently recognized. Unilateral pulmonary agenesis associated with EA-TEF is a rare condition; only 37 cases have been reported since 1874.[94–100] Usui and colleagues[101] reported a 47% incidence of tracheobronchial abnormalities such as ectopic or absent right upper lobe bronchus, congenital bronchial stenosis, and a decreased ratio of circumferential cartilaginous trachea to membranous trachea; these abnormalities could play an important role in such respiratory conditions as tracheomalacia and atelectasis associated with EA.[101] Several reports also suggest that EA is associated with abnormalities in vagal innervation that are not related to surgical intervention to repair the esophageal defect.[102]

# Classification

As noted previously, numerous classification schemes have been proposed and used to describe EA. The most useful and practical classifications are perhaps simple anatomic descriptions, even though many institutions and surgeons still use the Gross classification. It is important to note, however, that there are many variations to the fairly straightforward anatomic descriptions given in Table 69-3. In 1976 Kluth[35] summarized and diagrammed many of the anatomic variants not described by the many classifications mentioned here.

Waterston's 1962 classification was based on risk factors (see Table 69-1). The classification affected the surgical care of these patients. Infants in the "good"-risk category (A) were

**TABLE 69-3**

**Incidence of Various Esophageal Atresia—Tracheoesophageal Fistula Anomalies**

| | |
|---|---|
| 1. Esophageal atresia with a distal tracheoesophageal fistula | 84% |
| 2. Esophageal atresia without tracheoesophageal fistula | 6% |
| 3. Tracheoesophageal fistula without esophageal atresia | 4% |
| 4. Esophageal atresia with a fistula to both pouches | 1% |
| 5. Esophageal atresia with a proximal tracheoesophageal fistula | 5% |

typically treated with immediate operative repair, "moderate"-risk infants (B) were managed by delayed repair, and "high"-risk infants (C) were treated by staged repair. Although the Waterston classification continues to be used to compare results between centers, many investigators have questioned its current validity in caring for these infants.[68,92,103] With modern neonatal critical care, more low-birth-weight infants are surviving and more treatment options are available for infants with multiple congenital anomalies. As a result, a search for modern criteria for survival has produced several new classification schemes.

In 1989 Randolph and colleagues[103] suggested a refinement in Waterston's classification on the basis of the overall physiologic status of an infant with EA. According to a report analyzing the results of 39 infants managed with the physiologic status criteria, more and earlier primary repairs were performed, and excellent survival rates were maintained in stable infants in comparison with 87 infants previously managed by using Waterston's criteria.[103]

Other prognostic classifications have recently been proposed. Poenaru and colleagues[92] suggested that only severe pulmonary dysfunction with a preoperative mechanical ventilation requirement and severe associated anomalies were independent predictors of survival. Brown and Tam[104] suggested that the measured length of the esophageal gap provides a method of classification to predict morbidity and long-term outcome. In a review of 357 cases of EA treated at the Hospital for Sick Children on Great Ormond Street in London between 1980 and 1992, Spitz and colleagues[93] found that birth weight and major cardiac disease were important predictors of survival. The Spitz classification is currently the system most commonly used.[65,105] Okamoto and colleagues[196] recently suggested a revision to the Spitz classification (Table 69-4). Using receiver-operating characteristic (ROC) curves to compare the two classifications, these authors suggest that as overall care of low- and very-low-birth-weight infants improves, the cardiac anomalies play an increasing role in assessing prognosis for infants with EA.

## Diagnosis and Clinical Findings

Unlike many congenital pediatric surgical problems, prenatal EA is not commonly diagnosed. Prenatal detection of EA by ultrasonography relies on the finding of a small or absent stomach bubble and associated maternal polyhydramnios.[106] However, with these criteria, the predictive value of prenatal ultrasonography in the diagnosis of EA is only 20% to 40%.[107,108] The ultrasonographic finding of an esophageal pouch in the middle of the fetal neck in association with polyhydramnios and a small stomach may increase the accuracy of prenatal diagnosis of EA.[109,110] A recent report suggests that real-time fetal magnetic resonance imaging may be a useful adjunct in the prenatal diagnosis of EA anomalies suspected on ultrasound.[111]

Most infants with EA are symptomatic in the first few hours of life. The earliest clinical sign of EA is usually excessive salivation that results from pooling of secretions in the pharynx. Typically, the first feeding is followed by regurgitation, choking, and coughing. Other features are cyanosis with or without feeding, respiratory distress, inability to swallow, and inability to pass a feeding or suction catheter through the mouth or nose into the stomach. If a distal fistula is present, the abdomen distends as inspired air passes through the fistula into the stomach. Pulmonary compromise can become significant as gastric fluid refluxes through the TEF, spills into the trachea and lungs, and subsequently leads to chemical pneumonitis. As the abdomen distends with air, the diaphragms (the principal muscles of respiration in the newborn) elevate and pulmonary status worsens. Aspiration of saliva from the upper pouch into the trachea further exacerbates the pulmonary compromise.

The diagnosis of EA can be confirmed by passing a firm catheter through the mouth into the esophagus to the point at which resistance is met. A few milliliters of air can be injected through the tube and used as a contrast agent to distend the upper esophageal pouch as frontal and lateral films are obtained (Fig. 69-3). A flexible catheter such as a feeding tube will often curl up in the upper pouch, also suggesting the diagnosis of EA (Fig. 69-4). If necessary, 0.5 to 1.0 mL of diluted barium can be used as a contrast agent and injected into the upper pouch to confirm the diagnosis (Fig. 69-5). Under carefully controlled fluorography, barium may also detect a proximal TEF; in the usual circumstance of a portable film performed in the neonatal unit, however, barium identified in the tracheobronchial tree is more likely to represent contrast aspirated through the larynx rather than through a proximal TEF. A very small or short upper blind pouch may also suggest the presence of a proximal TEF. Air in the stomach and bowel confirms the presence of a distal TEF. Absence of air in the abdomen typically represents isolated EA without distal TEF (Fig. 69-6), but the presence or absence of a proximal TEF must be confirmed by bronchoscopy. The incidence of proximal TEF is much higher than thought in the past. However, it is possible to have absence of intestinal air in the circumstance of a narrow or occluded distal fistula, which is identified at the time of operation.[112,113] The diagnosis of TEF without EA is more difficult and requires a high index of suspicion on the basis of clinical symptoms. The diagnosis is often delayed, and investigations are triggered by repeated coughing or choking during feedings, often with pulmonary infiltrates on chest radiograph suggesting aspiration. The diagnosis can be made by barium esophagography in the prone position (Fig. 69-7); however, bronchoscopy with or without esophagoscopy is often required to confirm the diagnosis.

**TABLE 69-4**
**Okamoto modification of the Spitz Classification: Predictors of Survival in Cases of Esophageal Atresia**

| *Class* | *Description* | *Risk* | *Survival* |
|---|---|---|---|
| Class I | No major cardiac anomaly, BW $\geq$ 2000 g | Low | 100% |
| Class II | No major cardiac anomaly, BW $<$ 2000 g | Moderate | 81% |
| Class III | Major cardiac anomaly, BW $\geq$ 2000 g | Relatively high | 72% |
| Class IV | Major cardiac anomaly, BW $<$ 2000 g | High | 27% |

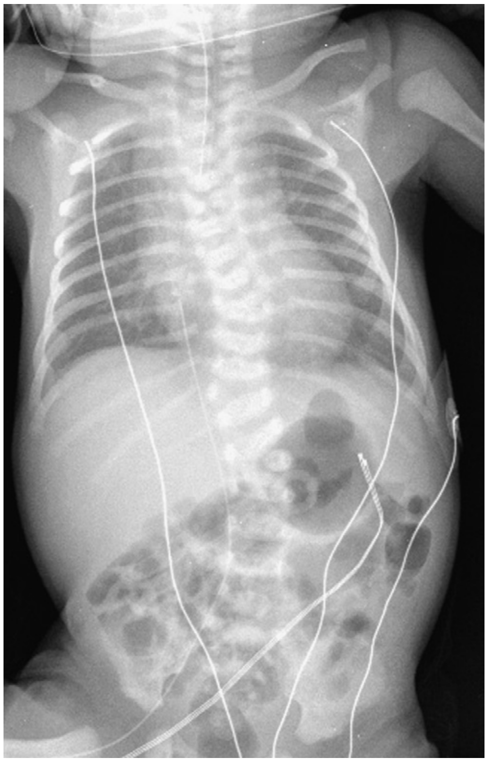


FIGURE 69-3 Upper esophageal atresia pouch with air. Also note vertebral anomalies.

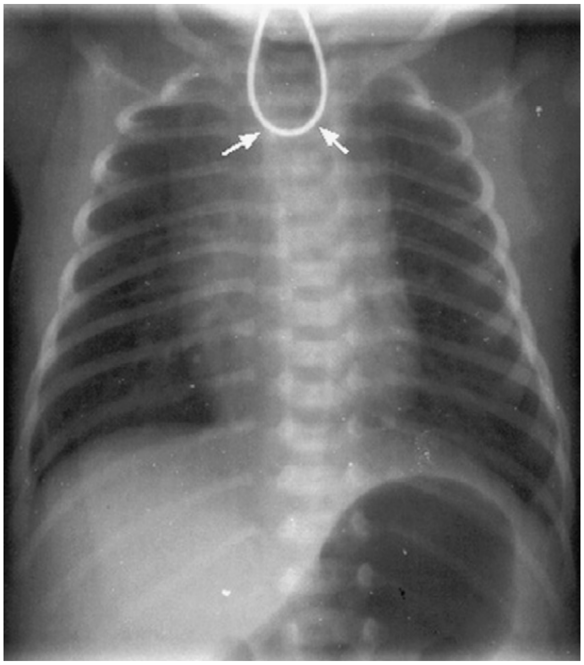


FIGURE 69-4 Upper esophageal atresia pouch with coiled feeding tube.

As previously discussed, the incidence of recognizable congenital defects associated with EA is between 50% and 70%. The clinical evidence of these other anomalies should, therefore, be considered in the diagnostic evaluation for EA. In addition to a physical examination focused on seeking known associated defects (such as those of the VACTERL association), additional testing usually includes echocardiography, renal ultrasonography, and chromosomal analysis. In fact, it is not unusual for the finding of an anorectal malformation, for example, to precede the clinical signs and symptoms of a concomitant EA.

## Preoperative Treatment

Pneumonitis from aspiration of upper pouch secretions and reflux of gastric acid through the TEF causing worsening respiratory distress is the most critical preoperative problem for an infant with EA-TEF. Immediate management includes measures to prevent further aspiration and treatment of pneumonitis. A sump catheter should be positioned in the upper esophageal pouch to continuously aspirate saliva under low-pressure suction. The double-lumen Replogle type of catheter is best for this purpose because the perforations along the side of the catheter are located only near the tip, which minimizes the possibility of suctioning oxygenated air away from the larynx. The infant should be positioned to minimize reflux of gastric fluid up through the TEF. An upright sitting position has traditionally been advocated, but some authors argue that the head-up, prone position is most effective at minimizing reflux. Broad-spectrum antibiotic coverage and pulmonary physiotherapy are also initiated. Intravenous fluid therapy with 10% dextrose and hypotonic saline should be started to maintain fluid, electrolyte, and glucose balance. Vitamin K analogue should also be administered before surgery. Routine endotracheal intubation should be avoided because of the risk for gastric perforation and worsening respiratory distress as the abdomen becomes distended from ventilation through the TEF.

## Operative Repair

The operative approach to an infant with EA depends greatly on the specific type of anomaly present and the occurrence of associated anomalies.

### ESOPHAGEAL ATRESIA WITH DISTAL TRACHEOESOPHAGEAL FISTULA

Emergent operation for EA with distal TEF is seldom necessary, and a period of 24 to 48 hours between diagnosis and operation permits full assessment of the infant and treatment of pulmonary insufficiency including atelectasis and pneumonitis. In most infants, open thoracotomy or thoracoscopic division of the fistula with primary anastomosis of the esophagus is possible and is the operative procedure of choice.

For the open approach, the infant is usually positioned for a standard right posterolateral thoracotomy, with the right arm extended above the head and the head slightly flexed. If a right-sided aortic arch (2.5%) is identified on a preoperative echocardiogram, a left-sided thoracotomy is preferred; however, a double aortic arch is not unusual and makes a left thoracic approach difficult as well.[114] A curved skin incision is made around the lower border of the scapula and extends from the anterior axillary line posteriorly to the paravertebral region (Fig. 69-8). Subcutaneous tissue and chest wall muscles are divided using electrocautery; this allows elevation of the scapula and identification of the fourth intercostal space.

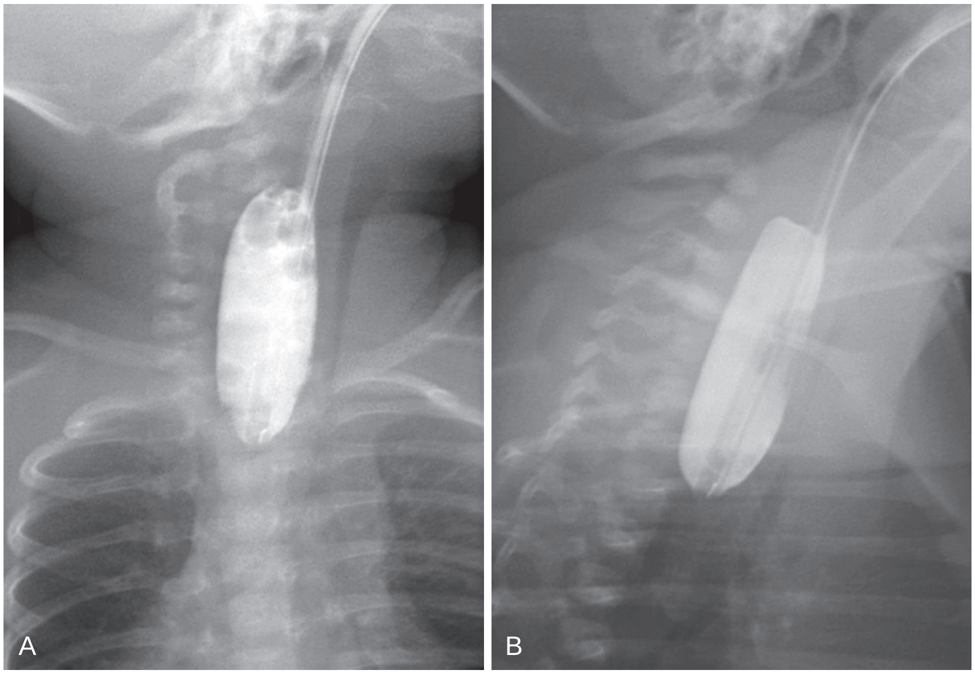



**FIGURE 69-5** The upper esophageal pouch is outlined by 0.5 to 1 mL of thin barium in the frontal **(A)** and lateral **(B)** projections.

**FIGURE 69-6** Absence of intestinal air suggests isolated esophageal atresia without tracheoesophageal fistula. Also note vertebral anomalies.

**FIGURE 69-7** An H-type tracheoesophageal fistula is shown as contrast is injected through a nasoesophageal tube. Contrast is noted passing from the esophagus, through the fistula (*arrow*), and filling the upper part of the trachea and larynx.

Some surgeons advocate a muscle-sparing thoracotomy using an approach between the latissimus dorsi and the serratus anterior muscles in an attempt to minimize postoperative shoulder function morbidity.[115,116] The thorax is entered through the fourth intercostal space by dividing the intercostal muscles, with care taken to avoid incising the pleura. Most pediatric surgeons continue to advocate the extrapleural approach for EA-TEF repair because a substantial anastomotic leak does not result in empyema but merely causes an esophagocutaneous fistula, which typically closes in 1 to 2 weeks. Surgeons who use the transpleural route argue that the operative time is shorter and, with current antibiotic options, the risk for empyema after a leak is minimal. With the extrapleural approach, the pleura are gently pushed away from the chest

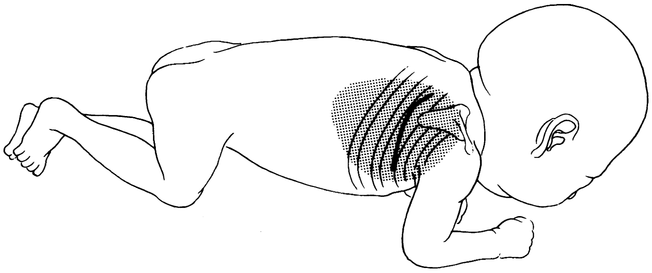


**FIGURE 69-8** Positioning of an infant for repair of esophageal atresia with or without a tracheoesophageal fistula. The thorax is entered.

wall; this in turn allows insertion of a rib-spreading retractor. Moist pledgets, tissue applicators, or gauze can be used to dissect the pleura anteromedially as the rib spreader is sequentially opened (Fig. 69-9). With further retropleural dissection, the azygos vein is exposed and may be divided between ties as the lung and pleura are gently retracted medially. When the posterior mediastinum is exposed, the upper pouch, distal TEF, trachea, and vagus nerve are identified. The lower part of the esophagus is dissected circumferentially at the level of the fistula, and every effort is made to preserve the vagal fibers that supply the distal portion of the esophagus. Traction on a heavy silk suture, tape, or vessel loop passed around the distal end of the esophagus controls gas flow through the fistula into the stomach and allows meticulous dissection and exposure for fistula closure (Fig. 69-10). The latter can be performed with 5-0 or 6-0 permanent or absorbable suture placed in interrupted fashion (Fig. 69-11). Because occasional intratracheal granuloma has occurred with permanent sutures, we recently chose to close the fistula with absorbable suture such as polydioxanone (Fig. 69-12). It is important to leave 1 to 2 mm of esophagus on the tracheal end of the fistula to minimize the risk for postoperative tracheal stricture, while not leaving an excessive amount that would act as a tracheal diverticulum. The air-tightness of the tracheal closure can be tested by filling the thoracic cavity with warm saline and watching for bubbles with positive-pressure ventilation.

A small tube should be passed through the distal end of the esophagus to ensure that the lumen is adequate and open and to aspirate air distending the stomach. Occasionally,

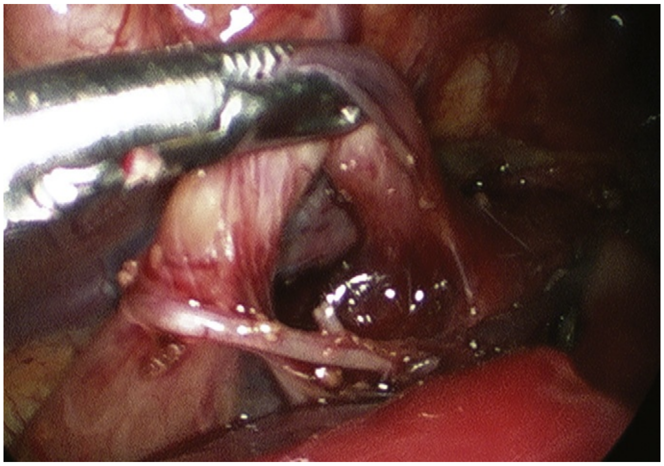


**FIGURE 69-10** Distal esophageal pouch mobilization up to the tracheoesophageal fistula at the tracheal bifurcation. Note the clear view of vagal branches. *(See Expert Consult site for color version.)*

a congenital distal esophageal stricture will be encountered. Two fine stay sutures on the distal esophageal opening allow gentle traction for dissection. The extent of distal mobilization should be minimized to avoid damaging vagal branches and the segmental blood supply. However, distal mobilization should be undertaken if it is necessary to ensure a primary low-tension anastomosis. Identification of the proximal esophageal pouch can be facilitated if the anesthesiologist gently pushes on a suction catheter, which is passed through the mouth into the upper pouch. A traction suture can be placed through the tip of the pouch, and even through the suction catheter, to assist in proximal dissection and avoid the trauma caused by repeatedly applying forceps to the proximal pouch. Mobilization of the upper pouch should be sufficient to bring the upper pouch down to the distal esophageal segment. This usually necessitates dissection up to the thoracic inlet (Fig. 69-13). Extensive circumferential dissection of the proximal pouch also allows for identification of an undiagnosed proximal TEF. Because the cervical blood supply to the proximal part of the esophagus is excellent, this type of extensive dissection does not run a significant risk for ischemic injury. Great care must be taken during the dissection between

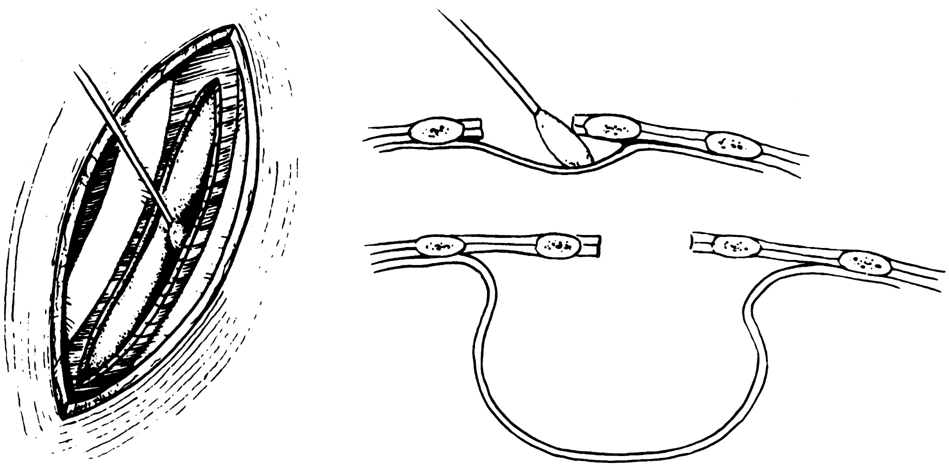


**FIGURE 69-9** Extrapleural dissection is facilitated by using moistened tissue applicators or pledgets to push the parietal pleura away from the chest wall and subsequently away from the posterior mediastinum.

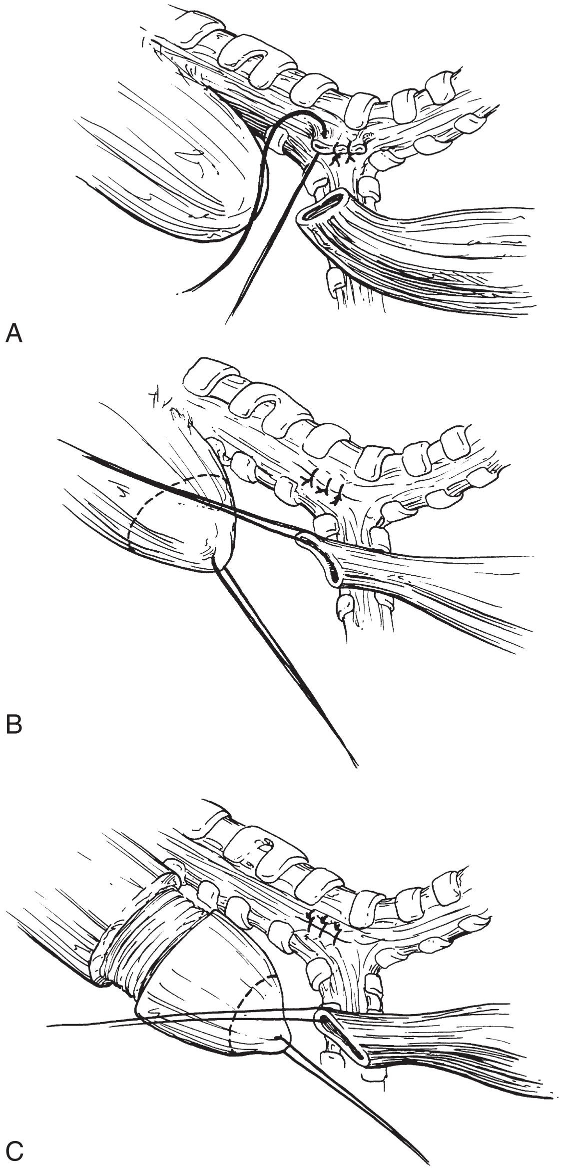



FIGURE 69-11 **A,** The opening of the tracheoesophageal fistula is closed with 5-0 or 6-0 nonabsorbable suture. **B,** The feasibility of primary anastomosis between the two esophageal segments is being assessed. **C,** A proximal esophagomyotomy being used to gain additional length. (From Rowe M, O'Neill JA, Grosfeld JL, et al: Essentials of Pediatric Surgery. St Louis, Mosby-Year Book, 1995.)

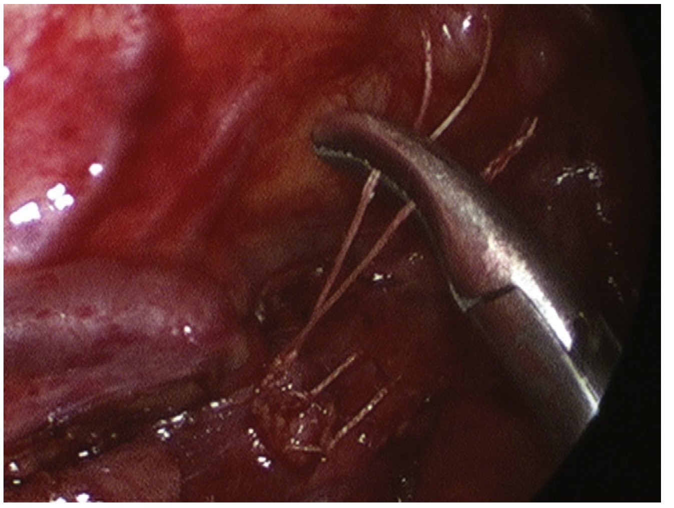


FIGURE 69-12 Interrupted suture closure of tracheoesophageal fistula. *(See Expert Consult site for color version.)*

FIGURE 69-13 Dissection of the upper esophageal pouch. *(See Expert Consult site for color version.)*

the esophagus and the membranous trachea, however, to avoid inadvertently opening the trachea. Unfortunately, the more extensive the proximal dissection, the greater the likelihood of disturbance to vagal branches.

The tip of the upper esophageal pouch is excised or simply opened and stretched at its lowest point to a diameter corresponding to the distal esophageal lumen. Traction sutures are placed opposite each other, and an end-to-end anastomosis is begun by placing interrupted 5-0 or 6-0 sutures in the back wall with the knots tied on the inside of the lumen; great care should be taken to include full-thickness esophageal wall including the mucosa and muscularis (Fig. 69-14). The upper pouch mucosa often retracts and can easily be missed if the surgeon is not vigilant. Unless the two ends of the esophagus are very close, it is best to insert the entire back row of sutures before tying them. A small feeding tube can then be passed and advanced across the anastomosis into the stomach to ensure distal esophageal patency and the potential for early postoperative enteral feeding if desired. The anterior layer of the anastomosis is then completed over the tube, with the knots tied on the outside (Fig. 69-15). The effect of the type of suture material used in the esophageal anastomosis on subsequent stricture formation has been a point of debate. In a review of patients in whom anastomotic strictures developed, Chittmittrapap and colleagues[117] reported a statistically significant increased rate of stricture when braided silk was used versus polypropylene or polyglycolic acid suture.

Once the anastomosis is complete, the position of the tube should be confirmed if it is to remain in place for postoperative gastric decompression and feeding. A chest tube or closed suction drain is usually placed in the retropleural space and secured to the lateral chest wall by a loose absorbable suture. The drain should be placed away from the anastomosis. Some surgeons leave no chest tube or drain in the chest after a retropleural dissection.[118]

In infants with EA and distal TEF, another technique for handling the fistula and uniting the esophageal ends is the end-to-side anastomosis developed by Sulamaa and colleagues[119] and championed by Duhamel and others.[109,120,121] With this technique, a single ligature is used to ligate the

fistula; the upper pouch is mobilized down to the lower esophageal segment, and a wide, oblique, end-to-side anastomosis is performed. Because of concern for recurrent TEF formation, this method has not been widely accepted. In a review from a center where both techniques were used, Poenaru and colleagues identified end-to-side anastomosis as a significant risk factor for mortality, specifically because of recurrent TEF, but noted a lower rate of gastroesophageal reflux (GER).[122]

In another series of 68 infants treated with this technique, Touloukian and colleagues[121] reported a TEF recurrence rate of 7%, a rate similar to or lower than that seen in large series of end-to-end reconstructions. In addition, the rate of other complications such as stricture (5%), anastomotic leak (8%), and GER (6%) was lower than in most other series using end-to-end esophageal reconstruction.

Thoracoscopic repair of EA-TEF is being adopted more widely. This technique typically uses three 2.5- to 5-mm transpleural access trocars, an angled telescope, a video camera, and small-diameter (2.5 to 5 mm) instruments to identify and ligate the TEF (often with a 5-mm clip), mobilize the proximal esophageal pouch, and perform an end-to-end esophagoesophagostomy in a fashion that is similar to the open thoracotomy approach (see Figs. 69-10, 69-12, 69-13, 69-15, and 69-16). Advocates of this approach have suggested that benefits include superior visualization, improved cosmesis, and elimination of the morbidity of neonatal thoracotomy including scoliosis, winged scapula, chronic pain, shoulder weakness, chest wall asymmetry, and maldevelopment.[123,123a] However, the thoracoscopic EA-TEF repair is technically demanding and requires advanced endosurgical skills. The thoracoscopic end-to-end esophageal anastomosis is technically challenging because of limited working space, lack of articulation at the end of the instruments (the needle driver in particular), and the necessity of tying sutures under tension.[123]

Particular attention must be given to infants with EA and a large distal TEF with severe respiratory distress syndrome. Under these circumstances, preoperative endotracheal intubation is often necessary. However, high-pressure ventilation may worsen lung ventilation and abdominal distention as inspired air is diverted through the TEF into the stomach, thus exacerbating respiratory compromise. Affected infants may require emergency surgical intervention to stabilize the pulmonary status and avoid gastric perforation, which is typically fatal in these circumstances.

Several operative approaches have been described to manage this problem including gastric division,[124] banding of the gastroesophageal junction,[125] and positioning the tip of the endotracheal tube below the fistulous orifice.[126] The latter technique may be dangerous if not combined with fiberoptic bronchoscopy to locate the TEF; a fistula at or close to the carina precludes the safe use of this technique, and inadvertent intubation through a large fistula may be fatal.[127] Bronchoscopic placement of a Fogarty balloon catheter through the fistula has been successfully used to ablate the flow of ventilated air through the fistula.[128] This approach may be used to stabilize a rapidly deteriorating infant; however, concern has been raised about potential technical difficulties with this approach and problems with injury to the distal end of the esophagus in which the balloon is inflated.[129] Emergency gastrostomy to decompress the air-filled stomach

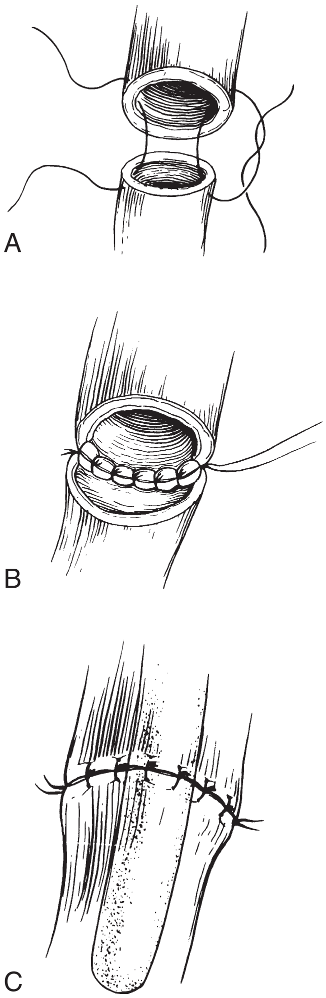



**FIGURE 69-14** Single-layer esophageal anastomosis. **A,** Corner stitches are placed and the knots are tied on the outside. **B,** The posterior row is placed with the knots tied on the inside. **C,** The anterior row completes the anastomosis over a tube with the knots tied on the outside. (From Rowe M, O'Neill JA, Grosfeld JL, et al: Essentials of Pediatric Surgery. St Louis, Mosby-Year Book, 1995.)

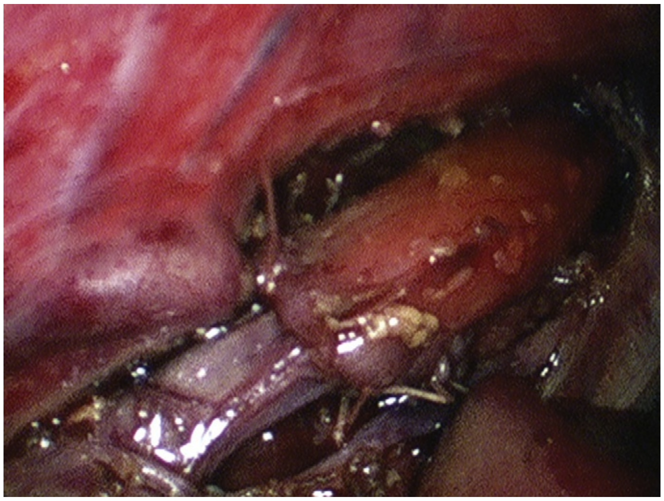


**FIGURE 69-15** Completed end-to-end esophageal anastomosis. *(See Expert Consult site for color version.)*

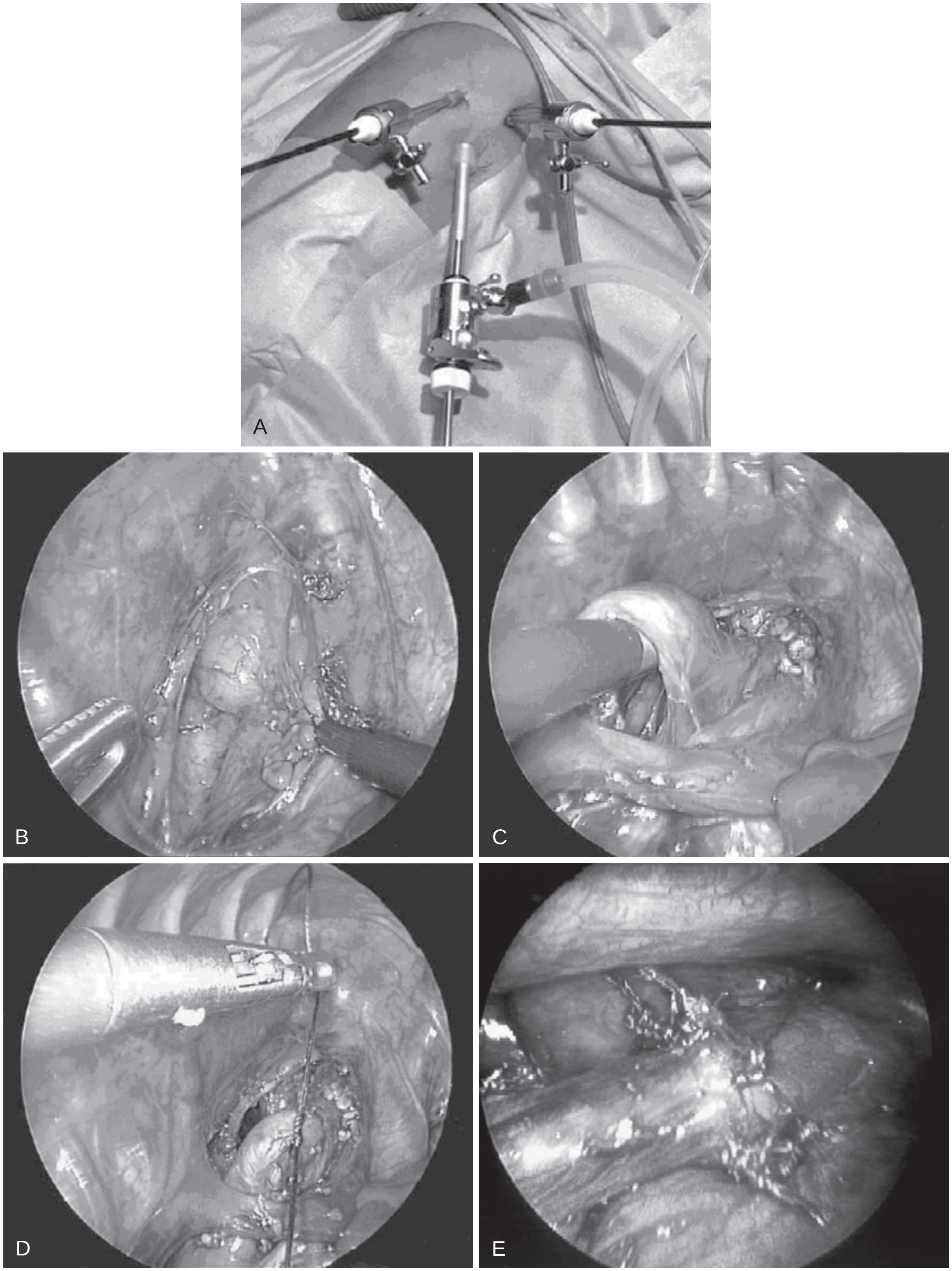



**FIGURE 69-16** Thoracoscopic repair of esophageal atresia with a distal tracheoesophageal fistula. **A,** Position of the trocars, a 6-mm trocar for the telescope and two 4-mm trocars for instruments. **B,** The posterior pleura has been incised and the upper pouch is being mobilized. **C,** The distal fistula has been dissected free with the azygos vein left intact. **D,** Fistula being ligated close to the trachea. **E,** Completed end-to-end esophagoesophagostomy. (From Bax KMA, Van der Zee DC: Feasibility of thoracoscopic repair of esophageal atresia with distal fistula. J Pediatr Surg 2002;37:192.)

and small bowel has also been used in this situation. This approach, however, places the infant at risk for pulmonary collapse because each ventilator breath volume bypasses the lung by preferentially passing through the TEF and escaping via the low-resistance gastrostomy tube. The use of a gastrostomy tube with an underwater seal may increase air resistance and decrease runoff through the fistula. A small balloon catheter passed through the gastrostomy into the lower esophagus can provide excellent palliation for days to weeks.[129a]

Emergent thoracotomy and fistula division in an infant with severe respiratory distress syndrome who requires high-pressure ventilation is generally the best approach; in a premature baby, the decision to operate should be made early because the hyaline membrane disease will worsen in the first 24 to 36 hours and will make the lungs even less compliant. In many circumstances, the infant remarkably improves after emergency fistula ligation; this improved condition may allow primary repair of the esophagus and thus eliminates the need for a second operation.

## LONG-GAP ESOPHAGEAL ATRESIA

Occasionally in infants with EA-TEF, the upper pouch is high and the distance between the upper and lower esophageal segments limits the ability to easily complete end-to-end esophagoesophagostomy with acceptable tension. The same is true for most neonates with isolated EA because the lower esophagus is not "attached" to the trachea. Although much has been said and written about the subject, there is no precise definition of "long-gap" EA. What is amenable to primary anastomosis by some surgeons may be considered "long gap," "very long gap," or "ultralong gap" by others. In addition, measurement of gap length can be biased by the method used to measure the distance between the proximal and distal ends of the esophagus. Some reports describe preoperative measurement of the gap by inserting a radiopaque tube or bougie into the upper pouch and placing contrast or a flexible endoscope into the distal pouch through a previously placed gastrostomy tube.[130,131] Other definitions of gap length are based on intraoperative measurements obtained before or after mobilization of the proximal pouch and, on occasion, the proximal and distal pouches. These variations on the method of determining gap length contribute to the confusion and debate about how long is long.[132]

In the case of isolated EA, in which a "long gap" is expected, most pediatric surgeons would proceed with the operative placement of a gastrostomy tube, a period of observation, and an attempted delayed primary repair. It is well documented that during the first several months of life, the gap between the two ends of the esophagus tends to lessen because of spontaneous growth, possibly related in part to reflux of bolus gastric feedings into the lower esophagus, which makes primary repair more feasible.[133,134] In addition, many preoperative mechanical techniques have been described as a means to facilitate narrowing of the esophageal gap. The most commonly used method is that of upper pouch bougienage, in which a weighted bougie is passed through the mouth into the upper pouch, with forward pressure applied daily or twice daily for 6 to 12 weeks before attempting delayed primary repair.[135] The use of preoperative upper and lower pouch bougienage to decrease gap length has also been described,[136] but some of the early proponents have abandoned this technique.[136a] In 1975 Hendren and Hale[137,138] reported using an electromagnetic field to pull together metallic "bullets" placed in the two ends of the esophagus in order to shorten the gap.

Other innovative operative techniques designed to narrow the long gap before attempted surgical esophageal anastomoses have been advocated. In 1971 Rehbein and Schweder[139] described the use of a nylon thread bridging the gap between the two ends of the esophagus and attached to silver olives[136] residing within each lumen. The olives were pushed toward each other over time until the two ends of the esophagus pressed together and created a fistula. Shafer and David[140] used a similar technique to create a fistula between the two ends of the esophagus by simply approximating the two ends of the mobilized esophagus with tacking sutures, then placing a bridging silk suture. A modification of this technique has recently been reported successful in five infants.[141] Another method that facilitates esophageal lengthening is the multistaged, extrathoracic elongation technique of Kimura, in which the upper part of the esophagus is mobilized and initially brought out as an end cervical esophagostomy. Every 2 to 3 weeks, the esophagus and its cutaneous stoma are surgically mobilized and translocated down the anterior chest wall until enough length is achieved to perform an end-to-end esophageal anastomosis.[142,143] Foker has described a novel technique in which traction sutures on both the proximal and distal esophageal pouches exit through the chest wall and are serially pulled in opposite directions until the pouches approximate (Fig. 69-17). The external traction technique is reported to induce esophageal growth and expedite approximation of the pouches, thus allowing for earlier primary repair (10 to 14 days).[144,145] Internal traction sutures have also been used to promote esophageal growth in cases where the gap is such that an initial anastomosis would perhaps be under too much tension. Successful thoracoscopic esophageal elongation for long-gap EA has also been reported.[146] There is also a report of using the Kimura technique for proximal pouch lengthening and the Foker technique for distal pouch lengthening.[147]

In addition to preoperative attempts to elongate the esophagus, many intraoperative techniques have been used to establish a primary esophageal anastomosis, either at an initial operation in the newborn period or at the time of a delayed operation after the elongation methods previously described have been used. Bagolan advocates using the "Foker traction" principle intraoperatively, finding that significant length can be obtained after 20 to 30 minutes of traction on the esophageal ends.[147a] Livaditis and colleagues[148,149] described the use of a circular myotomy of the upper part of the esophagus to decrease the tension on an end-to-end esophageal anastomosis in a piglet model of EA and, in 1973, reported the clinical use of this technique to lengthen the upper esophageal segment in order to allow for a primary anastomosis in an infant with long-gap EA (see Fig. 69-11).[150] Since that time, proximal esophageal circular myotomy to lengthen the upper esophageal pouch and achieve a primary anastomosis in long-gap EA has been widely used. The use of balloon catheters or cuffed endotracheal tubes inflated in the upper esophageal pouch to facilitate mobilization and subsequent circular myotomy seems to be a useful modification of this method.[151–154] We have occasionally made an additional right cervical incision to mobilize the upper esophageal pouch up and out of the neck and perform a more proximal second or third circular myotomy.[132]

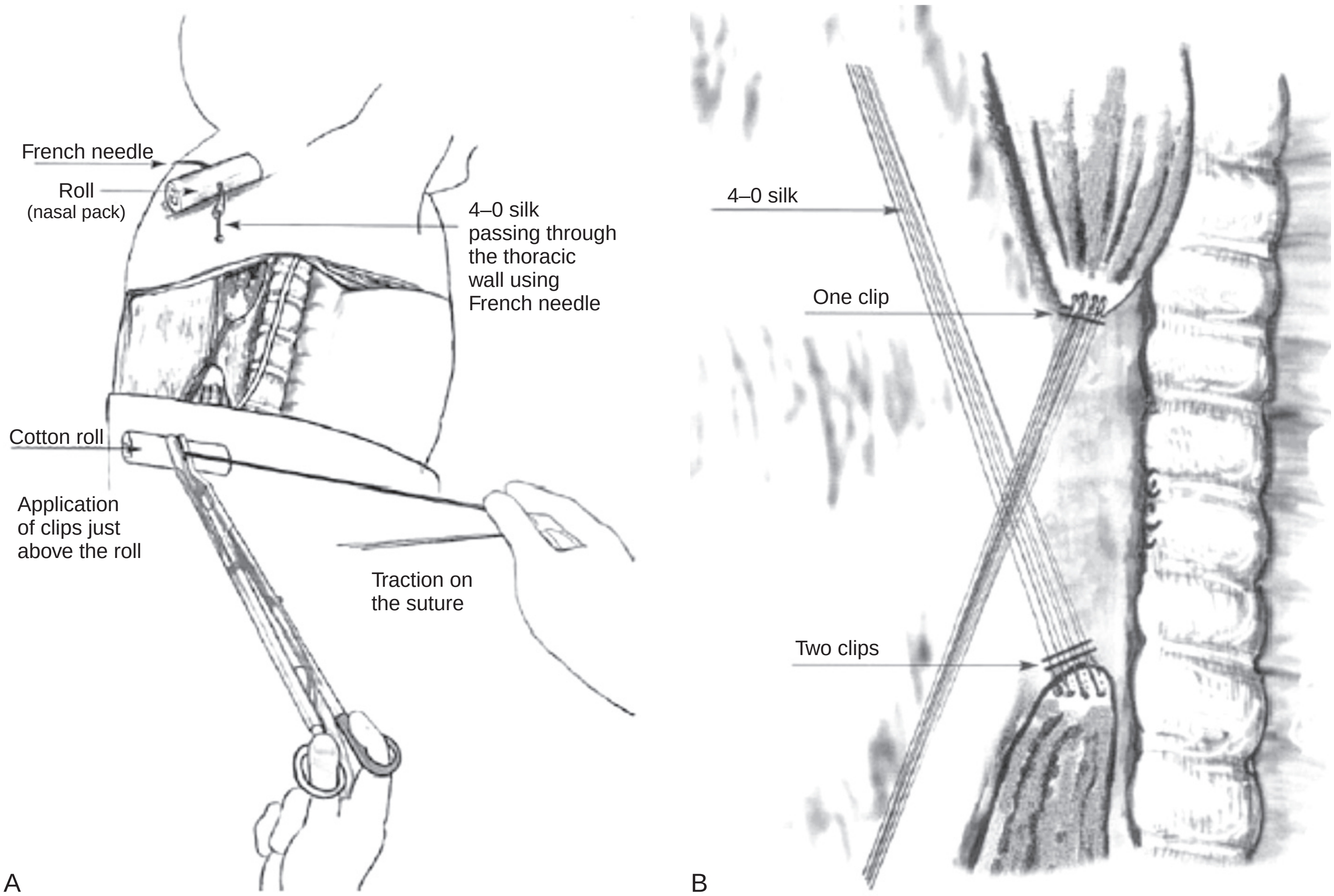


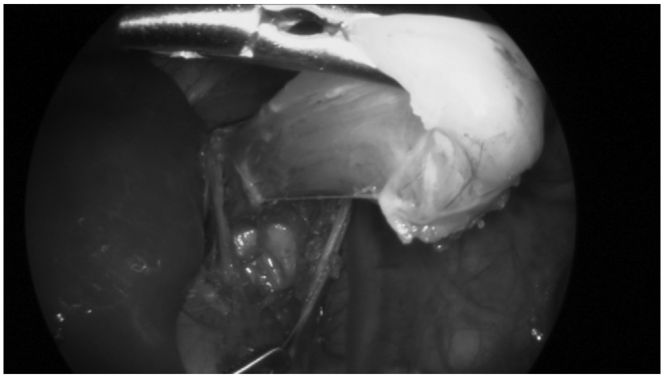

**FIGURE 69-17** Foker technique for lengthening the upper and lower esophageal pouches by external traction sutures. **A,** External view of crossed traction sutures and bolsters. **B,** Internal view. (From Foker JE, Linden BC, Boyle EM Jr, et al: Development of a true primary repair for the full spectrum of esophageal atresia. Ann Surg 1997;226:533.)

However, significant complications of circular myotomy have been described and have created a debate among surgeons regarding its safety. Complications include esophageal leak, impaction of food particles in the myotomized segment,[155] and mild ballooning of the myotomized segment. Severe ballooning resulting in an esophageal pseudodiverticulum has been reported to be a potentially serious complication. Several reports have noted the formation of a pseudodiverticulum with a distal anastomotic stricture, as might be expected.[152,155,156] If the stricture is not treated, the pseudodiverticulum can enlarge so much that it causes complications such as dysphagia and life-threatening respiratory obstruction.[156]

Several reports have suggested the use of a distal esophageal pouch circular myotomy in addition to proximal myotomy to achieve a primary esophageal anastomosis.[157,158] Many technical modifications have been suggested to minimize the risk for potential serious complications from circular myotomy. The use of a spiral upper pouch myotomy with oblique suture closure of the muscular layer has been advocated as a technique that minimizes the chance of diverticulum formation and, theoretically, improves motility.[159,160] Another method used to elongate the upper pouch involves the creation of a full-thickness anterior flap of the upper pouch wall as described by Gough; when folded distally, the flap can be rolled into a tube and attached to the lower esophageal segment.[161] In 1989 Bar-Maor and colleagues[162] emphasized the technical details of this method to elongate the upper pouch. Davenport and Bianchi[163] reported good follow-up results in 25 infants with EA treated by this method over a 5-year period. Variations of this technique have been described and consist of the creation of a 5-mm posterior flap[164] or anterior esophageal flap,[165] followed by an end-to-end oblique anastomosis with a spatulated distal esophagus.

At the time of attempted initial or delayed primary repair, the esophageal segments sometimes do not reach together even though one or more of the methods just presented have been tried. Several additional techniques have been described to facilitate an esophageal anastomosis. Despite the long-held opinion that the blood supply to the distal end of the esophagus is tenuous and may be compromised by mobilization, many surgeons have found that the distal esophagus can be, and often is, mobilized to facilitate a primary anastomosis (Fig. 69-18).[166] We have successfully achieved primary end-to-end esophageal anastomosis by completely mobilizing the distal esophagus down to and even through the esophageal hiatus of the diaphragm. With this approach, some of the fundus of the stomach can be brought up into the chest to facilitate anastomosis.[132]

Taking this concept further, Schärli described a combined abdominal and thoracic procedure in which distal esophageal elongation was achieved by ligation and division of the left gastric artery, transverse or diagonal division of the lesser



FIGURES 69-18 Aggressive mobilization of distal esophageal pouch in a case of isolated esophageal atresia.

curvature of the stomach, and mobilization of the gastric cardia and upper fundus into the chest to achieve primary esophageal anastomosis.[167,168] A partial fundoplication is recommended to treat the anticipated GER. Not surprisingly, postoperative GER has been reported to be a significant problem after this procedure.[169] By use of a similar approach, a Collis gastroplasty with Nissen fundoplication has also been described as a means of lengthening the distal end of the esophagus to avoid esophageal replacement.[170,171]

In addition to the surgical techniques used to facilitate saving the native esophagus as the conduit of choice for the repair of long-gap EA, the use of postoperative head flexion, paralysis, and mechanical ventilatory support has been strongly advocated by some to minimize the risk for anastomotic disruption when the esophageal anastomosis is under substantial tension.[68,136,172,173]

The rationale for this approach is the prevention of disruptive force at the anastomotic site by flexion of the neck and paralysis of the striated muscles in the proximal part of the esophagus.[136,174]

## ESOPHAGEAL REPLACEMENT

For an extensive discussion of esophageal replacement, see Chapter 71. Despite the many methods and innovations developed to achieve esophageal continuity in infants with EA, the esophagus may need to be replaced if these methods fail. Numerous operative procedures have been described for esophageal replacement in infants with EA, as well as children with caustic injury.

The choice of esophageal substitute depends on many factors. Colon replacement, or ileocolon, has been widely practiced for many years as a method of esophageal replacement. Either the right or left colon can be placed substernally or behind the hilum of the lung on the right or left side. Vagotomy and a gastric drainage procedure are typically performed to avoid stricture or ulceration at the cologastric anastomosis. Several complications occur after colonic interposition including cervical anastomotic leak (30% to 50% of cases), stricture, and intrathoracic redundant colon with stasis, gastric reflux, respiratory problems, and diarrhea. Some surgeons favor a reversed gastric tube as a substitute; in this procedure, a tubularized portion of the greater curvature is brought up to the cervical esophagus in the substernal or retrohilar position. Complications are similar to those described for colonic interposition. A modified gastric tube has also been described in which a portion of the greater curve is fashioned into a "free" tube graft based on the right gastroepiploic artery.[175] The jejunum has also been used for esophageal replacement both in a Roux-en-Y fashion and as a free graft with microvascular anastomosis.[176]

Gastric transposition has more recently become a well-established and successful esophageal substitute in infants with EA.[136,177,178] Spitz and colleagues[40] have reported good to excellent outcomes in 90% of 138 infants and children with EA in whom this method of replacement was used (age at operation ranged from 7 days to 17 years).[179] The survival rate was 95.4%, the incidence of anastomotic leak was 12%, the incidence of strictures requiring dilation was 20%, and there was no deterioration in function over a 10-year follow-up. A recent review by one of us (AGC) reports excellent outcomes in more than 110 infants treated with gastric transposition for long-gap esophageal atresia.[180] The technical aspects are demonstrated in Figure 69-19. A laparoscopic approach to gastric transposition has recently been reported and appears to be a viable, less invasive option.[181]

## ESOPHAGEAL ATRESIA WITHOUT TRACHEOESOPHAGEAL FISTULA

Infants born with isolated EA have almost no esophagus in their thorax. It is important to be aware of this fact in order to institute an appropriate treatment plan and avoid fruitless exploratory thoracotomy. The preoperative and operative treatment of this lesion was discussed extensively earlier in this chapter. In a review of 69 infants with isolated EA treated over a period of 50 years, Ein and Shandling[182] reported a 52% incidence of prematurity, an 11% incidence of Down syndrome, and a 10% incidence of duodenal atresia; all these rates are higher than typically reported in patients with EA-TEF. A recent 24-year review of the experience from Great Ormond Street Hospital for Children in London found that 71% of patients were male. Among the associated anomalies were 19% cardiac, 16% urogenital, 14% vertebral, and 7% anorectal malformation. A more recent review reports an 85% esophageal salvage rate but also describes the complicated preoperative and postoperative course for these infants including 60% anastomotic leak rate and severe gastroesophageal reflux disease.[183]

The clinical manifestations of an infant with isolated EA are similar to those of an infant with EA-TEF in terms of inability to swallow; in the former, however, the abdomen is typically scaphoid, and plain radiographs of the abdomen show no air in the gastrointestinal tract. A gastrostomy tube should be placed within the first 24 to 48 hours of life, and delayed primary repair using the various methods previously discussed should be attempted. Placement of the gastrostomy tube allows the early institution of enteral feedings, which leads to subsequent enlargement of the diminutive stomach and stretching of the distal esophageal pouch (Fig. 69-20). Enlargement permits the stomach to be used as an esophageal substitute if necessary. At the time of placement, a contrast imaging study can be performed to evaluate the unusual possibility of an occluded but present distal esophageal fistula to the trachea, which might suggest the potential for early esophageal repair.[112,113] A rigid bronchoscopy can also be done to eliminate the possibility of a proximal or occluded distal fistula. A period of observation and enteral nutritional support

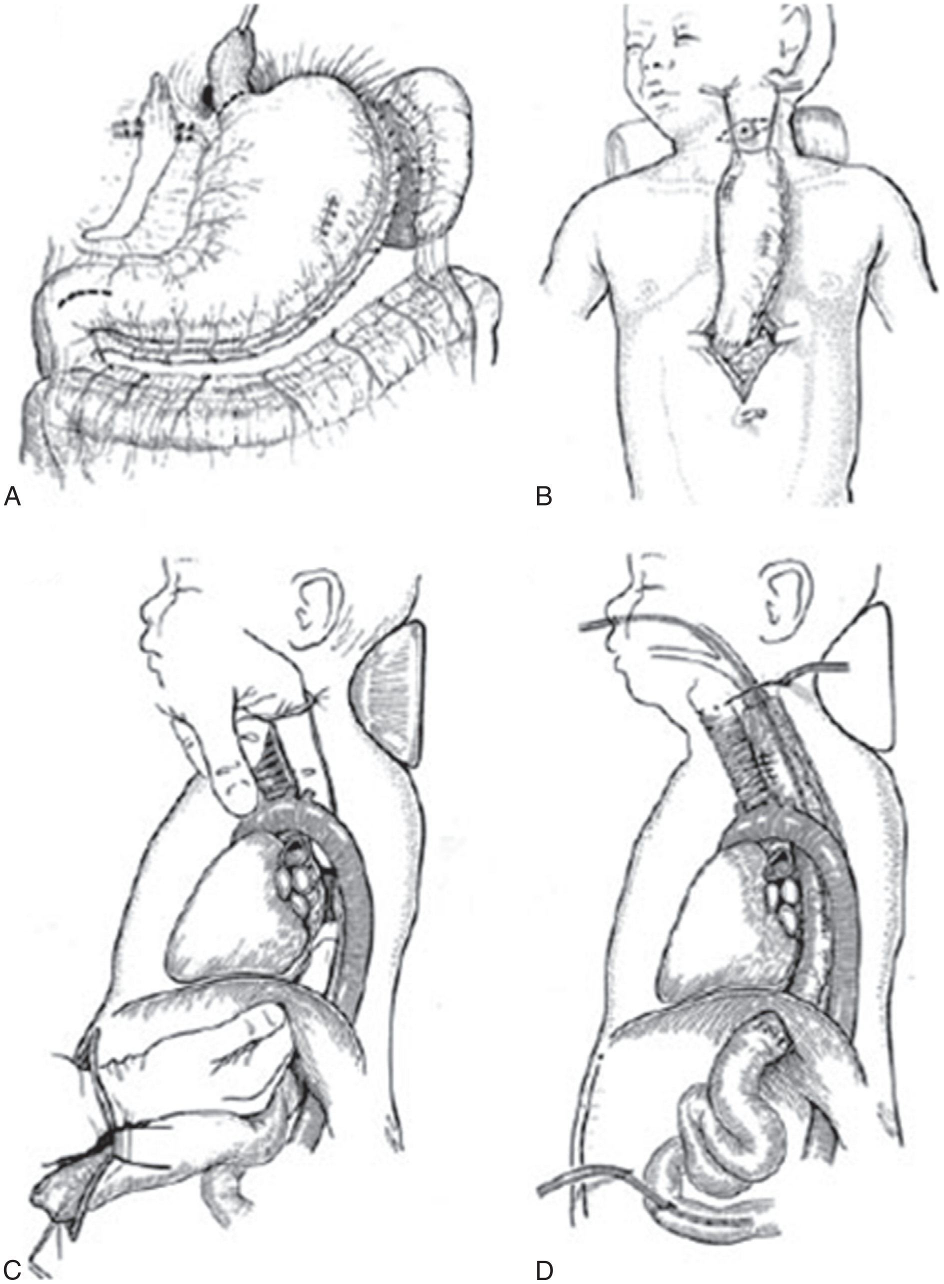



**FIGURE 69-19** **A** to **D,** Gastric transposition technique. (From Peditr Surg Int. 2010 Dec;26(12):1129-1134.)

is instituted with or without daily upper pouch bougienage. Over an 8- to 12-week period, the process of esophageal elongation can be monitored by imaging studies that use contrast material, metallic probes, bougies, or flexible endoscopy placed in the upper and lower esophageal segments (Fig. 69-21, *A* and *B*).

When no further elongation progress is evident or when the two ends of the esophagus can be brought to close proximity, an operation is performed. Thoracotomy or a thoracoscopic approach with dissection and mobilization of the proximal and distal esophageal segments is done and primary anastomosis is attempted. If these efforts do not allow primary anastomosis, circular myotomy, hiatal mobilization, Kimura procedure, proximal pouch flap esophagoplasty, or Foker's traction-elongation technique can be undertaken. When the two ends of the esophagus are clearly too distant for primary esophageal anastomosis despite preoperative attempts at elongation and consideration of these methods (i.e., lower esophagus does not reach above the diaphragm), we have proceeded with a primary gastric transposition to the cervical esophagus, typically without a thoracotomy. In these latter circumstances, many surgeons prefer to proceed to a cervical esophagostomy, preferably on the left side, with plans for a future esophageal replacement procedure. Postoperative complications are similar to those in infants with repaired EA-TEF (see the later section on outcomes); these adverse effects primarily include anastomotic leak and stricture, dysphagia, and gastroesophageal reflux disease (GERD).

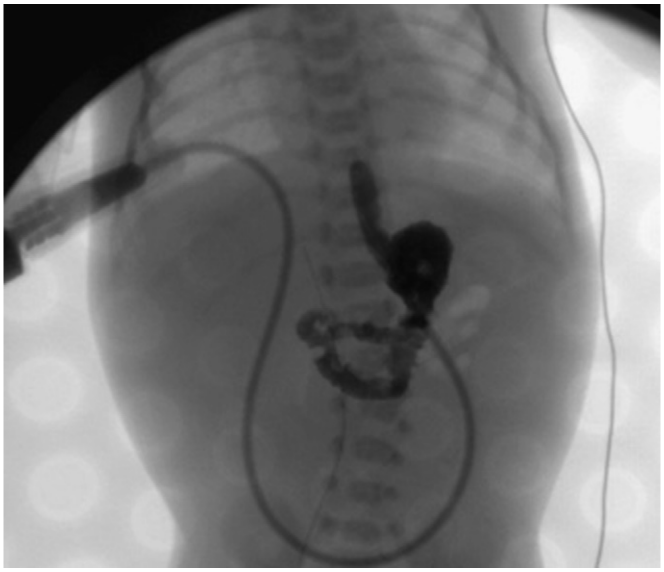


**FIGURE 69-20** Gastrostomy tube with contrast injection in an infant with isolated EA.

## ISOLATED (H-TYPE) TRACHEOESOPHAGEAL FISTULA

Congenital TEF without EA or the "H" type of TEF (perhaps more anatomically accurately called the "N" type) occurs in approximately 4% of esophageal anomalies reported. This anomaly is usually manifested in the first few days of life when the neonate repeatedly chokes on attempting to feed or has unexplained cyanotic spells.[184] When the infant is coughing or crying, intermittent abdominal distention can occur as air passes through the fistula into the stomach. Older infants and children are more likely to have recurrent bouts of pneumonia, typically involving the right upper lobe. A high index of suspicion is necessary in considering this diagnosis.

The diagnosis of isolated TEF can be suspected if plain radiographs of the chest show evidence of aspiration pneumonitis with gastric distention. A reliable way to establish the diagnosis is by tube video esophagography performed while the infant is prone; a small nasogastric tube is passed into the distal end of the esophagus, and contrast medium is gradually injected as the tube is slowly withdrawn. The radiologist performing the study must be familiar with this diagnostic approach because more than 50% of H-type fistulas may be missed on routine esophageal contrast swallow studies. Bronchoscopy with esophagoscopy can typically confirm the diagnosis and, if done immediately before surgery to divide the fistula, allows for the passage of a fine catheter or guidewire through the fistula to aid in subsequent identification at surgical exploration.[185]

Most isolated TEFs can be successfully divided through a cervical approach.[186] The site of a right-sided, low cervical incision is determined, and the infant is placed with the head extended and turned to the left. The sternocleidomastoid muscle is retracted posteriorly, with division of the sternal head if necessary; dissection then proceeds medially to the carotid sheath. Identification of the trachea and esophagus is facilitated by palpating the endotracheal and

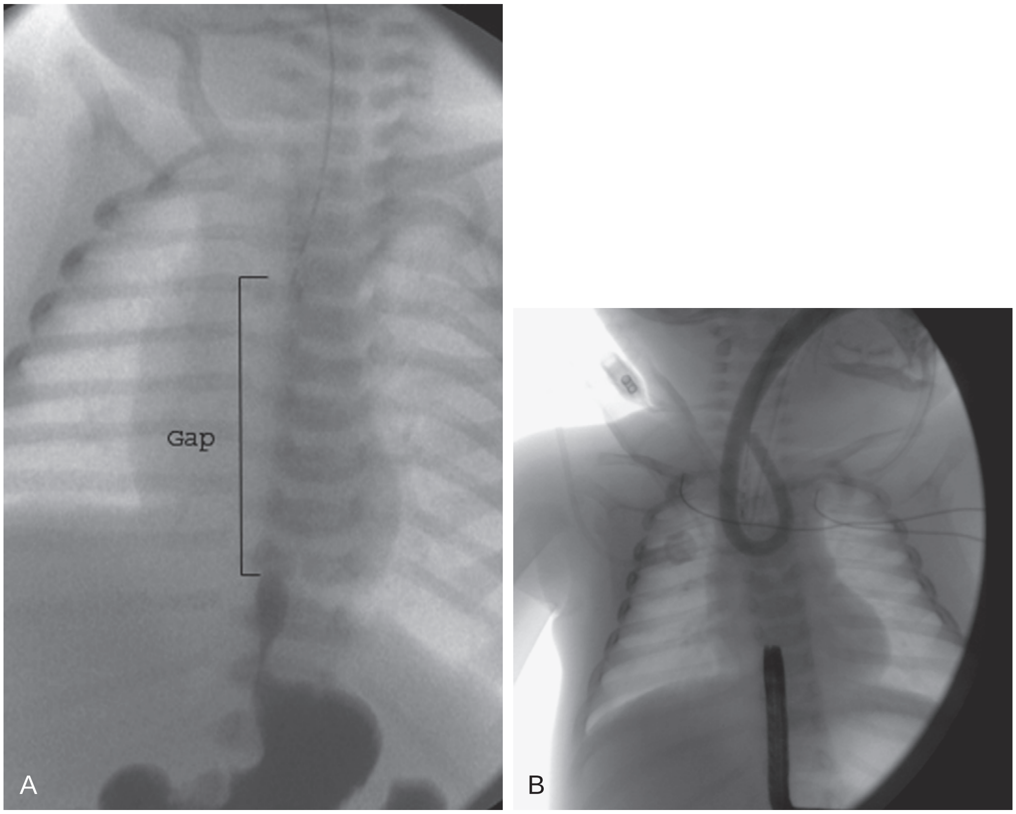



**FIGURE 69-21** A chest film taken with a Replogle tube pushing in on the upper esophageal pouch and a contrast injection through the gastrostomy tube demonstrates a long-gap isolated esophageal atresia **(A).** After 8 weeks, a repeat study with a bougie coiled in the upper esophageal pouch and a neonatal flexible endoscope passed through the gastrostomy site and up the distal esophageal pouch allows for assessment of interval narrowing of the gap **(B).**

nasogastric tubes. Division of the inferior thyroid artery and middle thyroid vein may be necessary to expose the plane between the trachea and esophagus. The recurrent laryngeal nerve must be identified and preserved. Identification of the fistula is facilitated by encircling the esophagus with Silastic slings, but it is important to be aware that the contralateral recurrent laryngeal nerve can be damaged during this maneuver. Once the fistula is identified (it is often higher than expected), traction stitches should be placed close to the esophagus through the superior and inferior extent of the fistula to avoid rotation of the esophagus after division of the fistula. On the tracheal side, 5-0 polypropylene sutures are placed at the superior and inferior limits of the fistula. The fistula is now divided close to the esophagus, and interrupted 5-0 Vicryl or PDS sutures are placed on the tracheal side to close the fistula. The esophageal side of the fistula is closed with absorbable polyglycolic acid sutures (Fig. 69-22). Some surgeons advocate interposing muscle tissue between the two opposing suture lines to reduce the likelihood of recurrence of the fistula. A right thoracotomy or thoracoscopic approach can be used on the rare occasion when the fistula is located well within the thorax or when a recurrent fistula from a previous EA repair is being approached.[187]

Postoperative complications include respiratory distress secondary to edema of the trachea or injury to the recurrent laryngeal nerves. The degree of preexisting lung disease and concerns about tracheal edema may warrant leaving the endotracheal tube in place for several days after the operation. Esophageal leak and recurrence of isolated TEF are rare.

## ESOPHAGEAL ATRESIA WITH AN UPPER POUCH FISTULA

There are two versions of this anomaly: (1) proximal pouch fistula in association with distal TEF (double fistula) and (2) proximal pouch fistula without distal TEF. Several reports have cited varying incidences of a fistula between the upper esophageal pouch and the trachea. The exact incidence of this type of fistula has probably been underestimated because some initially unrecognized proximal pouch fistulas have been reported as recurrent TEFs after repair of EA with distal TEF,[188] and some of these cases have been diagnosed as pure EA because the upper TEF was missed. A recent report by Bax and colleagues suggests that proximal pouch fistula without distal fistula is as high as 5.6% of all patients with EA.[189] The diagnosis can be made by a preoperative proximal pouch contrast study, preferably performed by a skilled pediatric radiologist under optimum conditions in the radiology suite using fluoroscopy and video recording or in the neonatal unit if necessary.[190] This study usually shows a small upper pouch in addition to identifying the fistula. However, a frequent point of confusion during this study and in the interpretation of results is the occurrence of spillover of contrast from the pouch up into the larynx and down into the trachea. Because of the potential for inaccurate interpretation, some surgeons rely on preoperative bronchoscopy to make or confirm the diagnosis of a proximal pouch fistula (Fig. 69-23).[190] Unfortunately, a small proximal fistula can also be missed when endoscopy is used. Another common approach to the diagnosis of this anomaly is complete mobilization of the upper pouch during repair of the EA in order to localize and repair

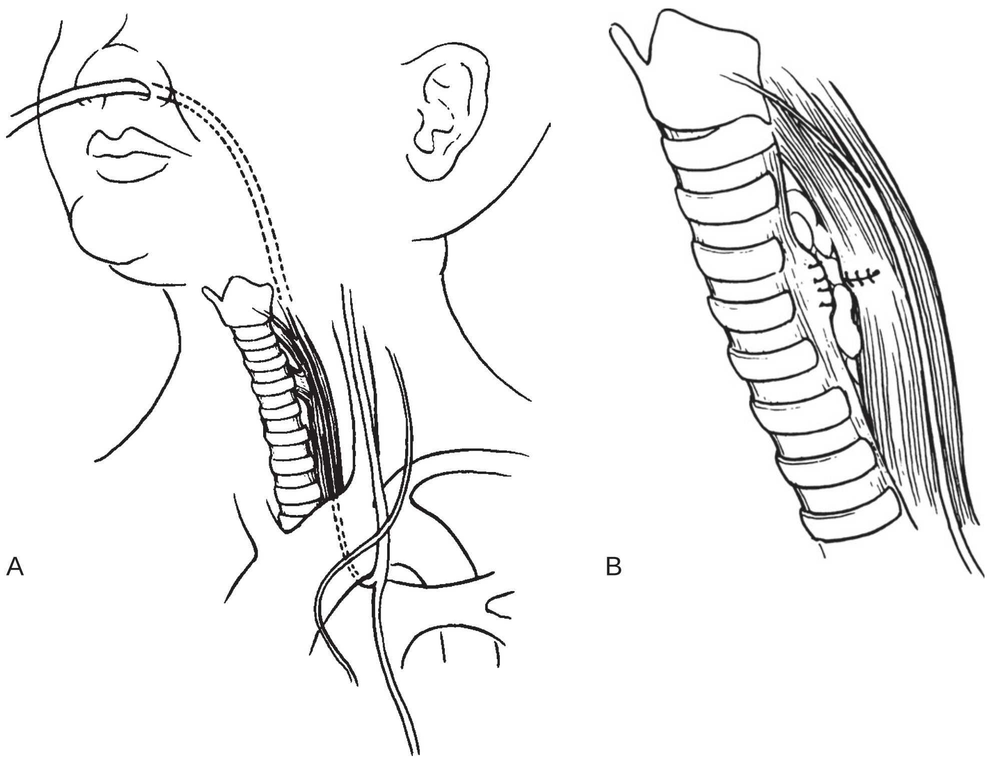



FIGURE 69-22 H-type tracheoesophageal fistula. **A,** Anatomic relationship between the fistula and the recurrent laryngeal nerve. **B,** After division, the fistula is closed by interrupted suture on both the trachea and esophagus.

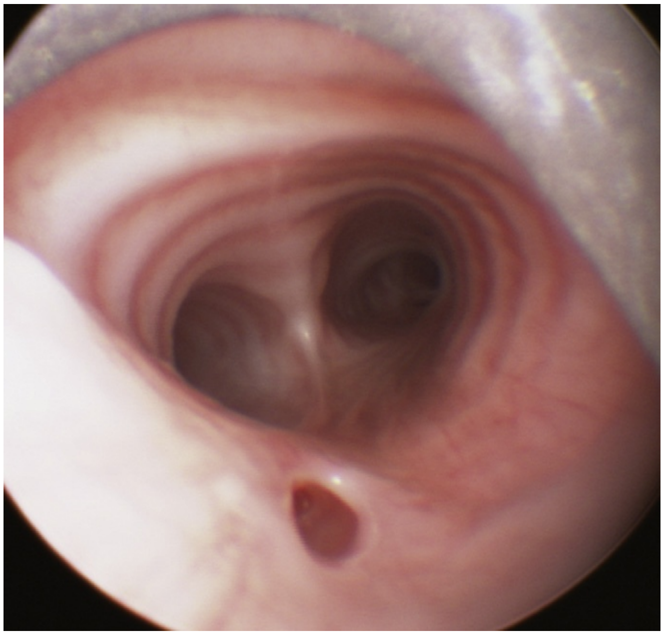


**FIGURE 69-23** Bronchoscopic view of an unexpected upper pouch tracheoesophageal fistula. *(See Expert Consult site for color version.)*

an unsuspected upper pouch fistula. As with the other diagnostic methods mentioned, proximal pouch fistulas may also be unrecognized during surgical exploration, in part because of the extreme proximal nature of some of these fistulas. A proximal pouch fistula should be suspected and specifically looked for if the upper pouch is unusually narrow or short at the time of preoperative imaging studies or at surgical exploration because such findings suggest decompression through a fistula.

Once identified, a proximal fistula should be surgically ligated and divided as with a distal TEF. If an upper pouch fistula is diagnosed after the initial repair of EA with or without distal TEF, a cervical approach can often be used as previously described for an H-type TEF.

# Outcomes

Survival rates for infants who have EA with or without TEF have improved dramatically in the past 50 years. Recent reviews reported 85% to 95% overall survival as compared with rates less than 40% before the 1950s.[64,65,105,191–194] However, subsets of infants with EA still have a worse prognosis. Waterston's risk classification scheme historically helped identify infants with EA who were at particular risk for a poor outcome and as such helped direct treatment options.[195] In recent years, other risk classification schemes have been proposed. A recent modified classification scheme suggests that revised class I (low-risk group) consisted of patients without major cardiac anomalies and birth weight greater than 2000 g; class II (moderate-risk group) consisted of patients without major cardiac abnormalities and birth weight less than 2000 g; class III (relatively high-risk group) consisted of patients with major cardiac anomalies and birth weight greater than 2000 g; and class IV (high-risk group) consisted of patients with major cardiac anomalies and birth weight less than 2000 g (Table 69-4).[196] Other recent evaluations suggest that infants with EA who appear to be at increased risk for death and long-term morbidity include those with (1) lower birth weight (<1500 g)/prematurity,[64,136] (2) major CHD,[66,191,193a] (3) severe associated anomalies and ventilator dependency,[92] and (4) a long gap length between the two ends of esophagus.[104]

# Complications

Despite excellent long-term survival for infants with EA, many significant complications can occur. In a recent evaluation of 134 EA patients older than 15 years, 49% had complications in the first year and 54% had complications after 1 year. Predictors of complications included twin birth, preoperative intubation, birth weight less than 2500 g, long-gap atresia, anastomotic leak, postoperative intubation longer than 4 days, and inability to feed at the end of 1 month.[197] Complications can generally be classified as early (including anastomotic leak, anastomotic stricture, and recurrent tracheoesophageal fistula) and late (including GERD, tracheomalacia, respiratory disease, and disordered esophageal peristalsis).

## EARLY COMPLICATIONS

### Anastomotic Leak

Whether open or thoracoscopic techniques are used, anastomotic leak at the esophagoesophagostomy occurs in approximately 13% to 16% of patients with EA.[123,198,199] Most leaks are clinically insignificant and can be managed with adequate drainage and nutritional support (Fig. 69-24). When a retropleural approach is undertaken and a patent mediastinal drain is in place, up to 95% of anastomotic leaks close spontaneously.[200] Even when transthoracic repair is followed by disruption and the pleural space is contaminated, adequate

**FIGURE 69-24** Anastomotic leak at the esophagoesophagostomy. The leak is contained and adequately drained. Right upper lobe atelectasis is common.

drainage can usually be achieved. This in turn allows spontaneous closure of the leak. Breakdown of the anastomosis is frequently followed by the formation of a stricture at the site of the leak and is sometimes associated with a recurrent TEF. Major disruptions of the esophageal anastomosis account for only 3% to 5% of postoperative leaks and are typically recognized early (24 to 48 hours) after the initial repair. The infant frequently deteriorates from tension pneumothorax or mediastinitis uncontrolled by drainage and antibiotics. Factors that probably contribute to anastomotic leak include poor surgical technique, ischemia of the esophageal ends, use of myotomy, and excessive tension at the anastomotic site.[201,202] In this critical setting, reoperation for control of sepsis with adequate drainage and attempted repair of the anastomotic leak are warranted. A pleural or pericardial patch, with or without an intercostal muscle flap buttress, may help secure anastomotic closure.[203,204] If the esophageal anastomosis is not repairable, cervical esophagostomy and delayed esophageal replacement may be required.

### Esophageal Stricture

Esophageal stricture is a common complication of anastomosis of the esophagus in EA, but the reported incidence varies widely depending on the criteria used to define a stricture. In a recent large series, stricture requiring dilatation is reported to occur in up to 80% of patients.[68,105,116,147a] Spitz and Hitchcock[91] proposed that stricture be defined as the presence of symptoms (dysphagia and recurrent respiratory problems from aspiration or foreign body obstruction) and narrowing noted on endoscopy or contrast esophagography (Fig. 69-25). Factors that have been implicated in the pathogenesis of esophageal stricture include poor anastomotic technique (excessive tension, two-layered anastomosis, and silk suture material), long gap, ischemia at the ends of the esophagus, GERD, and anastomotic leak. Reports of thoracoscopic repair of EA note stricture rates similar to many open operations (11% to 13%).[123,206] Up to 13% of infants and children will require removal of an esophageal foreign body after repair of EA with or without TEF, even in the absence of a stricture on contrast studies.[207] Parents have to be counseled about slow introduction of solids and keeping the food minced until the child has enough molar teeth to grind the food adequately because the scar in the area of anastomosis always remains.

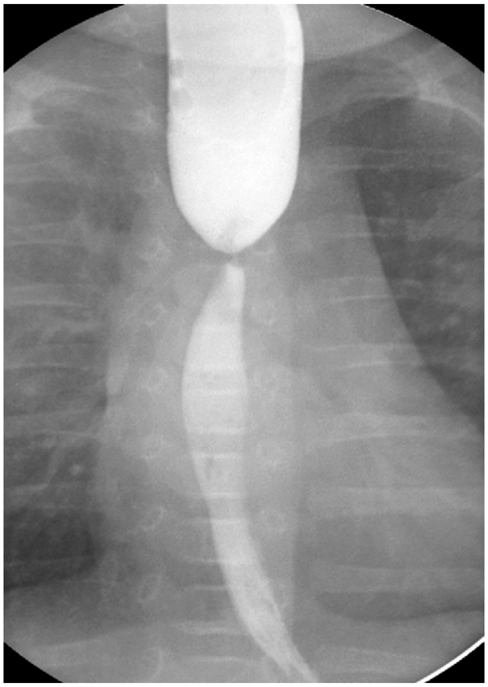


**FIGURE 69-25** Barium esophagogram showing an anastomotic stricture.

Clinically significant narrowing at the site of the esophageal anastomosis is traditionally treated by dilation performed via antegrade or retrograde bougienage. We have found that passing Savary-Gilliard type dilators prograde over a guidewire has many advantages: This method allows fluoroscopic assessment during sequential dilations, enables the use of contrast injection during the dilation session, and typically eliminates the need for rigid esophagoscopy. More recently endoscopic balloon dilators have been frequently used with good results.[208,209] This technique has the theoretic advantage of producing a uniform and radial force at the site of the stricture rather than the shearing axial force applied with traditional bougienage.[210–213] Many strictures respond to one to three dilations (53%) in the first months after esophageal repair. However, a recalcitrant stricture resistant to repeated dilations will require resection and reanastomosis or even esophageal replacement. Injection of triamcinolone at the stricture site during flexible esophagoscopy is used in many centers, mostly by pediatric gastroenterologists, but repeated injections may lead to adrenal suppression. Recently, the application of mitomycin C to the stricture under endoscopic control has been reported to reduce stricture formation after dilation. It is crucial to determine whether the esophageal stricture is associated with GERD by investigation with contrast esophagography, endoscopy, pH monitoring, or any combination of these studies. Because all EA patients demonstrate GER to some degree, children are routinely prescribed histamine-2 blockers at the time of discharge. In the presence of an anastomotic stricture or persistence of acid reflux, proton-pump inhibitors may be preferable. Many strictures do not respond to dilation attempts if severe GERD continues to bathe the stricture with acid.[212] When medical management of GER fails and the stricture does not respond to esophageal dilations, an antireflux procedure may be indicated. The stricture is often successfully treated with dilations after the antireflux operation; however, care must be given to not dilating the fundoplication because that significantly increases the possibility of recurrent GERD. The most recalcitrant strictures have been treated by resection and reanastomosis, or more recently by stenting. However, experience is still limited with the latter, and a fatal arterio-esophageal fistula from an unrecognized aberrant right subclavian artery has been reported.*

### Recurrent Tracheoesophageal Fistula

Recurrent TEF occurs in 3% to 14% of patients after initial operative division or ligation.[105,121,214–217,200] Recurrent TEF has been attributed to anastomotic leak with local inflammation and erosion through the previous site of TEF repair.

*From a poster presentation, “Arterio-esophageal Fistula from an Aberrant Right Subclavian Artery after Esophageal Stenting for Stenosis after Atresia Repair,” at the Annual Meeting of the Canadian Association of Paediatric Surgeons, Saskatoon, September 2010, by Lo and colleagues.

Techniques that have minimized the likelihood of recurrent TEF include the use of a pleural flap,[215] vascularized pericardial flap,[218–220] and azygos vein flap[221] interposed between the esophageal and tracheal suture lines. Although recurrent TEF typically occurs in the early postoperative period, it may not be recognized for months to years. Symptoms can be typical of those seen with a congenital H-type TEF including coughing and choking or cyanosis with feedings; however, less obvious symptoms such as recurrent pulmonary infections are more common. The diagnosis may be suggested by an air-filled esophagus on plain radiographs of the chest. Routine contrast swallow studies will miss up to 50% of recurrent fistulas. As with a congenital H-type fistula, contrast esophagography performed in the prone position under videofluoroscopy is a reliable method of establishing the diagnosis. Bronchoscopy with cannulation of the fistula with a 2- to 3-French catheter is also a reliable diagnostic approach and is invaluable in locating the fistula during the operative procedure. A recurrent TEF rarely closes spontaneously and typically requires surgical repair. Thoracotomy with fistula ligation and division is the operation of choice. To minimize the chance of recurrent fistulization, which has been reported in 10% to 20% of patients with a first-time TEF recurrence, pleura, intercostal muscle, or pericardium should be interposed between the esophagus and trachea.[222] A recent large series from the University of Michigan of 26 patients over 27 years reports postoperative complications to include leak (27%), esophageal stricture (15%), and recurrent TEF (11%).[223]

Endoscopic eradication of TEF by means of various chemicals or diathermy has been increasingly reported.[224–226] Diathermy or laser deepithelialization followed by fibrin glue has been reported in case reports and series with success rates as high as 85%[227,228]; however, others continue to report failure with chemical techniques.[229] A recent report of using argon plasma coagulation reports a 66% success rate.[230]

## LATE COMPLICATIONS

### Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) in infants and children with repaired EA is common, and the incidence seems to be increasing as suspicion and diagnostic investigation have become more common. In addition, the trend to preserve the native esophagus with many of the techniques described earlier in this chapter also promotes GERD. The magnitude of the problem is reflected in the finding that GERD occurs in 30% to 70% of patients after repair of EA.* The cause of GERD in this group of infants probably relates to shortening of the intra-abdominal portion of the esophagus because of anastomotic tension and/or esophageal motor dysfunction, either acquired as a result of operative manipulation or intrinsic to the congenital anomaly itself.[232–234] The consequences of GERD are then magnified by the poor or absent esophageal peristaltic pump, thus exposing the esophagus to prolonged acid contact. Esophagitis is frequently observed in older children and adolescents on long-term follow-up of patients with EA.[232,235–238] In several recent long-term follow-up studies, it appears that adults who had EA repaired as infants continue to be at risk for GERD and its complications,[239,240] including an apparent increased risk for the development of Barrett esophagus, perhaps as high as 9%.[239–241] In a recent case control study, 101 patients post EA repair with a mean age of 36 years (range 21 to 57) were compared with 287 controls. The authors found symptomatic GERD in 34% (vs. 8%), dysphagia in 85% (vs. 2%), and at endoscopy found an increased incidence of hiatal hernia (28%), Barrett esophagus (11%), esophagitis (8%), stricture (8%), and epithelia metaplasia (21%); manometry showed nonpropagating peristalsis in 80% and low distal wave amplitudes in all.[242] One case of esophageal adenocarcinoma was reported in a 20-year-old patient in whom an EA had been repaired during infancy.[243]

The diagnosis of pathologic GERD is suspected in patients with symptoms of vomiting, dysphagia, and recurrent anastomotic stenosis, which is occasionally associated with the impaction of a foreign body or food bolus. In addition, respiratory symptoms such as stridor, cyanotic spells, recurrent pneumonia, and reactive airways disease may indicate GERD rather than other conditions such as tracheomalacia.

The diagnosis of pathologic GERD in infants and children after repair of EA is suggested by upper gastrointestinal contrast study. Twenty-four-hour pH probe data, though not as standardized for children as they are for adults, typically document pathologic reflux.[232] Extensive esophageal manometric studies have consistently documented abnormal esophageal peristalsis and decreased lower esophageal sphincter pressures after EA repair; as a result, this test is probably not helpful in diagnosing GERD.[244] Multichannel esophageal impedance combined with pH monitoring may emerge as a superior test but is not widely available yet.[245]

In infants and children with pathologic GERD, aggressive medical management typically consists of thickening of feedings, positioning of the infant in a prone or upright posture, and administration of acid reduction agents such as histamine-2 blockers, proton pump inhibitors, and prokinetic agents. However, 45% to 75% of these infants ultimately undergo antireflux operations because of failed medical management, failure to thrive, chronic pulmonary infection, refractory anastomotic stricture, or the development of a distal esophageal stricture.[200,215,220] The choice of antireflux operation is controversial. The Nissen fundoplication has typically been considered the best option.[234,246–248] However, debilitating dysphagia and significant complications including wrap disruption and recurrent GERD in a third of patients have been frequent after the 360-degree wrap.[200,220,249,250] Because of the generally poor results with Nissen fundoplication in this setting, some surgeons have used the anterior Thal partial-wrap fundoplication in these patients. However, as other surgeons have modified the Nissen fundoplication to create a short, floppy wrap (1 to 1.5 cm over a large dilator), this operation continues to be commonly used.[246] In addition, because the esophagus is frequently shortened in the setting of repair of EA, some surgeons have used the Collis-Nissen fundoplication to gain intra-abdominal esophageal length.[171]

### Tracheomalacia

Substantial respiratory symptoms occurring after repair of EA-TEF can be due to tracheomalacia. Tracheomalacia has been noted to affect up to 75% of pathologic specimens from patients suffering from EA-TEF; however, the condition is problematic or significant in approximately 10% to 25% of

*References 105, 147a, 200, 215, 220, 231, 232.

infants after repair of EA-TEF, approximately half of whom require surgical correction.[215,251–253] It is often difficult to clinically distinguish these symptoms from those of recurrent TEF, anastomotic leak, or GERD.[254] Tracheomalacia is defined as generalized or localized weakness of the trachea that allows the anterior and posterior tracheal walls to come together during expiration or coughing. In infants with associated TEF, structural anomalies of the trachea were identified in 75% of 40 infants at autopsy, thus suggesting that embryologic events leading to TEF may contribute to the development of tracheomalacia.[254] The cartilage was shorter than normal and thereby failed to provide the support necessary to maintain a patent airway.[254] In infants, the trachea may also be easily compressed between the aorta anteriorly and the often dilated upper esophagus posteriorly after repair of EA-TEF; such compression has been considered a significant contributor to the pathophysiology of tracheomalacia. Kimura and colleagues[255] studied tracheomalacia with cine computed tomography and suggested that the primary cause of tracheomalacia is related to intrinsic tracheal weakness. This has been confirmed in the Adriamycin-induced EA-TEF rat model and may also provide more insight into the pathogenesis of the anomaly. The level of tracheal collapse is usually in the region of or just above the original site of the TEF in the distal third of the trachea, generally at the level of the aortic arch. Perhaps surprisingly, severe tracheomalacia appears less common in infants with pure EA,[256] but it has been reported.[182]

The clinical manifestations of tracheomalacia are broad and range from a "brassy" or "barking" cough in mild cases to recurrent pneumonia or acute, life-threatening apneic spells. Infants with tracheomalacia are often reluctant to feed because of difficulty breathing during feeding or cyanotic attacks. These symptoms usually appear after discharge from the hospital, when the infant is a few weeks to a few months of age.[256] Life-threatening apneic spells were noted in 27 of 32 children with tracheomalacia described by Filler and colleagues.[257] These spells occur during or within 5 to 10 minutes of a meal and are characterized by cyanosis progressing to apnea, bradycardia, and ultimately, cardiorespiratory arrest if not interrupted. The diagnosis is established by bronchoscopy with spontaneous ventilation, which reveals a slitlike lumen of the trachea at the involved area (Fig. 69-26). Because the symptoms overlap those of a stricture or GER, the initial investigation usually consists of a contrast esophagram; close attention to the tracheal air column on the lateral views during such a study will often reveal complete tracheal collapse during forced expiration (i.e., crying) or when contrast fills a distended upper esophagus just above the anastomosis.

Treatment of tracheomalacia remains controversial. Most infants with mild to moderate symptoms of tracheomalacia do not require operative intervention because the symptoms tend to improve with time. In infants with severe symptoms including acute life-threatening events, the operative treatment of choice is aortopexy.[258–261] This operation is usually performed through a left anterior mediastinotomy (Chamberlain approach) or anterolateral thoracotomy, and the ascending aorta and arch are sutured up to the posterior surface of the sternum after partial thymectomy. Lifting the aorta up in this fashion raises the anterior wall of the trachea and opens the tracheal lumen.[256,261] A proposed modification of this operation has been the use of a flap of pericardium based at the root of the aorta to be sutured to the sternum in cases in

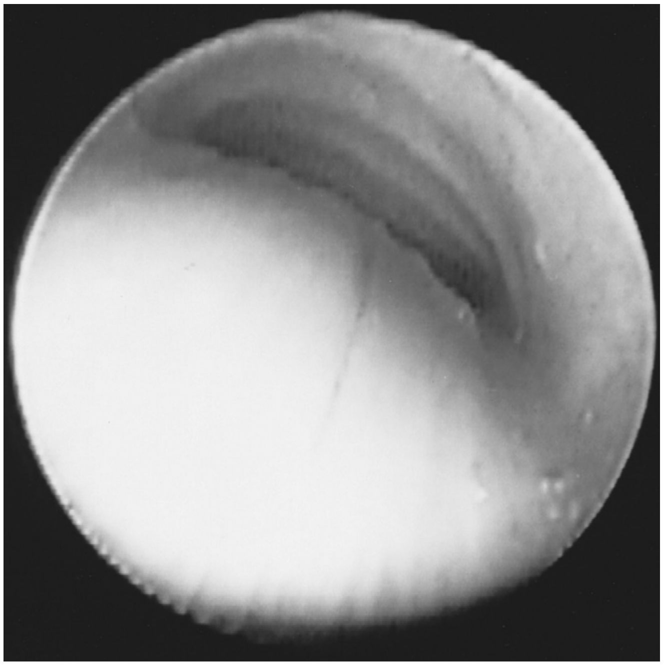


**FIGURE 69-26** Tracheomalacia after repair of esophageal atresia-tracheoesophageal fistula. A bronchoscopic view of the tracheal lumen during spontaneous respirations shows almost complete collapse of the trachea during expiration.

which the aortic arch would not reach the posterior aspect of the sternum without undue tension. An anterior mediastinal approach via a low transverse cervical incision for aortopexy and trachelopexy has recently been advocated.[263] Recently, a thoracoscopic approach for aortopexy has been reported to be a good alternative to thoracotomy.[264–266] Many surgeons use intraoperative bronchoscopy to document the adequacy of aortopexy with regard to opening the tracheal lumen as sutures are being tied or even before suture placement. Other surgical treatment options for tracheomalacia associated with EA have been suggested. The role of various stents in the treatment of tracheomalacia after repair of EA, though successful in case reports, has yet to be validated as a standard treatment method.[267–270] Filler and colleagues[257] recommend that an airway stent be considered for children in whom aortopexy fails to relieve tracheal collapse or for the rare cases of diffuse tracheobronchomalacia, for which aortopexy is not useful. Recently, glossopexy has been suggested as an early alternative to aortopexy to treat infants with suspected retrodisplacement of the tongue (glossoptosis).[271] Tracheostomy is a final treatment option if aortopexy fails, which is uncommon. It is fairly common to detect significant GER in patients with severe tracheomalacia; in such cases, we would advocate aortopexy before considering a fundoplication.

### Other Long-Term Quality-of-Life Issues

As previously discussed, the esophagus of an infant with EA has abnormal peristaltic activity that is secondary to the congenital defect itself, as well as secondary to operative repair of the lesion. The incidence of the problem approaches 75% to 100% in children and adults who have been studied with esophageal manometry. Dysphagia is worse after intestinal interposition for esophageal replacement. Occasional dysphagia has been reported to occur in up to 50% to 90% of adults,

with 30% having additional problems with choking.[253,272,273] This disorder is clinically significant in that it is responsible for many long-term symptoms after EA repair including dysphagia, esophageal foreign body obstruction, GERD, and recurrent respiratory problems. Although these symptoms may improve with time, early problems with feeding intolerance and food bolus obstruction can lead to failure to thrive. Many children must eat slowly and be selective with food choices. In a series of EA patients followed for 10 years, Lacher and colleagues[274] found 72% swallowed without problems; however, 41% had poor weight gain (<25$^{th}$ percentile).

In addition, recent reports have examined long-term respiratory outcomes after EA repair. One recent paper reports a greater than 60% incidence of recurrent respiratory infections, a 25% decrease in FEV1, and decreased maximal exercise performance at greater than 5 years beyond EA repair.[275] Another long-term follow-up study found respiratory symptoms in all patients including pneumonia 16%, bronchitis and asthma 52.3%, cyanosis episodes 9%, and cough 90%.[194] In our experience using small incisions and muscle sparing, thoracic deformities are extremely rare.

# Congenital Stenosis of the Esophagus

True congenital esophageal stenosis (CES) is a rare condition that has historically been confused with esophageal strictures secondary to inflammation, especially GERD. CES has been reported to occur once in every 25,000 to 50,000 births[276,277]; as of 2004, fewer than 600 cases have been described in the world literature. For unknown reasons, the incidence of CES seems to be higher in Japan than in other parts of the world.[278,279] The incidence of other anomalies associated with CES is reported to be 17% to 33%; these anomalies include EA with or without TEF; H-type TEF; cardiac anomalies; intestinal atresia; midgut malrotation; anorectal malformations; hypospadias; malformations of the head, face, and limbs; and chromosomal anomalies.[277] In addition, a report by Vasudevan and colleagues[280] noted that 5% of their patients with EA-TEF anomalies had CES with tracheobronchial remnants, whereas other reports suggest an incidence as high as 12% to 14% of patients with EA had associated CES.[278,281]

Classification schemes for CES have been numerous and confusing, in part because of the difficulty in differentiating congenital from acquired lesions. The definition and classification proposed by Nihoul-Fekete and colleagues[277] are perhaps the most clear. CES is defined as an intrinsic stenosis of the esophagus, present at birth, that is caused by congenital malformation of esophageal wall architecture.[277] This classification delineates three forms of CES: (1) a membranous web or diaphragm, (2) fibromuscular thickening, and (3) stricture secondary to tracheobronchial remnants in the wall of the esophagus.

A congenital membranous web or diaphragm is reported as the rarest of the three forms of CES.[282] It has been considered to represent a missed form of EA[25] and may be analogous to membranes in other parts of the gastrointestinal tract. It is usually a partially obstructing lesion located in the middle or lower portions of the esophagus. The membrane is covered on both sides with squamous epithelium and often has an eccentric opening. Symptoms typically occur at several months of age as the infant begins consuming solid food.

The second type of CES has been called *idiopathic muscular hypertrophy* or *fibromuscular stenosis* and in some reports has been the most common form of CES.[277] Its histologic characteristics are submucosal proliferation of smooth muscle fibers and fibrous connective tissue with normal overlying squamous epithelium.[277] A resemblance to hypertrophic pyloric stenosis has been suggested,[277,283] but no clear embryologic or pathogenic factors explain these lesions.

CES caused by tracheobronchial remnants is described as the most common type of CES in some reports and is certainly the most described and understood of the three types of CES. It is believed that CES caused by tracheobronchial remnants occurs as part of a spectrum of anomalies, including EA-TEF, related to separation of the foregut from the respiratory tract around the twenty-fifth embryonic day.[121] Tracheobronchial tissue is believed to become sequestered in the wall of the esophagus and comes to reside in the typical distal location because of the faster growth rate of the esophagus.

CES secondary to tracheobronchial remnants was first reported in 1936 by Frey and Dusche[284] in a 19-year-old woman who died with the diagnosis of achalasia.[121] In 1964 Holder and colleagues[62] reported three cases of distal esophageal stenosis in their review of 1058 infants with EA, TEF, or both. After several additional reports,[285,286] Spitz, in 1973, first demonstrated a clear congenital basis for this disorder.[287] In addition, 71 cases of CES have been reported in the Japanese literature as of 1981[279]; 6 cases were reported in the Chinese literature (out of 76 total cases of CES in 1987).[288] An additional three cases of CES have been reported, one of each type described earlier.[289]

## DIAGNOSIS

Symptoms of CES usually begin in infancy with progressive dysphagia and vomiting, generally after the introduction of semisolid or solid foods around the age of 6 months. Some case reports, however, describe severe symptoms of regurgitation and respiratory distress in the newborn.[277] In some patients, a foreign body in the esophagus may be the first symptom noted.[290] The correct diagnosis is frequently difficult to establish. Contrast esophagography typically reveals an abrupt distal esophageal narrowing, most often interpreted as a stricture related to GERD. Stenosis secondary to fibromuscular hypertrophy can result in a more tapered narrowing (Fig. 69-27). CES caused by webs or fibromuscular hypertrophy can be manifested as midesophageal or even upper esophageal stenosis.[291] Over time, the esophagus proximal to the stenosis can dilate, and contrast study results can be interpreted as achalasia.[292] Additional studies helpful in differentiating CES from achalasia and strictures caused by GERD include esophageal manometry and pH monitoring. Esophagoscopy typically shows esophageal narrowing with normal-appearing mucosa at the level of the stenosis in cases of CES. Recently, high-frequency endoscopic ultrasonography has been reported to be helpful in the diagnosis of CES.[293]

## TREATMENT

Treatment of CES should relieve the symptoms of stenosis and maintain the antireflux mechanism of the gastroesophageal junction. Bougienage has been successful in treating CES secondary to esophageal webs and fibromuscular

FIGURE 69-27 Barium esophagogram showing narrowing of the midesophagus as a result of congenital esophageal stenosis.

hyperplasia. Antegrade and retrograde tapered dilators have been the traditional form of bougienage, but more recent use of hydrostatic balloon dilation has been successful.[277,292,294,295] A series of dilations may be required for resolution of the stenosis. Membranous webs are typically adequately treated with dilation, and one report described successful endoscopic excision of a congenital web.[280,289,296,297]

Traditionally, most cases of CES secondary to fibromuscular hypertrophy and tracheobronchial remnants have been treated by surgical excision, either as the primary approach or after failed attempts at dilation.[294]

More recent recommendations suggest dilations should be aggressively attempted before committing to resection.[295] When resection is required, it is important to clearly identify the location of the stenosis before surgery by contrast esophagography in order to plan the operative approach. A right thoracotomy is typically used for stenosis in the midesophagus and a left thoracotomy for stenosis in the lower part of the esophagus. An abdominal approach should be used for CES in the abdominal portion of the esophagus. At exploration, the extent of the stenosis can be difficult to determine; the use of a balloon catheter passed beyond the stenosis, inflated, and pulled back against the stenosis has been suggested as a helpful technique.[298] Alternatively, a bougie passed from above or preoperative flexible upper endoscopy may demonstrate the stenotic area. In most cases, the stenosis is less than 3 cm in length and segmental resection and end-to-end esophageal anastomosis can be accomplished. Care should be taken to preserve the vagus nerves. Case reports have documented innovative surgical approaches including stenosis resection using limited myectomy, leaving the mucosa intact,[299] as well as thoracoscopic[300] and laparoscopic[301] approaches. In cases of long fibromuscular hypertrophy unresponsive to dilation, resection and esophageal replacement with the colon, stomach, or jejunum may be necessary. If the stenosis is near the gastroesophageal junction, most surgeons advocate segmental resection with esophageal anastomosis and an antireflux procedure to prevent postoperative reflux. Modified Hill gastropexy and Nissen fundoplication, with or without pyloroplasty, have been most commonly used[277,298]; however, Collis gastroplasty in combination with Nissen fundoplication has been reported to be effective for managing esophageal shortening and postoperative GERD.[278,294,302]

### RESULTS

Good long-term results have been reported for dilation and operative resection.[269] In patients who have undergone distal esophageal CES resection without an antireflux procedure, significant GERD has developed and required a subsequent antireflux operation. Reported complications from treatment by dilation include esophageal perforation and failure of therapy. Complications of resection and anastomosis include esophageal leak with mediastinitis, which can be successfully treated by mediastinal drainage.[270,272]

## Laryngotracheoesophageal Cleft

A laryngotracheoesophageal cleft (LTEC) is a rare congenital anomaly consisting of a midline communication between the larynx, trachea, and esophagus. The malformation was possibly first described in 1792 by Richter in his doctoral thesis, in which he described an infant who choked and vomited on feeding.[303] The infant died, but because no autopsy was performed, the diagnosis was unconfirmed. An infant with LTEC was next described in 1949 by Finlay.[304] In 1955 Pettersson[305] performed the first successful correction of a laryngotracheal cleft.

As with EA-TEF, the embryogenesis of LTEC is not completely understood. The long-held theory is that there is an arrest of the cranial extension of the tracheoesophageal septum that permits the persistence of an esophagotrachea.[306–308] More recent studies have suggested that as with EA-TEF, initial normal development is followed by a far-reaching fusion of the trachea and esophagus.[32] Although no consistent pattern of inheritance has been seen, sporadic familial associations have occurred; LTEC is reported with the “G” syndrome and the Pallister-Hall syndrome.[309] The incidence of LTEC favors males by a ratio of 5:3.[310]

Various associated congenital anomalies occur in the setting of LTEC including gastrointestinal, genitourinary, and cardiac malformations.[310] EA with TEF occurs in 20% to 37% of patients with LTEC.[310,311,312] Other associated gastrointestinal malformations include anal defects (21%), anomalies of rotation and fixation (13%), and meconium ileus (8%).[310,313] Genitourinary anomalies occur with an incidence of 14% to 44% and include hypospadias, inguinal hernias, undescended testes, and renal agenesis.[310,313] Cardiovascular anomalies, identified in 16% to 33% of patients, include ventricular septal defects, coarctation of the aorta, and transposition of the great vessels.[310]

To more adequately delineate therapy, several classification schemes have been described. In reporting the first surgical repair in 1955, Pettersson described three types of clefts: type I, limited to the larynx and involving part or all of the cricoid plate; type II, extending beyond the cricoid lamina to the cervical trachea; and type III, involving the entire trachea down to the carina. In 1991 Ryan and colleagues[314] suggested a type IV in which the cleft extends beyond the carina to involve one or both mainstem bronchi.

Symptoms of LTEC vary depending on the extent of the cleft, but most patients immediately after birth exhibit respiratory distress aggravated by feeding. Additional symptoms can include a characteristic toneless or hoarse cry, cyanosis, choking, increased secretions, and recurrent aspiration pneumonia. It is not unusual for the severity of associated anomalies to obscure the presence of LTEC, especially if it is a minimal type I or II lesion. On the basis of the common symptoms of LTEC, the diagnostic evaluation typically proceeds along the line of the more commonly suspected diagnosis of EA-TEF or tracheomalacia. Contrast esophagography demonstrates rapid confluence of contrast material in the upper part of the esophagus and trachea; however, it is often difficult to know whether this is secondary to spillover at the level of the larynx or passage of contrast through a cleft. Rigid endoscopy under general anesthesia is the definitive method for diagnosis of LTEC, but it can still be difficult to identify a cleft unless the index of suspicion is high and unless the frequent mucosal infolding at the level of the subglottic region is pushed open to reveal the cleft (Fig. 69-28).

Management of infants with LTEC begins by maneuvers to minimize aspiration and stabilize the airway. Ryan and colleagues[314,315] recommended avoiding endotracheal intubation before surgery if possible, but it is often necessary to intubate the trachea and perform tube gastrostomy before definitive surgical repair of extensive LTECs. Operative procedures vary depending on the severity of the cleft. Asymptomatic type I clefts may require no operative intervention, and symptomatic clefts have been successfully repaired endoscopically.[310] Type II LTEC can be approached through a lateral pharyngotomy, posterior pharyngotomy, or anterior laryngofissure. The lateral exposure has been most often reported; this method permits easy access to the cleft and allows asymmetric incisions in the mucosa, thereby avoiding contiguous suture lines. The major disadvantage to this approach is its risk to the recurrent laryngeal nerves. The anterior laryngeal approach exposes the larynx and upper part of the trachea and has no risk for recurrent laryngeal nerve injury. Concern about postoperative laryngeal stability has been raised, and some surgeons recommend the use of stents during the healing process.[310,316]

Operative management for types III and IV LTEC requires a combined cervical and thoracic approach. Donahoe and colleagues[311,314,315] have described the use of a specifically designed bifurcated endotracheal tube with flanged ends that can be positioned during bronchoscopy to suspend the trachea anteriorly with a ureteral catheter sling (Fig. 69-29). The endotracheal tube allows for confident airway control during the multiple position changes frequently required during the operation. A right thoracotomy is performed, and the tracheoesophageal cleft is exposed retropleurally. The tracheoesophageal groove is incised on the right and opened from the carina to the thoracic inlet. Separation of the two tubes is completed by incising along the left side of the common esophagotracheal wall, and an approximately 1-cm flap of esophagus running the length of the trachea should be left to help create the neomembranous portion of the trachea. It is important to size the esophageal flap correctly in order to avoid stenosis or a floppy posterior wall, which can result in tracheal obstruction. As the dissection proceeds, it is also important to push away and thus protect the left vagus and recurrent laryngeal nerves. Closure of the trachea and esophagus is accomplished in a caudal-to-cranial fashion with running polypropylene suture for the esophagus and interrupted polypropylene for the trachea. A right cervical incision is then made to expose the upper portion of the esophagus, trachea, pharynx, and larynx; the repair is continued with inclusion of a three-layer repair of the larynx and placement of a tracheostomy tube, which can be custom-designed to avoid undue pressure against the posterior tracheal repair. Some surgeons prefer an anterior approach and divide the larynx and trachea in the midline, as described for type II defects.[317] Cardiopulmonary bypass has been used both as a supporting technology

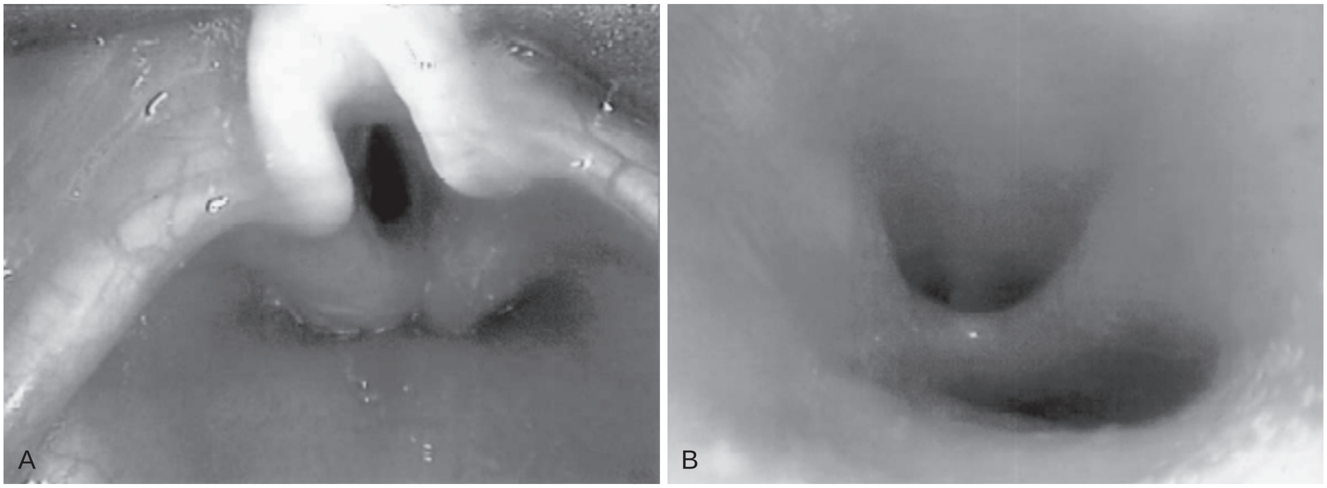



**FIGURE 69-28** Endoscopic view of a type III laryngotracheoesophageal cleft. **A,** Proximal end of cleft may be difficult to appreciate at first glance. **B,** Distal end of cleft ends just proximal to the tracheal bifurcation.

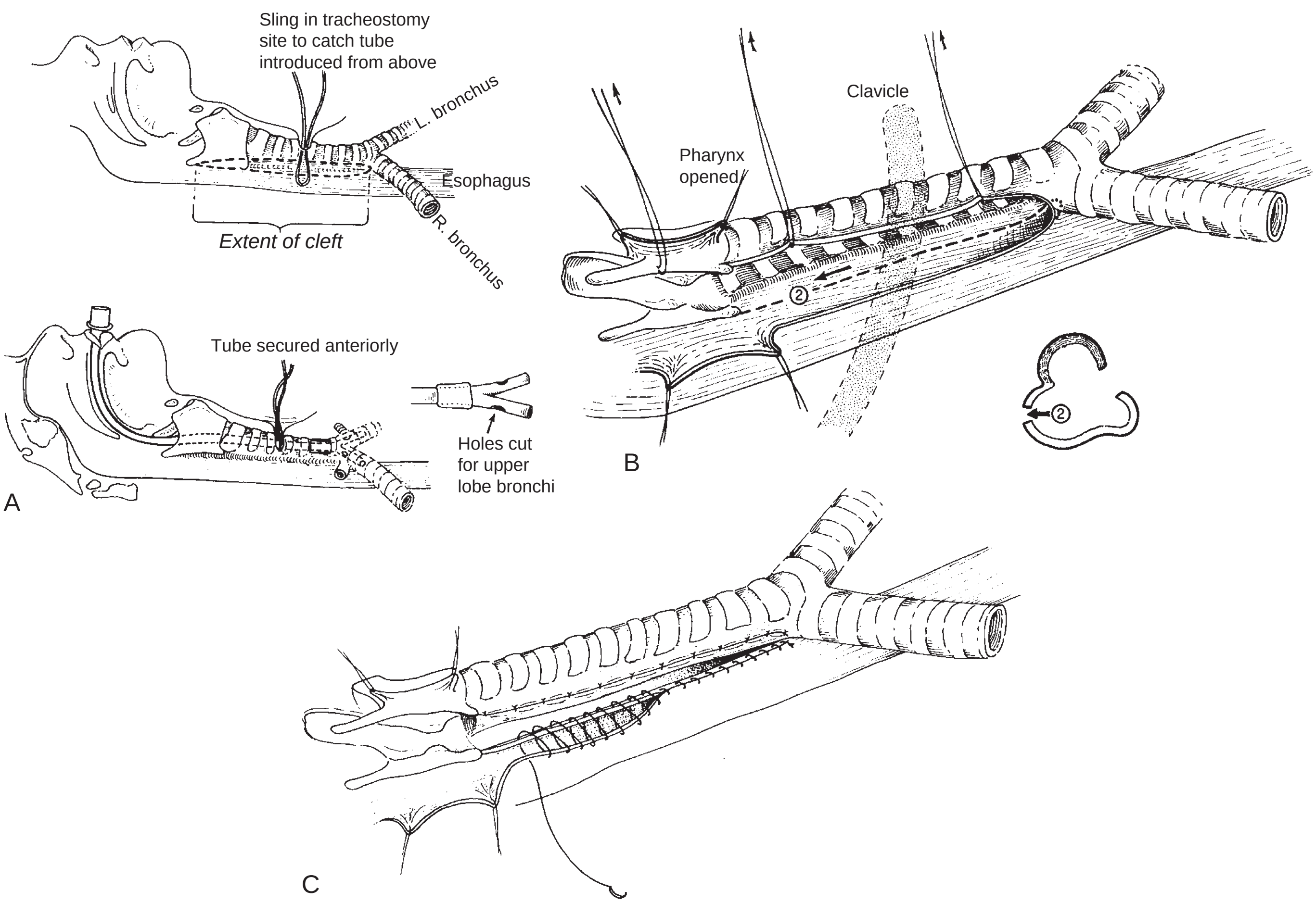



**FIGURE 69-29** Repair of a type III laryngotracheoesophageal cleft. **A,** Stabilization of a bifurcated endotracheal tube is done at bronchoscopy with a loop passed through a tracheotomy, which draws the endotracheal tube forward. **B,** A cervical and thoracic approach allows retropleural exposure of the cleft. A longitudinal incision is made in the right tracheoesophageal groove below the tracheal rings. The incision is extended inferiorly and across the esophagus and up the left side, with approximately 1 cm of esophageal wall left attached to the trachea to allow adequate tissue to close the trachea. **C,** The trachea has been closed with interrupted sutures, and the esophagus is closed in running fashion up to the thoracic inlet. Closure of the laryngeal portion of the cleft and the lateral pharyngeal wall is not yet accomplished. (From Donahoe PK, Gee PE: Complete laryngotracheal cleft: Management and repair. J Pediatr Surg 1984;19:143.)

during the anterior approach[318] to repair a type IV cleft and as support in the form of extracorporeal membrane oxygenation for one patient treated via a lateral thoracic and cervical approach.

Few patients with these complex anomalies are treated at any single institution.[310,315,319] Postoperative survival rates continue to be rather poor and range from 50% to 75%, depending on the severity of the malformation, associated anomalies, and prematurity. Anastomotic leakage is reported to occur in approximately 50% of repairs and typically requires reoperation via a different approach.[310] In addition, an inability to wean patients from the ventilator, pharyngoesophageal dysfunction, and GER are common postoperative complications. A reduction in morbidity and mortality depends, in part, on earlier recognition so that secondary complications can be prevented. At present there is no clear consensus about the best surgical approach; however, treatment is clearly complex and should be undertaken at centers with multidisciplinary expertise.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 70

# Caustic Strictures of the Esophagus

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## Historical Note

Corrosive ingestion is a disease of the industrial age.[1] The tragic consequences of ingesting caustic substances and the evolution of treatment methods have been well summarized by Tucker and colleagues.[2] Esophageal dilatation of the resulting stricture, initially using blind bougie dilatation through the mouth, has changed little in principle but greatly in practice as a result of technologic advances.[3,4] Development of the distally lighted esophagoscope, introduction of string-guided retrograde dilatation via gastrostomy, and improvements in general medical and nutritional support have nearly eliminated early mortality.[2,5–7] On the basis of experimental evidence, the use of steroids and antibiotics became widespread in the 1950s and 1960s in an attempt to reduce the incidence of stricture by inhibiting inflammation, scar formation, and infection.[8–19] There has been some recent progress in managing the fibrotic healing process (e.g., mitomycin C and increasing use of stents). However, mortality still occurs from pharyngeal and laryngeal burns resulting in edema and airway obstruction, massive ingestion with perforation, and complications after stricture dilatation or surgical bypass of an irreversibly damaged esophagus.[20–26]

## Epidemiology

The ingestion of corrosive substances remains a major health hazard in children, despite aggressive educational programs aimed at both children and adults, preventive labeling and packaging, and even legislation limiting the strength and availability of caustic substances.[1,2,6,27–30] In rural areas and in developing countries, caustic soda in both crystal and liquid form is used in home industry for soap making, fruit drying, and container cleaning on farms.[31] In addition, the availability of innumerable over-the-counter caustic cleaning agents virtually ensures that children will continue to be at risk. The most distressing aspect is that most ingestions occur in children younger than 3 years and are entirely preventable. Boys are more frequently involved.[1,23,27] Toxic ingestion in children older than 5 years is suspect, and ingestion in adolescents (where girls predominate) is usually intentional[1,32]; in these cases, larger volumes and more potent corrosive and caustic materials tend to be used. Although mortality is rare, morbidity is often devastating and can be associated with lifelong consequences. Comprehensive statistics dating back to the 1970s indicate a decrease in the incidence of ingestion; however, in developing countries, the many reports of esophageal replacement procedures bear witness to this serious worldwide public health problem.[1,24,31,33–35] This is particularly true in areas where corrosive substances are available in containers that are not childproof or where such substances have been decanted from larger containers for use in homes.[1] There is still a great need for adult education and for legislation to ensure correct labeling and safe packaging and to restrict the strength and availability of caustic agents.[27,29,30]

Approximately 20% of ingestions of caustic substances result in some degree of esophageal injury.[15,32,36] Early management strategies for ingestion are now well defined, particularly the use of fiberoptic endoscopy to assess the extent and severity of injury.[37–39] However, controversy still surrounds the use of steroids, antibiotics, and esophageal stents, as well as the timing, frequency, and method of esophageal dilatation in the prevention and management of caustic strictures. Indications for definitive esophageal surgery or bypass and the type of procedure to use are also subjects of ongoing debate.[22]

## Cause

Strong alkalis that are sold in both liquid and granular form are the principal cause of severe injury (Table 70-1).[27] Household bleach, dishwasher detergents, and other cleaning agents, all of which are moderately alkaline, are the most frequent corrosive materials ingested. However, these burns are usually limited to the esophageal mucosa, without extensive necrosis or subsequent stricture formation.[27,40] A wide variety of caustic substances can cause direct injury to living tissues, particularly to moist mucous membranes, including corrosives such as potassium and sodium hydroxide (lye) and phenols; reducing agents such as hydrochloric and nitric acids; desiccants such as sulfuric acid; oxidizing agents such as chromic acid, sodium hypochlorite, and potassium permanganate; and protoplasmic poisons such as acetic and formic acids.[6,41,42] The physical form of the substance ingested and its pH play a substantial role in the site and type of

**TABLE 70-1**
**Common Caustic Substances Ingested**

| *Caustic Substance* | *Type* | *Commercially Available Form* |
|---|---|---|
| Acids | Sulfuric | Batteries |
| | | Industrial cleaning agents |
| | | Metal plating |
| | Oxalic | Paint thinners, strippers |
| | | Metal cleaners |
| | Hydrochloric | Solvents |
| | | Metal cleaners |
| | | Toilet and drain cleaners |
| | | Antirust compounds |
| | Phosphoric | Toilet cleaners |
| Alkali | Sodium hydroxide | Drain cleaners |
| | Potassium hydroxide | Oven cleaners |
| | | Washing powders |
| | Sodium carbonate | Soap manufacturing |
| | | Fruit drying on farms |
| Ammonia | Commercial ammonia | Household cleaners |
| | Ammonium hydroxide | |
| Detergents, bleach | Sodium hypochlorite | Household bleach, cleaners |
| | Sodium polyphosphate | Industrial detergents |
| Condy's crystals | Potassium permanganate | Disinfectants, hair dyes |

postingestion esophageal injury, with a pH greater than 12 or less than 1.5 being associated with severe corrosive injuries.[1,12,41,43,44] Crystalline drain cleaners in the form of concentrated sodium hydroxide tend to adhere to the oropharynx or become lodged in the upper esophagus, where injury is most severe.[12,45–47] Highly concentrated caustic liquids usually pass rapidly through the oropharynx and cause injury to the entrance of the esophagus, the midesophagus, and immediately proximal to the esophagogastric junction.

Unlike alkaline solutions, which do not have much taste, strong acids are bitter, burn on contact, and are usually expectorated. However, when swallowed, they pass rapidly through the esophagus and cause the most substantial damage in the antrum of the stomach. The injury tends to be worse when the stomach is empty.[48] The duodenum and proximal small intestine are relatively protected by pylorospasm.[6,49–51] Ferrous sulfate as tablets (Clinitest) or capsules may also induce caustic injury to the esophagus or stomach.[52] Disk batteries contain concentrated potassium or sodium hydroxide, but they rarely lodge in the esophagus because of their small size.[53] If charged, these batteries may also cause injury to adjacent mucosa because of hydrolysis at the negative electrode.

# Pathophysiology

Much of what is known about the pathology of caustic injury in children has been derived from adult experience with self-inflicted injury and experimental studies in animals.[44–46,54–59] Injury to mucosal surfaces occurs within seconds after contact with a strong acid or alkali.[44,46] The nature of the injury caused by acidic and alkaline substances differs considerably. With acid ingestion, coagulation necrosis of the mucosa, hard eschar formation, and usually limitation of acid penetration through the mucosa occur. With alkali ingestion, tissue penetration with liquefactive necrosis is followed by destruction of the epithelium and submucosa, which may extend through the muscle layer.[8,41,44] Ischemia and thrombosis are dominant early processes.[60] A friable discolored eschar develops, under which tissue destruction continues until the alkali is neutralized. The esophagus is damaged principally at the areas of holdup: the cricopharyngeal area, the midesophagus where it is crossed by the aortic arch and left mainstem bronchus, and immediately above the esophagogastric junction. Immediate spasm and disorganized motility occur; these events may result in delayed emptying and even gastric regurgitation.[61] Hemorrhage, thrombosis, and marked inflammation with edema may be seen in the first 24 hours after injury. Depending on the degree of burn, inflammation may extend through the muscle layer until perforation occurs. After 48 hours, there is evidence of thrombosis of submucosal vessels, which gives rise to local necrosis and gangrene. Bacterial contamination leads to the development of small intramural abscesses, which may extend to the mediastinum with full-thickness injury.[9] After several days, necrotic tissue is sloughed, edema decreases, and neovascularization begins. This early reparative or subacute phase is evident from the end of the first week through the second week after injury. Scar formation begins in the third week, when fibroblast proliferation replaces the submucosa and muscularis and stricture formation commences. Mucosal re-epithelialization begins during the third week and is usually complete by the sixth week. It is during this period that adhesions may form, narrowing or obliterating the esophageal lumen. The end result may be a fibrotic stricture and a shortened esophagus.[8,62] If the injury is transmural, necrosis may extend to the surrounding mediastinum, leading to mediastinitis, or in an anterior direction into the trachea, giving rise to tracheoesophageal or even aortoesophageal fistulas.[21,26,63,64]

Steroids have been used to modify the inflammatory response both at the site of the burn and in the deeper tissues, with the ultimate goal of less extensive scarring.[9,12,44,47,65,66] However, the extent of the initial injury largely determines the outcome of the healed injury; this can range from mucosal re-epithelialization, with loss of esophageal glands and some submucosal fibrosis but preservation of the muscularis, to complete replacement of the esophageal wall by fibrous tissue.[46,67] Once the muscle of the esophagus has been destroyed, it cannot regenerate; at that point, maturation of the fibrous replacement with epithelialization of the luminal surface is the only "positive" outcome.[11] Reduction of scar tissue formation by induced inhibition of intermolecular covalent bonding of collagen with lathyrogens and other antifibrotic agents has been demonstrated experimentally, and recently mitomycin C has been reported to be efficient at a dose of 1 mg/mL concentration applied locally with a soaked swab for 4 minutes immediately after dilatation.[10,19,22,38,65,68–73]

# Clinical Presentation

Most infants and children who ingest caustic substances present with few symptoms or signs.[36–38,74] Only approximately one quarter have substantial objective evidence of corrosive ingestion.[36,75] The extent and severity of injury depend on

the concentration and form of the ingested substance. Crystalline alkalis tend to adhere to moist surfaces and cause immediate pain; in this case, oropharyngeal burns and primarily upper esophageal and laryngeal injury result. Esophageal burns in the absence of objective oropharyngeal evidence may occur in a small percentage (≤10%) of patients and should not deter the clinician from taking the appropriate diagnostic steps.[76] However, most patients with extensive oropharyngeal injury present with substantial esophageal damage; esophageal injury is unlikely if only the tongue and soft palate are involved.[36–38,75]

The viscosity and specific gravity of corrosive acids are lower than those of liquid alkalis. As a result, acid ingestion is associated with rapid transit through the esophagus; thus this organ may be largely spared. Damage occurs primarily in the antrum of the stomach because of the pooling of swallowed acid proximal to the pylorus, which goes into spasm on contact with the ingested acid.[25,50,58,77]

Obvious signs and symptoms of injury may be evident, with inflammatory mucosal edema in the oropharyngeal area and severe pain in the mouth and in a retrosternal direction.[74,75] This is often associated with agitation and tachycardia. Drooling and inability to swallow indicate severe posterior pharyngeal or upper esophageal injury.[47,65] Acute obstruction of the upper airway may result from posterior pharyngeal and laryngeal edema caused by spillage of the caustic agent into the upper airway.[32,78]

Concentrated ammonia fumes may be inhaled, causing nasopharyngeal edema and leading to respiratory injury.[32] Although rare, esophageal perforation with mediastinitis, peritonitis, and shock may occur.[21,47]

## Initial Management and Diagnosis

Initial management is directed at maintaining an adequate airway and oxygenation and ensuring cardiovascular stability. A few patients may require immediate intervention to maintain the airway. Once respiratory and hemodynamic stability has been achieved, the noxious agent, its composition and concentration, and the circumstances of ingestion should be investigated. Although the caregiver should be able to identify the ingested substance, this information is often lacking. Many health regions have poison centers where detailed product information is available.[79] In cases of caustic ingestion, inducing vomiting or encouraging the ingestion of any liquid is contraindicated because the alkali is mostly neutralized by gastric acids, and the consequences of acid regurgitation may cause further injury. Also, inhaled or aspirated vomitus may introduce corrosive matter into the upper airway, leading to acute inflammation and edema with airway obstruction.

Because the history and physical examination are unreliable in assessing the degree of esophageal involvement, endoscopic examination of the oropharynx and upper gastrointestinal tract is crucial.[37] Fiberoptic endoscopy is both accurate and safe, especially when done within 24 to 48 hours after ingestion.[3,7,38,39,54] Unnecessary treatment is avoided when esophageal injury can be excluded; however, there is still debate about which patients with a history of ingestion require endoscopy. Some advocate endoscopy only in symptomatic patients.[80,81]

Technetium-labeled sucralfate radioisotope scanning of the esophagus has been used successfully as a screening device, with lack of sucralfate adherence indicating the absence of significant injury (Fig. 70-1).[82] Using endoscopy findings to grade the severity of the injury, one can predict the long-term outcome, particularly with regard to subsequent stricture formation; however, it is sometimes difficult in practice to obtain an accurate assessment (Table 70-2).[32,54,83] An attempt is made to visualize the entire upper gastrointestinal tract, but identifying circumferential or grade III injuries provides sufficient information to initiate treatment protocols; attempts at further visualization are unnecessary and potentially dangerous.[32,67] Perforation in this situation is a severe complication that may be accompanied by mediastinitis and even mortality. In the presence of visual evidence of a pharyngeal burn with stridor, early esophagoscopy is contraindicated because of the risk of aggravating the airway obstruction.[30] Indirect fiberoptic laryngoscopy is useful to assess the upper airway.[47] Esophagoscopy may be done at the same time if esophageal intubation is required, or it may be done later, when edema of the upper airway has resolved. Initial radiographic studies should be restricted to the neck, chest, and abdomen if aspiration or respiratory burn is suspected. If fever, systemic sepsis, and upper abdominal signs are present, perforation may have occurred and a water-soluble contrast esophagogram may be useful to provide evidence of perforation.[38] A contrast esophagogram is usually done after 10 to 14 days, when an assessment of the entire esophagus and upper

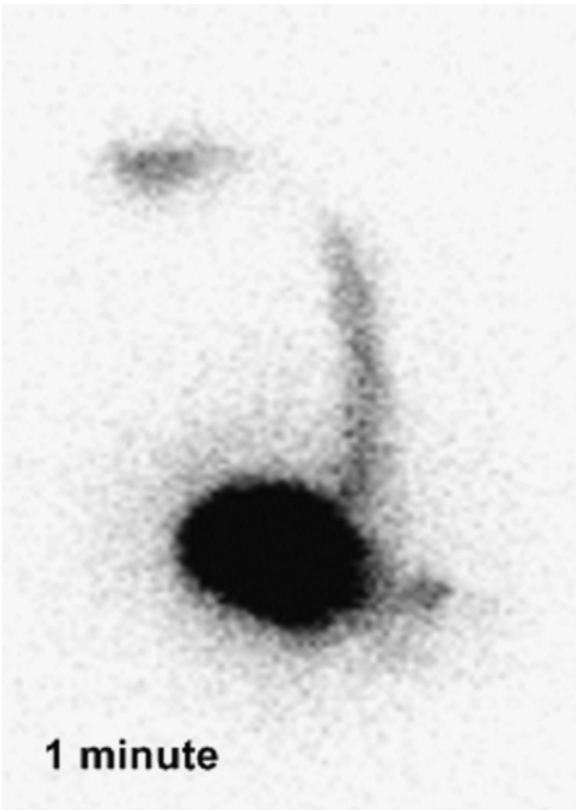


FIGURE 70-1 Technetium-99m–labeled sucralfate isotope scan after caustic ingestion. There is abnormal adhesion of sucralfate to the entire esophagus. Residual buccal activity is noted. The findings are in keeping with a caustic injury to the entire oesophagus. Endoscopy confirmed grade 2 injury to the distal two thirds of the esophagus.

**TABLE 70-2**
**Endoscopic Grading of Injury Severity**

| *Grade* | *Description* |
|---|---|
| 0 | Normal |
| I | Edema and hyperemia of mucosa |
| IIa | Friability: hemorrhage; erosion blisters, exudates, or whitish membranes; superficial ulcers |
| IIb | Grade IIa plus deep, discrete, or circumferential ulceration |
| IIIa | Small scattered areas of necrosis; areas of brownish black or gray discoloration |
| IIIb | Extensive necrosis |

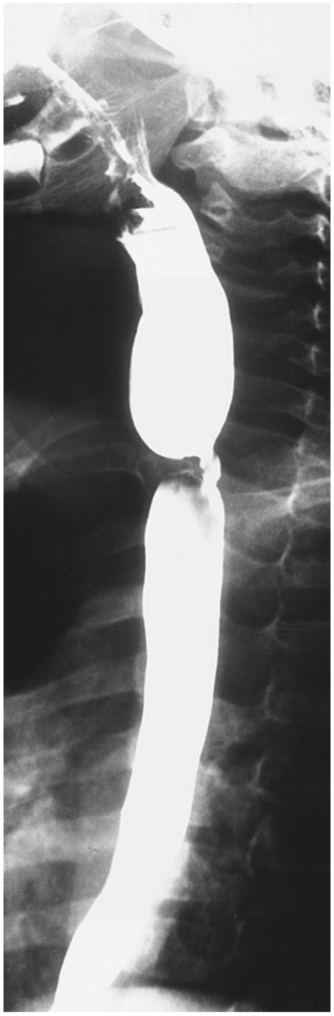

FIGURE 70-2 Localized stricture from ingestion of caustic crystals in a 4-year-old. The patient was managed successfully by local resection and primary esophageal anastomosis.

gastrointestinal tract can identify the extent of injury and may help in choosing the appropriate therapy (Fig. 70-2).[84]

# Treatment

If a known mild irritant such as hypochlorite bleach has been ingested without evidence of injury, treatment can be expectant.[4,39,75] If the substance ingested is not known and symptoms are apparent, endoscopy is indicated.[4,83,85,86]

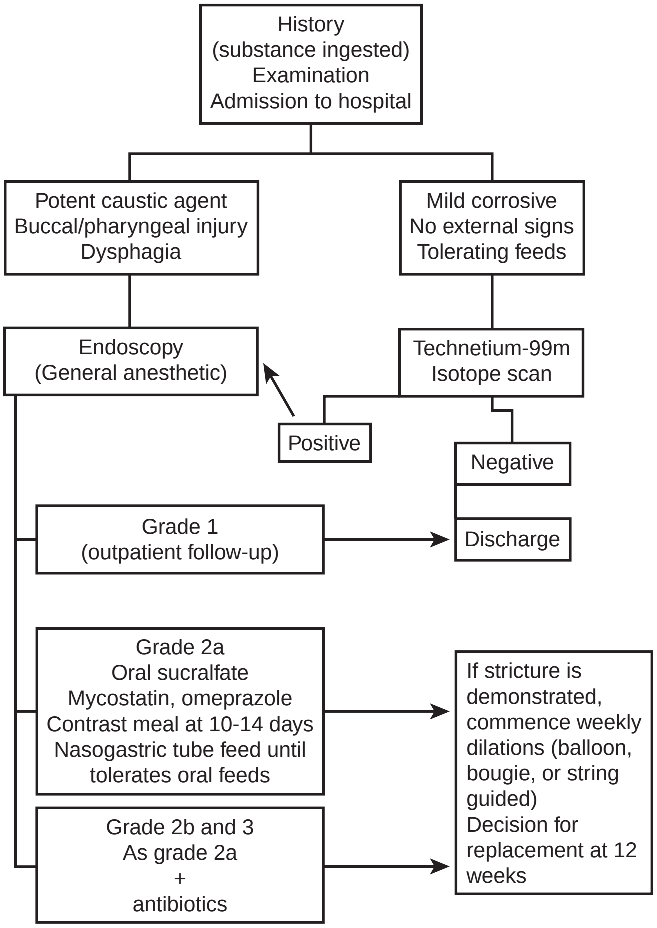


FIGURE 70-3 Management protocol for caustic strictures of the esophagus.

For patients with first-degree burns (grade I injury), no specific treatment is necessary. Liquid oral intake is initiated and extended to solids. If solid foods are tolerated, the child can be discharged. Clinical follow-up at 2 to 3 weeks is indicated, and contrast examination is done if residual clinical symptoms of dysphagia are noted. Our management protocol is summarized in Figure 70-3.

Patients with moderate (grade IIa) or severe (grade IIb and III) injuries require further treatment aimed at the prevention of stricture formation because up to 50% will develop strictures.[76,87] Although most patients with grade IIa injuries recover completely, close follow-up is required and endoscopy and dilatation must be done as prophylactic measures.[3,4] Major controversy surrounds the treatment options for severe injuries—namely, the use of steroids and antibiotics, esophageal stents, and esophageal dilatation.[88] Grade IIIb injuries are rare in the pediatric age group and usually occur in adolescents attempting suicide. These injuries may require immediate and aggressive surgery if extensive necrosis and perforation are present, especially if the stomach is also involved.[54,57,89]

The use of systemic steroids is based on the knowledge that they inhibit the inflammatory response, which is backed up by animal experiments.[8,9,12,28,44] However, in clinical trials using a variety of dosing regimens, no statistical difference in the prevention of stricture formation was evident.[90,91] Extensive retrospective reviews have also failed to show any significant

benefit of steroid therapy for patients with severe injuries.[47,54,92] More recently, the use of high-dose steroids (dexamethasone 1 mg/kg/day) has been advocated.[11,65,93] However, the number of patients in these studies was small, and morbid conditions such as mycotic infection of the esophagus, osteitis, peptic ulceration, and osteoporosis were significant.

For patients with severe injuries, a nasogastric tube may be passed for early feeding purposes. In patients who are unable to swallow, the tube can be used for enteral feeding, to serve as a guide for prograde dilatation and to maintain patency of the esophageal lumen.

In most cases, oral feeding commences as soon as the patient can swallow saliva. If dysphagia occurs, an esophagogram can identify the extent of involvement. Concomitant use of antifungal agents, antacids, and acid-secreting inhibitors ($H_2$ receptor blockers or proton pump inhibitors) is widespread, but their efficacy has not been proved.[3,4,6,30]

## Complications of Injury and Treatment

If a stricture is demonstrated on contrast radiography done 10 to 14 days after injury, a program of dilatation is commenced (Fig. 70-4).[4] Various methods can be used, ranging from mercury-filled bougies, flexible-graded bougie dilatation, guidewire-directed metal olives (Eder-Puestow system), or various balloon dilators.* Dilatation should always be attempted with great care. Initial passing of bougies for prograde dilatation should never be done blindly. If there are several strictures and visualization is difficult, it is much safer to place a transesophageal string, which is then used to guide the dilators either retrograde through the gastrostomy or antegrade through the mouth.[2] This is best done by initially passing a soft-tipped, flexible guidewire into the distal esophagus through a gastrotomy.[16,101] Easy access to the gastroesophageal orifice is gained by advancing a polyvinyl chloride endotracheal tube up the lesser curve through the gastrotomy or passing a guidewire under vision using a transgastric fiberoptic endoscope.[103] For satisfactory dilatation of a stricture, a general anesthetic is required in the early stages to protect the airway.

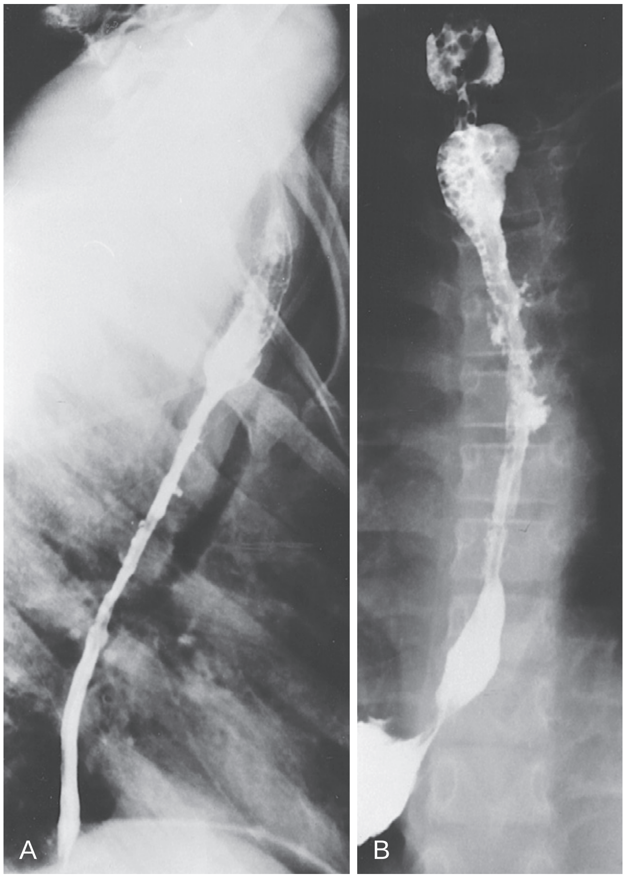


**FIGURE 70-4** **A,** Early esophagogram after caustic ingestion. **B,** Several areas of full-thickness ulceration progressed to extensive strictures, which required esophageal bypass.

To be effective, dilatations should be done at least once a week, commencing with catheters that are one or two French sizes smaller than the estimated diameter of the stricture. It is generally prudent not to dilate more than two to three sizes larger than the size of the first dilator meeting resistance. Initially, dilatation should be continued as long as esophageal healing and a progressive increase in esophageal caliber are noted, along with reestablishment of normal feeding. Factors indicating a poor prognosis are delay in presentation, extensive grade III injury, ongoing esophageal ulceration, a densely fibrotic stricture that cracks on dilatation, a stricture longer than 5 cm, and inadequate lumen patency despite repeated dilatations over a 9- to 12-month period.[23,104] No data support the routine use of prophylactic antibiotics; however, if systemic infection or transmural necrosis occurs, appropriate antibiotic therapy should be commenced.[44,75,96] During recovery, it is essential to provide adequate nutrition; in most cases the gastrointestinal tract can be used, with access through the nasogastric tube or by placement of a feeding gastrostomy or jejunostomy tube.

If dilatation fails and a dense stricture develops, it requires treatment.[94] As with other benign esophageal strictures, the incidence and severity of gastroesophageal reflux must be investigated and excluded as a contributing cause of the persisting stricture.[23,63,95,105–107] Gastroesophageal reflux should be managed surgically, if necessary, before definitive procedures to resect a stricture or replace the esophagus are attempted (Fig. 70-5).[47,108] Localized strictures may be resected with an end-to-end anastomosis. However, the whole esophagus must first be carefully assessed endoscopically to confirm that the stricture is indeed localized, because histologic evidence of fibrotic injury may be much more extensive than is evident on radiography.[23,35] A healthy color of the esophageal mucosa and distensibility with air insufflation at esophagoscopy are useful signs when assessing the esophagus. Local injection of steroids (1% triamcinolone acetate) into short strictures has had some success when combined with dilatation but has not been assessed prospectively. Likewise, application of mitomycin C has also been used with reported success (vide supra).[13,16,19,63,109–111]

*References 3, 4, 23, 29, 85, 94–102.

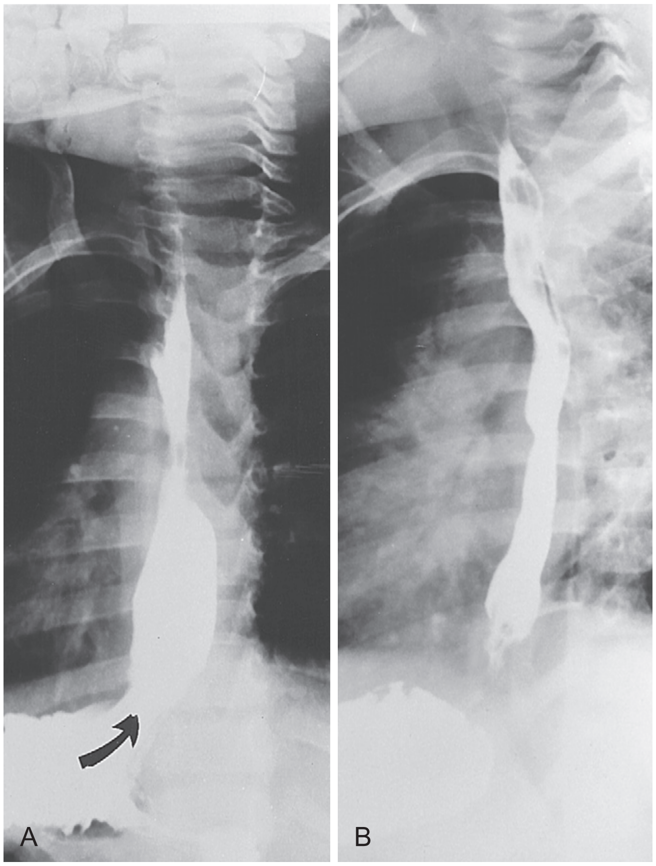


FIGURE 70-5 **A,** Contrast esophagram of a persistent caustic stricture of the midesophagus, with esophageal shortening and marked gastroesophageal reflux (*arrow*). **B,** This resolved after antireflux surgery and dilatation.

Some investigators advocate the use of esophageal stenting by means of an indwelling nasogastric tube.[112–114] The lumen is maintained, and adhesion of de-epithelialized areas of the esophagus is prevented; simultaneously, tube feedings can be given. Over the years, various types of stents have been used (e.g., silicone, polytetrafluoroethylene).* If used, stents should remain in place for at least 6 weeks, at which time epithelial healing should be complete and fibrosis will have begun to mature. However, in many cases these tubes are not well tolerated; they may promote gastroesophageal reflux, and if an extensive inflammatory response through the muscle occurs, the stent must be in place for much longer to be effective. Stents have also been used in the management of esophageal fistulas resulting from caustic injury or dilatation therapy, mainly as a temporizing measure before surgical repair or esophageal bypass.[64,120]

## Long-Term Outcome

Extensive caustic injury may heal without stricture or may respond to the various prophylactic and therapeutic measures outlined. However, residual motility dysfunction can be expected, and an achalasia-like picture has been described.[121–123]

Carcinoma of the previously injured esophagus is a real risk, but the disease usually has a latency period of 15 to 40 years.[4,56,124–130] However, a lethal squamous cell carcinoma of the esophagus has been reported just 1 year after injury.[131] Also, Barrett esophagus has been observed following lye-induced injury.[87,132] Thus long-term surveillance with esophagoscopy is advocated. In this regard, two prudent questions arise: To what extent should the clinician try to preserve the damaged esophagus? When should attempts at dilatation be abandoned?[133,134]

Currently, there is a trend toward earlier esophageal bypass in a severely injured esophagus, with the addition of resection of the damaged esophagus.[3,28,66,104] Complications such as abscess or cyst formation in the bypassed but retained esophagus are rare, and carcinoma has not been reported.[23,104]

Esophageal perforation, as evidenced by pain, fever, and tachycardia, is a life-threatening iatrogenic complication of esophageal dilatation (Fig. 70-6).[46,103] With immediate recognition by endoscopy or contrast swallow, many patients with a perforated esophagus can be treated conservatively with systemic antibiotics and parenteral nutrition.[135–137] Established methods of management with either thoracostomy drainage or primary repair with proximal and distal esophageal and gastric diversion are reserved for patients with delayed recognition or extensive disruption. Transesophageal water irrigation with chest drainage as a supplement to conservative measures has also been advocated.[135] If dilatation has failed or if the esophagus cannot be salvaged, esophageal bypass or substitution is indicated. Operations currently used are colonic interposition, gastric tube esophagoplasty, jejunal interposition, and gastric advancement (see Chapter 71).* Colonic patch procedures have also been used for less extensive but persistent strictures.[86,103,141–143] Deciding which procedure to use and whether to bypass or resect the injured esophagus is influenced by local practice and the morbidity and mortality from esophageal resection. Clearly, the risks associated with resection must be less than the risk of cancer in the retained but bypassed esophagus.[86,124,144–146]

## Results

Between 1957 and 2010, 522 children with caustic injuries of the esophagus were treated at the University of Cape Town teaching hospitals (Red Cross War Memorial Children's Hospital and Groote Schuur Hospital). The average age was 35 months, with a range of 7 to 206 months. Forty-five percent were younger than 2 years. In recent years (1990 to 2010) there has been a trend toward an increasing number of patients presenting to hospitals with caustic ingestions (1432), but only 500 patients (35%) required hospitalization. Of these, only 39 (8%) developed strictures. The mean age was 4.5 years, with equal gender distribution. Most children ingested household cleaners or disinfectants.

*References 18, 105, 107, 112, 113, 115–119.

*References 23, 28, 35, 68, 86, 104, 138–140.

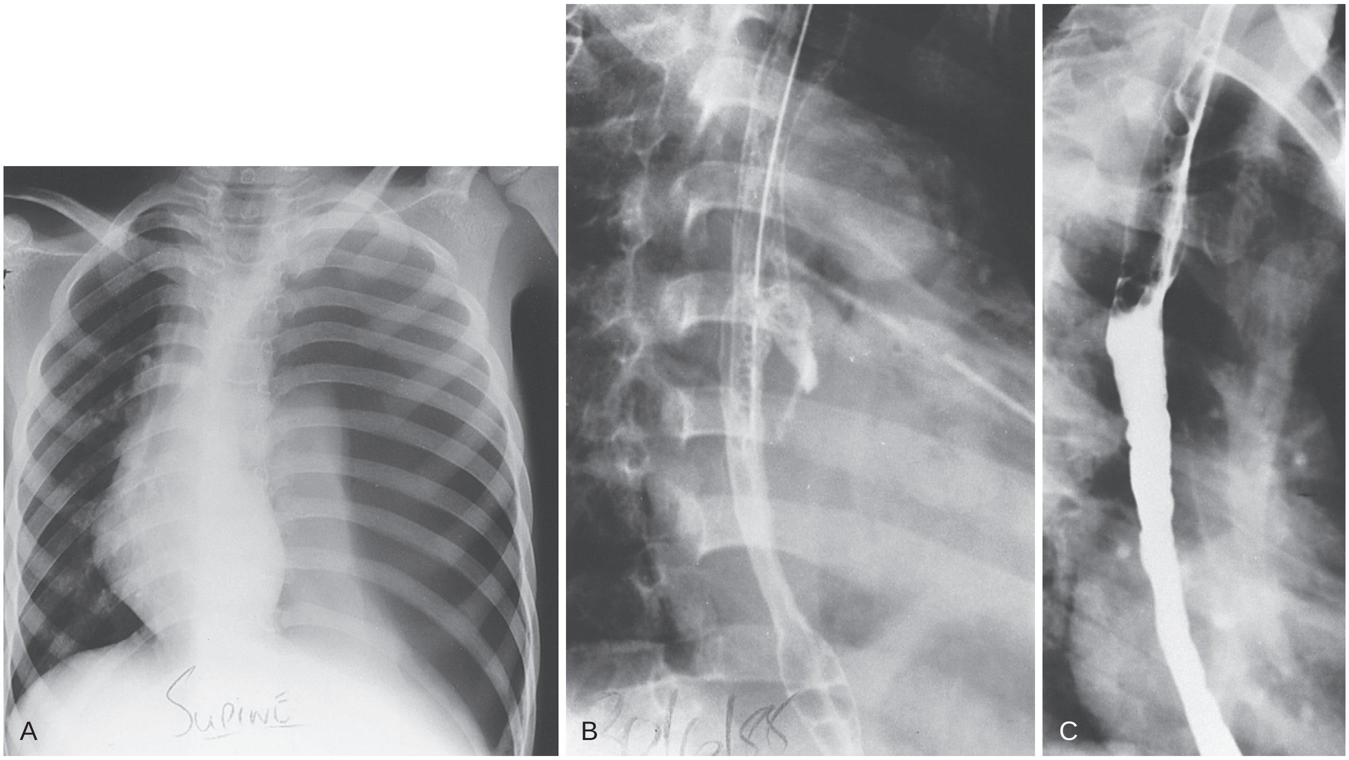


**FIGURE 70-6** Left-sided tension pneumothorax secondary to perforation after dilatation of an upper esophageal caustic stricture. **A,** Treatment by tube thoracostomy drainage. **B,** Contrast study 10 days later shows that the leak has been contained. **C,** Healed esophagus 12 weeks after perforation. Esophageal replacement was not required in this case.

Overall, 97 of the 522 (18.5%) patients developed fibrous strictures of the esophagus. Caustic soda was the most common corrosive agent (92 of 97 patients) and was taken in the crystal form by 31 children. Acid burns were responsible for only four strictures. One patient with an acid burn who had extensive esophageal injury developed a severe stricture of the stomach antrum and upper jejunum; another patient presented 8 months after ingesting soldering acid with a near-complete antral stricture. Of the 97 patients with strictures, 49 (50%) responded to repeated dilatations, whereas the other 48 required operative management. Ten of the 48 had severe oropharyngeal burns in addition to the scarred esophagus, and 6 of these patients required tracheostomy. The 97 patients had an average of 18 dilatations (range, 1 to 38). The 49 who responded to dilatation had an average of 17 dilatations over a period of 13.6 months (range, 0.5 to 20 months); the 48 children with strictures who required esophageal replacement were dilated an average of 12.7 times (range, 1 to 31) over a 13.7-month period (range, 0.5 to 87 months). The outcome was poor when presentation was delayed for more than 1 month, with 8 of 10 such patients requiring esophageal bypass. Length of stricture greater than 5 cm was another adverse factor; 17 of 18 patients with this finding did not respond to dilatation.

Complications in the 97 patients with stricture are summarized in Table 70-3. The most significant complication was esophageal perforation, which occurred in 13 patients. Perforation occurred after an average of six dilatations.

**TABLE 70-3**

**Complications of Caustic Strictures of the Esophagus ($N = 97$)**

| *Complication* | *No. of Patients* |
|---|---|
| Perforation | 13 |
| Tracheoesophageal fistula | 1 |
| Gastroesophageal reflux | 7 |
| Pneumonia | 8 |
| Cerebral abscess | 1 |
| Hemorrhage | 1 |
| Tracheostomy | 6 |

Two perforations occurred during the first dilatation, and others occurred after as many as 14 dilatations, indicating that perforation can occur at any stage. With early recognition, perforation was associated with minimal morbidity and some patients could be treated conservatively with intravenous antibiotics alone. If extension of the inflammatory process or perforation into the mediastinum or pleura occurred, these areas were drained. One patient developed a tracheoesophageal fistula and had esophagectomy of an extensively scarred esophagus, followed by posterior mediastinal left colonic interposition. No complications such as cyst or abscess formation have occurred in the retained esophagus in patients receiving a retrosternal interposition. Seven patients developed gastroesophageal reflux, six of whom underwent antireflux surgery. Four subsequently responded to dilatations, whereas the other three required esophageal replacement (Table 70-3).

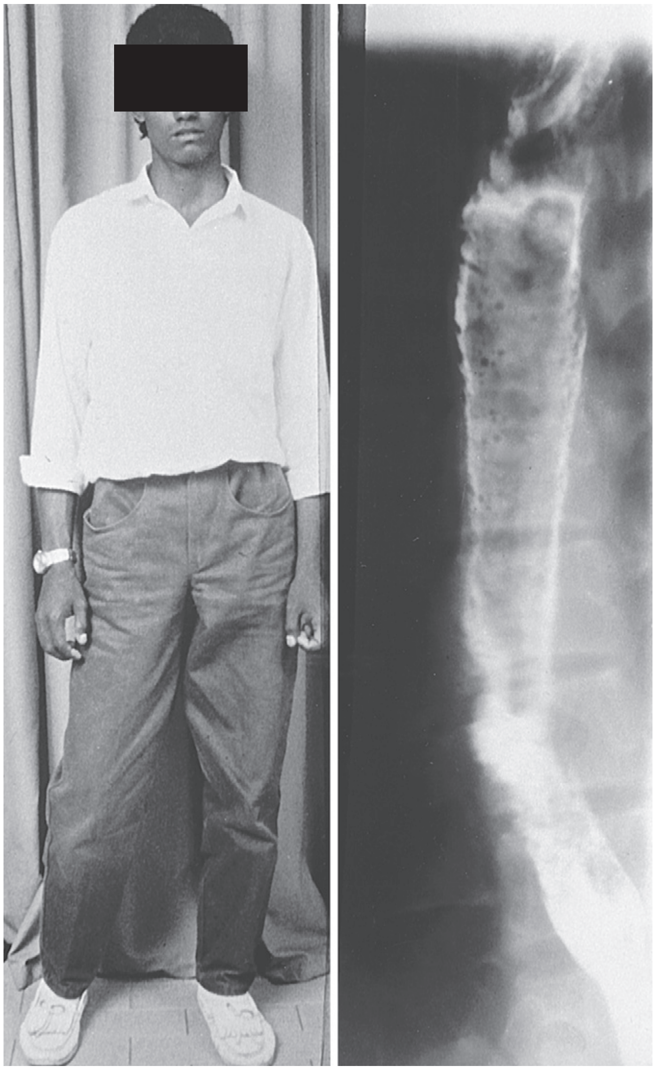

**FIGURE 70-7** Young man 21 years after substernal left colonic esophageal replacement for caustic injury, with accompanying esophagogram. He recently developed fatal squamous carcinoma of the cricopharynx nearly 30 years after caustic ingestion.

Since 1969, we have performed an isoperistaltic retrosternal left transverse and left descending colon interposition based on the ascending branches of the left colonic vessels in 39 cases and local resection with end-to-end anastomosis in 1 case. Details of the operative procedure have been reported.[23] Colonic interposition has proved to be a successful conduit for all nutritional needs, with satisfactory long-term results (Fig. 70-7). Recently following an international trend, we have moved to resection of the damaged esophagus and the transmediastinal placement of the graft (see Chapter 71).[68,140]

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 71

# Esophageal Replacement

Lewis Spitz and Arnold G. Coran

The need to replace the esophagus is becoming increasingly rare. This mainly results from improved methods of retaining the native esophagus in infants born with long-gap esophageal atresia. In addition, general awareness of the damage that can occur as a consequence of intractable gastroesophageal reflux has resulted in more aggressive approaches in antireflux surgery, and with the introduction of childproof containers, fewer lye and caustic injuries to the esophagus occur. Nevertheless, there continue to be instances where substitution of the esophagus is required and it is important for the pediatric surgeon to be aware of the various options available for replacement.

## Indications for Esophageal Replacement

### ESOPHAGEAL ATRESIA

Infants with long-gap esophageal atresia (EA) constitute the main group that requires esophageal replacement because of failure to achieve end-to-end anastomosis. Numerous maneuvers have been adopted to overcome the long-gap EA and obtain a primary anastomosis, thereby allowing retention of the infant's native esophagus. A list of these techniques is shown in Table 71-1. For infants with an isolated esophageal atresia, it is important to exclude an upper pouch tracheoesophageal fistula. Where there is only a small nubbin of distal esophagus above the hiatus, or no intrathoracic esophagus at all, a replacement is clearly going to be required and it is best at an early stage to perform a cervical esophagostomy and allow the infant to go home pending a later replacement procedure. The infant is now free from the danger of aspiration, and appropriate bonding with the family can take place at home. Where the gap between the proximal and distal esophagus is between four and eight thoracic vertebral bodies or if at thoracotomy an anastomosis cannot be achieved even under extreme tension, delayed primary repair should be attempted. The infant is fed by gastrostomy while suction is applied to the upper esophageal pouch for a period of 6 to 12 weeks. During this time, the gap between the two ends of the esophagus gradually diminishes. If primary anastomosis is still impossible at this stage, further delay is unproductive and esophageal substitution is required. It would now be possible to perform a primary interposition procedure, or if circumstances do not permit, then a cervical esophagostomy is performed with later replacement procedure. Although it is obvious that the patient's own esophagus is the best esophagus, persisting with futile attempts to retain the native esophagus in the presence of major complications (e.g., empyema, intractable stricture, repeated recurrent fistulas) is occasionally detrimental to the well-being of the infant. In such situations, it is clearly in the patient's best interest and safety to abandon the esophagus and perform a replacement procedure at a later stage.

### PEPTIC STRICTURES

Antireflux surgery is usually performed for pathologic gastroesophageal reflux before intractable strictures develop. The majority of severely scarred and inflamed strictures of the esophagus will resolve with effective antireflux surgery followed by regular postoperative esophageal dilations. A small percentage requires limited "sleeve" resection of the strictured area, but some will fail to respond and will require esophageal replacement.

### CAUSTIC STRICTURES

Although uncommon in developed countries as a result of legislation mandating childproof containers for caustic substances, many children in developing countries continue to sustain caustic esophageal injuries. Most cases are mild and respond to repeated dilations. Full-thickness injury to more than a short segment of the esophagus invariably results in an intractable stricture, which fails to respond to dilations and usually requires substitution. Continuing with dilatations at regular intervals for longer than 6 to 12 months is unproductive. The need to resect the damaged esophagus continues to be disputed. The risk for malignant conditions and the ease with which esophagectomy can be performed in children favors resection and substitution rather than bypass procedures. Caustic strictures are discussed extensively in Chapter 70.

**TABLE 71-1**
**Surgical Maneuvers in Long-Gap Esophageal Atresia**

| |
|---|
| **During the Initial Procedure** |
| Anastomosis under tension[87–89] |
| Tension-relieving procedures[90–93] |
| Flap technique[94,95] |
| Suture fistula[96–98] |
| **Delayed Primary Anastomosis** |
| With bougienage: proximal,[99,100] proximal and distal,[101] magnetic[102] |
| Without bougienage[103] |
| Esophageal lengthening techniques: flap,[94,95] spiral myotomy,[104] gastric division,[105] traction sutures[106–108] |
| **Transmediastinal "Thread"** |
| With and without "olives"[103,109] |
| Kato technique[110] |
| **Esophageal Replacement** |
| Colonic interposition[19,24,111] |
| Gastric tube esophagoplasty[51,109] |
| Jejunal interposition[66,67,112] |
| Gastric transposition[77,79,80,86,113] |

## MISCELLANEOUS INDICATIONS

The need for replacement because of bleeding esophageal varices is virtually obsolete as a result of the success of alternative techniques, particularly sclerotherapy, banding, and portosystemic shunts. Tumors of the esophagus may require resection of extensive lengths of the esophagus. Examples of such tumors in children are diffuse leiomyoma and inflammatory pseudotumor. The esophagus may be extensively damaged by prolonged impaction of foreign bodies such as aluminum can ring pulltops, which are radiolucent and may escape detection on conventional radiography. Other unusual indications for esophageal replacement include intractable achalasia, diffuse candidiasis in children with immune deficiency, scleroderma,[1] epidermolysis bullosa,[2] and human immunodeficiency virus (HIV) strictures.[3]

# Characteristics of an Ideal Esophageal Substitution[4]

- The substitute must function as an efficient conduit from mouth to stomach to satisfy the nutritional needs of the child.
- Gastric acid reflux into the conduit must be minimal; if reflux does occur, the substitute should be resistant to gastric acid.
- The substitute should not impair respiratory or cardiac function.
- The operative technique should be technically unchallenging and adaptable to small children.
- The conduit should not produce any external deformity.
- The conduit must grow with the child and continue to function into adult life.

# Types of Esophageal Replacement

Although the colon has been the most frequently used organ for esophageal substitution in children, dissatisfaction by some surgeons has led to use of other alternatives. The methods most commonly used are shown in Figure 71-1.

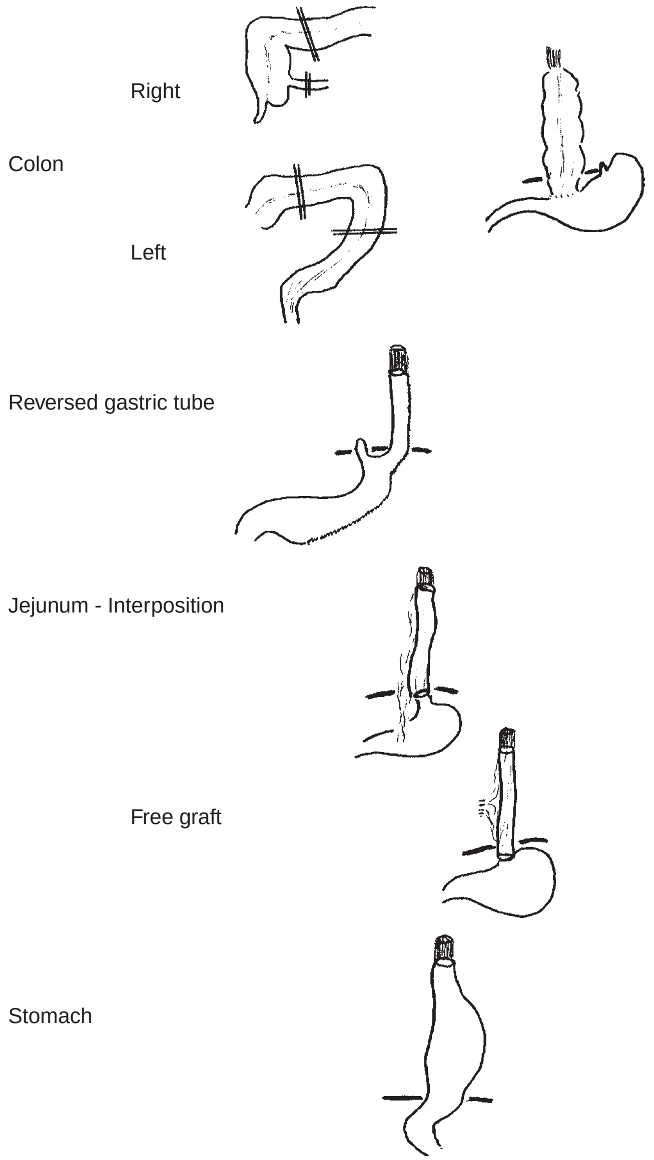


**FIGURE 71-1** Methods for esophageal replacement.

The advantages and disadvantages of the various substitution procedures are outlined in Table 71-2.

Several artificial prostheses have been used as substitutes for the esophagus. All of these have only functioned for short periods.[5,6]

# Route for Positioning the Esophageal Substitute

The posterior mediastinum is the shortest distance between the cervical region and the abdomen for esophageal replacement.[7] Colonic interpositions were originally placed subcutaneously on the anterior chest wall, but the cosmetic appearance with this method is unacceptable and it has been abandoned. The advantages and disadvantages of the other routes are outlined in Table 71-3.

# Timing

Although esophageal replacement is possible in newborns, the procedure should generally be delayed until the infant is thriving and weighs at least 5 kg. In the interim, it is important to stimulate the swallowing reflex by offering sham oral feedings during regular gastrostomy feedings. Infants who achieve good sham-feeding will undoubtedly rapidly accept oral nutrition when the esophageal substitute has been successfully connected. In all cases, adequate mechanical preparation of the intestine is essential because the organ that had been selected for esophageal replacement may be unsuitable and an alternative technique may be required.

Excellent comprehensive reviews of the history of esophageal replacement have been documented by May and Samson in 1969[8] and Postlethwait in 1983.[9]

# Colonic Interposition

Colonic interposition continues to be a widely used procedure for esophageal replacement in children. In adults with carcinoma of the esophagus, the currently preferred technique is gastric transposition, with colonic interposition being reserved as a secondary procedure.

## HISTORY

In 1911 Kelling[10] used a segment of transverse colon based on the left colic artery to bypass the esophagus. Unfortunately, the patient died before an attempt could be made to join the cervical esophagostomy to the upper end of the colon. In 1911 Vulliet[11] preserved the mesenteric pedicle to the right end of the colon transplant in a cadaver. In 1914 Von Hacker carried out the first successful colonic interposition in an adult.[12] The first successful colonic bypass in a child was reported by Lunblad in 1921.[13] The patient underwent the procedure for an esophageal stricture at 3 years of age and lived until he was 37 years old, at which time he died accidentally. Ochsner and Owens[14] reviewed the literature in 1934 and could find only 20 reported cases of colonic esophagoplasty. In 1951 Rudler and Monod-Broca[15] described the retrosternal ileocolonic graft. In 1955 Dale and Sherman[16] described two infants with EA who had reconstruction of the esophagus at 2 years of age using a right colonic retrogastric anterior mediastinal interposition. Four years later, Battersby and Moore[17] reported five cases of right colon replacement for congenital atresia of the esophagus. The three children who had substernal placement of the colon survived. They recommended delaying the procedure until the infant was at least 9 months of age. Major advances in the use of the colon for esophageal replacement were documented by Sherman and Waterston in 1957,[18] by Waterston in 1964,[19] Azar and colleagues in 1971,[20] and Belsey in 1965.[21] Waterston and Belsey[22] were strong proponents of the transpleural route using the left colon supplied by the left colic vessels. In 1967 Otherson and Clatworthy[23] stated that the colon was the best organ for esophageal replacement in children and recommended delaying the operation until the child was 18 to 24 months old so that gravity in the erect position would assist in food passage through the colonic interposition. Freeman

**TABLE 71-2**
**Substitution Procedures**

| *Method* | *Advantages* | *Disadvantages* |
|---|---|---|
| Colon | Adequate length | Precarious blood supply |
| | Reflux seldom occurs | Graft necrosis |
| | | High incidence of leaks and strictures |
| | | Involves three anastomoses |
| | | Redundancy over long-term |
| | | Slow transit of food |
| Gastric tube | Adequate length | Long suture line |
| | Good blood supply | High incidence of leaks and strictures |
| | Size of conduit appropriate | |
| | Rapid transit | Reflux—Barrett syndrome |
| Stomach | Adequate length easily attained | Bulk of stomach in thorax |
| | | Reflux common early on |
| | Excellent blood supply | Poor gastric emptying |
| | Single anastomosis | Affects pulmonary function |
| | Ease of procedure | Affects growth |
| Jejunum | Appropriate size | Precarious blood supply |
| | Retention of peristaltic activity | |
| | Length can be a problem | Three anastomoses |
| Free jejunal graft | Appropriate size | Specialized technique for |
| | Good peristaltic activity | microvascular anastomosis |
| | | Prolonged operating time |
| | | Precarious blood supply |
| | | High failure rate |

**TABLE 71-3**
**Routes for Positioning the Esophageal Substitute**

| *Route* | *Advantages* | *Disadvantages* |
|---|---|---|
| Retrosternal | Ease of procedure | Longest route from neck to abdomen |
| | Useful when transpleural and mediastinal routes are unavailable because of inflammation or previous surgery | Angulation of graft |
| | | Problems with access if cardiac surgery required |
| Transpleural | Convenience and ease of procedure | Displacement of lung |
| | | Requires thoracotomy |
| **Posterior Mediastinal** | | |
| Most direct route | Organ contained in mediastinum | Mediastinum may be unavailable because of previous surgery, fibrosis, or inflammation |
| | Little or no compression of lung | |
| | Thoracotomy not always required | |

and Cass, in 1982,[24] advocated placing the transposed colon in the route of the native esophagus in the posterior mediastinum and reported an impressively low rate of complications.

## SURGICAL TECHNIQUE

Colonic interposition entails use of either the right colon based on the ileocolic vessels placed in the retrosternal position or the left/transverse colon based on the left colic vessels positioned in a retrohilar position in the left pleural cavity or in the posterior mediastinum (Fig. 71-2).

## RIGHT COLON RETROSTERNAL TECHNIQUE

The abdomen is opened either through a midline upper abdominal incision or a transverse upper abdominal muscle-cutting incision that transects both rectus abdominis muscles. The entire colon must be mobilized and exposed to provide detailed and accurate assessment of its blood supply. In a study of 600 specimens, Sonneland, Anson, and Beaton[25] reported that only 24% of specimens showed the typical textbook picture of three vessels to the right side of the colon arising from the superior mesenteric artery.[25] The middle colic artery was absent in 3.6% of cases. The marginal artery was occasionally absent. In individual children, the anatomy of the vascular supply determines the section of colon most appropriate for the interposition procedure. The blood supply to the right colonic interposition is based on the middle colic artery. However, if a segment of terminal ileum is to be used in the interposition,[26] the ileocolic vascular supply to the graft must be preserved if possible. The length of intestine to be used is carefully estimated, and bulldog clamps are placed across all vessels that require division. The clamps are left in position for at least 10 minutes to ensure that the blood supply is adequate, that the marginal vessels continue to pulsate, and that the color of the section of colon selected for the interposition remains normal. The blood supply can be further evaluated by removing the appendix and observing the flow of blood in the appendicular artery. If the blood supply seems to be satisfactory, the vessels that require division are carefully and securely ligated and divided. It is important to preclude hematoma formation in the mesentery. The ileum is divided between the clamps, and the distal stump is closed in preparation for its relocation into the neck. The transverse colon is then divided to the left of the middle colic artery, and intestinal continuity is restored by an end-to-end ileotransverse colostomy.

A transverse cervical incision that encircles the previously constructed cervical esophagostomy is made. The incision should extend to the midline of the neck approximately 1 cm above the manubrium sterni. The upper border and posterior surface of the manubrium is exposed by dividing the cervical fascia and the origin of the sternomastoid muscle. It may be necessary to enlarge the opening into the retrosternal space by removing the upper part of the manubrium, sternoclavicular joint, or both.

The retrosternal tunnel is developed from above through the cervical incision in a plane directly posterior to the sternum and anterior to the thymus and pericardium and from below following division of the anterior attachments of the diaphragm. The tunnel must be wide enough to accommodate at least two to three fingers.

The stomach is then mobilized to allow the colon and its vascular pedicle to pass behind the stomach, over the anterior

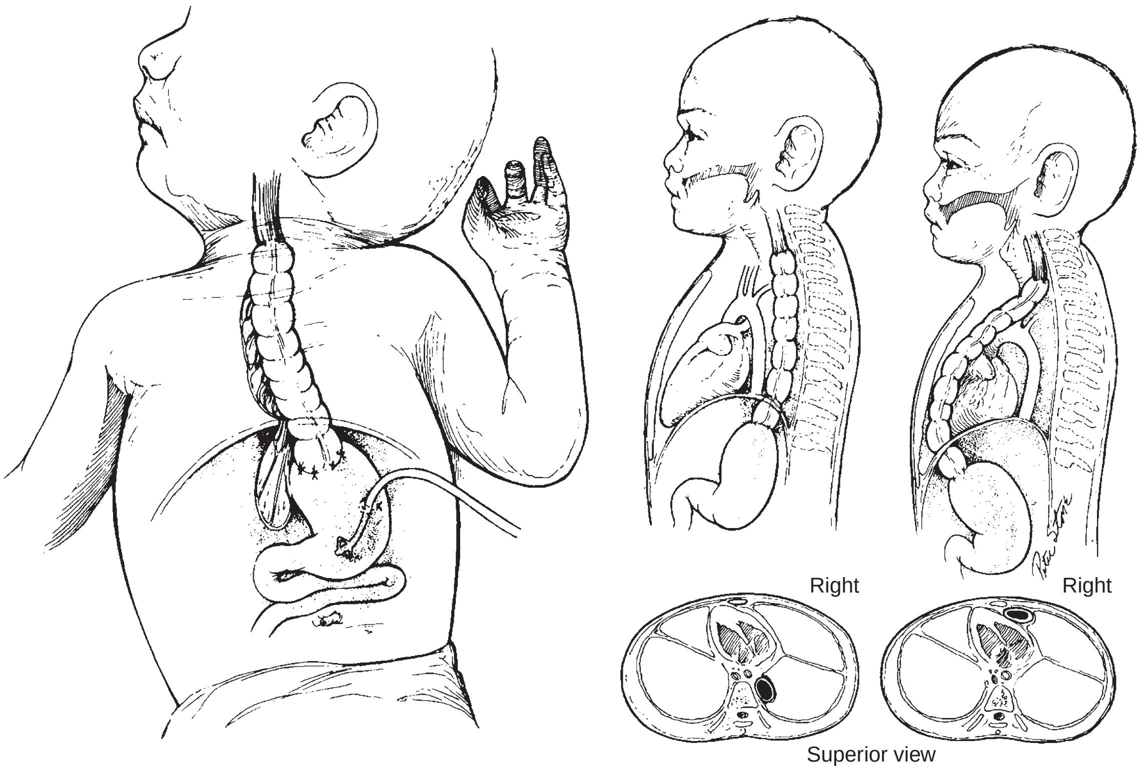


FIGURE 71-2 Colon esophagoplasty. The colon may be placed in retrosternal or retrohilar position with equal success. (From Randolph JG: Surgical problems of the esophagus. In Sabiston D, Spencer F [eds]: Gibbon's Surgery of the Chest, 3rd ed, Philadelphia, WB Saunders, 1976. Used with permission.)

surface of the liver, and through the retrosternal tunnel into the neck. It is vital to ensure that there are no kinks or twists in the graft that may impair the blood supply. The distal end of the colonic interposition is anastomosed to the anterior wall of the stomach close to the lesser curvature. An antireflux submucosal gastric tunnel has been devised as a method of preventing reflux of gastric acid into the colon graft.[27] The proximal end of the graft, which will comprise the ascending colon or the terminal ileum, is anastomosed end to end to the distal end of the cervical esophagus. During preparation of the esophagus for anastomosis, it is imperative to preserve its blood supply and to meticulously mobilize the full thickness of the esophagus. The length of the colonic interposition must be just sufficient to bridge the gap between the esophagus and the stomach. Excess colon should be resected before anastomosis while the blood supply to the remaining graft is preserved. Redundancy is a problem that increases with time and can lead to stasis. Pyloroplasty or pyloromyotomy is generally recommended to prevent this complication.

## LEFT/TRANSVERSE COLON TRANSPLEURAL TECHNIQUE

The left colon transpleural technique was originally described by Waterston.[19] For this method, the left transverse colon based on the ascending branch of the left colic artery is placed isoperistaltically in the retrohilar position. In the original description, the entire procedure was performed through a left thoracic incision with access to the abdomen provided by detaching the diaphragm peripherally from the chest wall. An alternative approach is to use separate abdominal and thoracic incisions or a thoracoabdominal incision.[21] Intestinal continuity is restored by end-to-end colo-colic anastomosis. The colon graft is passed in a retrogastric and retropancreatic direction and then through a separate lateral incision in the posterior diaphragm into the left pleural cavity. The colon is passed behind the hilum of the left lung and into the neck by tunneling through the Sibson fascia in a posterior direction to the subclavian vessels and lateral to the carotid sheath. The proximal end of the colonic interposition is anastomosed end to end to the cervical esophagus, and the distal end is anastomosed either to the distal stump of esophagus (in cases of esophageal atresia) or preferably to the posterior wall of the stomach. Pyloroplasty is again recommended. Freeman and Cass[24] modified the procedure by placing the colon in the posterior mediastinum in the site of the normal esophagus.

## RESULTS

With modern anesthetic techniques and postoperative management, mortality from colonic interposition alone should be negligible.[28] Graft necrosis should also be rare, particularly if meticulous attention is paid to ensuring that the graft has an adequate blood supply and that the vessels do not kink as the graft is passed behind the stomach. Venous obstruction may result in gradual infarction of the colonic interposition weeks or months after surgery. The most common complications are anastomotic leakage, particularly that which involves the esophagocolonic anastomosis in the neck and stricture formation. Leaks are attributed to a poor blood supply to the proximal end of the colon or to damage to or impairment of the blood supply to the esophageal wall. Most leaks resolve spontaneously within a few weeks, but some progress to stricture formation. Strictures at the cervical anastomosis generally resolve with dilations, but resection of the strictured area and revision of the anastomosis are occasionally necessary.

The incidence of complications subsequent to colonic interposition in the various large series in the literature is shown in Table 71-4.

**TABLE 71-4**
**Results of Colon Interposition**

| *Yr* | *Author* | *No. of Patients* | *Deaths* | *Leaks (%)* | *Strictures (%)* |
|---|---|---|---|---|---|
| 1967 | Gross[114] | 47 | 4 | 6 (13) | 7 (15) |
| 1967 | Otherson and Clatworthy[23] | 11 | 0 | 4 (36) | 3 (27) |
| 1971 | Azar[20] | 60 | 5 | 15 (25) | 18 (30) |
| 1972 | Soave[115] | 32 | 5 | 28 (87) | — |
| 1972 | Martin[116] | 21 | 2 | 4 (19) | 6 (28) |
| 1978 | Rodgers[42] | 13 | 0 | 5 (38) | 3 (23) |
| 1976 | German and Waterston[39] | 32 | 1 | 7 (21) | 7 (21) |
| 1982 | Freeman[24] | 33 | 2 | 2 (6) | 2 (6) |
| 1982 | Campbell[117] | 23 | 1 | 8 (34) | 4 (17) |
| 1985 | Hendren[28] | 32 | 1 | 2 (6) | 0 |
| 1986 | Rode et al[118] | 35 | 4 | 8 (23) | 5 (14) |
| 1986 | West et al[119] | 25 | 0 | 10 (40) | 11 (44) |
| 1986 | Ahmed and Spitz[120] | 112 | 15 | 54 (48) | 34 (30) |
| 1989 | Mitchell et al[121] | 79 | 9 | 23 (29) | 17 (22) |
| 1993 | Carneiro and Doig[122] | 11 | 2 | 5 (45) | 2 (18) |
| 1994 | Cheng[123] | 240 | 7 | 25 (10.4) | — |
| 1995 | Raffensperger[124] | 59 | 2 | 11 (19) | 13 (22) |
| 1998 | Khan[125] | 25 | 0 | 10 (40) | 7 (28) |
| 2000 | Erdogan[126] | 18 | 4 | 11 (61) | 3 (17) |
| 2003 | Hamza[127] | 475 | 5 | 47 (10) | 25 (5) |
| 2007 | Tannuri[128] | 99 | 1 | 27 (27) | 14 (14) |

Gastric reflux into the colonic interposition may occur and occasionally results in peptic ulceration of the colon. This may progress to hemorrhage or, on rare occasions, perforation with resultant empyema. Late deaths from perforation and empyema have been reported.

Complications after bypass procedures have also been described in the retained esophagus.[29,30] Shamberger[31] described eight patients who developed chronic inflammation in the esophageal remnant, including three cases of Barrett syndrome. Others have documented mucocele and empyema developing in the retained esophagus.[32]

Peristalsis in the colonic segment is usually absent, and food is conducted through the colon by gravity.[13,33–36] The intrathoracic colon may become increasingly redundant with time, and this may result in delayed emptying and stasis, which increases the risk for regurgitation and aspiration. It may be necessary to resect the redundant portion of colon, but in so doing, care must be taken to avoid damage to the blood supply of the remaining colon. This can be done by resecting the mucosal/submucosal tube of the redundant distal colon, opening the remaining muscular tube of the redundant colon on its antimesenteric side, and creating a new cologastric anastomosis on the top of the open muscular cuff where the blood supply to the proximal colon runs. One of us (author AGC) has done this in 12 cases, and the results have been excellent with removal of all the redundancy and elimination of all symptoms.

The nutritional state of children after colonic interposition seems to be satisfactory.[37] Children who originally had EA tend to be in the lower percentiles for height and weight, whereas those who had esophageal replacement for caustic stricture fall into a normal growth curve.[4,34,38–41] Nearly half of patients with colonic interposition have depleted stores of iron.[42] Coopman and colleagues[43] reviewed the long-term outcome following colonic interposition in 32 children. Complications were identified in 58% in the first year postoperatively, and in the long term 85% experienced problems including abnormal lung function (58%), feeding difficulties (50%), scoliosis (35%), and nutritional deficiencies in 25%.

# Gastric Tube Esophagoplasty

## HISTORY

In 1905 Beck and Carrell[44] constructed tubes of the greater curvature of the stomach in dogs and cadavers; the tubes were brought antethoracically into the neck. In 1912 Jianu[45] successfully used this tube intrathoracically in two patients with strictures. In 1948 Mes[46] showed that a tube of the greater curvature of the stomach could reach the neck. Later, Gavriliu in Hungary[47–49] and Heimlich[50,51] in the United States popularized this method of esophageal replacement. More recent advocates for gastric tube esophagoplasty include Burrington and Stephens,[52] Cohen,[53] Ein,[54] and Anderson.[55,56]

## SURGICAL TECHNIQUE

The abdomen is opened through a transverse supraumbilical incision, and the gastrocolic omentum is divided at a safe distance from the gastroepiploic arcade (Figs. 71-3 and 71-4).[55] The right gastroepiploic artery is divided at the point of origin of the gastric tube; the site of division must be chosen carefully to avoid narrowing the pyloric outlet. The optimum location is usually approximately 2 cm proximal to the pylorus, where a vertical incision is made through the anterior and posterior walls of the stomach. With an 18-French to 24-French chest tube placed in the stomach along the greater curvature to act as a guide to ensure the construction of an appropriately sized gastric tube, a gastrointestinal anastomosis (GIA) stapler[57] is applied 1½ to 2 cm from the greater curvature, encompassing both anterior and posterior gastric walls. The staple line is placed, and the stomach is cut parallel to the greater curvature. Three to four applications of the stapler are usually required. The short gastric vessels are divided, and the spleen is protected during the construction of the tube. Splenectomy is *never* necessary. The staple lines on the gastric tube and on the native stomach are reinforced simultaneously with interrupted Lembert sutures of 4-0 nonabsorbable material. If the left gastroepiploic artery has been previously ligated and is unavailable to supply the antiperistaltic tube, an isoperistaltic tube based on the right gastroepiploic artery can be constructed.

The route to the neck is selected at this point, and either a retrosternal tunnel is created or a left thoracotomy is performed in the sixth intercostal space. The neck incision is placed in the suprasternal notch for a substernal tube and in the left anterior triangle for the transthoracic route. Finger dissection from cervical and thoracic approaches assists selection of the safest place to incise the Sibson fascia. This position may be anterior or posterior to the subclavian vessels, depending on which space is larger. An incision is made in the diaphragm in a medial and anterior direction to the aortic hiatus, and the gastric tube is drawn into the chest and passed in a proximal direction into the neck. The orientation of the pedicle is maintained to prevent twisting or kinking of vessels. Anastomosis with the cervical esophagus is done with a single layer of nonabsorbable sutures. A few sutures placed between tube and diaphragm anchor the tube in the chest. The gastrostomy is reestablished in the remnant of the stomach. The chest and neck are drained, and the abdomen is closed without drainage. If the left gastroepiploic artery was damaged during a previous operation, the right gastroepiploic artery can be used to support the vascular pedicle and the tube would be constructed in the reverse (isoperistaltic) direction. In this instance, after creation of the gastric tube, the stomach is rotated in a posterior direction so that the tube can be brought to the neck.

## RESULTS

The gastric tube tends to retain its shape without the redundancy and dilation that tends to occur in colon grafts. Reflux is almost always present and may cause Barrett changes in the proximal esophageal stump.[58] Peptic ulceration has been reported as a long-term complication associated with gastric tubes.[59,59a,60] Nocturnal coughing is a common problem that can be alleviated by elevating the head of the bed and avoiding fluids shortly before bedtime. The gastric tube supports nutrition well. Children with lye strictures fall into normal growth curves, whereas those with EA tend to fall in lower percentiles for weight and height but grow satisfactorily and maintain good nutrition.[38]

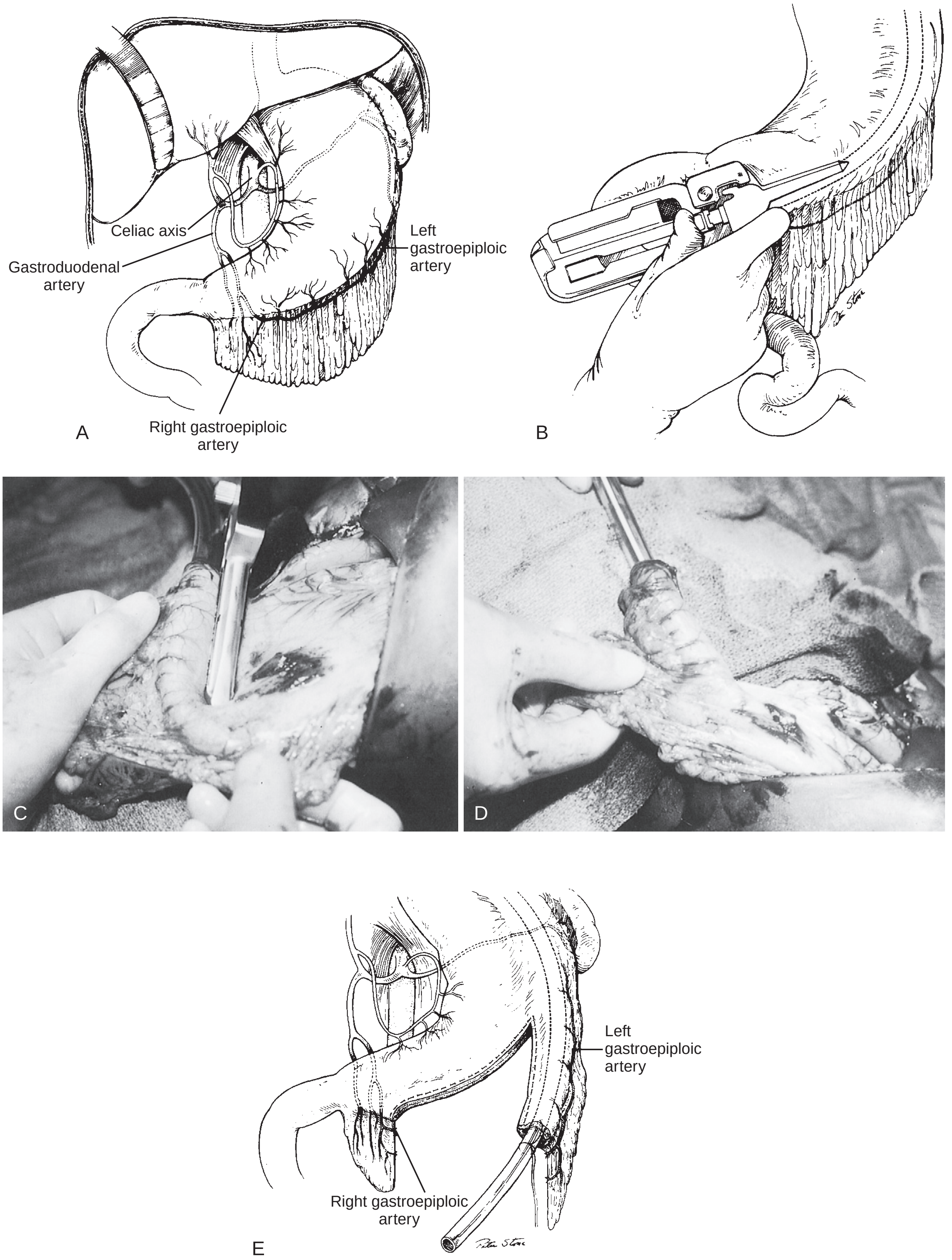


**FIGURE 71-3** Reverse gastric tube construction. **A,** Tube is vascularized by the left gastroepiploic artery. The right gastroepiploic artery is divided where shown, and the arcade is carefully preserved. **B** through **E,** Step-by-step division of the stomach by the gastrointestinal anastomosis stapler, using a chest tube along the greater curvature as a guide to ensure uniform size of the gastric tube. Oversewing of the staple line on the tube and stomach is also shown.

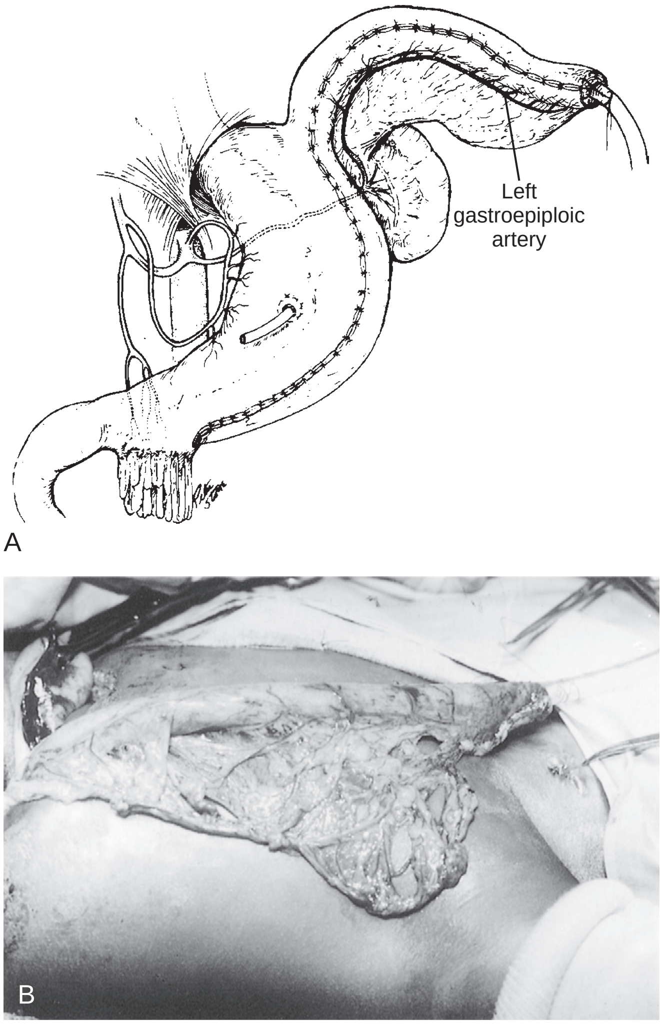


FIGURE 71-4 Reverse gastric tube. **A,** The spleen has been preserved; staple closures of the tube and stomach have been reinforced by interrupted sutures. **B,** The tube is placed over the chest and reaches the cervical esophagostomy, to which the clamp is pointing. The intrathoracic course is even shorter.

Mortality associated with gastric tube esophagoplasty is low, but leaks and strictures are common. Perforation of the gastric tube occasionally occurs.[60] Peristalsis is generally absent, and the tube empties by gravity (Table 71-5).

**TABLE 71-5**
**Results of Gastric Tube Esophagoplasty**

| *Yr* | *Author* | *No. of Patients* | *Deaths* | *Leaks (%)* | *Strictures (%)* |
|---|---|---|---|---|---|
| 1968 | Burrington[52] | 8 | 1 | 3 (37) | — |
| 1973 | Ein[129] | 15 | — | 7 (47) | 9 (60) |
| 1978 | Anderson[130] | 15 | — | 5 (33) | 5 (33) |
| 1985 | Goon[131] | 46 | 1 | 35 (76) | 27 (59) |
| 1987 | Ein[132] | 36 | 3 | 24 (67) | 15 (42) |
| 1998 | Ein[54] | 11 | — | 9 (81) | 8 (72) |
| 2004 | Borgnon[133] | 21 | 1 | 2 (10) | 2 (10) |

# Jejunal Interposition

## HISTORY

In 1906 Roux[61] used the jejunum in an antethoracic direction to bypass a caustic stricture in a 12-year-old child. Follow-up of this patient was published by Picot-Roux and Hase in 1950.[62] The patient did well until 1940, when a large fistula developed subsequent to trauma, and in 1941, an epithelioma was found in the cutaneous portion of the esophagus; this disorder was successfully treated with radiation therapy. The patient died of unrelated causes at 53 years of age. In 1913 Lexer[63] combined the Roux isolated jejunal loop with a cutaneous skin tube when the jejunum was not long enough to reach the neck. Approximately 20 years later, Ochsner and Owens[14] reviewed the literature of antethoracic esophageal replacement and found that of 240 patients, 56% had tubes constructed of jejunum. In 1946 Reinhoff[64] performed the first intrathoracic jejunal replacement of the esophagus. He recommended the shorter intrathoracic route and stated that the jejunum was long enough to reach the neck. Longmire[65] reported a jejunal interposition for caustic stricture in which the inadequate blood supply to the upper end of the jejunum was supplemented by an anastomosis between the internal mammary artery and the mesenteric artery of the jejunum in 1951. The advantages of the jejunum as an esophageal substitute are that peristaltic activity is preserved, and its caliber is similar to that of the normal esophagus. The results of jejunal interposition are shown in Table 71-6. The most recent series is reported by Bax[66,67] where there was no mortality and a 20% leak rate in 24 cases.

**TABLE 71-6**
**Results of Jejunal Interposition**

| *Yr* | *Author* | *No. of Patients* | *Deaths* | *Leaks (%)* | *Strictures (%)* |
|---|---|---|---|---|---|
| 1958 | Jezioro[134] | 14 | 2 | 3 (21) | 1 (7) |
| 1982 | Ring[112] | 16 | 0 | 4 (25) | 2 (12) |
| 1988 | Saeki[135] | 19 | 2 | 3 (15) | 2 (10) |
| 1993 | Cusick[136] | 6 | 2 | 1 (17) | 2 (33) |
| 2007 | Bax[66,67] | 24 | 0 | 5 (20) | 1 (4)* |

*One stricture required resection, and 10 patients required dilatations (>4 times in 6 patients).

## SURGICAL TECHNIQUE

Two methods of jejunal replacement of the esophagus are used[64,68]: (1) transection of the jejunum distal to the ligament of Treitz, in which the proximal end of the loop is brought up through the thorax into the neck to join the esophagus, the distal end is anastomosed to the stomach, and intestinal continuity is restored by a jejuno-jejunal anastomosis; and (2) interposition of an isolated jejunal segment, either pedicled[66] or with microvascular anastomosis of the jejunal pedicle is done.

# Gastric Transposition

## HISTORY

In 1922 Kummell mobilized the esophagus in two patients by bluntly freeing it with the fingers introduced from the cervical and abdominal wounds.[69] Next, the stomach was

transplanted into the esophageal bed and the esophagus was anastomosed to the stomach. Although both patients died, this was the first attempt at gastric transposition by means of the mediastinal route. In 1938 Adams and Phemister[70] successfully resected a carcinoma in the lower thoracic esophagus of a 53-year-old patient and restored continuity by esophagogastrostomy. In 1944 Garlock's successful reestablishment of esophagogastric continuity after resection of the esophagus for carcinoma of the middle third in a 58-year-old male was reported.[71] At follow-up, the only complication was regurgitation in the recumbent position. This problem was controlled by sleeping on two pillows. In 1945 Sweet[72] recorded 12 esophageal resections with esophagogastric anastomosis above the arch of the aorta, and in 1948[73] he described the successful application of his technique following resection of a carcinoma of the upper thoracic esophagus with anastomosis of the stomach to the cervical esophagus. Soon thereafter, successful pharyngogastrostomy was described. Replacement of the esophagus by gastric transposition is currently the procedure of choice in adults with carcinoma, but its use in children has been limited.[74] Atwell[75] reported six children who had gastric transposition; two died, but good long-term results were achieved in the other four patients.

## SURGICAL TECHNIQUE

Transhiatal gastric transposition without thoracotomy is the procedure of choice (Fig. 71-5).[74,76–79] This procedure is sometimes contraindicated in the presence of extensive scarring from previous surgery or mediastinal inflammation.[80]

To preserve the vascular arcades of the gastroepiploic vessels, the initial feeding gastrostomy should ideally be sited on the anterior surface of the body of the stomach, well away from the greater curvature.

The stomach is exposed through an upper midline or left subcostal abdominal incision. Alternatively, a left oblique muscle-cutting incision that may extend into a left thoracotomy may be used, particularly if resection of a fibrotic esophagus or previous colonic interposition is required.

The gastrostomy is carefully mobilized, and the defect in the stomach is closed in two layers with interrupted 4-0 polyglycolic acid sutures.

Adhesions between the stomach and the left lobe of the liver are lysed while care is taken to preclude damage to the major blood vessels. The greater curvature of the stomach is mobilized by ligating and dividing the vessels in the gastrocolic omentum and the short gastric vessels. These vessels should be ligated well away from the stomach wall to preserve the vascular arcades of the right gastroepiploic vessels. Meticulous care must be taken to avoid damaging the spleen. The lesser curvature of the stomach is freed by dividing lesser omentum from the pylorus to the diaphragmatic hiatus. The right gastric artery is carefully identified and preserved while the left gastric vessels are ligated and divided close to the stomach (see Fig. 71-5, *A*).

The lower esophagus is exposed by dividing the phrenoesophageal membrane, and the margins on the esophageal hiatus in the diaphragm are defined. The inevitably short blind-ending lower esophageal stump in patients with isolated EA is dissected out of the posterior mediastinum by a combination of blunt and sharp dissection through the diaphragmatic hiatus. The vagal nerves are usually divided during this part of the procedure. The body and fundus of the stomach are now free from all attachments and can be delivered into the wound. The esophagus is transected at the gastroesophageal junction, and the defect is closed in two layers with 4-0 polyglycolic acid sutures. A Heineke-Mickulicz pyloroplasty or pyloromyotomy is usually performed, although whether it is necessary continues to be controversial.[81] The second part of the duodenum may need to be Kocherized to obtain maximum mobility of the pylorus. The abdominal part of the procedure and dissection into the posterior mediastinum through the esophageal hiatus may be carried out laparoscopically.[82]

The highest part of the fundus of the stomach is identified, and stay-sutures of different material are inserted to the left and the right of the area selected for the anastomosis. These sutures help to avoid torsion of the stomach as it is drawn through the posterior mediastinum into the neck (see Fig. 71-5, *B*).

Attention is now turned to the neck, where a previously constructed cervical esophagostomy is mobilized through a 3- to 4-cm transverse incision. Care must be taken not to damage the muscular coat of the esophagus. The recurrent laryngeal nerve that courses upward on the posterolateral surface of the trachea is identified and preserved. A plane of dissection between the membranous posterior surface of the trachea and the prevertebral fascia is established, and a tunnel is created into the superior mediastinum by blunt dissection immediately in the midline. A similar tunnel is fashioned from below in the line of the normal esophageal hiatus in the tissues posterior to the heart and anterior to the prevertebral fascia.[40] When continuity of the superior and inferior posterior mediastinal tunnels has been established, the space to be occupied by the stomach is developed into a tunnel the width of two to three fingers (see Fig. 71-5, *C*).

If thoracotomy was required for resection of a fibrotic esophagus (e.g., in cases of caustic or reflux esophagitis) or a nonfunctioning prior interposition, or when blunt dissection would be hazardous because of fibrosis from previous surgery or infection, the transthoracic part of the procedure is carried out under direct vision. The remainder of the operation is done in the same manner as that for the mediastinal procedure.

A long, blunt hemostat is passed into the posterior mediastinal tunnel from the cervical incision, and the two stay-sutures on the fundus of the stomach are grasped. The hemostat is gently withdrawn, which pulls the stomach up through the esophageal hiatus and the posterior mediastinal tunnel into the cervical incision. Alternatively, a large, stiff chest tube may be passed from the cervical incision into the mediastinum and abdomen and then sewn to the fundus of the stomach and drawn back into the neck, maintaining the sutures in the right orientation. Orientation of the fundus is checked by realigning the stay-sutures in their correction position. The end of the esophagus is anastomosed to the highest part of the stomach using a single layer of interrupted 4-0 polyglycolic acid sutures.

A large-caliber (12-gauge) nasogastric tube is inserted into the stomach through the esophagogastric anastomosis. The tube remains in place to allow free drainage and is aspirated at regular intervals to prevent acute gastric dilatation in the early postoperative period. A soft rubber drain is placed at the site of the anastomosis, and the wound is closed in layers.

The surgeon then returns to the abdomen, where the margins of the diaphragmatic hiatus are sutured to the antrum of

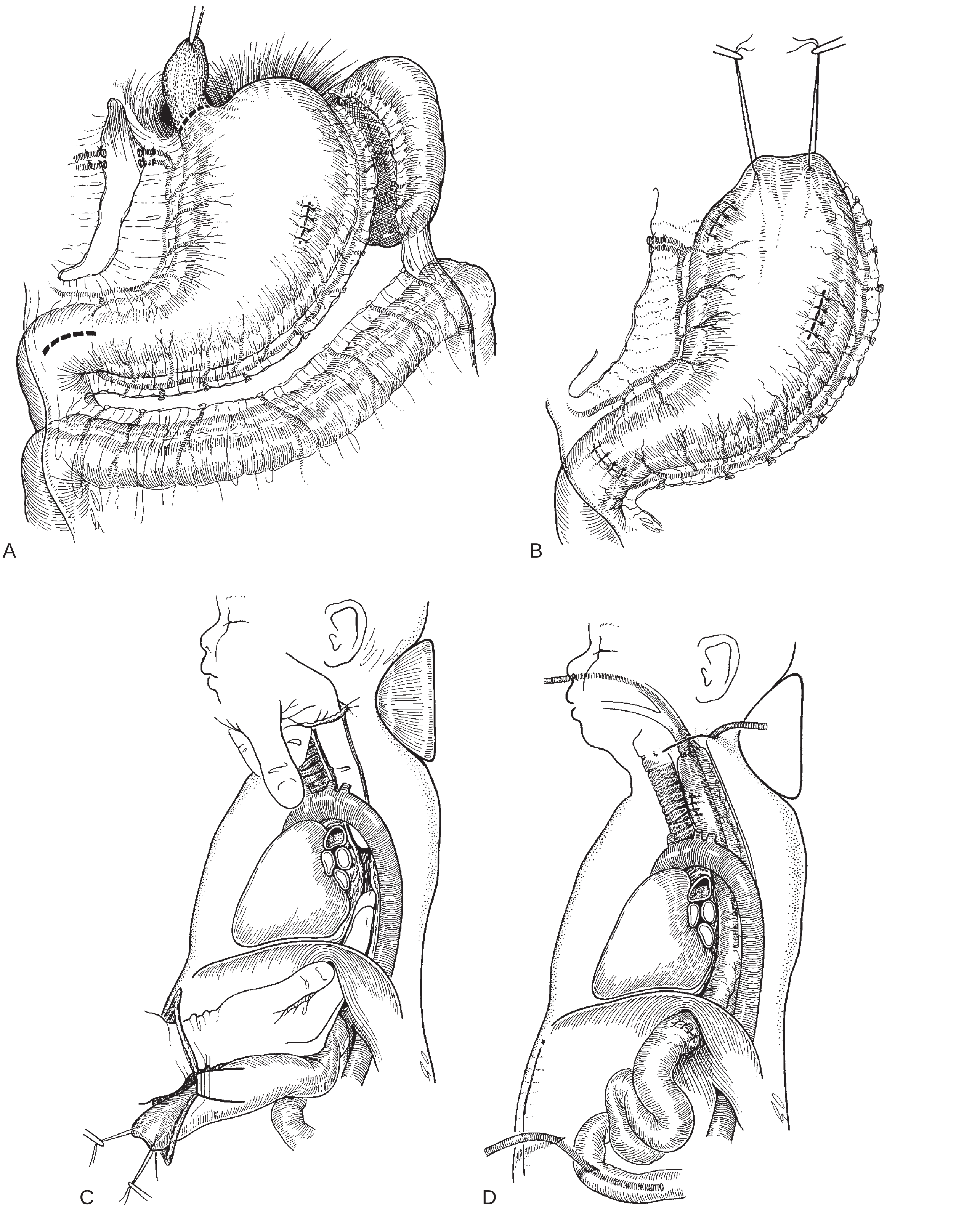


**FIGURE 71-5** **A,** Technique of gastric transposition. Mobilization of the stomach along the greater and lesser curvatures, preserving the right gastroepiploic and right gastric vessels. The short gastric vessels are carefully divided, with care being taken to avoid trauma to the spleen. The left gastric vessels have been ligated and divided. The duodenum (to which the Kocher technique has been applied) and the site of pyloroplasty are indicated. The short stump of esophagus in a case of isolated atresia is shown being mobilized from within the esophageal hiatus of the diaphragm. The gastrostomy site has been sutured. **B,** Pyloroplasty has been completed, the distal esophageal stump has been resected, and the two sutures on the fundus of the stomach indicate the highest point of the stomach at the proposed site for the esophagogastric anastomosis. **C,** Fashioning of the posterior mediastinal tunnel by blunt dissection from above by means of a cervical incision to mobilize the esophagostomy or expose the esophagus in the case of caustic injury and from below by means of the esophageal hiatus in the diaphragm. The dissection is done strictly in the midline in the prevertebral plane. **D,** The final position of the stomach in the posterior mediastinum with the esophagogastric anastomosis in the lower neck and pyloroplasty situated immediately within the peritoneal cavity below the esophageal hiatus. A jejunostomy tube has been placed for postoperative enteral feeding.

the stomach with a few interrupted sutures so that the pylorus lies immediately below the diaphragm in the midline. A fine-bore or button loop feeding jejunostomy has been found to be of considerable value in providing enteral nutrition in the first few weeks after gastric transposition before full oral nutrition is established (see Fig. 71-5, *D*).

## POSTOPERATIVE MANAGEMENT

Careful monitoring of vital functions is essential in the early postoperative period. Extensive dissection of the soft tissues in a posterior direction to the trachea has been done, and the resulting edema may cause respiratory compromise. Elective endotracheal or nasotracheal intubation with or without assisted ventilation for a few days may simplify the postoperative course and reduce the incidence of respiratory problems.

Jejunal feedings are instituted on the second or third day after surgery. The safest method of delivery of nutrition by this method is a slow, continuous infusion rather than by a bolus technique, which can provoke a "dumping" effect. Contrast swallow is done 7 days after surgery, and if no leak is identified at the anastomosis, careful oral feeding may begin. The cervical drain is removed when the integrity of the anastomosis has been demonstrated.

The results of gastric transposition in the larger series in the literature are shown in Table 71-7. In the period 1981-2005, 192 gastric transpositions were performed at Great Ormond Street Hospital, London.[83] The most common indication for esophageal replacement was EA in 138 cases, 76 of whom had failed primary repair, while 48 had isolated atresia without fistula. Twenty-nine children had intractable caustic strictures. More than 80% of patients were referred from abroad or from other centers within the United Kingdom. The method of replacement was via the posterior mediastinum without thoracotomy in 98 patients (51%). In the remainder a thoracotomy was necessary because of dense mediastinal scarring secondary to the original injury (caustic, perforation) or as a result of previous failed attempts at esophageal reconstruction. All patients are currently routinely paralyzed and mechanically ventilated for at least 48 to 72 hours postoperatively.

There have been nine deaths (4.6%), eight of whom had had complex courses before the transposition. Anastomotic leakage at the esophagogastric connection occurred in 12% of cases, all except one of which closed spontaneously. Strictures developed in 20% of cases, all but three of whom responded to endoscopic dilatation.[84] In these three cases, stricture resection and reanastomosis was successfully carried out through a cervical approach. Strictures were more common after caustic injury (38%). Swallowing problems postoperatively were encountered in 30% of cases.

Establishing oral feeding can be extremely difficult, particularly in infants with EA who have not been properly sham-fed. The jejunal feeding tube greatly simplifies postoperative nutrition and avoids the need for parenteral nutrition. Vomiting, which may be bilious in nature as a consequence of pyloroplasty, is common in the early postoperative period, especially when the child is recumbent.

A follow-up of 17 patients who had gastric transposition more than 5 years previously has shown that the intrathoracic stomach functions as a conduit as opposed to a reservoir for both liquids and solids.[85] Rapid emptying (>50%) of both liquids and solids occurred within 5 minutes of ingestion in 82% of patients. Dumping symptoms are occasionally an early feature, but these symptoms resolve within a few weeks in most cases. Of 17 children, 13 were within normal percentiles for height and 11 were within normal percentiles for weight. Low stores of iron are a feature in all types of esophageal replacements and were documented in all patients who had had gastric transposition. All but one child had restricted pulmonary function, with a mean total lung capacity of 68% and a mean forced vital capacity of 64% of expected values. It is uncertain at present whether these reduced values are a consequence of the primary condition or a direct result of gastric transposition.[85]

In 90% of our patients, the long-term outcome was judged to be good to excellent in terms of absence of swallowing difficulties and other gastrointestinal symptoms such as dumping or diarrhea. There has been no deterioration in function of the transposed stomach over time.[83]

One of us (author AGC) has had personal experience since 1985 with 169 gastric transpositions in infants and children. Follow-up has been obtained in 144 of these patients. These 144 patients consisted of 111 with EA, the vast majority of which were long-gap EA, 17 with lye strictures, 5 cases of diffuse leiomyomatosis, 2 patients with recurrent gastroesophageal reflux who had undergone multiple operations, 6 cases of failed colonic transpositions, and 3 recurrent tracheoesophageal fistulas who had undergone multiple previous operations with continued recurrence. More than 90% of patients had undergone previous esophageal surgery including previous esophageal replacements in 20%. After the initial early experience with this procedure in which a thoracotomy or thoracoabdominal approach was used, in the last 100 patients the posterior mediastinal dissection was done via the abdomen and the neck without any complications including serious bleeding. Ten patients with long-gap pure EA did not undergo a previous cervical esophagostomy before the gastric transposition. A feeding jejunostomy was done selectively but usually in infants with pure long-gap EA because of their difficulty in learning to feed postoperatively.

There has been no mortality in this series. There has been no loss of gastric conduit. In one patient, the gastric transposition was taken down due to a severe stricture, a result of failure to return for follow-up for more than 1 year. There have been two major complications: In one child with a lye stricture, the anastomotic leak tracked into the mediastinum and required drainage. She recovered but suffered a cardiac arrest 3 months later during dilation with residual brain

**TABLE 71-7**
**Results of Gastric Transposition**

| *Yr* | *Author* | *No. of Patients* | *Deaths (%)* | *Leaks (%)* | *Strictures (%)* |
|---|---|---|---|---|---|
| 1980 | Atwell[75] | 6 | 2 (33) | — | — |
| 1987 | Valente[137] | 21 | 1 (4.7) | 4 (19) | 3 (14) |
| 1991 | Marujo[138] | 21 | 1 (4.7) | 4 (17) | 3 (14) |
| 1995 | Spitz[78] | 83 | 6 (7.2) | 10 (12) | 10 (12) |
| 2002 | Hirschl[139] | 41 | 0 | 15 (36) | 20 (49) |
| 2009 | Spitz[83] | 192 | 9 (4.6) | 21 (12) | 36 (19) |
| 2007 | Tannuri[128] | 30 | 1 (3.3%) | 5 (17%) | 3 (10%) |
| 2009 | Coran[86] | 169 | 0 | 27 (16%) | 31 (18%) |

damage. The leak rate was 16%; all leaks closed spontaneously and required no further surgery. The stricture rate was 18%. All strictures have responded to dilations. Strictures were more common in caustic injuries. There was only one case of documented dumping syndrome, which responded to a carbohydrate-free diet. More than 90% of the patients are feeding orally. One of the most difficult problems was food aversion in babies with pure EA. In some cases, it took longer than 1 year for these infants to learn how to feed orally.[86]

In summary, there are several alternatives to esophageal replacement, with advantages and disadvantages for each, and the method chosen depends largely on the surgeon's experience and somewhat on patient-related factors, but good results can be obtained in a reproducible fashion with colon or gastric transposition or with gastric tubes.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 72

# Disorders of Esophageal Function

Juan A. Tovar

The esophagus acts as a conduit interposed between the pharynx and the stomach and has no significant secretory or absorptive functions. Its main function is propulsive, and its disorders induce several pathologic conditions that mirror their adult counterparts, although with specific pediatric features. Some of these disorders are related to malformations and manifest themselves during infancy and childhood. Most are incompletely understood due to our limited knowledge of the mechanisms of regulation of gastrointestinal motility and also because of the insufficiencies of the diagnostic tools that are difficult to apply in children due to size and collaboration problems. In the present chapter these motor disorders are addressed.

## History

In contrast with gastroesophageal reflux, the existence of disorders of esophageal function in children has been acknowledged only recently. With the exception of achalasia[1,2] and "esophageal diverticulum" likely corresponding to cricopharyngeal achalasia,[2] they were not even mentioned in the first modern textbooks of the specialty.[1–4] The nature of the functional disturbances involved in their pathogenesis and their sometimes elusive symptoms have been understood only recently, when the necessary miniaturized diagnostic tools were developed. Since these conditions were investigated, new clinical situations in which dysmotility plays a role were identified and examined.

## Embryology

The esophagus derives from the foregut or cranial part of the endodermal tube that runs longitudinally along the embryonal body. Cranially it starts at the lower end of the pharynx and caudally it is in continuity with the stomach, which is an expansion of the foregut.[5] The endodermal lining of this foregut is surrounded by muscle fibers that originate from the mesoderm and arrange themselves in two layers: the external, in which they are disposed longitudinally, and the internal, in which they adopt a circular pattern.

On the fourth week of gestation the respiratory anlage appears on the ventral side of the foregut and progressively undergoes branching until configurating the definitive tracheobronchial tree.[5] Endodermal-mesenchymal interactions and the influence of various genes, transcription factors, and growth factors contribute to shaping the lung and its multiple types of cells.[6,7] The endodermal lining undergoes changes leading to differentiation into either esophageal or tracheobronchial epithelia.[8] Tracheo-esophageal separation is crucial for normal organogenesis, and several malformations or dysfunctions of the esophagus have their origin at this point. On completion of these phases, the esophagus acquires its final configuration with two muscular layers, a submucosa and a polystratified, nonkeratinized mucosa. The reason why the muscle of the upper third of the organ is striated while that of the distal two thirds is smooth is unclear,[9] as is the mechanism by which this mucosa, which was originally endodermal, acquires its final ectodermal pattern. Esophageal glands derived from the endoderm form in the submucosal layer and secrete alkaline fluid that contributes to buffering acid.[10]

From weeks 4 to 11, neuroblasts issued from the cranial neural crest colonize the foregut in a cranio-caudal direction[11] and settle in the intermuscular and submucosal layers establishing fibrillar connections that will account for neural control of esophageal function by the parasympathetic and sympathetic systems.[12] Nonadrenergic noncholinergic (NANC) or nitrergic innervation is present in the myenteric plexus on week 12 and in the submucosal plexus on week 14. It is fully developed by week 22[13] or 23.[14] Both the vagus nerves and the sympathetic paravertebral chains are of neural crest origin, and their development parallels that of the intramural innervation.

The diaphragm is functionally related to the distal esophagus: The stomach and a part of the esophagus are located below the diaphragm, whereas most of the organ remains intrathoracic. Parts of the muscle fibers of the diaphragm have truncal mesodermal origin, and some are originally cervical.[15,16] The central tendon and other connective structures derive from the posthepatic mesenchymal plate that contributes to the closure of the pleuroperitoneal canals.[17]

## Anatomy

The upper end of the esophagus is in continuity with the pharynx. Its muscle fibers fuse with those of the cricopharyngeal muscle, the lower portion of the inferior pharyngeal constrictor that acts as an upper esophageal sphincter (UES). The esophageal body is located into the posterior mediastinum in close contact with the spine posteriorly, with the trachea and heart anteriorly, and with both pleural spaces on the sides. The vagal trunks run and branch on the surface of the esophagus. Esophageal length ranges from 10 cm in the newborn to 35 to 40 cm in adults. The lower end of the esophagus traverses the hiatus to become intra-abdominal before joining the stomach. On this end there is no distinct sphincter, but the circular fibers adopt at the gastroesophageal junction a horizontal U shape on the right side (clasp fibers), whereas on the left side they arrange themselves in another U-shaped structure that overrides the gastric incisura extending downward on the anterior and posterior faces of the stomach (sling fibers).[18] The diaphragmatic sling that forms the hiatus departing from the right crus overlaps the distal esophagus and the sphincter. Its striated fibers are closely attached to the esophagus separating the thoracic space lined by pleura from the abdominal one lined by peritoneum. These structures constitute altogether a zone of high pressure in which the lower esophageal sphincter (LES) and the crural sling are the main functional structures. In contrast with other segments of the gastrointestinal tract, the esophagus is devoid of serosal layer, although it is in part in close contact laterally with the right and left mediastinal pleurae in the thorax and anteriorly with the peritoneum in its short intra-abdominal portion. The muscle layers are quite similar to those of the intestine except for the nature of the muscle fibers, which are striated in the upper third and smooth for the remaining extent of the organ.

The intermuscular and submucosal plexuses contain ganglion cells connected among themselves and with the parasympathetic vagi and recurrent nerves, thoracic sympathetic trunks, and celiac plexus by a dense fibrillar network. The respective cholinergic and adrenergic mediators exert respectively positive and negative motor influences on the organ. Relaxation is mediated by nitrergic nerve endings that have their neurons in the intramural plexuses.[19] The c kit-positive interstitial cells of Cajal are distributed among the muscle fibers, where they may play a pacemaker role.[20–23] The extent to which these cells are related to neural control is not fully clear yet.[24]

## Physiology

The function of the esophagus is the transport of the alimentary bolus from the pharynx to the stomach. Secondarily, this organ takes in charge the clearance of the fluid that eventually refluxes from the stomach.

As a mechanism to avoid the invasion of the larynx by digestive juices and the insufflation of the esophagus by air during inspiration, the UES keeps a permanent tone that only relaxes during deglutition, when the glottis is closed and respiration ceases.[25] On the other hand, the unfavorable pressure conditions imposed on the esophagus by its intrathoracic location require permanent closure of the distal end to prevent reflux. This function is ensured by the LES, which also maintains its permanent tone except during deglutition.[26] The balance between the cholinergic and the nitrergic mediators regulates the permanent closure of the sphincter and its relaxations.[27]

The intrathoracic location of most of the esophagus and the intra-abdominal location of the stomach maintain an abdomino-thoracic pressure gradient. The intermittent negative inspiratory thoracic pressures coupled with the permanently positive abdominal pressures thus tend to push the gastric contents back into the esophagus.[28] The resting tone of the LES opposes this gradient assisted by the rhythmic contractions of the diaphragmatic crural sling, which further close the lumen during inspiration. At this moment the unfavorable gradient is more powerful and the sling displaces the cardia downward, accentuating the angle of His and lengthening the intra-abdominal segment of the esophagus.[29] The synergic play of these smooth and striated muscular structures has been extensively studied in animals[30–32] and bears some resemblance with the mechanism of anorectal continence in which the permanent resting tone is provided by the internal sphincter, and the intermittently required additional closure is achieved by voluntary contraction of the striated muscle complex and the external sphincter.

Deglutition is only possible if the upper and lower esophageal sphincters relax. This happens whenever the pharyngeal muscles mount a propulsive wave, and relaxation lasts until the peristalsis of the esophageal body triggered by pharyngeal contractions reaches the lower end of the organ. In order to effect these propulsive waves, the muscles of the esophagus contract in a coordinated craniocaudal manner progressing along the entire length of the organ to push the esophageal contents into the stomach. These are *"primary"* waves. Normal muscle layers and neural control are necessary for achieving this complex function, and motor disorders of the esophagus are likely the result of their anomalies.

Reflux is the retrograde passage of gastric contents into the esophagus and it is to a certain extent normal because the permanent tone of the LES fails several times every day, particularly during meals, allowing the permanent gastroesophageal pressure gradient to push gastric juice backwards. This sphincter may be permanently insufficient in some patients, particularly in neurologically impaired ones,[33] but it is presently acknowledged that most episodes of reflux in adults and children are due to nondeglutitory extemporaneous relaxations of the sphincter.[26,34,35] During these relaxations, the esophageal lumen is invaded by acid gastric juice. The mucosa is not prepared for this insult, and it has to clear this fluid promptly in order to avoid permanent damage. For this purpose the esophagus mounts peristaltic contractions that may be independent of deglutition, that arise at different levels of the organ and that are progressive and therefore able to force the refluxed material back into the stomach. These are *"secondary"* waves[36] aimed at clearing the esophagus of the bulk of the refluxed fluid. Complete clearance is only achieved after several swallows of alkaline saliva with some help from the alkaline secretion of esophageal glands.[37,38] The normal esophagus may also produce a limited number of simultaneous nonpropulsive motor waves that close the lumen along its entire length. These are known as *"tertiary"* waves, and when they are too frequent they contribute to some of the motor disturbances of the esophagus.[39–43]

## Methods Used for Evaluating Esophageal Function

For many years the barium swallow has been the main tool for investigating the esophagus. It shows not only anatomic anomalies of the organ but also abnormal contractility and relaxation of the upper or lower esophageal sphincters. However, irradiation is unavoidable if prolonged assessment is required and this has progressively limited its use. This method remains necessary for some of the conditions alluded to in this chapter, as we show later.

Scintigraphy with liquid or solid radionuclide-tagged meals has helped to clarify the normal mechanisms of esophageal clearance and is useful for assessing esophageal transit and esophageal and gastric emptying. However, it is of relatively limited use in children.[44–47]

Endoscopy with suitable fiberscopes allows direct inspection of the esophageal lumen and mucosa. Some contractility disorders may be detected by this procedure, but its main usefulness resides in the information obtained by inspection and biopsy of the mucosa. Some of the functional disorders are related to esophagitis and this can be adequately detected by endoscopy and biopsy.

Extended pH-metry is primarily intended to quantitate the extent of acid exposure of the esophagus. Because there is a clear correlation between the motor function and the clearance capacity of the organ, the information gained by pH probes may be crucial for understanding some of the motor disturbances.[34,44,48–50]

Manometry is the main tool for examining the motor function of the esophagus. This procedure is based on the principle of Pascal that states that the pressures exerted on any point of a liquid are transmitted in all directions with similar strength. Using tip-occluded probes with lateral holes perfused at constant rates, the pressure at any point of the esophageal lumen can be recorded through pressure transducers connected in a "T" to the perfusion system. Assemblies of several probes with spaced holes can explore the progression of pressure waves along the organ (Fig. 72-1).[34,35,40,50–60] Solid-state sensors can replace the perfused probes, but their fragility and high cost limit their use.

Manometry is also helpful for assessing the sphincteric function. Using one single perfused probe or assemblies of several of them with radially arranged orifices and withdrawing the recording orifices at a constant speed through the gastroesophageal junction allows recording of the pressure profile of both the UES and LES.[35,40,52,61,62] For the LES the profile shows the gastric pressure followed by a "plateau" corresponding to the overlapping LES pressure and the crural sling contractions.[63] Furthermore, it allows detection of the point at which the esophagus becomes intrathoracic because there is an "inversion point" at which the positive pressure inspiratory deflections become negative (Fig. 72-2). Stationary sphincter manometry with one of the orifices at the sphincteric level allows detection and assessment of the extent of relaxation.

However, because it was understood that reflux is possible with normal sphincteric pressures, more attention was paid to relaxations; therefore continuous sphincteric recording probes with constantly perfused sleeves located at the appropriate level were developed.[26,34,35,64,65] This, coupled with the availability of fine extruded Silastic probes, has permitted the study of gastroesophageal physiology in small and premature babies during relatively long periods of time.[66,67]

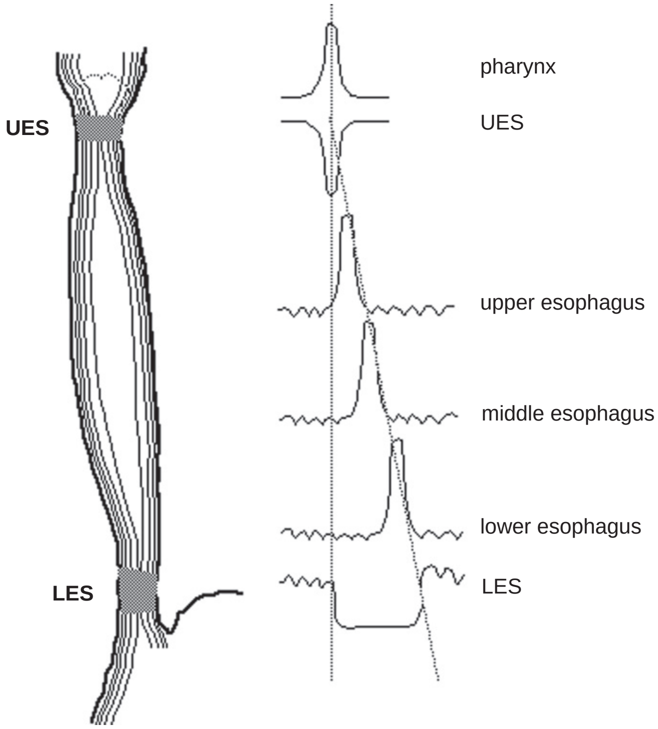


**FIGURE 72-1** Schematic drawing of the pressures recorded manometrically within the lumen of the esophagus during deglutition. Contraction of the pharyngeal constrictors is accompanied by relaxation of the cricopharyngeal muscle or upper esophageal sphincter (UES). Progressive peristaltic waves are generated in the body of the esophagus. The lower esophageal sphincter (LES) remains relaxed during the entire process and closes subsequently with a postrelaxation peak.

Manometry requires bulky, expensive, and delicate equipment and some collaboration on the side of the patient that may be difficult to obtain in children in whom sedation might change the registered pressures.[68,69] High-resolution manometry could provide more detailed data on esophageal motor function in children.[70]

The recently introduced 24-hour ambulatory manometry coupled with pH-metry generated important information on several esophageal disorders in adults and also in children.[71–80] However, the size of the solid-state sensor probes and the bulk of the equipment have limited these tests to older children for the moment.[43,50,59,81] These techniques benefit from the development of extended recording of pressures or pH, reduced to electrical signals that can be analyzed and measured with the assistance of purposefully designed software. It is likely that these diagnostic tools will be further miniaturized and adapted to children in the near future, thus enlarging the scope of manometric studies.

The more recent tool available for the assessment of esophageal function is multichannel intraluminal impedance (MII) coupled with manometry and/or pH-metry.[82,83] Changes in esophageal width cause proportional changes in luminal impedance and, with the assistance of several electrodes and adequate storing systems, a long-duration recording is possible. MII allows sequential analysis of the impedance variations caused by the passage of gas or liquid in either

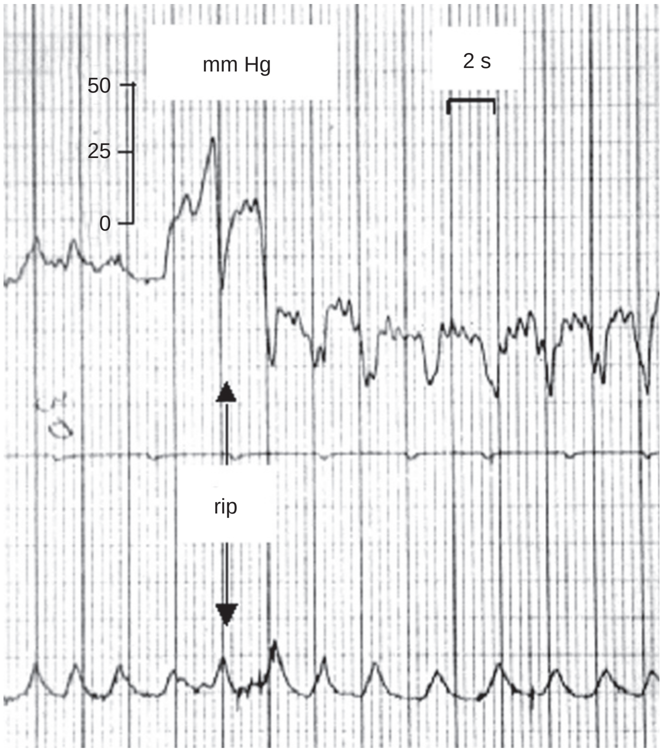


FIGURE 72-2 Pull-through manometric recording of the lower esophageal sphincter (LES) in a normal child (*upper tracing*) with simultaneous recording of the abdominal pressures (*lower tracing*). Intragastric pressures are first recorded with positive inspiratory deflections. A "plateau" corresponds to the high pressure zone of the LES. When the probe enters the thoracic esophagus, intraluminal inspiratory deflections become negative (respiratory inversion point, rip). From then on the pressure baseline is lower and the inspirations are recorded by negative waves. Withdrawal speed is 1 mm/sec, and time between vertical marks is 2 seconds.

direction. Reflux detection is possible and, when the measurements are coupled with pH recordings, its acid or nonacid nature can be ascertained. Furthermore, MII allows assessment of deglutition and esophageal motor activity (Fig. 72-3).

However, there are several limitations for the use of MII: Although this procedure sheds light on the little known field of nonacid or alkaline reflux, analysis of 24-hour tracings requires ample expertise and specialist time that considerably limit its use. Computer-assisted analysis has been used for reflux studies, but little has been done in terms of esophageal function investigation.[84–91] Furthermore, these limitations are even greater in children because of size, the need for patient cooperation, and the ethical restraints for establishing baseline control values, which also apply to other invasive functional tests in children.

# Disorders of the Upper Esophagus

The cricopharyngeus occasionally fails to maintain its permanent tonus or to relax during deglutition. This leads to difficult swallowing and consequent choking that may threaten life during early infancy.

Permanent *cricopharyngeal relaxation* is sometimes seen in neurologically impaired patients who undergo repeated episodes of aspiration.[92] *Delayed* or *incomplete relaxation* may be observed in children with Chiari syndrome,[93,94] 22q11.2 deletion,[95] or after diazepam medication.[96] Absence of relaxation *(cricopharyngeal achalasia)* occurs rarely as a primary phenomenon or secondary to neuromuscular disorders.[92,97] In all these conditions the leading symptoms are choking during feeding and respiratory distress during early infancy, which may prompt urgent diagnostic workup. Barium meal or cineradiography depicts simultaneous opacification of the respiratory and digestive tracts in cases of permanent relaxation and dilated pharynx with permanent upper esophageal closure and occasional passage of contrast into the trachea in cases of delayed or absent relaxation.[97,98]

Manometry is useful for the diagnosis of cricopharyngeal disorders because it shows the incompleteness or absence of relaxation of the muscle during deglutition.[92,93,99,100] However, it is particularly difficult to perform in infants because the use of perfused catheters in the upper esophagus is unpleasant for the baby who chokes, coughs, and does not collaborate. Recordings with sphincteric sleeves depict better the lack of relaxation with less risk of fluid aspiration.[101]

Gastrostomy may be necessary for feeding babies with permanent cricopharyngeal relaxation and also in those with UES achalasia.[94,102] Achalasia of the muscle can be treated by balloon dilatation,[103–105] but extramucosal myotomy is more effective.[99,106] If reflux is present, a concurrent fundoplication should be considered because insufficiency of both the upper and lower esophageal closure mechanisms may be devastating.[107] Some nonspecific histologic changes of the muscle obtained during myotomy have been reported in cricopharyngeal achalasia.[108]

# Disorders of Esophageal Body

## PRIMARY MOTOR DISORDERS

Abnormal motility of the body of the esophagus is a frequent cause of symptoms in adults in whom *diffuse esophageal spasm*,[72,109–112] *nutcracker esophagus*,[113,114] or other abnormal motor patterns impairing the propulsion of the bolus are occasionally diagnosed after investigation for dysphagia, noncardiac chest pain, or suspected reflux. Simultaneous, nonpropulsive contractions or an excessive proportion of long-duration waves alternating with normal ones are found in the first of these conditions, whereas extremely powerful, high-amplitude waves that can be peristaltic or retrograde are demonstrated in the second one.[72,76,115] Nutcracker esophagus has been seen to evolve into achalasia.[116]

Manometry is the main diagnostic tool, and its accuracy has improved considerably since 24-hour ambulatory recordings became available because the disturbances may not be permanent and appear only occasionally at some point of the circadian cycle. Because of the difficulties of performing this procedure in children, primary motor disorders of the esophageal body were practically unheard of in them until recently, although apnea, bradycardia,[117] and bizarre posturing[118] had been considered as expressions of motor disturbances. However, introduction of better manometric techniques produced growing evidence of their existence at this age. Food impaction in the absence of stenosis has been found in association with manometric patterns similar to those of adult nutcracker esophagus (Fig. 72-4), but this

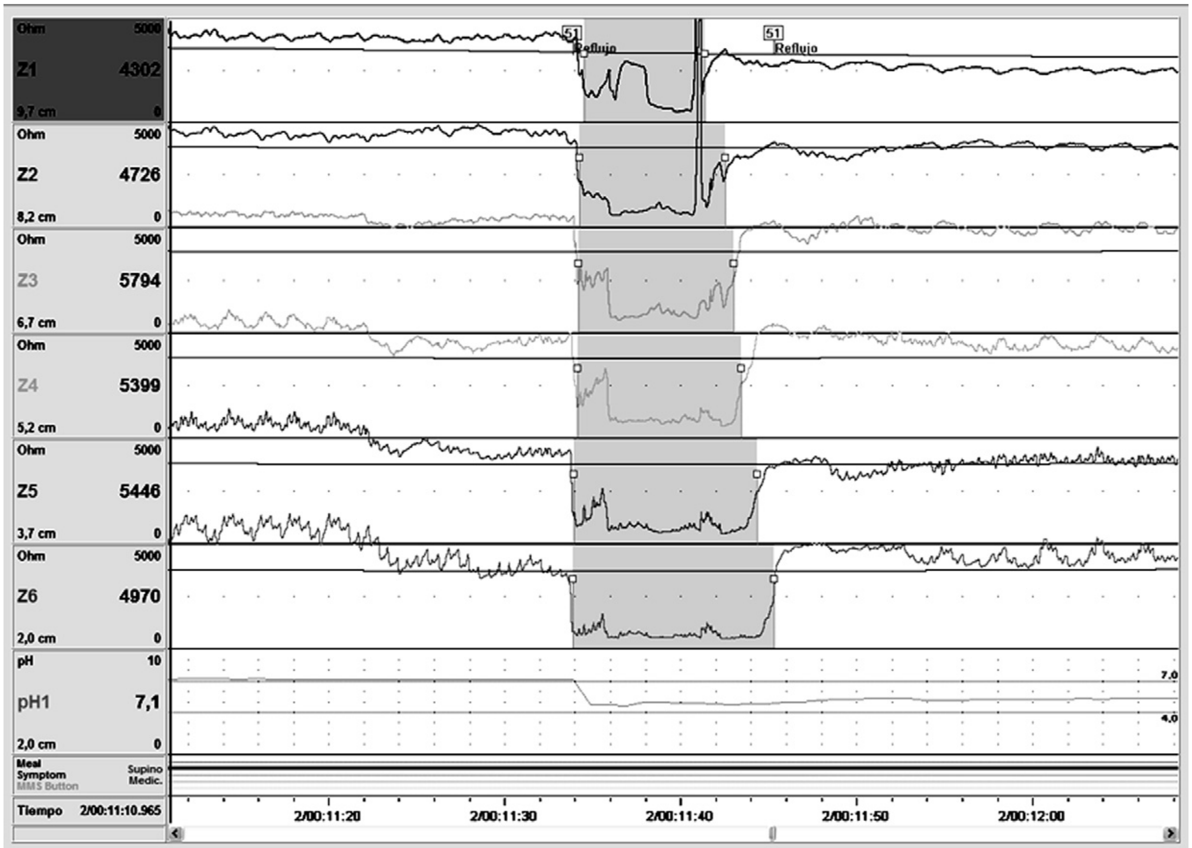


**FIGURE 72-3** Multichannel intraluminal impedance (MII) tracing in a 6-year-old child with gastroesophageal reflux. The lower pH tracing reveals a pH fall that unchains a retrograde fall of impedance revealing increased esophageal lumen width (reflux episode). Shortly after, the baseline width is nearly recovered in an antegrade sequence revealing swallowing. However, this event does not clear completely the refluxed acid because the pH tracing does not come back to normal. Using a pH of 4 as a threshold for defining reflux, this episode would have been disregarded. With this technique, it is considered as a weakly acidic reflux episode.

disorder might not be primary because most patients have either reflux[58,59,119,120] or eosinophilic esophagitis.[121,122]

Pharmacologic treatment of primary motor disorders with prokinetics or calcium channel blockers[123,124] is rarely indicated in children with these conditions.[125] Sildenafil, a drug that helps to induce NO-related relaxation of the esophageal body and LES, has been introduced for the treatment of motor disorders in adults,[126–128] but it has not been used in children until now. Balloon dilatation or extended myotomy, procedures occasionally used in adults, have not been used in children.

## SECONDARY MOTOR DISORDERS

Abnormal esophageal motility has been demonstrated in several syndromes and chromosomal disorders: Damaged peristalsis sometimes associated with reflux was found in children with both *Down syndrome*[129–131] and *Cornelia de Lange syndrome*.[132–136] *Scleroderma*,[137–139] *polymyositis-dermatomyositis*,[140] and *lupus*,[141] which are well-known causes of esophageal dysmotility in adults, may rarely start during childhood. *Babies breast-fed by mothers with silicone implants*[142] may also undergo esophageal motor disturbances similar to those of scleroderma.


**FIGURE 72-4** Nocturnal ambulatory manometric recording of intraluminal lower esophageal pH (1) and upper (4), middle (5), and lower (6) esophageal pressures in a 10-year-old boy with recurrent episodes of nonobstructive food impaction. The tracing demonstrates a pattern of nutcracker esophagus with long-duration, apparently peristaltic waves that are extremely powerful, particularly at the lower end of esophageal body (>200 mm Hg or 3 to 4 times above normal). This happens during sleep and without reflux, as seen in the pH tracing.

More relevant for pediatric surgeons are the motor disturbances of the esophagus suffered by survivors of neonatal operations for *esophageal atresia with or without tracheoesophageal fistula*.[47,143–147] In this malformation the structure of the muscle layers[148] and the abnormal extrinsic[149,150] and intrinsic[151,152] innervations impair the peristaltic pump for life. This is particularly harmful in this condition in which the function of the LES is also abnormal because both failures make gastroesophageal reflux (GER) a nearly constant part of the disease independently of the type of repair.[61,153] In addition, esophageal shortening due to the neonatal anastomosis,[154] abnormal hiatus,[155] and perhaps operative denervation may influence dysmotility. Many studies demonstrated that the LES function is abnormal in survivors of neonatal operations for esophageal atresia,[61,146] and some others showed that peristalsis is permanently damaged even many years after the anastomosis.[60,89,144,147,156,157] The clinical relevance of these disorders is probably greater than it was previously thought. Patients operated on for esophageal atresia have swallowing problems that are perceived by them as minor but that are almost constant when specifically searched for.[144,158] Their esophagus cannot fight reflux and, because of the structural basis of these dysfunctions, not much benefit can be expected from prokinetic medication. Furthermore, the spontaneous improvement of reflux with age that is part of the natural history of the disease in children cannot be expected in patients operated on for esophageal atresia, whether by thoracotomy or through a minimally invasive approach.[159]

GER should be treated in patients with esophageal atresia when it is symptomatic and/or when it causes esophagitis. Dysmotility, a constant problem with this malformation, does not preclude a complete fundoplication, which should be loose. Gravity is probably the main esophageal emptying force before or after the plication and there should be no problem if the wrap is loose enough. However, the proportion of long-term failures of the plication is high in this group of patients because all the causes of GER and dysmotility remain active in spite of the new valve.[160,161]

Other conditions relevant to pediatric surgeons involve esophageal motor disorders: *chronic intestinal pseudoobstruction,* a heterogeneous group of gastrointestinal dysfunctions with myogenic or neural basis, is characterized by distal esophageal dysmotility with simultaneous, short-lasting, low-amplitude waves[162–164] that may help in the diagnosis. However, dysmotility is widespread and the esophageal part is not the most significant.[165] Patients with *Hirschsprung disease* have simultaneous and double-peaked esophageal waves,[166] and children with *congenital central hypoventilation syndrome*[167] or *Goldenhar syndrome*[168] also have dysmotility. Survivors of neonatal operations for *congenital diaphragmatic hernia* have radiologic and clinical evidence of abnormal esophageal motor function[157,169–172] that might be related to innervation anomalies.[173] Esophageal dysfunction involving lowered sphincteric pressures or abnormal distal esophageal contractility has been described in children with *chronic renal failure*,[174] *Noonan syndrome*,[175] and *Pierre-Robin sequence*.[176] The same anomalies were found in adults with *celiac disease*.[177] A number of children with this disease also have eosinophilic esophagitis, and this could explain the esophageal disturbances.[178]

Children with *corrosive injuries* of the esophagus have impaired peristaltic activity both in the acute postinjury period[179] and when scars are established.[180] These manometric findings were confirmed by radionuclide[181] and combined studies.[182] The contribution of dysmotility to the clinical course and prognosis in this condition is still unclear, although it is believed that secondary esophagitis aggravates them.

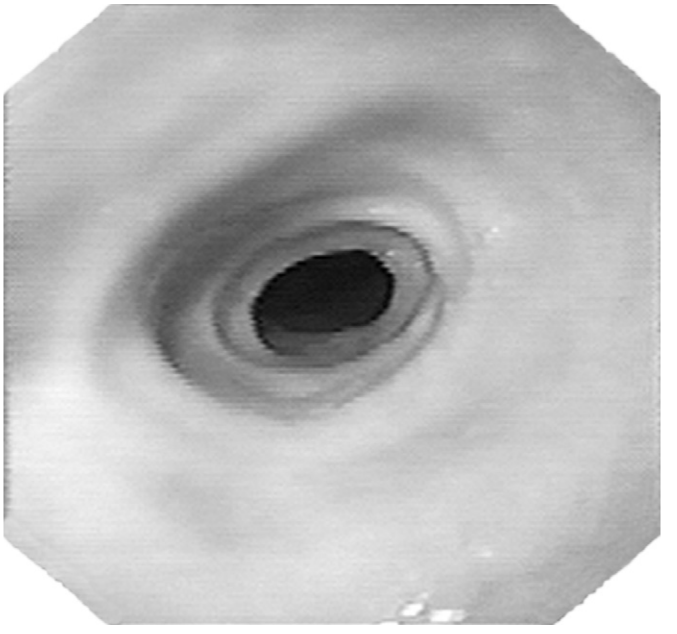

**FIGURE 72-5** Typical "multiple-ring" pattern of the esophagus on fiberoptic endoscopy in an 11-year-old girl with dysphagia due to eosinophilic esophagitis. On biopsy the mucosa was heavily infiltrated with eosinophils. pH-metry was normal, and the patient did well after a course of treatment with steroids.

In the past few years we have treated a growing number of patients with *eosinophilic esophagitis,* a condition of probably allergic origin in which there are symptoms of reflux or food impaction.[121,183–186] Reflux and stenosis are usually ruled out, and a typical aspect of Schatzki ring[187] or multiple rings[188] is seen on endoscopy (Fig. 72-5); heavy infiltration of the mucosa by eosinophils is found on biopsy, particularly with the Luna eosinophil granule stain.[189] Strictures are rarely observed in eosinophilic esophagitis, and they respond to treatment.[190,191] Dilatations may be indicated even in cases of severe dysphagia without stenosis.[192] Eosinophilic esophagitis has been seen in patients previously operated on for esophageal atresia in whom reflux is common.[193] Oral corticosteroids,[183] fluticasone,[194,195] and eosinophil stabilizers like montelukast[196,197] are usually helpful in the management of this condition.[190] However, there seems to be a dissociation between the symptoms and the histologic findings during treatment.[198]

## Disorders of the Distal Esophagus

*Primary gastroesophageal reflux* involves both the failure of the gastroesophageal barrier and abnormal esophageal motility. The causes for the sphincteric failure are not completely understood, but there is increasing evidence of prolonged nondeglutitory relaxations as the main mechanism.[26,34,35] They permit the creation of a "common cavity" phenomenon

that allows the full action of the untoward gastroesophageal pressure gradients between the stomach and the esophagus. The gastric fluid refluxed into the esophagus must be pushed back to the stomach by peristalsis, but this second defensive mechanism is also damaged with the consequent risk of esophagitis. The proportion of peristaltic contractions after deglutition or reflux and the amplitude of the waves are decreased, particularly at the lower end of the organ.[40,43,57] Whether dysmotility in gastroesophageal reflux disease is a primary phenomenon or secondary to esophageal inflammation is unclear. There are solid clinical and experimental arguments to maintain that chronic esophagitis damages previously healthy peristalsis,[199,200] but at least in some cases motor function remains abnormal even after medical or surgical cure of reflux and esophagitis.[40,51,199,201,202]

The success of prokinetic treatment used extensively in the past decades illustrates the relevance of the dysmotility in GER disease. These drugs act by reinforcing the failing sphincter, hastening gastric emptying, and improving peristalsis.

The more characteristic motor disorder of the lower end of the esophagus is *achalasia* in which the LES is hypertonic and does not relax during deglutition. In addition, in part by dilatation of the esophagus and also because of primary hypoperistalsis, its propulsive function is totally ineffective. This condition is rare in young children and, although some cases have early onset, most are diagnosed in late childhood or early adolescence. Only a few pediatric studies include more than a limited number of cases,[81,203–210] and the largest multicenter series involves only 175 cases.[211]

The cause of achalasia is unknown, but there is increasing evidence of a progressive disturbance of the intrinsic innervation with reduced or absent nitric oxide synthase (NOS) activity.[19,23] This enzyme is in charge of synthesizing NO, the nonadrenergic-noncholinergic neurotransmitter of smooth muscle relaxation.[19] nNOS(−/−) mice with nitric oxide synthase disruption have hypertensive, nonrelaxing LESs.[212] Recent evidence indicates a correlation between paucity of c-kit positive interstitial cells of Cajal and depletion of neuronal nitric oxide synthase (N-NOS) immunoreactivity in the esophagus of patients with achalasia showing that these cells are in some way related to relaxation.[213] The progressive degeneration of the intrinsic innervation has some bearing with that seen in Chagas' disease, a South American parasitic condition caused by *Trypanosoma cruzi* that causes degeneration of the neural structures leading to megaesophagus[214,215] and abnormal esophageal function. However, in Chagas' disease the pressures in the LES are not increased but rather reduced.[216]

Achalasia may be associated with Allgrove syndrome, an autosomal recessive familial condition[217] caused by a mutation of the AAAS gene on chromosome 12q13[218–223] in which, in addition to the esophageal motor dysfunction, there are adrenocortical insufficiency and alacrima. This association is also addressed as ALADIN syndrome (alacrima, achalasia, adrenal insufficiency, and neurologic disorder).[224] Achalasia is more frequent in boys and is occasionally associated with Down syndrome.[130,131,225]

Achalasia patients complain of progressive dysphagia and regurgitation of food retained in the esophagus that should not be confounded with vomiting. Some have retrosternal pain that may become distressing. They lose weight and often have foul breath and respiratory symptoms like nocturnal cough or repeated pneumonia due to frequent microaspiration.[208,226,227] In cases of Allgrove syndrome there are also symptoms of adrenocortical insufficiency such as progressive pigmentation and asthenia and eventually absence of tears (alacrima), but these symptoms and other manifestations of neurologic disease[224] may appear later after the full clinical picture of achalasia has developed.

Barium meal is often diagnostic: The esophagus is large (megaesophagus) and contains stagnant fluid above the barium column. There is a marked aperistalsis and the esophagogastric junction is filiform, adopting a classical "bird's beak" shape.[208] The contrast progresses into the stomach after a long time, and most of it is retained in the esophagus for hours (Fig. 72-6). Radionuclide scintigraphy may depict the lack of progression of the esophageal content and allows more prolonged observation with less irradiation, but it is less informative of the shape of the distal esophagus.[130,228]

Fiberoptic endoscopy rules out the presence of stricture, and the instrument can be advanced in the stomach with relative ease. After suctioning of the retained fluid, a picture of esophagitis may be seen but it is secondary to fermentation of the stagnant fluid. pH-metry is not useful at this stage and can be misleading because this fluid is often acid and the probe reading may suggest GER, which is in fact impossible.

Manometry is the best diagnostic tool for achalasia: The sphincter is hypertonic and does not relax or does it incompletely during deglutition. The esophageal peristalsis is absent and the scarce contractions present, particularly during meals, are recorded simultaneously at all points of the lumen, which is in fact a common chamber (Fig. 72-7).[70,203,207] Twenty-four-hour ambulatory recordings performed with probes equipped with multiple solid-state sensors show that the aperistalsis is constant along the entire circadian cycle

**FIGURE 72-6** Barium meal in a 9-year-old patient with achalasia. The esophagus is enlarged and contained stagnant fluid before the contrast was given. Emptying is slow and the cardia has a typical pattern of "carrot" or "bird's beak" (*left*). Some feeble esophageal contractions are seen (*right*), but peristalsis is impossible because the esophageal walls remain widely separated.

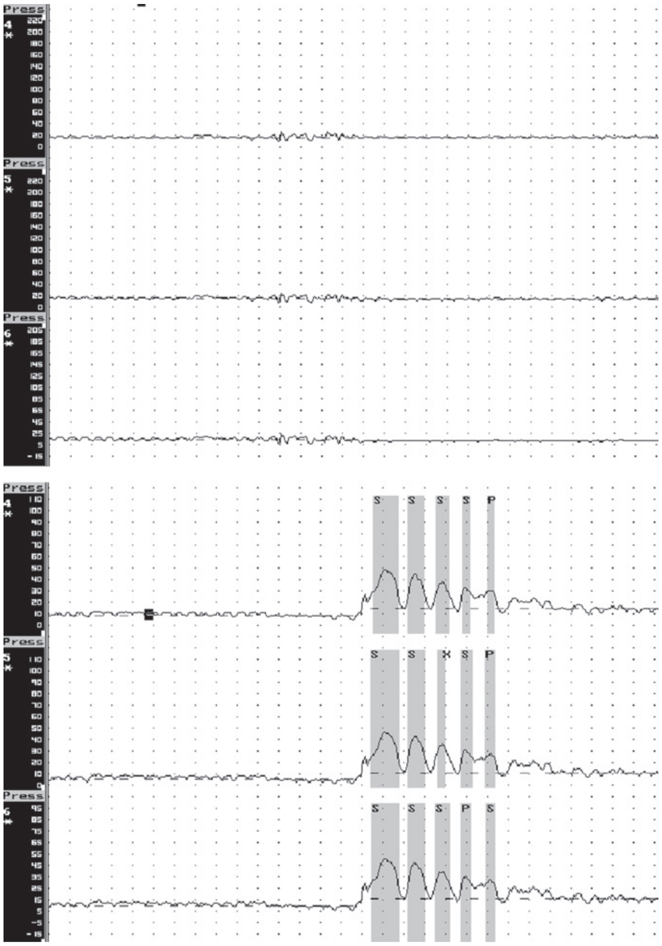

**FIGURE 72-7** Ambulatory esophageal manometry in an 8-year-old boy with achalasia. In the upper picture, the pressures at the upper (4), middle (5), and lower (6) levels of the esophagus are identical and no waves are seen. In the lower picture, corresponding to a meal, some waves are generated but they are simultaneous and nonpropulsive (time between vertical marks, 5 seconds).

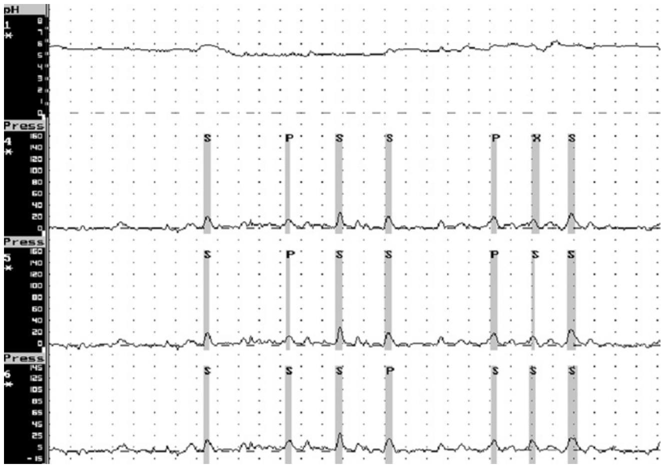

**FIGURE 72-8** Ambulatory esophageal manometry during meal in a 24-year-old woman 12 years after Heller myotomy for achalasia. She was asymptomatic, but esophageal motility remained poor. The motor waves at the upper (4), middle (5), and lower (6) levels of the esophagus showed peristaltic organization, but they were weak (<25 mm Hg, roughly half the normal). Time between vertical marks is 5 seconds.

including meals, when motor waves are normally more active.[81] Impedance studies confirmed and reinforced these data.[83]

The differential diagnosis includes extrinsic and intrinsic causes; in the latter group, acquired strictures and congenital stenosis from tracheobronchial remnants are usually easily eliminated by endoscopy. Leiomyomas and leiomyomatosis, either isolated or as part of Alport syndrome (hereditary X-linked nephropathy and deafness), may be suspected on endoscopy but require cross-sectional imaging with computed tomography or magnetic resonance imaging for confirmation.[228a]

Medication, particularly calcium channel blockers such as nifedipine, may alleviate the spasm in some cases,[229] but they cannot be relied on as a long-term treatment in children with achalasia.[124] Forceful balloon dilatation of the distal esophagus is often successful in adults, but this modality of treatment has not brought permanent relief in children,[203,204,230] although some favorable results were reported,[209,231] particularly older than the age of 6.[232] The local injection of botulinum toxin has been also tried in children, but its success has been limited as well.[226,233–236] Like in adults,[237] extramucosal Heller myotomy remains the best treatment at this age and it can be performed through either the thorax or the abdomen.[81,203,204,207,208,211,238] Perioperative lower esophageal manometry[239] or endoscopy[240] may ensure the completeness of the myotomy. An abdominal approach probably allows for a more complete myotomy on the gastric side and facilitates fundoplication. In fact, if sought after, reflux is rather constant after Heller myotomy and some form of fundoplication is probably indicated in children, whose long life expectancy after the operation supports the use of this procedure to prevent complications of GER.[81,204,206,207,226,241,242] A Nissen procedure may be inadequate due to the often large diameter of the thickened esophagus; the posterior Toupet or anterior Thal-Dor hemifundoplications are preferred.[81,207,242] Some authors prefer to omit antireflux procedures in these patients.[209,243] All these procedures can be performed laparoscopically, and this approach has become the gold standard.[209,238,242,244–247]

Postoperatively patients are relieved of their symptoms at once and they can feed properly and regain weight. However, the esophagus remains dilated for months or even years and its function only rarely returns to normal. Most patients maintain scarce and ineffective peristalsis in spite of the decrease in sphincteric pressure provided by myotomy (Fig. 72-8).[81,204,241,248,249] Some patients continue to have minor symptoms such as dysphagia and often require a few swallows of water during meals, but surgery brings back a good quality of life. Esophageal replacement has been reported in some rare cases of achalasia in which all other treatments failed.[250,251]

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 73

# Gastroesophageal Reflux Disease

Michael E. Höllwarth

The esophagus is a rather simple organ with no digestive features but serves the function of conveying food from the pharynx to the stomach. Gastroesophageal reflux (GER) is the term used to describe the usually undetected backflow of gastric contents into the esophagus, rarely reaching the pharynx or the mouth, and causing regurgitation. It is a physiologic phenomenon and occurs in otherwise normal individuals several times during the day and night, especially postprandial after ingestion of fluids such as soup, tea, coffee, or milk. In healthy individuals a number of mechanisms such as resistance of the esophageal squamous epithelial layer, rapid clearance of the refluxed material by propulsive peristalsis, and buffering of refluxate by swallowed saliva ward off any negative effects of reflux on the esophagus.

Pathologic reflux or gastroesophageal reflux disease (GERD) is a situation in which reflux causes major symptoms and complications such as failure to thrive, disturbance of sleep, recurrent aspiration in very young infants, epigastric or retrosternal pain, heartburn, esophagitis, stenosis, or Barrett esophagus in older children. Problems concerning esophageal function and reflux disease have been extensively investigated, as evidenced by the 300 to 400 reports published each year. Epidemiologic data in adults show that approximately 20% of the Western population is affected and GERD is now the most common upper gastrointestinal disorder in the Western world.[1] Risk factors are either genetic (family history, monozygotic twins); demographic (pregnancy, age, body mass index); or behavioral (smoking, alcohol, drug therapy). Recent genetic investigations have shown collagen type III alpha I and the male gender to be risk factors for hiatal hernia.[2] Epidemiologic data concerning the incidence of GERD in children are scarce. According to Vandenplas, troublesome GERD occurs in 5% to 8% of infants.[3] In Italy 313 (12%) of 2642 infants (age range 1 to 12 months) had clinical symptoms of GER, but only 1 of 210 infants followed closely over a period of 24 months developed GERD.[4]

## Esophagogastric Junction

The esophagogastric junction is a complex system that effectively separates the abdominal compartment with its higher pressure from the thoracic compartment with a significantly lower pressure, thereby preventing constant reflux from the stomach to the esophagus. It consists of several structures such as the crura of the diaphragmatic hiatus, the angle of His with the mucosal flutter valve inside the stomach, and the lower esophageal sphincter (LES).

The crural diaphragm forms an oblique slit encircling the esophagus from cranial-ventral to dorsal-caudal and constitutes an external pinchcock mechanism.[5] The medial wall of the esophagus continues directly into the lesser curvature of the stomach while the lateral wall forms with the stomach a type of incisure—the so-called angle of His. Oblique muscle fibers of the stomach, located below the LES, are arranged in a C-like fashion with the open part toward the lesser curvature.[6] Corresponding to the external anatomy, a mucosal fold (flutter valve) lies within the lumen of the esophagogastric junction. The flutter valve is passively pressed against the end of the lower esophagus when the gastric fundus is filled (Fig. 73-1, *A* and *B*).[7] The flatter the angle of His, the less developed is the valve mechanism and the more readily a reflux occurs.

The LES lies within the diaphragmatic hiatus, which forms a firm tunnel in which the esophagus is secured by the phreno-esophageal membrane. Manometric studies show that its upper portion belongs to the thoracic cavity and its lower portion to the abdominal pressure zone (Fig. 73-2). Under normal circumstances, an abdominal section of the esophagus does not exist. The tone of the LES lies in the range of 12 to 15 to 25 mm Hg not only in adults but also in neonates and infants.[8,9] It is approximately 1 cm long in the newborn and 3 cm long in adults (Table 73-1). The LES maintains its basic tonus but relaxes with the ongoing peristaltic wave of the swallow and closes with a brief increase in tone to 35 or 40 mm Hg. It should be noted that, during propulsive peristalsis, the esophagus exhibits a longitudinal contraction of 3 to 5 cm and the LES moves upwards together with the esophageal body.[10] Thus a sleeve device is necessary to register the pressure of the sphincter over a longer distance in order to demonstrate the true relaxation on manometry.[11] LES tone and relaxation are modulated through the central nervous system via the vagus nerve.[12]

One specific characteristic of the LES is the fact that its tone relaxes through a propulsive peristaltic wave, and transient lower esophageal sphincter relaxations (TLESRs) of 5 to

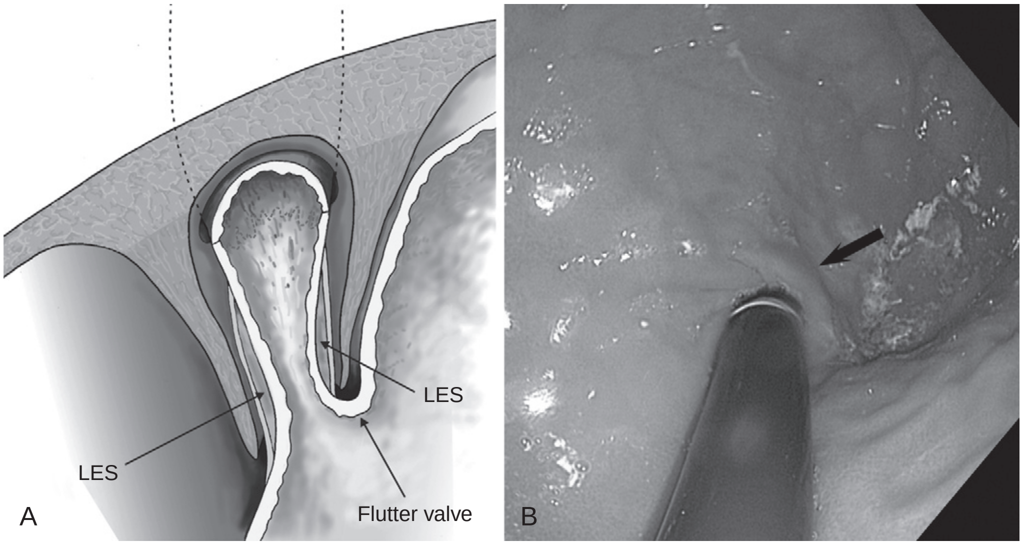


**FIGURE 73-1** **A,** Sketch of the anatomic structures of the esophagogastric junction. **B,** Endoscopic view of the mucosal "flutter valve" at the site of the angle of His. *(See Expert Consult site for color version.)*

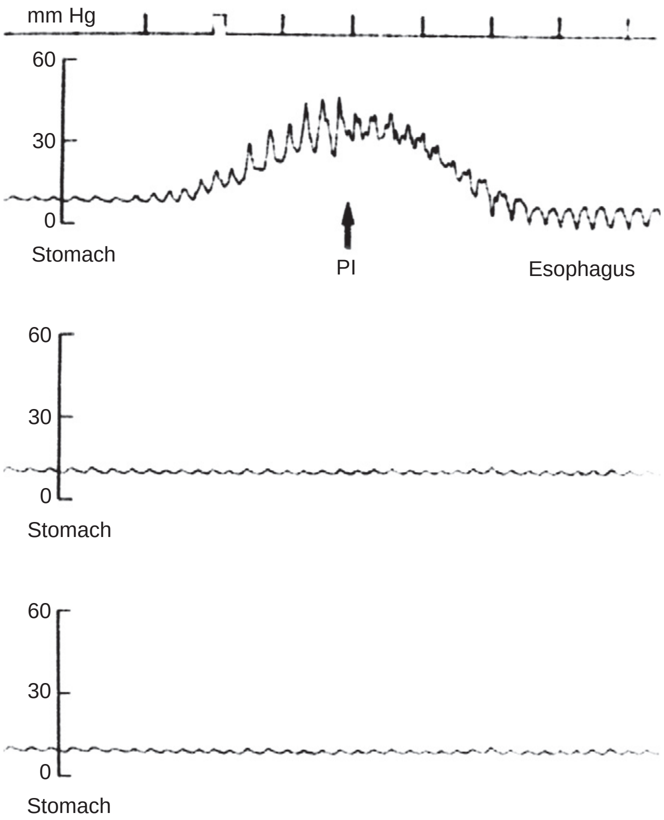


**FIGURE 73-2** Lower esophageal sphincter (LES) during a slow pull-through manometry in a newborn child. The LES lies within the hiatus with one part belonging to the abdomen and the upper part to the thorax. Except for the sphincter, there is no abdominal esophagus. *PI,* Pressure inversion.

30 seconds' duration occur even in the absence of any other esophageal peristalsis in healthy individuals.[13] A common space is created between the stomach and the esophagus and is seen on manometry as a sudden change of the typical esophageal tracing into an abdominal pressure curve, also known as the "common cavity phenomenon" (CCP) (Fig. 73-3).[14] Most of these relaxations remain unrecognized in healthy individuals because the refluxed material only reaches the lower esophagus. The volume is immediately returned to the stomach by a secondary peristalsis (volume clearance). Any drop in pH, however, that might accompany the refluxed gastric contents is neutralized only in a stepwise manner by the alkaline saliva during subsequent acts of deglutition (acid clearance) (Fig. 73-4). Therefore volume clearance is usually rather fast, whereas neutralization of the acidic reflux may take between 30 seconds and several minutes, the latter especially during sleep, because of the reduced frequency of swallowing.

Recent investigations show that nitric oxide is an important intramuscular transmitter for TLESR.[15] Glutamate is a different transmitter that affects the afferent vagal nerve. Its release can be inhibited by γ-aminobutyric acid ($GABA_B$) receptors, which exist on both ends of the neurons—at the gastric mechanoreceptors and the hindbrain control mechanisms—thereby achieving effective inhibition of TLESR.[16,17] Recently, metabotropic glutamate receptor 5 (mGluR5) antagonists were described as further potent inhibitors of TLESR.[18]

## Pathologic Reflux

TLESR is the primary pathophysiologic mechanism in all individuals with GERD. Relaxation is triggered by gastric mechanoreceptors that signal distension to the hindbrain. The latter generates motor signals to the LES and the esophagus via the vagus nerve. Additionally, these signals inhibit selectively the inspiratory contraction of the diaphragm suspending the pinchcock effect of the crura.[19] We have shown that the high incidence of GER in newborns and young infants is not caused by a low tone of the LES but by TLESR. Babies with pathologic reflux experienced more prolonged TLESR with CCP, significantly more often, but their LES pressure was normal (Table 73-2).[8,9] These findings were confirmed later by Omari.[20] Because any ingested fluid triggers TLESR by gastric distension, the largely liquid food (milk) given to infants is another factor that may cause more frequent TLESR.

**TABLE 73-1**
**Lower Esophageal Sphincter Tone and Length in Newborns and Small Infants**

| | n | *Age (days)* | *LES Tone (mm Hg)* $\dot{x} \pm SD$ | *LES Length (mm)* $\dot{x} \pm SD$ | *PS (n = 10)* |
|---|---|---|---|---|---|
| Prematures (GA 30-36) | 7 | 7-28 | 23,0 ± 3,6 | 10,0 ± 1,1 | — |
| Newborns | 24 | 1-10 | 20,4 ± 8,0 | 10,7 ± 0,8 | 5,2* |
| Newborns | 19 | 11-28 | 21,8 ± 10,0 | 11,0 ± 0,5 | 7,3 |
| Infants | 20 | >28 | 18,0 ± 7,0 | 11,3 ± 1,1 | 7,9 |

With permission from Höllwarth ME, Uray E, Pesendorfer P, et al: Esophageal manometry. Pediatr Surg Int 1986;1:177-183.
*$P < 0.05$.
*GA,* gestational age.

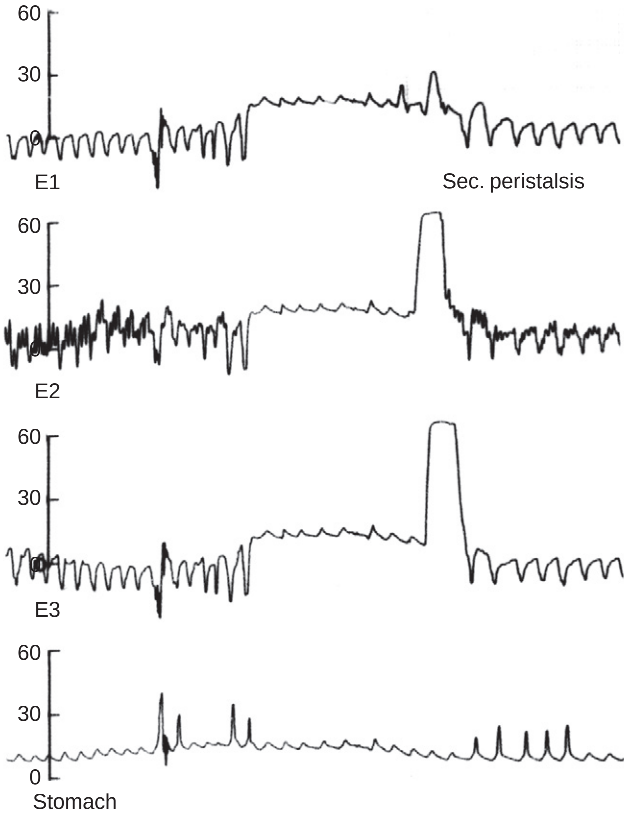


**FIGURE 73-3** Spontaneous pressure inversion of the esophageal tracings to an abdominal tracing indicating the opening of the lower esophageal sphincter due to a transient lower esophageal sphincter relaxation, the manometric "common cavity phenomenon." It is always terminated by a secondary propulsive peristaltic wave generated within the esophagus.

Furthermore, delayed gastric emptying with pathologic TLESR is observed in children with neurologic disorders and may increase the incidence of reflux episodes after a meal.[21] Given these functional disturbances in early infancy, as well as in children with neurologic disorders, we concluded that pathologic reflux may be regarded as a sign of delayed maturation or disturbed coordination of control centers in the hindbrain, disrupting the function of esophageal peristalsis, the LES, and in some patients also gastric motility.

The characteristic symptoms of pathologic reflux in infancy usually disappear at the age of 1 or 2 years. However, we and other authors have found that the disappearance of clinical signs does not necessarily mean that esophageal function has been normalized.[3,22–24] Orenstein studied prospectively a group of infants with histologically proven GERD but with no therapeutic intervention; although GER symptoms resolved in the majority of cases, the histopathologic results revealed a lack of improvement at the 1-year follow-up investigation.[23] Martin showed that infants with significant regurgitation on 90 days or more during their first 2 years had an increased risk of GER symptoms at the age of 9 years.[25] El-Serag interviewed a group of patients suffering from GERD in childhood (mean age, 10 years) to adulthood (mean age, 18 years): At least weekly, symptoms (heartburn or regurgitation) were reported in 46%, 94% of whom were taking proton pump inhibitors (PPIs) or other antisecretory medication. The authors concluded that approximately one half of young adults with a history of childhood GERD needed antisecretory therapy.[26] We recommend a 24-hour follow-up study in infants with a history of GERD even when the symptoms of reflux have disappeared at the age of 1 or 2 years, in order to identify children who still suffer from pathologic reflux. Our clinical experience confirms El-Serag's findings: Any pathologic reflux pattern that is still present at the age of 5 years will persist into adulthood.

## Symptoms of Gastroesophageal Reflux Disease

Mild regurgitation, a flaccid leak-out, or occasional vomiting as a sign of GER may be found in approximately one half of all newborns and young infants mainly fed on milk. The infants' subsequent development shows that the symptoms become less frequent after the first 4 to 6 months and are no longer observed at 12 months, when the child starts to receive solid food. Pathologic reflux at this age may be characterized by frequent regurgitation episodes, effortless leak-out of milk or food after meals, between meals, and when asleep. A moist pillow is another sign of reflux during sleep. Additional symptoms are restless sleep with sudden unexplained wake-up and excessive crying episodes. Reflux-related problems while feeding the baby may significantly disturb the interaction between mother and child.[27] In case of significant vomiting of food, the child may even develop malnutrition and fail to thrive. Further suspicious symptoms are developmental disorders, recurrent respiratory tract infections due to microaspiration, greater irritability, and agitation.[28] However, clinical symptoms in infants are not reliable indicators of GERD and are often poorly correlated with the results of 24-hour pH monitoring or histology.[29,30] Esophagitis is rare in newborns and infants as long as the babies are predominantly fed on milk, because gastric juices are largely buffered during the first 2 hours after feeding and the exposure time to acids is relatively short (Fig. 73-5).

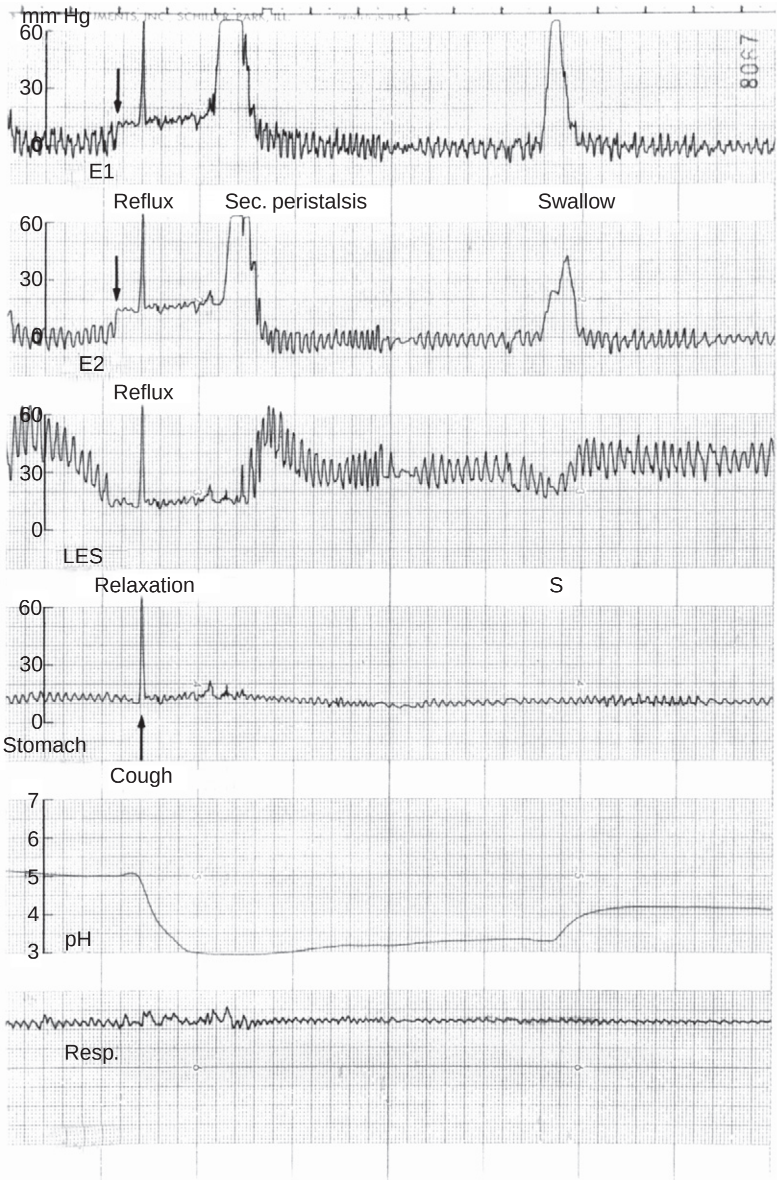


**FIGURE 73-4** Combined manometry and pH monitoring shows a 10-second "common cavity phenomenon" (CCP) with a fall of the pH from 5 to 3 and an increase with the next swallow to nearly pH 4. Note that a short cough during CCP indicates that reflux probably reached the pharynx and larynx.

**TABLE 73-2**

**Transient Lower Esophageal Sphincter (LES) Relaxations in Infants**

| | *Seconds* | *Infants with Reflux,* n | *Controls* n |
|---|---|---|---|
| Common cavity phenomenon (CCP) | <7″ | 12,4 ± 2,6* | 3,3 ± 0,5 |
| | 7-15″ | 9,6 ± 1,1* | 3,4 ± 0,4 |
| | >15″ | 3,0 ± 0,8* | 0,7 ± 0,2 |
| Total CCP time (%) | | 2,0 ± 0,3* | 0,5 ± 0,005 |
| LES tone (mm Hg) | | 25,3 ± 2,6 | 30,2 ± 1,4 |

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*Infants with pathologic reflux have a normal LES tone comparable with normal controls, indicating that the pathologic mechanism is not a weak LES pressure but a disturbed function with too many and too lengthy transient lower esophageal sphincter relaxations (TLESRs) indicated by more and longer CCPs ($P < 0.05$ compared with controls).

Apnea and sudden infant death syndrome (SIDS) are the most common causes of death between the age of 2 and 6 months. The association between reflux and apneic spells has been investigated with unequivocal results. There is no evidence that the typical apneic spells and near-miss events in infants between the ages of 2 and 6 months are caused by reflux events.[31,32] Although preterm infants had a higher rate of GER after feeding, a corresponding increase in apneic spells was not registered. In contrast, Wenzl showed a correlation between apnea and reflux in infants using the

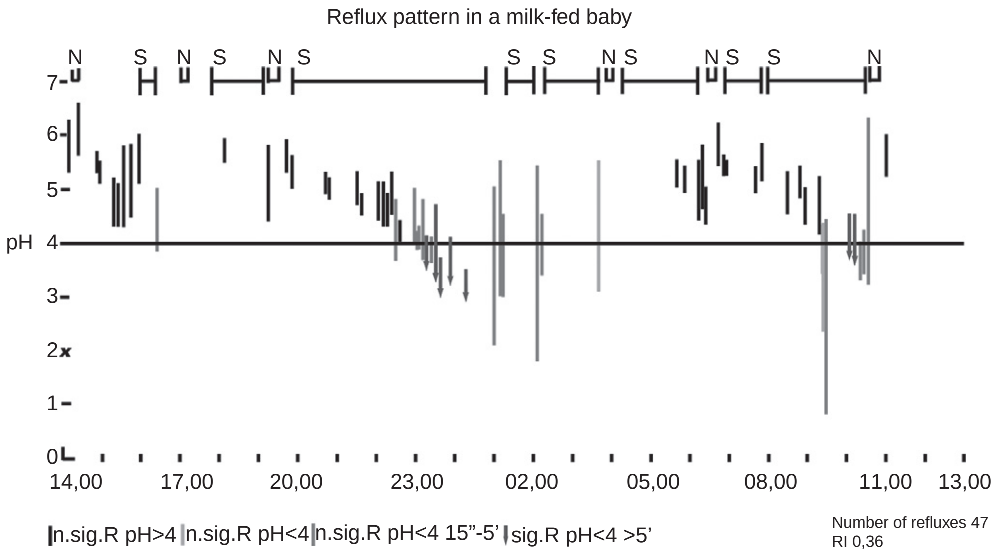


**FIGURE 73-5** Combined manometry and pH monitoring of a milk-fed 2-month-old infant. The lines indicate reflux episodes with the "common cavity phenomenon" and the related pH changes. In mainly milk-fed infants, gastric acid is effectively buffered and most of the reflux episodes for 2 to 3 hours after feeding do not fall lower than pH 4. *N,* Nutrition, *S,* sleep.

impedance technique. However, only 30% of the apneas were associated with reflux episodes while 70% were not.[33] Our investigations with manometry and simultaneous pH monitoring in infants with pathologic sleep apneas revealed no direct association between apneic spells and acidic refluxes. However, we did register a markedly delayed maturation of motor function of the esophagus in babies with sleep apneas or apparent life-threatening events (ALTEs).[34] Further studies have shown that infants with a pathologic sleep apneic pattern frequently suffer from pathologic reflux, whereas infants with a primary history of pathologic reflux have no remarkable prolonged apneic spells (Table 73-3).[35] These investigations support the hypothesis that infants with sleep apnea syndrome or ALTE suffer from a deeper localized underlying immaturity of the regulating hindbrain centers, whereas the causes for delayed maturation of esophageal motor function are located in higher brain regions and therefore not necessarily associated with disorders of respiratory regulation.

Symptoms in children beyond infancy are recurrent regurgitation of acid gastric juice, effortless vomiting, or night-time symptoms during sleep.[36] Recurrent respiratory tract diseases may occur due to microaspiration of reflux during sleep or may be complications of swallowing disorders in mentally handicapped patients. Clinical symptoms of esophagitis in most children are epigastric pain and, in adolescents, retrosternal pain or heartburn. Chronic inflammation of the mucosa may lead to microscopic bleeding and chronic anemia. If the inflammation spreads to deeper layers of the esophageal wall, it may eventually cause stenosis due to scarring. Late complications of GERD include replacement of the squamous epithelial layer by columnar epithelium, also known as Barrett esophagus. Chronic reflux in conjunction with unrecognized esophagitis, either with or without a hiatal hernia, may cause the Sandifer syndrome, which is characterized by behavioral problems such as spastic torticollis or dystonic body movements.

Hypopharyngeal refluxes at night with microaspiration may lead to laryngitis, laryngeal pseudopolyps and wheezing, chronic cough, pneumonia, or moderately severe symptoms of asthma. Recent clinical studies show that there might be a subgroup of patients with reflux-related airway problems who benefit from antireflux therapy, but chronic cough may also be unrelated to GERD.[37–40] The condition is difficult to diagnose except in those cases in which the radiologic investigation reveals aspiration of contrast material during reflux phases. Neither bronchoalveolar lavage nor nuclear medicine investigations are unequivocal. pH monitoring with one recording point in the upper and one in the lower esophagus discloses indirect signs when a large number of reflux episodes extend into the upper esophagus.[41] Other causes such as cystic fibrosis, aspirated foreign bodies, H-type fistulas, or malformations of the respiratory tract must be excluded. In children with a cerebral handicap, disruption of pharyngoesophageal transport—disturbed swallowing—is a common cause of recurrent aspiration.

**TABLE 73-3**
**Reflux and Apneic Spells**

| | n | *MA (sec/min)* | *LES Tone* | *Reflux* | *P:S* |
|---|---|---|---|---|---|
| Controls | 10 | 3,2 ± 1,3 | 21,6 ± 11,6 | 1 | 9,2 ± 1,6 |
| Infants with history of reflux | 12 | 5,5 ± 4,4 | 23,8 ± 10,4 | 8 | 8,4 ± 1,7 |
| Infants with history of sleep apnea | 21 | 13,7 ± 7,9* | 22,3 ± 7,0 | 14 | 7,5 ± 1,4 |

*Infants with a history of long sleep apneas also have more frequent reflux and an immature peristalsis when compared with infants with reflux or controls. *MA,* mean apneic time in sec/min; *P:S,* how many out of 10 induced swallows are followed by a propulsive peristalsis ($P < 0.05$ compared with controls).

## Diagnostic Investigations

Several diagnostic tests may be used to determine the extent of a pathologic reflux. However, the need for an extensive diagnostic workup depends on the nature of the underlying problem. The principal diagnostic tests to determine a pathologic gastroesophageal reflux are described in this chapter.

An *upper gastrointestinal series* is conducted to investigate the morphology and peristaltic function of the esophagus and exclude different pathologies such as pyloric hypertrophy and malrotation. Visualization of the gastroesophageal junction, demonstration of a sliding or fixed hiatal hernia, assessment of the angle of His, the course of esophageal peristalsis, and any remarkable features in the epithelium as signs of inflammation constitute the essential information that needs to be obtained. The actual evidence of reflux is less important because the radiologic exposure time is short and the true extent of reflux may be overestimated or underestimated. Indirect signs of a pathologic reflux include air reflux, a positive water siphon test (reflux after taking a large sip of water as provocation), and the level at which the reflux occurs.

*Twenty-four-hour pH monitoring* has long been the gold standard to evaluate the function of the esophagus. Ideally, multichannel probes are used and pH values in the stomach, lower esophagus, and upper esophagus are registered. Thus a pH drop in the esophagus may be correlated with the pH in the stomach, and the number of acidic refluxes that reach the upper esophagus can also be determined.[41,42] All pH drops below 4 of at least 15 seconds' duration (number of refluxes), the time required for normalization of pH and/or the time needed to increase the pH to 4 (reflux clearance), the number of reflux episodes with a clearance time of more than 5 minutes, and the longest reflux are assessed. We use a reflux index (RI) of 4% (percentage of time when pH < 4 in 24 hours) as a threshold in children and 3% in infants fed largely on milk because that takes into account the lower number of acid refluxes during which the pH drops below 4. The weakness of pH monitoring is that it provides a quantitative value of acid exposure of the esophagus but cannot demonstrate reflux episodes with a neutral or mildly alkaline pH.

*Combined multiple intraluminal impedance and pH monitoring* enable the investigator to determine all refluxes and the direction of bolus movement. Thus even neutral and alkaline refluxes can be recorded over 24 hours (Fig. 73-6).[43–45] Because microaspiration of nonacid refluxes plays an important role in recurrent respiratory tract infection, combined impedance/pH monitoring may well replace simple pH monitoring in the near future as the new gold standard of investigation.

*Manometric investigations* of esophageal function were introduced in the late 1960s, primarily to measure pressure in the LES. However, manometry is an excellent method to demonstrate the motor function and peristalsis of the esophagus as well. The manometric sign of TLESR is the CCP, which is marked by an increase in esophageal pressure tracings to abdominal pressure and a characteristic reversal of fluctuations that accompany respiration (see Fig. 73-3). Manometry combined with pH monitoring shows that the reduced pH due to reflux is normalized in a stepwise manner by swallowing saliva and permits analysis of acid, neutral, and alkaline refluxes (see Fig. 73-4). Thus the investigator can draw similar conclusions as those derived from impedance/pH studies. The disadvantage of manometry is that it is a motion-dependent investigation and requires a quiet child. Therefore it is not suitable as a routine method but may well be indispensable for specific questions.

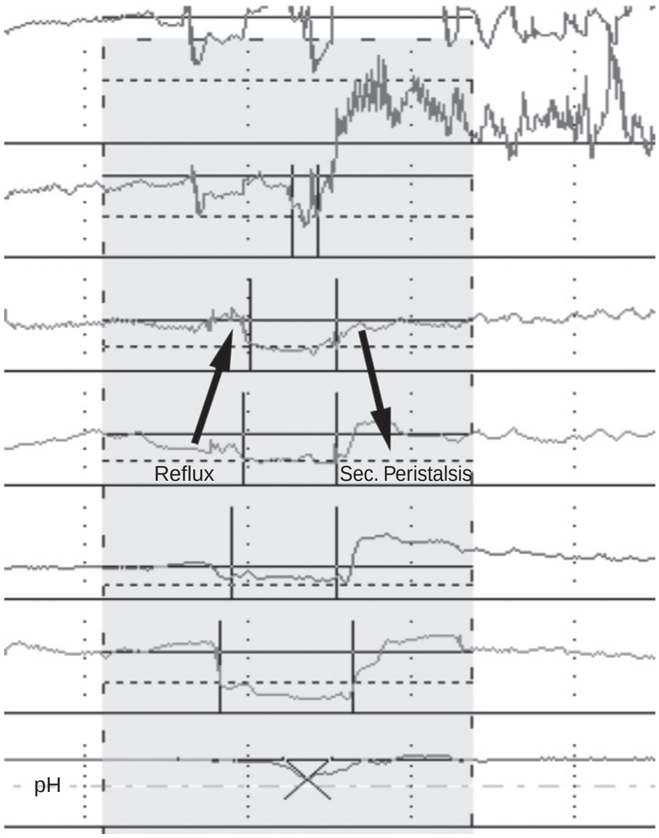


FIGURE 73-6 Combined impedance and pH monitoring shows a short reflux episode with a minimal decrease of the pH in the esophagus, which would not be detected by pH monitoring alone.

*Endoscopy and histology* are invasive investigations with flexible fiberoptic endoscopes and biopsies but an essential part of the diagnostic workup in GERD. Any endoscopic investigation is incomplete if the larynx is not inspected. Reddening, ulceration, or pseudopolyps on the vocal cords (Fig. 73-7) are typical signs of laryngeal reflux. Biopsy specimens are taken from the duodenum and the antrum of the stomach and tested routinely for *Helicobacter pylori*. The gastroesophageal junction is inspected by inversion of the tip of the endoscope in the stomach. Under normal circumstances the esophagus encloses the device tightly and the previously mentioned flutter valve can be seen at the lateral circumference. Sliding and paraesophageal hernias can be visualized (Fig. 73-8). The gastroesophageal junction and the Z-line can be accurately inspected by withdrawing the endoscope further. In normal cases the esophageal epithelium is smooth and milky red in color. In the presence of esophagitis one can quantify the degree of injury by using a scoring system such as the Savary-Miller interpretation: grade 1—erythema, grade 2—linear, noncircular ulceration, grade 3—confluent ulceration, grade 4—stricture. The more sophisticated Los Angeles classification of manifest esophagitis can also be used in children; it describes four grades of mucosal breaks, depending on the extension between mucosal folds.[46] It is essential to take several biopsy specimens, starting 1 to 2 cm proximal to the Z-line, upward into the upper esophagus. An optimal biopsy specimen includes

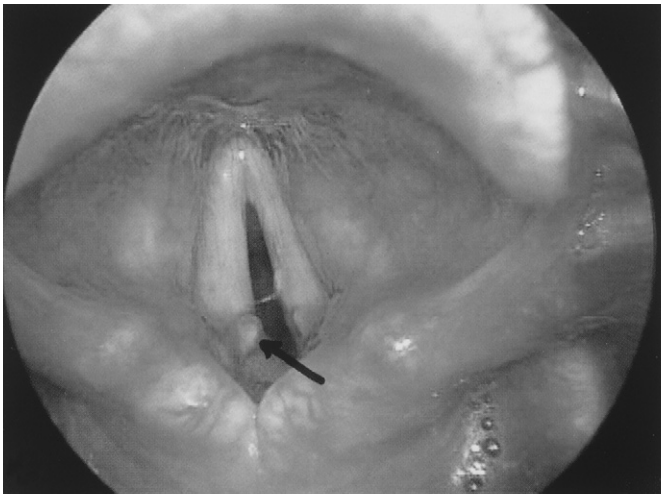

**FIGURE 73-7** Typical pseudopolyp on the vocal cord due to chronic reflux.

the entire epithelium with the basal cell layer. Hyperplasia of the basal cell layer and relative elongation of the papillae are signs of increased cell turnover due to reflux-related acid exposure or other pathologies. Dilated intracellular spaces are a relatively new parameter that is used in combination with other histologic features. Evidence of intraepithelial eosinophils then confirms the presence of obvious esophagitis, but it may be found even in the absence of corresponding symptoms.[47,48] On the other hand, the presence of more than 15 eosinophils per "high-power" field can be seen in infants with milk protein allergy and is a sign of a non-reflux-related allergic/atopic disease, also known as *eosinophilic esophagitis.*[49]

*Gastric emptying scans,*[51] *C-acetate breath test,* and *electrogastrography* have been used to evaluate gastric emptying time. However, doubts have been raised about their usefulness for the diagnostic workup of GERD.[28,50,51]

## Conservative Therapy of Reflux Disease

In infants, esophageal dysfunction and GERD resolve spontaneously in 90%. Therefore conservative measures are the treatment of choice. Former investigations have proposed the prone position, with the trunk raised as the most effective in preventing reflux because the hiatus is in the highest position.[52] However, the risk of sudden infant death is markedly increased in this position because vomiting during sleep may obstruct the nose and mouth, causing prolonged apneic spells and apparent life-threatening events (ALTEs). Currently, the supine position with the trunk elevated or the left-sided position during sleep and elevation of the head of the bed are given preference.[28,53] Additionally, frequent small-volume meals and thickening of food with rice gruel are recommended. However, the published literature provides no clear evidence of thickened formulas or specially manufactured milk formulas being effective in reducing the frequency of reflux events, but they do reduce visible regurgitation.[28,54–56] As mentioned earlier, the disappearance of symptoms does not necessarily mean that the reflux has subsided—it might just not reach the mouth. Therefore around the age of 2 years, a control 24-hour impedance/pH monitoring should be performed to prove or exclude persistent reflux.

In older children, there is no evidence of any specific change in food management reducing reflux. However, obesity, large-volume meals, and late eating have been associated with symptoms of GERD.[28]

$H_2$-receptor antagonists have been used for gastric acid buffering since the 1970s and have yielded beneficial effects in terms of providing symptomatic relief compared with placebo. Although their effect is inferior to that of a proton pump inhibitor (PPI), $H_2$-receptor antagonists are useful for PPI-intolerant patients.[57] Today, PPIs are the treatment of choice for curing GERD symptoms and esophagitis.[58] However, more studies are necessary to determine the specific symptoms and subgroups of juvenile patients who should be treated with PPIs.[58,59] Children on long-term PPI medication for GERD are exposed to a higher risk of acute gastroenteritis and community-acquired pneumonia, especially those with comorbidities such as diabetes or immunodeficiency.[60,61]

Although PPI therapy mainly reduces gastric juice acidity, a new and promising therapeutic option is the pharmacologic inhibition of TLESR by $GABA_B$ agonists such as baclofen. Recent experience with baclofen in adults and children with GERD has demonstrated a significant reduction in TLESR and reflux.[16,62–64]

Prokinetic therapy with cisapride has potential adverse effects (cardiac arrhythmias), and its clinical efficacy has not been conclusively established.[65] Domperidone and metoclopramide are other motility agents that are widely used, but their efficacy has not been demonstrated in randomized trials.[30]

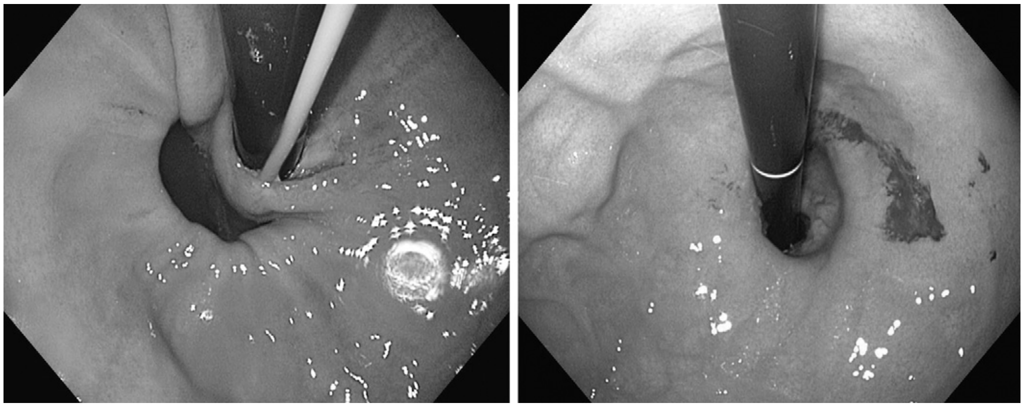

**FIGURE 73-8** *Left,* Typical paraesophageal hernia. *Right,* Axial hiatal hernia, with a view toward the higher-positioned lower esophageal sphincter.

## Surgical Therapy

Laparoscopic fundoplication is currently the treatment of choice. The procedure is safe and provides an excellent view due to magnification. Postoperative pain is significantly less, and the abdominal cosmetic aspect is clearly better when compared with a large laparotomy.

The most commonly used surgical procedures in children are the Nissen technique with a 360-degree wrap, the Toupet technique with a semicircular dorsal wrap, and the Thal technique with a semicircular ventral wrap.[66–68] The essential elements of all fundoplication techniques are mobilization of the gastroesophageal junction in order to achieve a 2- to 5-cm-long intra-abdominal esophagus (depending on the patient's age) and the creation of a partial or total fundus wrap around the esophagus over a large intraesophageal dilator (Figs. 73-9 to 73-11). When using the Nissen technique, the wrap should be loose and no longer than 1.5 to 2 cm in order to avoid complications such as the inability to belch or vomit and gas bloat. According to Nissen's original technique, the wrap must be created such that the surgeon can introduce his or her finger between the wrap and the esophagus.[66] Although a controversially discussed point, we advise fixation of the wrap to the esophagus with at least one suture and anchoring it to the diaphragm in order to prevent slippage or herniation. Most surgeons combine the technique with a hiatoplasty by approximating the crura with interrupted or figure-of-eight sutures to reduce the risk of wrap herniation into the thorax. We use onlay pledges to reinforce the hiatoplasty in cases of a large distance between the crura, or preexisting hiatal hernia. Great care should be taken to avoid injuring the vagus nerves. Modifications of Toupet's and Thal's techniques usually involve a 200- to 270-degree fundic wrap.

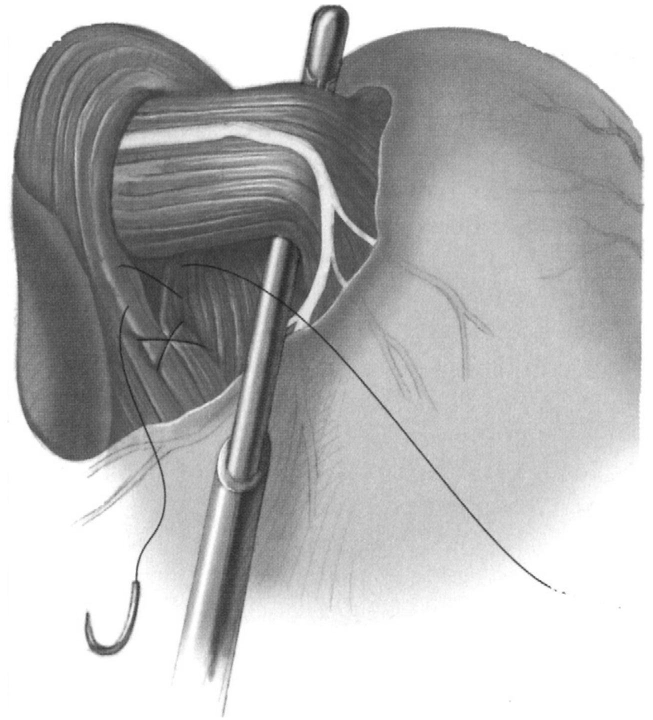

FIGURE 73-9 Laparoscopic Nissen. Hiatoplasty with figure-of-eight sutures. Great care should be taken to avoid closing the hiatus too tightly. (With permission from Georgeson KE: Gastro-oesophageal reflux and hiatus hernia. In Puri P, Höllwarth M [eds]: Pediatric Surgery, Springer Atlas Series, Berlin Heidelberg, New York, Springer, 2006, pp 49-60.)

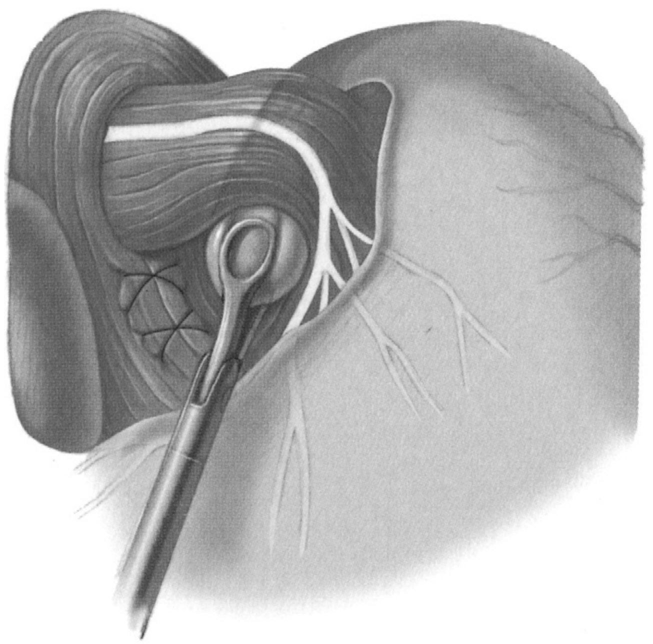

FIGURE 73-10 Laparoscopic Nissen. After ligation of the short gastric vessels, a part of the fundus is pulled with a Babcock to the right side. (With permission from Georgeson KE: Gastro-oesophageal reflux and hiatus hernia. In Puri P, Höllwarth M [eds]: Pediatric Surgery, Springer Atlas Series, Berlin Heidelberg, New York, Springer, 2006, pp 49-60.)

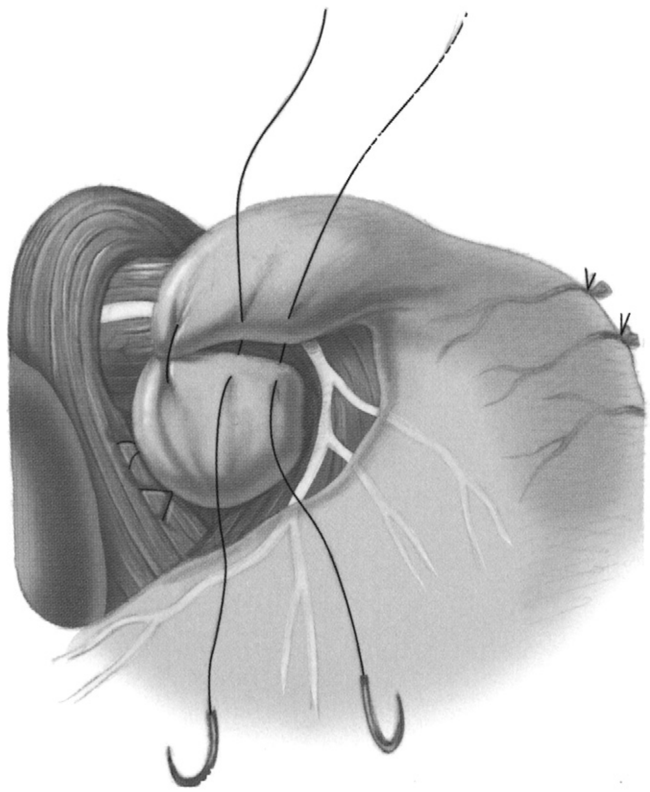

FIGURE 73-11 Laparoscopic Nissen. With a dilator in the stomach, a circular wrap is constructed and secured with one or two stitches to the esophagus and to the diaphragm. (With permission from Georgeson KE: Gastro-oesophageal reflux and hiatus hernia. In Puri P, Höllwarth M [eds]: Pediatric Surgery, Springer Atlas Series, Berlin Heidelberg, New York, Springer, 2006, pp 49-60.)

## Mechanisms of Antireflux Procedures

Manometric studies in adult patients before and after Nissen fundoplication have shown the following: (1) TLESR was substantially reduced to 50% of the preoperative rate, (2) the rate of TLESR accompanied by reflux was reduced from 47% to 17%, and (3) the mean residual pressure at the gastroesophageal junction during swallowing-induced relaxation increased significantly from 0.7 mm Hg to 6 mm Hg while the basal LES pressure was not affected.[69,70] Further investigations have shown that gastric distension causes an increased number of TLESRs in normal subjects and GERD patients, which is significantly attenuated by Nissen fundoplication, but gastric accommodation to the change in volume was similar in all groups.[71] Manometric studies comparing Nissen's technique with Toupet's showed that the resting tone of the sphincter was significantly higher in patients who underwent total wrap fundoplication, although there was no difference in the intra-abdominal length of the LES. The nadir pressure during LES relaxation was higher in those with a total wrap (6.5 vs. 2.6 mm Hg). However, the difference did not achieve significance. Significantly more CCPs occurred during TLESR by the Toupet technique after gas insufflation into the stomach. The authors concluded that partial dorsal fundoplication appears to restore gastroesophageal function more adequately, permitting air to be vented from the stomach without jeopardizing the antireflux barrier.[72] Studies on motor dysfunction of the esophagus show that it is not correlated with postoperative dysphagia and is not corrected by fundoplication, suggesting that it could be a primary phenomenon.[73–75]

## Results of Fundoplication

Antireflux surgery is a common procedure in the United States. From an analysis of 9987 records, it has been estimated that 48,665 procedures were performed in children between 1996 and 2003 (≈9 procedures per 100,000). The highest population-based procedure rate (45%) was performed in infants younger than the age of 1 year (≈101 procedures per 100,000 population).[76] Given the option of spontaneous maturation of esophageal function and the transient nature of reflux in infants younger than the age of 1 year, concerns have been expressed about the necessity of antireflux procedures. Hassall discussed failure rates and results of fundoplication in children and favors long-term medical treatment with PPIs; he recommends antireflux surgery only in selected patients.[77] It has been suggested that treatment algorithms should be reassessed in order to standardize the diagnosis, treatment, and follow-up of GERD in patients younger than 18 years of age in the United States.[78]

Tovar has convincingly shown that fundoplication with a floppy wrap is a powerful means of controlling reflux in appropriately selected children in whom medical treatment fails, or in symptomatic refluxers with specific comorbidities such as neurologic disorders or congenital anomalies.[79] A systematic review of randomized controlled trials of laparoscopic versus open fundoplication in adult patients showed a significantly lower operative morbidity, shorter postoperative stays, and less prolonged sick leave following the endoscopic approach.[80] In a randomized multicenter trial with a 5-year follow-up, antireflux surgery was more effective than omeprazole with respect to failure rates. However, when the dose of omeprazole was adjusted in cases of recurrent symptoms, the failure rate still revealed the superiority of surgery but the difference was not significant.[81]

Limpert compared the results of Nissen's procedure with Toupet's technique and came to the conclusion that, for most patients with normal or mildly disturbed esophageal motility, either procedure is effective. However, patients with a severe motility disorder are better served with a partial fundoplication.[82] In some studies, a lower rate of dysphagia was registered after the Toupet procedure, but in all other respects the results were of similar quality as those after a Nissen operation; others demonstrated no advantage of one procedure over the other.[75,83,84] Patients with aerophagy have fewer gas-related problems and less impairment of their ability to belch after a Toupet procedure when compared with Nissen fundoplication.[85] Long-term results of the laparoscopic Thal procedure also show favorable results; in one study, none of the children who were followed for more than 5 years had any symptoms of reflux.[86]

## Complications

A complication rate of 5.9% was recorded in 10,735 adults who underwent primary minimally invasive antireflux procedures between 1993 and 2000. The most common complication was wrap herniation (1.3%), the reoperation rate was 2.7%, and the mortality rate 0.08%.[87] Persistent dysphagia after laparoscopic fundoplication is usually related to the tightness of the wrap. It was speculated that division of the short gastric vessels permits the creation of a relatively loose fundoplication. However, it has been shown, in a randomized controlled trial, that routine division of short gastric vessels during total fundoplication did not improve the clinical or objective postoperative outcome.[88] In contrast, after analyzing more than 10,000 cases of laparoscopic fundoplication, Carlson and colleagues came to the conclusion that there might be a tendency to create a tighter wrap if the gastric vessels are not taken down. The overall incidence of dysphagia was 2.5% but was interestingly related to division (2.57%) or not (4.65%) of the short gastric vessels. The overall incidence of bloating was 9.4%, but the rates ranged from 0% to 45% (median, 2.4%).[87]

In childhood, recurrent gastroesophageal reflux disease (rGERD) is the most common problem after fundoplication. The majority of reoperations are performed within 12 months after the initial operation.[89,90] Failure rates to control reflux after fundoplication range between 2.5% and 10% but may be as high as 25% in patients with neurologic impairment.[91–93] Significant risk factors for recurrence are age younger than 6 years, preoperative hiatal hernia, postoperative retching, neurologic impairment, and postoperative dysphagia requiring esophageal dilatation.[91,94,95] A detailed analysis performed by Kimber revealed 9% redo procedures after 676 fundoplications; the majority of neurologically normal children had an associated anomaly such as esophageal atresia, while 60% of the redo patients had a neurologic impairment. Only 2 children out of the 66 who had to undergo repeat surgery had no associated medical conditions. The second Nissen procedure was

successful in 80%.[96] Analysis of the technical aspects of surgery revealed fundoplication herniations to be another common cause of failure.[97] Cephalad migration of the gastroesophageal junction above the hiatus may be due to inadequate esophageal lengthening into the abdomen. Thus in cases of a short esophagus, careful mediastinal mobilization is necessary to achieve a sufficient abdominal length. Inadequate hiatal closure may cause recurrent sliding or paraesophageal hernia, which occurs most frequently in children with hypertonic cerebral palsy.[96] This may be prevented by meticulous attention to accurate apposition of the crura during the initial procedure and/or the use of pledgeted sutures in wide or weak crural tissues.[96,97] In contrast to the open procedure, small bowel obstruction from adhesions is an uncommon event after laparoscopic fundoplication (4.8%).[98]

## Barrett Esophagus

Barrett esophagus (BE) is a condition associated with severe chronic reflux by which the squamous epithelium is replaced by columnar-lined epithelia of three different types: cardia-type epithelium, gastric fundic-type epithelium, and intestinal-type metaplasia including goblet cells (Fig. 73-12). The latter subtype can gradually progress through dysplastic stages to esophageal adenocarcinoma (EAC). Thus the term Barrett esophagus is used mainly for this histologic subtype with the highest risk for malignancy. The presence of dysplasia is often patchy; therefore biopsy guidelines recommend four quadrant biopsies every 2 cm in order to detect the development of high-grade dysplasia or early stages of EAC.[99] The risk of EAC in adult patients with BE is clearly elevated when compared with the normal population; however, the majority will not develop EAC.[100] So far it is unclear whether this holds true for pediatric patients with chronic reflux (e.g., children with esophageal atresia). Systematic reviews have shown that acid suppression therapy (surgery or drugs) has little or no effect on reversing BE, but antireflux surgery appears to reduce dysplasia and protects against development of high-grade dysplasia.[101] In contrast, recent studies show that antireflux surgery cannot prevent the development of EAC and therefore endoscopic follow-up examination should be continued after fundoplication.[102] A number of endoscopic therapies have been developed in recent years to eradicate the dysplastic epithelial lining (Neodymium Yag laser, Argon plasma coagulation, photodynamic therapy). Recent reviews show that radiofrequency ablation appears to be the most promising therapy, but long-term follow-up data are still necessary.[101]

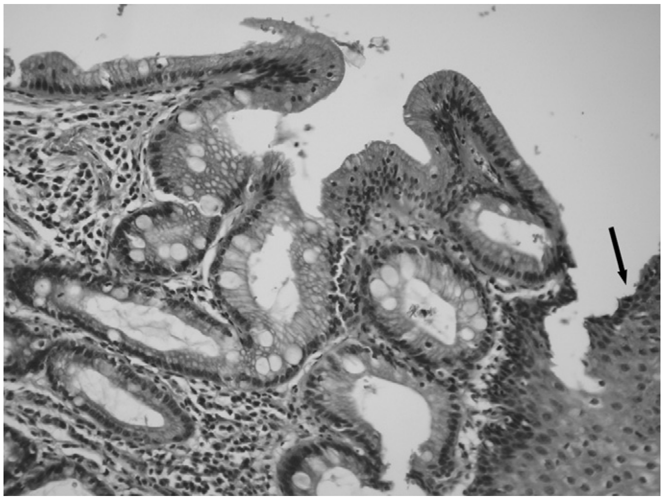

FIGURE 73-12 Barrett esophagus with intestinal metaplasia. On the right side of the histologic specimen is a part of the original esophageal epithelium visible (indicated by the *arrow*).

## Reflux in Children with Neurologic Impairment

Children with severe neurologic impairment (NI) frequently suffer from GERD, but the clinical symptoms may differ from those of neurologically normal children with reflux or may be concealed by more prominent symptoms such as recurrent respiratory tract infections. It has been shown that autoaggressive behavior and considerable agitation of these patients are valuable clinical signs of esophagitis and are significantly improved after successful surgical treatment.[103] Accordingly, analyses of quality of life proved the overall benefits of fundoplication and revealed fewer reflux-related short-term hospital admissions for aspiration pneumonia, GERD, and mechanical ventilation.[104,105] However, the rate of complications and recurrence after fundoplication was as high as 40%, with reoperation rates of 15% in long-term investigations.[106,107] Severe rumination and retching are known to be associated with reflux recurrence. Weber pointed to another important factor in these patients: Their preoperative nutritional status is a strong determinant of short- and long-term results, especially when steroids are administered additionally. He strongly recommends normalizing the child's nutritional status before performing any surgical procedure.[108]

Children with NI often suffer from oral motor impairment and need help with eating and drinking. Therefore a gastrostomy for feeding purposes with or without fundoplication is often necessary. Percutaneous endoscopic gastrostomy (PEG) is a useful procedure even in the presence of radiologic reflux.[109] Some studies have shown that PEG is associated with a greater frequency of symptomatic reflux and with significant complications, especially when combined with a laparoscopic antireflux procedure.[110,111] In other studies, good outcomes were reported with laparoscopic fundoplication and gastrostomy.[112,113] No randomized investigations have been performed to clarify whether it is better to combine gastrostomy with a fundoplication or with antireflux medication.[114] One study using decision analysis concluded that gastrostomy alone should be the favored approach in NI children without preoperative evidence of GER.[113] Experimental studies in cats have shown that gastrostomy causes a significant reduction in LES pressure, which can be prevented by preservation of the angle of His.[115] Technically, the gastrostomy should be performed in the lesser curvature or an anterior gastropexy should be added—both methods prevent flattening of the angle of His.[116,117]

Aspiration pneumonia is the most common cause of death in children with NI and GERD. Instead of fundoplication and

gastrostomy, a gastrojejunal feeding tube is used as an alternative treatment to reduce reflux episodes and provide adequate nutrition. However, an observational cohort study has shown that neither treatment option is clearly superior in preventing aspiration pneumonia or improving survival.[118] Bianchi described total esophagogastric disconnection as an alternative approach to treat NI children who are unable to swallow because it eliminates the risks of reflux and aspiration pneumonia.[119,120] Indications are either the inability to ingest food orally or recurrent respiratory disease and failure to thrive. Long-term results have shown that nutritional and metabolic complications including dumping and digestive malabsorption are common, and prolonged enteral nutrition is required.[121] This technique may be useful after failed fundoplication in NI patients.

## Impact of Delayed Gastric Emptying

Whether or not gastric emptying procedures are a valuable adjunct to fundoplication is controversial. Scintigrams with radioisotopes in the normal diet allow the investigator to quantify the magnitude of gastric retention before and after surgery. It has been estimated that 50% of children with GERD have delayed gastric emptying (DGE); the large majority suffer from disorders of the central nervous system.[122,123] It was speculated that children who develop complications after fundoplication (e.g., gas bloat, epigastric discomfort, recurrent reflux, paraesophageal hernia) may suffer from DGE.[122] Therefore gastric emptying procedures (GEPs) such as pyloroplasty or antroplasty have been proposed in addition to fundoplication, showing that recurrent reflux was significantly lower when a GEP was performed (18% vs. 35%) in children with GERD and DGE.[124] However, in Okuyama's investigation both GEPs were associated with a relatively high incidence of postoperative complications such as gas bloat, dysphagia, dumping, and wound infection.[123] In a carefully conducted study, Bais showed that the outcome of Nissen fundoplication was the same, regardless of whether the patient had a DGE or not. Patients with a DGE before the procedure had a normal emptying time after surgery, whereas patients with a normal emptying time had an increased rate of gastric emptying after surgery.[125] This study also showed that patients with a DGE do accumulate a greater portion of food in the fundus, which is normalized after fundoplication. Accordingly, recent investigations revealed no differences in outcome after fundoplication, regardless of whether a gastric emptying procedure had been performed in children with GERD.[126,127]

## Endoluminal Treatment of Gastroesophageal Reflux Disease

Although laparoscopic fundoplication remains the gold standard for surgical treatment of GERD, many new endoscopic techniques have emerged in recent times. The advantage of these purely endoluminal procedures is the fact that they can be performed on a day-clinic basis. The techniques can be divided into three groups: endoscopic suturing devices, endoscopic radiofrequency, and endoscopic implantation of inert material.

Endoscopic fundoplication has been performed thus far by using the *EndoCinch system* or the *EsophyX system*. The instruments introduced by the endoluminal approach permit construction of mucosal valves to prevent reflux.[128] The EsophyX system yielded good 12-month results in a multicenter trial and was approved by the U.S. Food and Drug Administration (FDA) in 2007.[129]

The *Stretta procedure* is a promising technique, delivering radiofrequency energy to the esophagogastric junction. Four small metallic prongs are embedded in the esophageal wall. Radiofrequency energy is applied to create small thermal lesions in the muscle wall at the LES. After FDA approval the procedure was tested in clinical trials, showing significant improvement in symptom scores and the use of PPI.[128] The procedure was successfully performed in 6 of 8 children.[130]

Endoscopic injection of *Enteryx,* an inert material at the esophagogastric junction, has also been associated with promising results. The material reduces the distensibility of the LES and decreases reflux events. A prospective multicenter trial showed excellent results in nearly 90% of patients who were able to discontinue PPI therapy, had improved symptoms, and had reduced esophageal acid exposure.[131]

## Hiatal Hernia

The history of hiatal hernia has dominated the reflux problem because it was synonymous with GERD until the 1970s.[132] It can be classified as axial—fixed or sliding—hernias, paraesophageal hernias, and mixed forms. An axial hiatal hernia is found in approximately 50% of adults older than 50 years of age.[133] Most individuals are asymptomatic or have nonspecific complaints within the spectrum of GERD. Reflux events occur due to delayed acid clearance and backflow of gastric juice during LES relaxations at the beginning of swallowing and after gastric distension.[133] Axial hernias in childhood are rare but can be observed in NI children or after surgical repair of an esophageal atresia with a long gap. The diagnosis can be established by radiologic procedures or even endoscopy after inversion of the scope. Surgical treatment consists of fundoplication with suture closure of the crura with or without reinforcing pledgets.

A paraesophageal hernia is a typical postoperative complication, with an incidence of 4.5% after fundoplication. It occurs less often after crural plication (3%) than without (10%).[134] It is generally believed today that children with asymptomatic paraesophageal hernias after fundoplication do not need surgical repair. However, patients with symptoms of dysphagia, postprandial pain, vomiting, or even gastric obstruction or strangulation need a laparoscopic redo fundoplication with closure of the hiatus.[134,135]

## Gastroesophageal Reflux Disease in Congenital Anomalies and Diseases

Gastroesophageal reflux is common in children after successful correction of esophageal atresia (EA). A recent survey of 132 adult patients who had undergone surgery for EA as newborns showed that 63% had reflux symptoms and 52%

reported dysphagia. Fifty-eight percent of 62 patients in whom endoscopy was performed suffered from reflux esophagitis, 42% had strictures, 11% had a Barrett esophagus, and one patient was diagnosed with a squamous cell carcinoma.[136] In the latter study it was concluded that patients older than 35 years of age and those with severe reflux symptoms are at high risk of having esophagitis or Barrett metaplasia. Specific problems associated with EA cause a significant reflux problem. First, many children with EA lack propulsive peristalsis in the distal segment of the esophagus, causing the ingested food to be transported by gravity. For this reason, the clearance time for refluxed gastric acid is significantly longer when compared with normal individuals, especially during sleep.[137,138] Second, experimental studies have shown that anastomosis of the esophagus under tension results in a significant decrease in LES pressure and length.[139] And third, nearly 20% of adult patients with EA as newborns have a hiatal hernia.[136] To avoid detrimental long-term complications and the development of Barrett esophagus, early investigations should be performed to assess esophageal function and the presence of reflux.[140] Around 30% of EA patients need an antireflux procedure. We give preference to the Toupet technique over the Nissen technique in order to avoid or reduce any additional barrier effect in the distal esophagus.

GERD occurs in up to 50% of children after repair of a congenital diaphragmatic hernia. This was found to be unrelated to the severity of the initial defect or the type of closure in some studies,[141,142] whereas wide defects requiring patch closure and need for extracorporeal membrane oxygenation (ECMO) were significant predictors of GERD in others.[143,144] The complex malformation of the diaphragm has an obvious detrimental effect on the anatomy and function of the esophagogastric junction. Investigations for GERD should be performed routinely during the follow-up of these patients.

Children with large congenital abdominal wall defects repaired in the neonatal period are known to suffer from pathologic reflux.[145] Children who have suffered caustic injury to the esophagus also show a higher frequency of GERD, which may be caused by a pathologic and prolonged acid clearance time due to disturbed peristaltic function of the esophagus or primary damage in the LES region.[146] GERD is also a major problem in the early life of children with cystic fibrosis but is known to improve with age.[147]

## Conclusion

Gastroesophageal reflux is common in neonates and infants. In most cases it is not caused by an insufficient LES but by delayed development of esophageal function and is characterized by several spontaneous relaxations of the LES. The mechanisms of reflux have been extensively studied in the past few decades. Esophageal function has been known to mature spontaneously by the end of 1 or 2 years in more than 90% of babies. Therefore unspecific and conservative lifestyle changes are usually sufficient. Reflux persisting into childhood requires sophisticated diagnostic procedures and close follow-up. If medical therapy fails, surgical correction is indicated. Fundoplication according to Nissen, Toupet, or Thal are the most commonly used procedures. Given the large number of postoperative complications, the patients should be followed for a long period of time.

*The complete reference list is available online at www.expertconsult.com.*

# Part VII

# ABDOMEN

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CHAPTER 74

# Disorders of the Umbilicus

Robert E. Cilley

## History

Umbilical malformations have been depicted in art and sculpture since antiquity, but the developmental basis for these abnormalities was not recognized until the late nineteenth century. Surgical textbooks, such as that by von Bergmann in 1904, clearly describe the embryology responsible for persistence of the vitellointestinal duct as a fistula, sinus, or cyst.[1] The symptoms of fecal drainage ("congenital umbilical anus") and prolapse of the intestine were well known. The surgeon was advised to avoid pitfalls such as excision of an "umbilical tumor" that exposed two intestinal lumens because it would indicate that the vitellointestinal remnant had been excised in excess back to the ileum. An umbilical polyp representing a persistent remnant of the duct was referred to as an "enteroteratoma."

Surgical management has changed little in the past 100 years. Interestingly, then as now, granulomas of the umbilical cord were treated by silver nitrate cauterization. The embryologic basis of developmental abnormalities of the urachus was similarly recognized, and their surgical treatment was described much as it is today. The natural history of spontaneous resolution of most umbilical hernias was also understood at the end of the nineteenth century. External compression was often recommended, and the importance of preservation of the appearance of the umbilicus rather than excision was emphasized. Repair of umbilical abnormalities was recognized as formidable in small children, and little is known of the true operative morbidity and mortality in the hands of the surgical pioneers who first attempted their correction.

The most complete work on the umbilicus is the classic text by Cullen, published in 1916.[2] This encyclopedic work is still the most definitive work on the subject. Cullen's curiosity was originally stimulated by a case of cancer at the umbilicus, and it inspired him to explore the entire topic of umbilical pathology. He stated, "The study of the umbilicus, which in the beginning had seemed so unimportant, became so fascinating that I covered most of the literature on the subject."[2]

The vital functions of the umbilicus in utero and the structures that pass through it in normal development contrast with its lack of physiologic importance after birth. Its psychologic importance throughout life is attested to by individuals who have endured surgical loss of their umbilicus. Pediatric surgeons are the first to be consulted whenever there is an unusual finding of the umbilicus in newborns and older children. Umbilical herniorrhaphy is among the more commonly performed operations in childhood. In addition, the umbilicus serves as a portal of entry for most laparoscopic procedures, and it may be used as an intestinal or urinary stoma site. Cannulation of its vessels, either in their native location or transposed surgically, provides vascular access in neonates. The umbilicus is considered to be aesthetically important,[3] and it may be an object of display and adornment. Exposure of the umbilicus is commonplace, as is the use of jewelry and piercings to enhance its appearance.

## Normal Embryology

The classic description of the formation of the umbilicus indicates that the abdominal wall forms by a combination of lateral infolding and ventral flexion of the disk-shaped trilaminar embryo that begins in the fourth gestational week. However, the actual growth of the embryo does not truly involve "bending" and "folding" of structures but rather represents differential growth of tissues. Initially, the amnion is located in a dorsal direction, whereas the yolk sac occupies a ventral position. The embryo is attached to the chorion, the forerunner of the placenta, by a connecting stalk composed of extraembryonic mesoderm in which the umbilical vessels develop and into which the allantois grows (Fig. 74-1, *A*). The yolk sac maintains its ventral position but is divided into intracoelomic and extracoelomic portions (Fig. 74-1, *B*). The intracoelomic portion, derived from the roof of the yolk sac, becomes the primitive alimentary canal and maintains a connection with the extracoelomic portion through the vitelline or omphalomesenteric duct. This connection is normally lost by the fifth to seventh week of gestation.[2,4] Persistence of this connection, as a remnant of either the developing alimentary tract or the accompanying vitelline vessels, accounts for some of the abnormalities described in this chapter.

Early in the third week of gestation, a diverticulum called the *allantois* forms from the posterior wall of the yolk sac and extends into the connecting stalk of the embryo (Fig. 74-1, *A* and *B*). The allantois serves as a reservoir for the developing renal system in lower vertebrates but has no

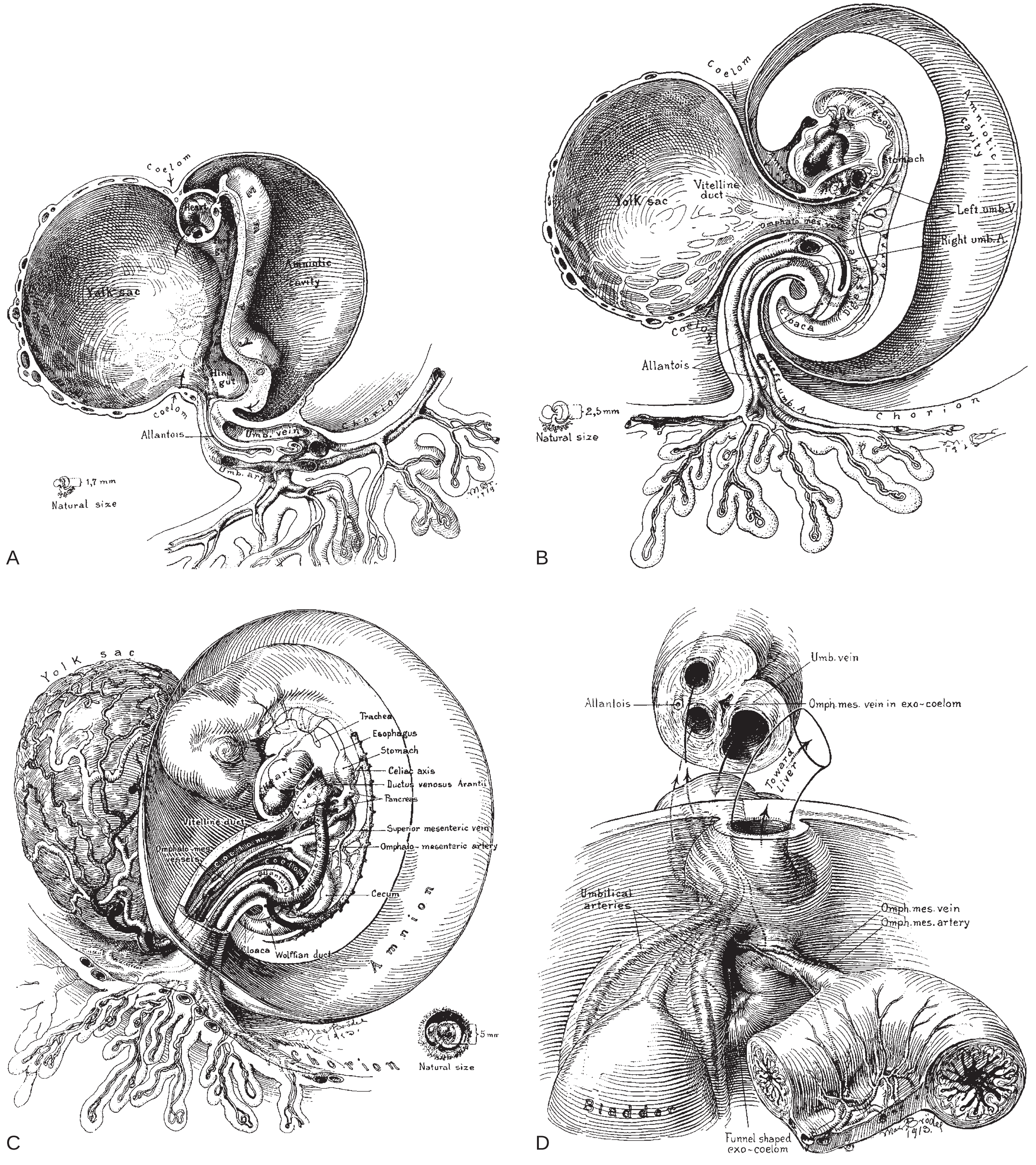


**FIGURE 74-1** **A,** A 1.7-mm embryo (third week). The primitive gut is not yet separate from the yolk sac. The amniotic cavity can be seen dorsally. The umbilical vessels develop in the extraembryonic mesoderm and connect the embryo to the developing placenta. **B,** A 2.5-mm embryo (fourth week). Infolding and flexion of the embryo draw the amnion around the body. The omphalomesenteric duct is part of the developing umbilical cord. (From Cullen TS: Embryology, Anatomy, and Diseases of the Umbilicus Together with Diseases of the Urachus. Philadelphia, WB Saunders, 1916.) **C,** A 5-mm embryo (fifth week) demonstrating a complete umbilical cord. The omphalomesenteric duct connection between the yolk sac and the alimentary tract is lost between the fifth and seventh weeks. **D,** A 45-mm embryo (10 weeks) viewed from inside. The intestines, which were extraembryonic coelomic (i.e., within the umbilical cord) between the sixth and tenth weeks, have returned to the peritoneal cavity.

known role in human development; it remains rudimentary as the transitory extraembryonic portion of the urachus. As the distal hindgut, or cloaca, partitions into the urogenital sinus ventrally and the anorectal canal dorsally, the developing bladder remains connected by the urachus to the allantois within the body stalk (see Fig. 74-1, *D*). The urachus is derived wholly from the developing bladder and may persist in various forms, which accounts for the abnormalities described later.

As the embryo develops, the amnion is drawn around it to surround the embryo and cover all the developing umbilical cord structures including the allantois, umbilical vessels, vitelline duct, and primitive mesenchymal tissue (Wharton jelly) (Fig. 74-1, *C*). During the period of rapid intestinal growth between the sixth and tenth weeks of gestation, the developing midgut is extracoelomic. As the body wall continues to develop, the intestines are incorporated into the coelomic cavity and intestinal rotation and fixation progress. The fibromuscular umbilical ring continues to contract and is nearly closed by the time of birth (Fig. 74-1, *D*). Persistence of the fascial opening as an umbilical hernia occurs frequently and is commonly seen in premature infants. Unlike other abdominal wall defects, umbilical hernias tend to resolve without specific treatment as a result of the ongoing development of tissues at the umbilical ring after birth. The fate of the structures that relate to the development of the umbilicus is shown in Table 74-1.

## Umbilicus at Birth

Modern obstetric practice uses plastic clamps that are placed a few centimeters from the umbilical skin during cord division at the time of delivery. Topical antimicrobials such as triple dye, bacitracin, silver sulfadiazine, povidone-iodine, chlorhexidine, hexachlorophene, alcohol, salicylic sugar powder, green clay powder, silver-benzyl-peroxide powder, and 1% basic fuchsin may be applied to the cord after birth.[5,6] All these agents are effective in reducing bacterial colonization rates, and their use is recommended when adequate cord care cannot be guaranteed. These agents may affect cord separation time, some cause discoloration, and repeated use of iodine-containing antimicrobials may result in systemic absorption of iodine and suppression of thyroid function. There is good evidence that, in developed countries, dry cord care, without the application of topical antibiotics, in association with routine soap and water bathing and meticulous hand washing practices is as effective as topical agents in reducing infection.[7] However, a recent randomized prospective study demonstrated fewer cord-related complications in infants treated with chlorhexidine powder compared with standard dry cord care.[8] In the undeveloped world, antiseptic cord cleansing with chlorhexidine may significantly reduce neonatal morbidity and mortality.[9]

Intestinal injury may result from injudicious placement of an umbilical cord clamp when an unrecognized small hernia of the umbilical cord (i.e., a small omphalocele) is present. Abdominal wall defects that relate to the umbilicus (i.e., gastroschisis and omphalocele) are covered in Chapter 75.

The normal time for separation of the umbilical cord after birth ranges from 3 days to 2 months.[10] Antimicrobial treatment may prolong cord separation by decreasing leukocyte infiltration. Delayed separation of the umbilical cord has been associated with heritable neutrophil mobility defects and widespread infections that are often lethal.[11] The abnormal neutrophils lack a membrane glycoprotein, which results in abnormal attachment, chemotaxis, and phagocytosis.[10] Although persistence of umbilical cord attachment beyond 3 weeks of age has been suggested to be a sign of such immunologic abnormalities, recent studies that have included more than 600 newborns have demonstrated the range of normal newborn cord separation to be broad (3 to 67 days), with a mean of 14 to 15 days.[10,12] In these studies, nearly 10% of normal newborns underwent cord separation after 3 weeks of age, thus indicating that delayed cord separation is not a reliable indicator of immunologic disease. If prolonged cord separation is associated with umbilical infection, leukocyte adhesion deficiency disorders should be suspected and an immunologic evaluation performed.[6,13,14]

**TABLE 74-1**
**Fate of Structures Related to the Developing Umbilicus**

| *Structure* | *Fate* | *Remnants, Pathologic Condition* |
|---|---|---|
| Urachus (connects the bladder to the allantois) | Obliterates | Median umbilical ligament, patent urachus, sinus, cyst |
| Omphalomesenteric duct (connects the midgut to the yolk sac) | Obliterates | Meckel diverticulum, patent omphalomesenteric duct, sinus, cyst, bands, polyp |
| Omphalomesenteric arteries | Most regress; fuse to form the celiac, superior mesenteric, and inferior umbilicus | Dominant artery may accompany Meckel diverticulum, fibrous band to the mesenteric arteries |
| Omphalomesenteric veins | Plexus around the duodenum becomes the superior mesenteric and portal vein (contribution from both the left and right vein) | Preduodenal portal vein if the ventral portion of the plexus persists |
| Umbilical arteries | Obliterate after birth | Medial or lateral umbilical ligaments* |
| Umbilical veins | Right obliterates; left returns placental blood to the inferior vena cava through the ductus venosus | Falciform ligament |

*Atlases and anatomy texts variably refer to the obliterated umbilical arteries as the *medial* or *lateral umbilical ligament*. When called the *medial umbilical ligaments*, the epigastric vessels are called the lateral umbilical ligaments. When called the *lateral ligaments*, the epigastric vessels are referred to as the *epigastric folds*.

After separation of the cord, the umbilicus may have many appearances. A normal umbilicus is characterized by a depression in which may be found the mamelon (a central eminence that contains the remnants of the solid portion of the umbilical cord) and the cicatrix (dense scar where the intraembryonic and extraembryonic coelom were in continuity). The cushion is the slightly raised margin that surrounds the umbilical depression. Cullen described more than 60 "normal" configurations of the umbilicus.[2]

# Umbilical Abnormalities

## ACQUIRED

### Umbilical Granuloma

After cord separation, a small mass of granulation tissue may develop at the base. These granulomas consist of true granulation tissue with fibroblasts and abundant capillaries; the granulomas range in size from 1 mm to approximately 1 cm. The surface often has a pedunculated appearance. Umbilical granulomas may be treated by cauterization with one or more applications of silver nitrate until the area epithelializes. Alternatively, the granuloma may be excised and silver nitrate or absorbable hemostatic material applied.[15] If the mass does not respond to cauterization, a true umbilical polyp or sinus tract must be suspected (see later). Care must be taken with silver nitrate application because burns and skin injury may occur.[16]

### Umbilical Infections

Although modern perinatal practice has dramatically reduced the incidence of omphalitis, infections of the umbilicus still occur with alarming morbidity and mortality, particularly in undeveloped countries.[17] Rigorous asepsis, hand washing, and cord care (either dry cord care or topical antimicrobials) have reduced the incidence of umbilical infections to less than 1% in hospitalized newborns.[18] Before the institution of such practices, the mortality rate for omphalitis was 65%. The primary pathogens implicated in these infections were *Staphylococcus aureus* and *Streptococcus pyogenes*. Currently, gram-negative bacteria play an important role in the pathogenesis of umbilical infections. Severe infections are often polymicrobial. Omphalitis may be manifested as a purulent umbilical discharge or periumbilical cellulitis. Delivery at home, low birth weight, use of umbilical catheters, and septic delivery are risk factors. Tetanus infection occurs on rare occasions. Intravenous antibiotic therapy is effective in eradicating most infections. Omphalitis is a common problem in developing countries, where it accounts for more than a quarter of neonatal hospital admissions.[19,20]

Cellulitis may progress to fasciitis, and such progression may be subtle. Signs of necrotizing fasciitis include abdominal distention, tachycardia, purpura, blistering, pyrexia, hypothermia, leukocytosis, and progression of cellulitis despite antibiotic therapy. Bacteriologic cultures demonstrate polymicrobial flora.[21] Necrotizing fasciitis and umbilical gangrene may be lethal and require immediate wide surgical debridement for patient survival.[18,22–27] Excision should be performed immediately on recognition; all infected skin, fat, and fascia should be excised back to viable, bleeding abdominal wall musculature. The umbilicus is obligatorily excised. Excision of preperitoneal tissue including the umbilical vessels and urachal remnant may be critically important to achieve eradication of the infection because these tissues harbor invasive bacteria and may provide a route for the progressive spread of infection seen after less extensive surgical debridement.[22] The defect may require a temporary prosthetic patch for closure, but ultimate fascial closure and umbilical reconstruction may leave an acceptable appearance. Hyperbaric oxygen therapy has been advocated as adjuvant therapy, but it is not of proven benefit.[26] The overall reported mortality associated with necrotizing fasciitis in collected series is 81%.[18,22–27]

Umbilical drainage resulting from chronic infection of umbilical remnants such as umbilical artery remnants has also been reported.[28] Excision and debridement are curative. Omphalitis can result in necrosis and breakdown of the umbilical stump with spontaneous evisceration within the first 2 months of life and may be associated with portal venous thrombosis and subsequent extrahepatic portal hypertension.

## CONGENITAL

### Omphalomesenteric Remnants

Remnants of the vitelline or omphalomesenteric duct account for a wide variety of umbilical abnormalities that may require surgical correction.[28a] These remnants include fistulas, sinus tracts, cysts, mucosal remnants, and congenital bands. Typical variations of the pathologic varieties are illustrated in Figure 74-2, *A* to *F*.[2,29,30]

If the omphalomesenteric duct is patent from the terminal ileum to the umbilicus, fecal umbilical drainage will be noted (Fig. 74-3, *A*). Although this event is dramatic to parents, the problem is immediately recognizable on examination and parents may be reassured that prompt surgical correction is curative. Prolapse of the proximal and distal ileum through the patent duct has a characteristic appearance. Although contrast injections are of interest, they do not change the surgical approach (Fig. 74-3, *B*). Anatomically unusual conditions such as an unexpected origin of the omphalomesenteric duct from the appendix will be recognized at the time of operation (Fig. 74-4).[31,32] Unless another, more serious medical condition exists, a patent omphalomesenteric duct should be excised promptly. A mechanical intestinal preparation is not necessary, although we customarily stop formula feeding; perioperative intravenous antibiotics are also given. The operation may be performed through the umbilicus itself or through an incision below the umbilicus. Full exploration and identification of all umbilical structures including one vein, two arteries, and the urachal remnant are indicated. The omphalomesenteric duct is traced to the ileum and divided. The ileum is closed, and care must be taken to control any dominant vitelline vessels that may be present. After the fascia is closed, umbilicoplasty is performed.

Small duct remnants and sinuses may have less characteristic drainage. Injection of contrast material may be helpful in delineating the nature of the problem in these instances, but surgical exploration remains the definitive diagnostic test. It is important that a full exploration is performed and that all umbilical structures including the intraperitoneal undersurface of the umbilicus are visualized to identify and remove any bands attached to the small intestine. If a Meckel diverticulum is attached to an omphalomesenteric band discovered at exploration, it is excised. Cystic remnants of the omphalomesenteric

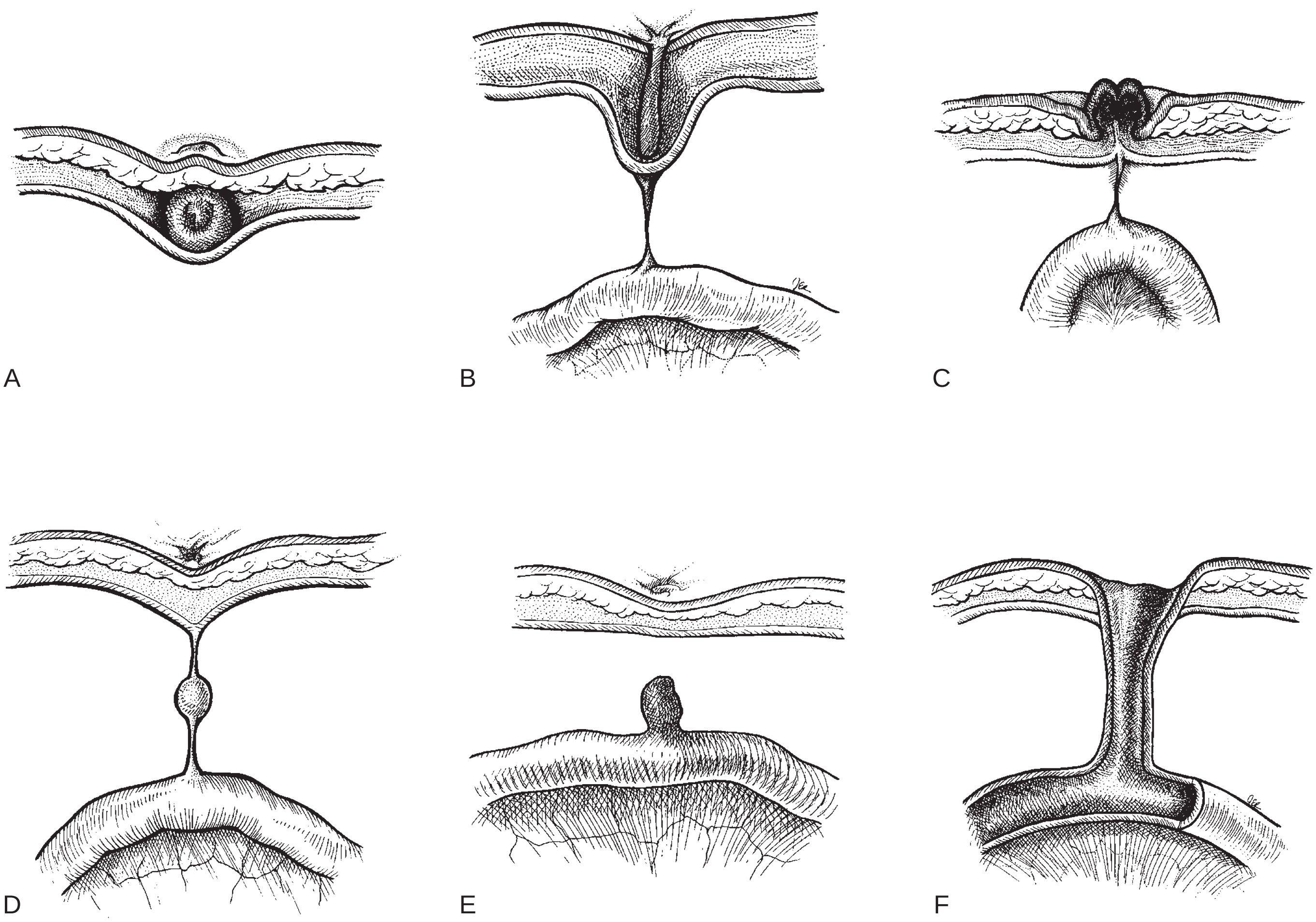


FIGURE 74-2 Various omphalomesenteric duct remnants. **A,** Umbilical cyst containing intestinal tissue. **B,** Umbilical sinus with a band. **C,** Umbilical polyp covered with intestinal mucosa. **D,** Fibrous band containing a cyst. **E,** Meckel diverticulum. **F,** Patent omphalomesenteric duct. Other varieties and combinations exist.

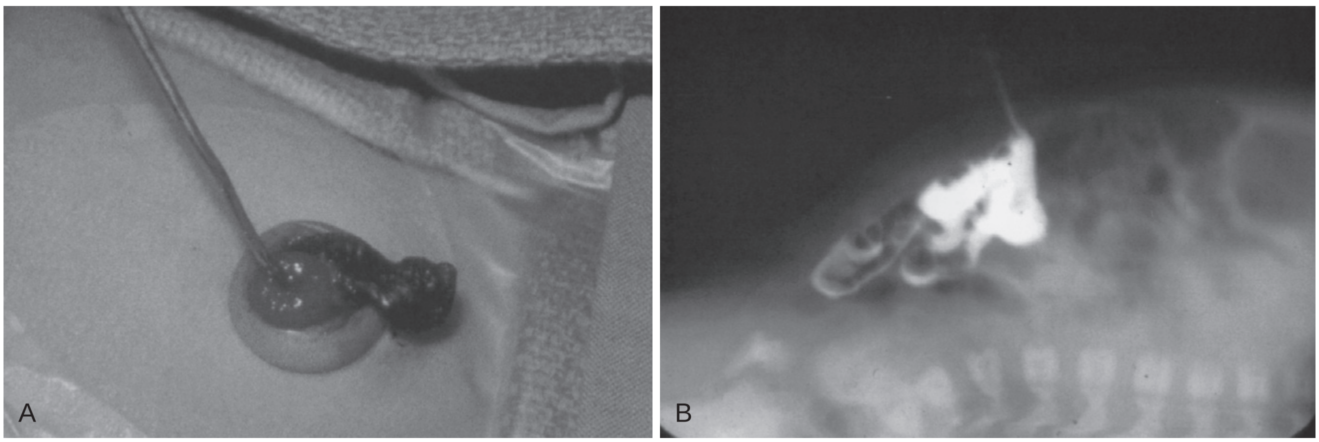


FIGURE 74-3 **A,** This photo of a newborn demonstrates probe patency of an omphalomesenteric duct into the ileum. **B,** A radiograph with contrast medium injected into a patent omphalomesenteric duct demonstrates filling of the small intestine. Studies of this sort are not usually necessary.

duct may become infected and cause acute symptoms, even in older individuals. If an abscess has formed, it may require surgical drainage; excision of any remnant may be accomplished at a later time. The omphalomesenteric duct or any remnant attachments between the abdominal wall and the intestine may cause angulation, volvulus, or herniation of intestinal loops, thereby resulting in mechanical intestinal obstruction. The nature of the obstruction will be discovered during laparotomy.

Rarely, spontaneous regression of a patent omphalomesenteric duct may occur.[33,34] In one case the defect was

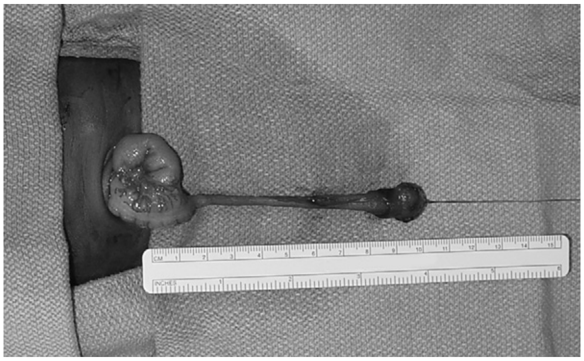

FIGURE 74-4 An unusual omphalomesenteric duct in continuity with the appendix. Presentation was as a large umbilical polyp. Correction was performed through the umbilicus.

documented by a fistulogram shortly after birth, but it was not operated on until the patient was 3 months of age. At that time, only a Meckel diverticulum was found, but it had no connection to the umbilicus, thus indicating that some regression had occurred in the interim. The Meckel diverticulum and its treatment are discussed in Chapter 84.

## Urachal Remnants

Various abnormalities of the urachus have been described.[2,35,36] The typical abnormalities are depicted in Figure 74-5. A patent urachus is associated with drainage of urine from the umbilicus. Clear drainage from the umbilicus should always raise suspicion of a patent urachus. Although the definitive anatomy is discovered during laparotomy, frank drainage of urine from the umbilicus requires an investigation of the urinary tract to look for bladder outlet obstruction in which the urachus is functioning as a relief valve (Fig. 74-6).[37] Such conditions are rare. A patent urachus may be approached either through the umbilicus or through an infraumbilical incision. It is important to identify all the umbilical structures for a definitive diagnosis. The patent urachus is ligated and transected at the level of the bladder; broad-based connections are closed in two layers with absorbable sutures. Excision of urachal remnants using laparoscopic techniques has been described.[38,39]

FIGURE 74-6 Radiograph with contrast medium injected into a patent urachus demonstrates filling of the bladder. (From Jona JZ: Umbilical anomalies. In Raffensberger JG [ed]: Swenson's Pediatric Surgery, 5th ed, Norwalk, Conn, Appleton & Lange, 1990. Used with permission.)

Urachal sinuses may give rise to umbilical drainage or be discovered on examination. Urachal cysts most often cause an infection manifested as a painful mass localized between

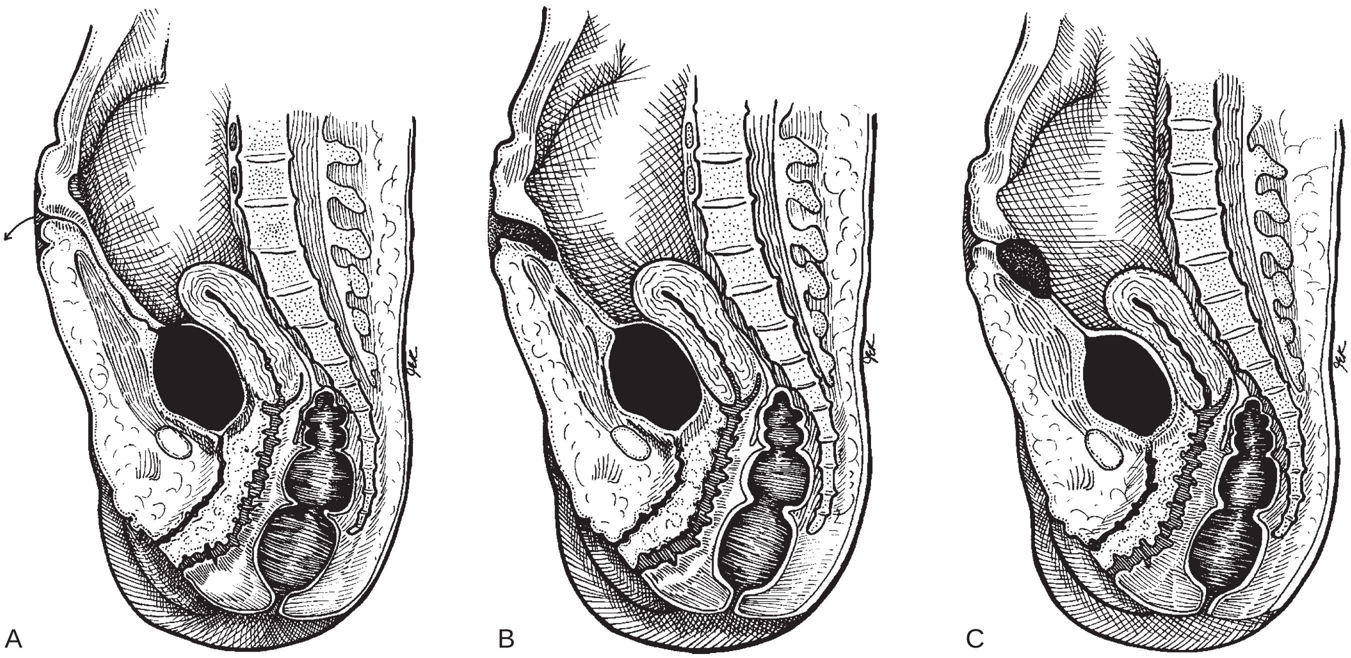

FIGURE 74-5 Various urachal remnants. **A,** Patent urachus with communication between the bladder and umbilicus. **B,** Urachal sinus. **C,** Urachal cyst, which is usually associated with infection.

the umbilicus and the suprapubic area. Ultrasonography or computed tomography may be helpful to confirm the diagnosis. Other unusual manifestations have been reported including a lateral mass.[40] The urachus has also been described as exiting from the midline below the umbilicus.[41,42] In addition, a patent urachus may be one of the causes of a giant umbilical cord in the newborn.[43] When a urachal cyst becomes infected and develops into an abscess, drainage of the acute process is required. After the abscess is drained, complete healing may take place. It is unknown whether subsequent operation to remove any residual cyst remnants is necessary.

Urachal remnants may cause complications later in life. Abnormal epithelium including colonic, small intestine, and squamous may be present in incidentally removed urachal remnants.[44] The fate of these tissues is unknown, but many different malignant tumors have been reported to originate from the urachus. A partial list of tumors in adults arising from the urachus is shown in Table 74-2. Pediatric tumors including rhabdomyosarcoma and neuroblastoma may originate from urachal remnants as well.[45,46]

Pain plus retraction of the umbilicus during micturition has been described as a sign of a urachal anomaly.[47,48] Resection of the urachal remnant is curative.

Diagnostic imaging including ultrasound, contrast injections, computed tomography, and magnetic resonance imaging may occasionally be helpful in diagnosing and treating umbilical abnormalities.[49] An infant with umbilical discharge caused by both a persistent urachus and an omphalomesenteric duct has been reported.[50]

### Umbilical Dysmorphology

A single umbilical artery may occur in conjunction with many syndromes and is associated with congenital abnormalities in a third of cases. Such abnormalities include trisomy 18 and renal and cardiac anomalies. Children with dysmorphic features may have characteristic findings that aid in diagnosis. Minor abnormalities that lack medical significance can nonetheless provide insight into the nature and timing of dysmorphologic events that occur during development.[51] Commonly, dermatoglyphics, hair patterning, auricular shape, and genital configuration are part of such observations. Minor abnormalities of the configuration of the umbilicus may be useful in the classification of dysmorphologic findings. For example, an umbilicus that is situated unusually high on the abdominal wall at the level of the lower rib cage and is flat and poorly epithelialized indicates Robinow syndrome, which is also characterized by a flat facial profile, mesomelic shortening, and genital hypoplasia. If the umbilicus is broad and prominent with a large stalk and redundant periumbilical skin, Rieger syndrome should be suspected, especially if these umbilical abnormalities occur in conjunction with goniodysgenesis and hypodontia. If the umbilicus is prominent with a button-like central portion in a deep longitudinally oriented ovoid depression or flat with radiating branches of the cicatrix, Aarskog syndrome, a condition classically characterized by short stature, facial dysplasia, syndactyly, and genital anomalies, is indicated.[52]

**TABLE 74-2**

| Tumors Arising from the Urachus |
|---|
| Adenocarcinoma |
| Transitional cell carcinoma |
| Squamous cell carcinoma |
| Mucinous (cyst) adenocarcinoma |
| Malignant fibrous histiocytoma |
| Fibrosarcoma |
| Pleomorphic sarcoma |
| Yolk sac tumor |
| Inflammatory pseudotumor |
| Villous adenoma (premalignant) |

## OTHER CONGENITAL AND ACQUIRED PATHOLOGIC CONDITIONS OF THE UMBILICUS

Suprapubic dermoid sinuses usually extend from the skin overlying the pubis and pass over the superior surface of the bladder to the umbilicus alongside the urachus.[53,54] The embryologic origin of such a sinus tract remains unclear, although it may be a variant of a dorsal urethral duplication.

Children with bladder and cloacal exstrophy may have an omphalocele or a low-set umbilicus incorporated into the upper portion of the open bladder plate, along with diastasis of the lower abdominal wall musculature and diastasis of the symphysis pubis.[55] Variants of exstrophy include superior vesicointestinal fissure, duplicate exstrophy, and pseudoexstrophy, in which the bladder is intact and only the musculoskeletal abnormalities are present.

Numerous unusual protrusions have been described at the umbilicus. Ectopic pancreatic tissue including islets is best explained by the pluripotential nature of cells of the vitelline duct.[56] Abnormal portions of liver connected to the main lobes of the liver have been described and probably represent entrapment by closure of the umbilical ring.[57] A giant, 10-cm hamartoma originating from the umbilicus without intra-abdominal involvement has been excised without incident.[58] The appendico-omphalic explanation of a fistula between the appendix and the umbilicus was noted earlier ("Omphalomesenteric Remnants"). Entrapment of the appendix in the umbilicus such as in a small omphalocele may also explain some fistulas from the appendix to the umbilicus.[59,60] Keloid formation has been observed after umbilical cord separation.[61] A giant umbilical cord may contain urachal remnants and ectatic vessels and may mask a small omphalocele. Care should be exercised during application of the cord clamp whenever the appearance of the cord is abnormal.

The umbilicus may be affected by any disease of hair-bearing skin including dermatoses and infections. It may be the site of ectopic tissue including endometriosis, as well as numerous primary and metastatic tumors, in addition to those of urachal origin (see Table 74-2). Many acquired pathologic conditions of the umbilicus are summarized in Table 74-3.

### Umbilical Piercing

Umbilical piercing is common and may present dilemmas in management. Trauma surgeons should be familiar with the opening mechanisms of body piercings to facilitate radiology studies and as needed for emergency procedures.[62] Removal of the piercing device is not necessarily recommended if infection occurs.[63] Local infections can be treated by warm compresses and antibiotic ointment. If infection persists, oral

**TABLE 74-3**
**Acquired Conditions of the Umbilicus**

| *Condition* | *Comment* | *Source* |
|---|---|---|
| Dermatoses | Seborrheic dermatitis, psoriasis, herpes gestationis, Fabry disease | Powell, 1988[a] |
| Foreign body reactions | Starch, talc, inserted objects | Powell, 1988 |
| Omphalith | Concretion of keratinous and sebaceous material | Powell, 1988 |
| Pilonidal disease | Related to hair-bearing sinus tracts | Steck, 1965[b]<br>Sroujieh, 1989,[c]<br>Gupta, 1990[d] |
| Infections | Bacterial, fungal, viral, parasitic | Powell, 1988 |
| Endometriosis | Ectopic endometrial tissue | Powell, 1988<br>Franklin, 1990[e] |
| Benign tumors | Nevi, pyogenic granuloma, inclusion cysts, hemangioma, dermatofibroma, neurofibroma, granular cell tumor, teratoma, desmoid tumor, lipoma | Powell, 1988 |
| Malignant tumors, primary | Melanoma, urachal adenocarcinoma, squamous cell carcinoma, basal cell carcinoma, sarcoma, leiomyosarcoma | Shetty, 1990[f]<br>Powell, 1988<br>Cornil, 1967[g] |
| Malignant tumors, metastatic | Stomach, pancreas, endometrium, ovary, cervix, colon, small intestine, gallbladder, lung, prostate, breast, unknown | Shetty, 1990 |
| Enteric fistulas | Originate from Crohn disease, perforated appendicitis, other such visceral perforations as colon, gallbladder | Park 1991[h]<br>Veloso, 1989[i]<br>Burchell, 1989[j] |
| Psychiatric disorders | Symbolic vagina | Waltzer, 1974[k] |
| Miscellaneous disorders | Perforation from a ventriculoperitoneal shunt; infections, dermatoses, and granulation tissue from piercing | Bryant, 1988[l]<br>Lena 1994[m] |

[a]From Powell FC, Su WP: Dermatoses of the umbilicus. Int J Dermatol 1988;27:150-156.
[b]Steck WD, Helwig EB: Umbilical granulomas, pilonidal disease and the urachus. Surg Gynecol Obstet 1965;120:1043-1057.
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antibiotics are prescribed. The site is cleansed with antibiotic soap, and the jewelry rotated and left in place to allow drainage. Infections that require surgical drainage or debridement are rare. Navel piercing jewelry may be temporarily removed during surgery while preserving the piercing sinus tract. A plastic intravenous catheter is placed in the sinus when the piercing is removed.[64]

### UMBILICAL LINT

The origin of umbilical lint has been a subject of curiosity and speculation. Experimental shaving on the periumbilical hair eliminates lint formation. Lint collected from the umbilicus after colored cotton shirts were worn by subjects with intact abdominal wall hair matched the color of the shirts indicating the source of the lint. Presumably umbilical lint collects as a direct result of the whorled umbilical hair acting on clothing-derived material. Hair encircles the umbilicus, and the keratin scales overlap with their bases pointing toward the hair follicle. This arrangement imposes direction on the random movement of the clothing lint that occurs when the material rubs back and forth across the abdomen with body movement. The periumbilical hairs act in a ratchet-like fashion to move the lint into the depths of the umbilicus.

## Umbilical Hernia

### ANATOMY

At birth the umbilicus is surrounded by a dense fascial ring that represents a defect in the linea alba. The umbilical opening is reinforced by strongly attached remnants of the umbilical arteries and urachus in an inferior direction and the more weakly attached umbilical vein in a superior direction. A layer of fascia (Richet fascia) derived from the transversalis fascia supports the base of the umbilicus. The peritoneum forms an intact undersurface of the umbilical ring, and skin overlies the umbilicus after the cord has separated. When the supporting fascia of the umbilical defect is weak or absent, a direct hernia results.[65] An umbilical hernia in children is surrounded by the dense fascia of the umbilical ring, through which a peritoneal sac attached to the overlying skin protrudes. The umbilical ring continues to close over time and the fascia of the umbilical defect strengthens, which accounts for the spontaneous resolution of this defect in most children.

An indirect umbilical hernia has also been described in which the peritoneal contents herniate from a point immediately superior to the umbilical ring. The hernia follows the umbilical canal along the umbilical vein, the linea alba in

an anterior direction, and a thin layer of preperitoneal fascia in a posterior direction.[66] This form of herniation has been suggested to cause proboscoid hernias in children; in this defect, the umbilical cicatrix is displaced progressively in an inferior direction as the hernia enlarges. This defect may also be responsible for umbilical hernias in some adults.

The umbilical hernia of childhood is distinguished from a "hernia of the umbilical cord," in which there is a defect in the peritoneum, as well as an open fascial defect at the umbilicus. Intestines herniate into the substance of the umbilical cord itself and are covered only by amnion. A hernia of the umbilical cord is, in effect, a small omphalocele.

## INCIDENCE AND NATURAL HISTORY

There is no doubt a molecular basis for umbilical ring closure.[67] Genetic heterogeneity accounts for the presence of an open umbilical ring in some children at the time of birth, whereas in others, the ring is essentially closed at the time of cord separation. Unlike inguinal and epigastric hernias, which have no real tendency to close after term, the umbilical ring is programmed to continue closure in many children for weeks, months, or years after birth.

Umbilical hernias in childhood occur with equal frequency in boys and girls. Numerous reports document a high incidence in African and African American infants.[68–70] The umbilical ring is open throughout most of gestation but becomes progressively smaller as gestation progresses. Most umbilical hernias in infants are recognized after cord separation in the first few weeks of life, and almost all are noted by 6 months of age. Most undergo spontaneous closure during the first 3 years of life. Umbilical defects are found in many premature infants after cord separation. Although umbilical hernias are commonly found in low-birth-weight infants (75% of infants weighing $< 1500$ g), most will resolve.[71] The lack of accurate longitudinal studies of children with umbilical defects does not allow definitive conclusions to be drawn about their natural history.[72] Umbilical hernias with a small ring diameter ($<1$ cm) are more likely to close spontaneously and close sooner than those with a large ring diameter ($>1.5$ cm). The diameter of the umbilical defect is prognostically important, whereas the length of the protrusion is not. Some umbilical hernias that are present at 5 years of age will close spontaneously without an operation.[73,74] The relationship between umbilical hernias that become symptomatic later in life and childhood umbilical defects is unknown. The protruding portion of the hernia generally remains unchanged while the fascial ring closes until it is too small to admit any contents into the hernia sac. The hernia thus tends to disappear abruptly.[74] Umbilical hernias are commonly observed in patients with Down syndrome, trisomy 18, trisomy 13, mucopolysaccharidoses, and congenital hypothyroidism. Umbilical defects (hernia or omphalocele) are part of the Beckwith-Wiedemann syndrome. Incarceration of intestine or omentum, strangulation, perforation, evisceration, and pain are rare events in the natural history of umbilical hernias in children. The most difficult task of the pediatric surgeon is to convince the family that observation alone will be successful in most cases and that an operation is not indicated for their child, especially in infancy. The large conspicuous skin-covered hernia sac with its characteristic and unsettling appearance is often associated with a small fascial defect. It may be helpful to demonstrate the size of the actual fascial defect to the parent.

Uncorrected umbilical hernias can become symptomatic at any time in life. Rupture and evisceration are rare but can occur.[75,76] Incarceration is rare, but the small bowel is most commonly affected when it does occur. Conditions that increase intra-abdominal pressure increase the likelihood of complications. Repair of umbilical hernias in patients with ascites is hazardous. Umbilical hernias may also become symptomatic during pregnancy, and if incarceration occurs, surgery is required. Unusual contents of umbilical hernias include uterine fibroids and endometrial elements.[77,78]

## SURGICAL INDICATIONS

Although repair of childhood umbilical hernias has been advocated to prevent the complication of incarceration in adults, the relationship between the two events is unclear.[79,80] Rare events such as incarceration requiring reduction, strangulation, perforation, and evisceration are absolute indications for surgery. In the absence of these absolute indications, persistence and appearance are relative indications for operative repair in developed countries. Infants with giant proboscoid hernias in whom the umbilical ring does not narrow during serial observations may be considered for repair in the first 2 years of life. Typical umbilical hernias should be observed at least until age 2. If there is no improvement in the size of the umbilical fascial ring, consider repair. Ample evidence supports the decision to postpone repair until later in childhood. Large defects ($>1.5$ cm) that persist past the age of 5 should be repaired. Evidence-based guidelines are lacking, and the decision may be individualized on the basis of such considerations as family history, parental desires, and local practices. The appearance of a hernia often drives families to insist that the hernia be repaired. In less developed parts of the world, it may be appropriate to actively observe umbilical hernias, with operation reserved for those with complications such as incarceration.[81,82]

If the child has a tender umbilical mass, the hernia may be reduced by milking the air out of the incarcerated loop of intestine and applying firm, steady pressure on the incarcerated mass. Admitting a patient for observation to rule out peritonitis and performing the operation the next day are appropriate. If the incarceration resists reduction, an emergency procedure is required. In an infant with an inguinal hernia and a concomitant umbilical hernia, the umbilical hernia should generally be left alone because it will probably close spontaneously.

## SURGICAL TECHNIQUE, RESULTS, AND COMPLICATIONS

Procedures described for the repair of umbilical hernias in children range from multiple layers of closure after opening the peritoneum to closed techniques in which the peritoneal sac is inverted or treated like an inguinal hernia sac and ligated with sutures.[83,84] Absorbable and nonabsorbable sutures have been advocated. The redundant skin of a large defect may be left in place and improves in appearance over time. Some have advocated excision of the skin and reconstruction when a large proboscoid hernia is present (see later). However, the fundamental technique of umbilical hernia repair has changed little since the 1953 description by Gross.[85] Secure closure of the fascia, usually in a transverse fashion, and preservation of the appearance of the umbilicus are common to all repairs. Strapping and taping of the defects have been discredited.[65,86]

Repair of an umbilical hernia is performed as an outpatient procedure with the patient under general anesthesia. Local anesthesia may be infiltrated into the wound before or after the procedure, but paraumbilical infiltration avoids distortion of tissues by the anesthetic.[87] Administration of local anesthesia before the incision conforms to the principles of preemptive analgesia. An infraumbilical skin crease incision is made (Fig. 74-7). The incision may be hidden within the umbilicus itself. Subcutaneous dissection is performed to circumscribe the sac. The sac is transected and may be dissected from the undersurface of the umbilical skin, but extensive and time-consuming dissection is unnecessary. Leaving a small remnant of the peritoneal sac on the undersurface of the umbilical skin causes no complications. The sac may be trimmed to a strong fascial edge or simply folded inward to allow placement of interrupted absorbable sutures in a transverse orientation. To ensure accurate placement of sutures, they are tied after placement is complete. A second layer of closure is unnecessary. Inversion of the umbilical skin is maintained with fine absorbable dermal suture between the underside of the umbilicus and the midportion of the fascial closure. The skin is closed with intradermal absorbable sutures and covered with a small dressing. Some surgeons apply a pressure dressing; however, a recent randomized study showed no benefit from application of a pressure dressing in standard childhood umbilical hernia repair.[88] Although infection predisposes to recurrence of the hernia, such complications are rare. Visceral injuries are possible but should not occur if the fascial edges are kept in view during the procedure.

Epigastric hernias can occur immediately adjacent to the umbilicus and may be difficult to distinguish from an umbilical hernia. Careful examination reveals a bulge at the upper margin of the umbilicus or just above it. A supraumbilical incision permits repair of an adjacent epigastric hernia and simultaneous repair if both umbilical and epigastric hernias are present.

## Use of the Umbilicus

Cannulation of the umbilical arteries and umbilical vein is commonly performed in sick neonates and provides a convenient means for intravascular access and monitoring.

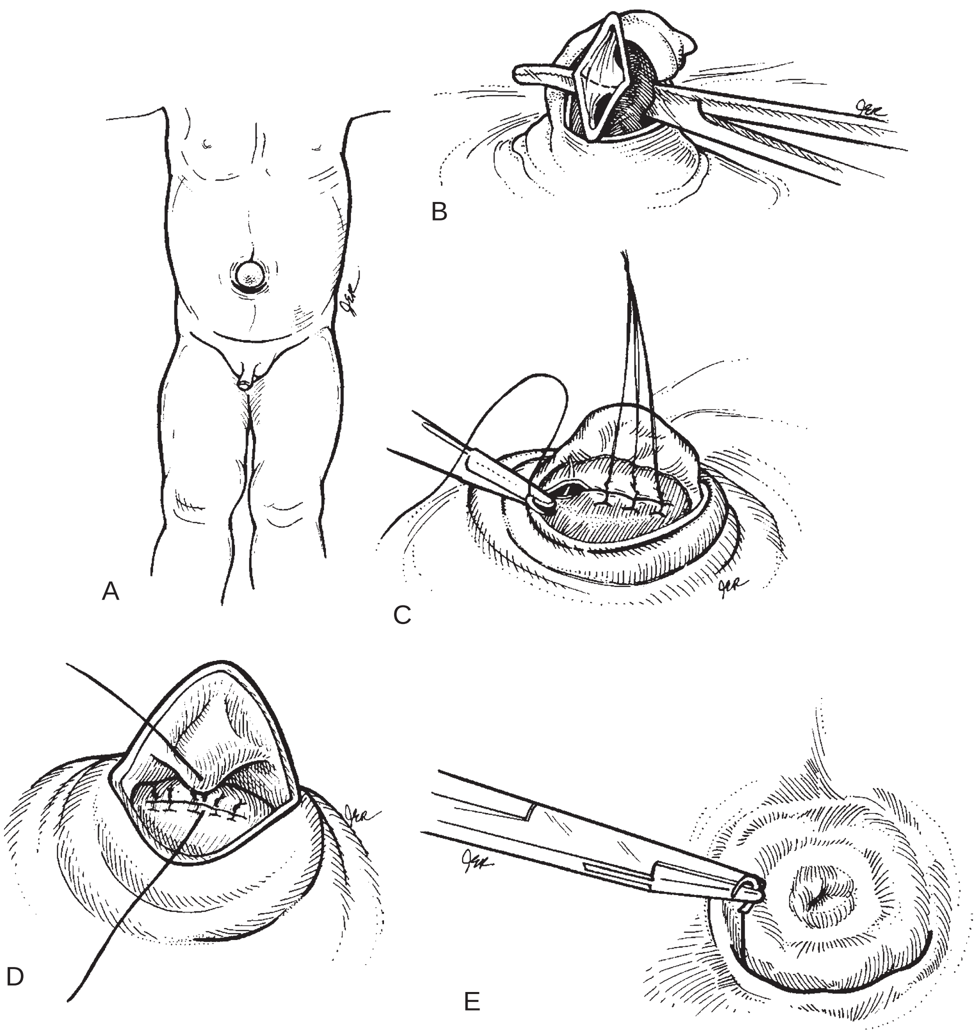


FIGURE 74-7 Repair of an umbilical hernia. **A,** An infraumbilical, curvilinear incision is marked. **B,** The sac is encircled and opened. **C,** The fascia is closed transversely. **D,** A tacking suture is placed between the undersurface of the umbilical skin and the fascia. **E,** Final result.

Associated risks are related to infection, vascular thrombosis, and direct injury from catheters.[89] There is insufficient outcome-based evidence to either refute or support the use of prophylactic antibiotics when umbilical artery or venous catheters are inserted in newborns.[90,91] There is little evidence that heparin coating of the catheter or catheter material lowers complication rates.[92] The umbilicus is frequently used as the entry site for laparoscopic equipment. The center of the umbilicus may be opened and the fascial ring probed and spread for access in infants, small children, and those with a shallow umbilicus. This technique leaves almost no detectable incision. In patients with a deep umbilicus, a separate infraumbilical incision may be preferable. The umbilical port is most often used as the primary site for placement of the viewing camera. Closure of the fascial defect after removal of the port is necessary to reduce the risk for formation of a hernia. Single-port laparoscopic procedures using the umbilicus as the only access site are gaining popularity in both pediatric and adult surgery.[93] The umbilicus has also been used to mask the abdominal incision used for pyloromyotomy in cases of hypertrophic pyloric stenosis.[94] This approach results in an almost undetectable scar.

The umbilicus can also be used as a stoma site.[95] No studies have compared the complication rate for intestinal stomas brought out of the umbilicus with those brought out from other locations in the abdominal wall; however, complications of umbilical stomas were reported by one study to be common.[96] After closure, the umbilicus is reconstructed and a nearly normal appearance is achieved. We have used the umbilicus as a temporary ostomy site and have found it satisfactory. Though providing no physiologic benefit, it leaves the patient with one less obvious incision site.

The umbilicus has also been used as an exit site for urinary diversion. In premature infants, a temporary cutaneous vesicostomy brought out of the umbilicus functions well and can be closed with excellent cosmetic results.[97] Intestinal conduits for urinary diversion have also been brought out of the umbilicus.[98]

# Reconstruction and Preservation of the Umbilicus

The umbilicus is aesthetically and psychologically important, and its abnormal appearance or absence may cause distress. Absence of the umbilicus may even be a source of grief and depression. The appearance of the umbilicus should be acceptable to the patient and family. A T-shaped or oval umbilicus with a superior hood may be the most aesthetically appealing configuration.[3] A broad or protruding umbilicus may be perceived to be less acceptable. One of the goals of all umbilical surgical procedures is to maintain or restore as normal an appearance as possible. Multiple techniques of surgical reconstruction or re-creation of the umbilicus have been described as noted later. Standard umbilical hernia repair produces minimal distortion of the umbilicus and generally results in a satisfactory appearance. Omphalomesenteric and urachal remnants can usually be excised through the umbilicus as noted earlier. After laparoscopy via the umbilicus, if the umbilical skin is secured to the fascial closure, a satisfactory umbilical depression is maintained. Patients may seek surgical correction for the perception of an unfavorable appearance of the umbilicus such as protrusion. Umbilicoplasty to address the appearance of the umbilicus has become a niche within the discipline of plastic and reconstructive surgery.

## UMBILICOPLASTY FOR GIANT HERNIAS WITH REDUNDANT SKIN

When large hernias (giant proboscoid hernias) are repaired, the redundant skin results in an unnatural appearance. Some improvement may occur with the passage of time, but a broad, flat, protruding configuration may persist. Reconstruction by a variety of techniques may improve the immediate and long-term appearance.[99–104] We have found the "tripartite umbilicoplasty" based on the technique described by Reyna and colleagues to be satisfactory for immediate reconstruction of giant umbilical hernias.[103] None of these described techniques has been widely adopted and shown to be superior in long-term follow-up.

## UMBILICOPLASTY FOR ABDOMINAL WALL DEFECTS AND CREATION OF A NEO-UMBILICUS

The umbilicus may be retained or reconstructed during the repair of abdominal wall abnormalities. The structures of the umbilical cord may be incorporated into a reconstruction of the umbilicus, or a neo-umbilicus may be fashioned.[105–111]

In gastroschisis and omphalocele, fascial repair may be performed through the circular skin defect that remains after the umbilical structures have been excised. This is the case for both primary and staged closures. The circular skin defect may then be closed with an intradermal purse-string suture that is incorporated into the middle of the fascial closure (Fig. 74-8, A).[106] Even if the fascial defect is enlarged for the application of a Silastic chimney, the lower portion of the defect can be closed in a similar circular fashion to create the appearance of an umbilicus.[105] Others have advocated preservation of the umbilicus in the repair of abdominal wall defects and leaving the umbilical remnants in place in continuity with the skin closure.[108,110,111] There is a trend toward preservation of the native umbilicus in gastroschisis repair (Fig. 74-8, *B*).

The umbilicus is abnormally located in all children with bladder exstrophy and is often associated with a small omphalocele defect. It may be transposed more cephalad at the time of bladder closure to create a more normal appearance.[112] In children with prune-belly syndrome, the umbilicus may be preserved on a vascularized pedicle and located appropriately after the removal of excess skin.[113]

In some circumstances a new umbilicus must be constructed when it is absent as a result of previous surgical removal or treatment of an abdominal wall defect. The normal location for the umbilicus is at the level of the iliac crests, overlying the third or fourth lumbar vertebrae. Umbilical reconstruction should create a round or oval depression with steep walls that

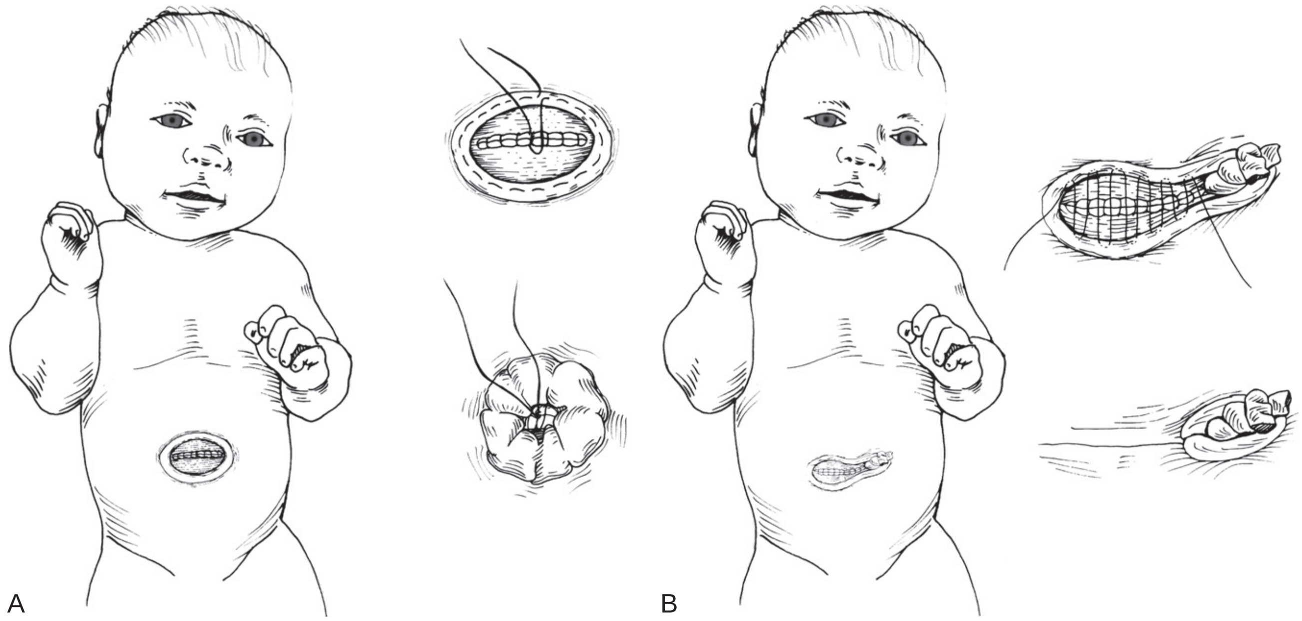


FIGURE 74-8 Technique of umbilicoplasty after excision of the cord structures or when a procedure is performed through the umbilicus (e.g., surgical repair of gastroschisis or a small omphalocele, excision of an omphalomesenteric remnant through the umbilical ring, excision of a urachal remnant through the umbilicus). **A,** Child with gastroschisis after fascial closure. Placement of a circumferential purse-string dermal suture is shown. Note that the suture passes through the fascia. **B,** Retention of the umbilical cord after repair of gastroschisis.

FIGURE 74-9 Creation of a neo-umbilicus using a tubularized defatted skin pedicle in a patient with a giant omphalocele in conjunction with abdominal wall reconstruction.

is centrally fixed to the abdominal wall fascia (Fig. 74-9). Some umbilical reconstructions tend to flatten over time. Tubularized skin reconstructions may be more durable and may also mimic the "cushion" or slightly raised area that surrounds the umbilical depression. Many techniques have been proposed to reconstruct an absent umbilicus.[106,109,114–122] They vary considerably in their complexity, but none have proved superior in long-term follow-up. Several techniques have been specifically described to reconstruct an absent umbilicus after exstrophy repair.[112,123–126]

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 75

# Congenital Defects of the Abdominal Wall

Michael D. Klein

## History

Newborns with abdominal wall defects were reported in the first century AD by Aulus Cornelius Celsus, a Roman physician, and then by Paulus Aegineta in the fifth century.[1] Omphalocele is described in the sixteenth century printed works of Ambrose Paré,[2] and Lycosthenes may have been the first to describe gastroschisis at about the same time.[3] Taruffi introduced the term *gastroschisis* in 1894.[4] For many years gastroschisis was confused with an omphalocele that had a torn sac.[5] Moore and Stokes are credited with limiting it to the specific clinical entity as we understand it today,[6] although they give credit to earlier authors who used the term, such as Bernstein,[7] but not to the earliest collected series of Massabuau and Guibal.[8]

The first successful repair of omphalocele was reported by Hey in 1802.[9] In 1873 Visick described the successful repair of gastroschisis.[10] Ahlfeld[11] in 1899 described painting an omphalocele sac with alcohol to produce an eschar and awaiting contraction and epithelialization. The use of mercurochrome for painting the sac was popularized by Max Grob.[12–14] Toxic effects of mercurochrome were described later.[15–17] A modern version was introduced by Ein and Shandling, who used an adhesive semipermeable artificial membrane.[18] Olshausen in 1887 first reported skin flap coverage of defects after removal of the membrane,[19] and Gross further demonstrated its effectiveness and popularized the technique.[20] Staged closure of the resultant hernia could be difficult because of failure of the abdominal cavity to grow without the impetus of the intestines within it, and because of intestinal adhesions to the skin flaps. For this reason, the skin was sometimes closed over an intact omphalocele sac.[21,22]

In 1967 Schuster introduced staged reduction of large omphaloceles with prosthetic material because he noted that the abdominal cavity did not grow with skin closure alone.[23] The fact that no operative technique has achieved universal success or acceptance is attested to by the many ingenious methods that continue to be devised including skin grafting,[24,25] pneumoperitoneum and tissue expanders to stretch the abdominal wall in preparation for closure,[26–28] partial hepatectomy,[29,30] lateral relaxing incisions in the fascia,[31] and division of the rectus abdominis muscles.[32]

## Spectrum of Clinical Congenital Abdominal Wall Defects

The clinically important defects are all umbilical with intact rectus abdominis muscles (Table 75-1). Omphalocele is a large defect (>4 cm) covered by amniotic membrane that contains midgut and other abdominal organs including the liver and often the spleen and gonad (Fig. 75-1). One unusual form of omphalocele is the cephalic fold defect, or pentalogy of Cantrell, in which the abdominal wall defect is supraumbilical and the heart is in the sac through a defect in the pericardium and the central tendon of the diaphragm.[33] The other elements of the pentalogy are an intracardiac defect and a sternal cleft. Ectopia cordis thoracis (when the heart is outside the chest with no pericardial covering as opposed to being inside the omphalocele sac) might be considered a form of a cephalic fold defect (Fig. 75-2).

Another unusual omphalocele is the caudal fold defect, cloacal exstrophy, in which the defect is infraumbilical and accompanied by exstrophy of the bladder, epispadias, diastasis of the pubic rami, and imperforate anus (see Chapter 120). The ileum prolapses between the two halves of the exstrophied bladder.

Gastroschisis is less than 4 cm in diameter, has no covering membrane, and usually contains only the midgut with the stomach and possibly a gonad. It is almost always to the right of the umbilical cord, although exceptions do occur (Fig. 75-3).[34] Occasionally, a skin bridge may be present between the cord and the defect, but the abdominal wall and its muscles are normal. At birth the bowel can appear perfectly normal, but more than 20 minutes after birth, the extruded intestine may be thickened and covered with a fibrinous exudate matted together so that individual loops cannot be distinguished. There have been several reports of gastroschisis with a small remnant of midgut appearing above a defect that has essentially closed, most likely caused by antenatal volvulus.[35,36] Most authors recognize patients with gastroschisis and an associated gastrointestinal condition such as atresia, perforation, necrosis, or volvulus as a separate entity with a poorer

**TABLE 75-1**
**Comparison of Congenital Abdominal Wall Defects**

| *Defect* | *Site* | *Sac* | *Contents* | *Frequency* | *Associated Anomalies* | *Outcome* |
|---|---|---|---|---|---|---|
| Omphalocele—lateral fold | Umbilicus | Yes | Liver, intestine, spleen, gonad | Common | Chromosomal, cardiac | Good (depending on associated anomalies) |
| Omphalocele—cephalic fold (pentalogy of Cantrell) | Superior umbilicus | Yes | Liver, intestine | Rare | Cardiac, sternal cleft, pericardial defect, central tendon diaphragm defect | Poor |
| Omphalocele—caudal fold (cloacal exstrophy) | Inferior umbilicus | Yes | Intestine | Rare | Bladder exstrophy, imperforate anus, epispadias | Fair |
| Umbilical cord hernia | Umbilicus | Yes | Intestine | Unusual | Uncommon | Good |
| Gastroschisis | Right umbilicus | No | Intestine | Common | Intestinal atresia | Good |
| Ectopia cordis thoracis | Midline sternum | No | Heart | Rare | Cardiac | Poor |

**FIGURE 75-1** Omphalocele.

**FIGURE 75-2** Ectopia cordis.

**FIGURE 75-3** Gastroschisis.

**FIGURE 75-4** Umbilical cord hernia.

outcome.[37] This is usually called *complicated gastroschisis*. Gastroschisis in the fetus is probably associated with intrauterine distress. Neonates with gastroschisis are more frequently premature and commonly have respiratory problems. Even term babies with gastroschisis are more likely to be small for gestational age[38–40] and to have younger mothers.[41]

Umbilical cord hernia is least common. It is also less than 4 cm and contains only the midgut, but it is covered by a membrane (Fig. 75-4). It is often confused with omphalocele. The differences are that it contains only midgut, never liver, and the abdominal wall above the defect is normal, with the rectus muscles meeting in the midline at the xiphoid. Few associated anomalies are reported with this defect. Like all abdominal defects in which the midgut has not returned to the abdominal cavity before birth to allow for rotation and fixation, these patients have malrotation, although it is not usually a cause of intestinal obstruction.

Umbilical hernia is distinguished from these anomalies by two features: (1) The defect is covered by normal skin, and (2) it is only rarely present at birth, instead usually

becoming apparent in the first weeks or months of life. In the literature before 1970 and in the literature outside pediatric surgery even today, these three forms are often confused, particularly omphalocele/gastroschisis and omphalocele/umbilical cord hernia.

Infants with congenital abdominal wall muscular deficiency, or prune-belly, syndrome have all the normal layers of the abdominal wall but little muscle in the loose areolar tissue. Much of the morbidity is related to similar muscular deficiency in the genitourinary and gastrointestinal tracts.

Other abdominal wall defects, often incompatible with life,[42–44] have been described in humans[45,46] including true absence of abdominal wall structures with evisceration of bowel.[47,48]

# Embryology

## EMBRYOLOGY OF THE ABDOMINAL WALL

At 3 weeks' gestation the flat disk of the embryo develops four folds that will enclose the body cavities (Fig. 75-5, *A* and *B*). Two lateral folds form the pleuroperitoneal canals once they meet anteriorly in the midline. The cephalic fold brings down with it the developing heart, which actually began distal to the brain, but now takes its place within the anterior chest wall. It also carries the septum transversum, which continues posteriorly and divides the pleuroperitoneal canals into the pleural and peritoneal cavities. The caudal fold brings with it the developing bladder or allantois, which started off distal to the anus. During this process the gut tube has formed along the length of the embryo with a communication at the umbilicus to the yolk sac; the yolk sac will eventually disappear, sometimes leaving a vitelline duct remnant on the distal ileum. At about 5 weeks' gestation, this gut tube elongates and develops within the umbilical coelom (Fig. 75-5, *C*), a cavity in the body stalk on the anterior surface of the embryo. At about 10 weeks' gestation the gut returns from the space within the umbilical stalk to the peritoneal cavity and undergoes rotation and fixation.

## EMBRYOGENESIS OF THE DEFECTS

Omphalocele represents a failure of the body folds to complete their journey.[49] Most omphaloceles are lateral fold defects and are always at the umbilicus. The rectus muscles often insert far apart on the costal margins and for this reason cannot be

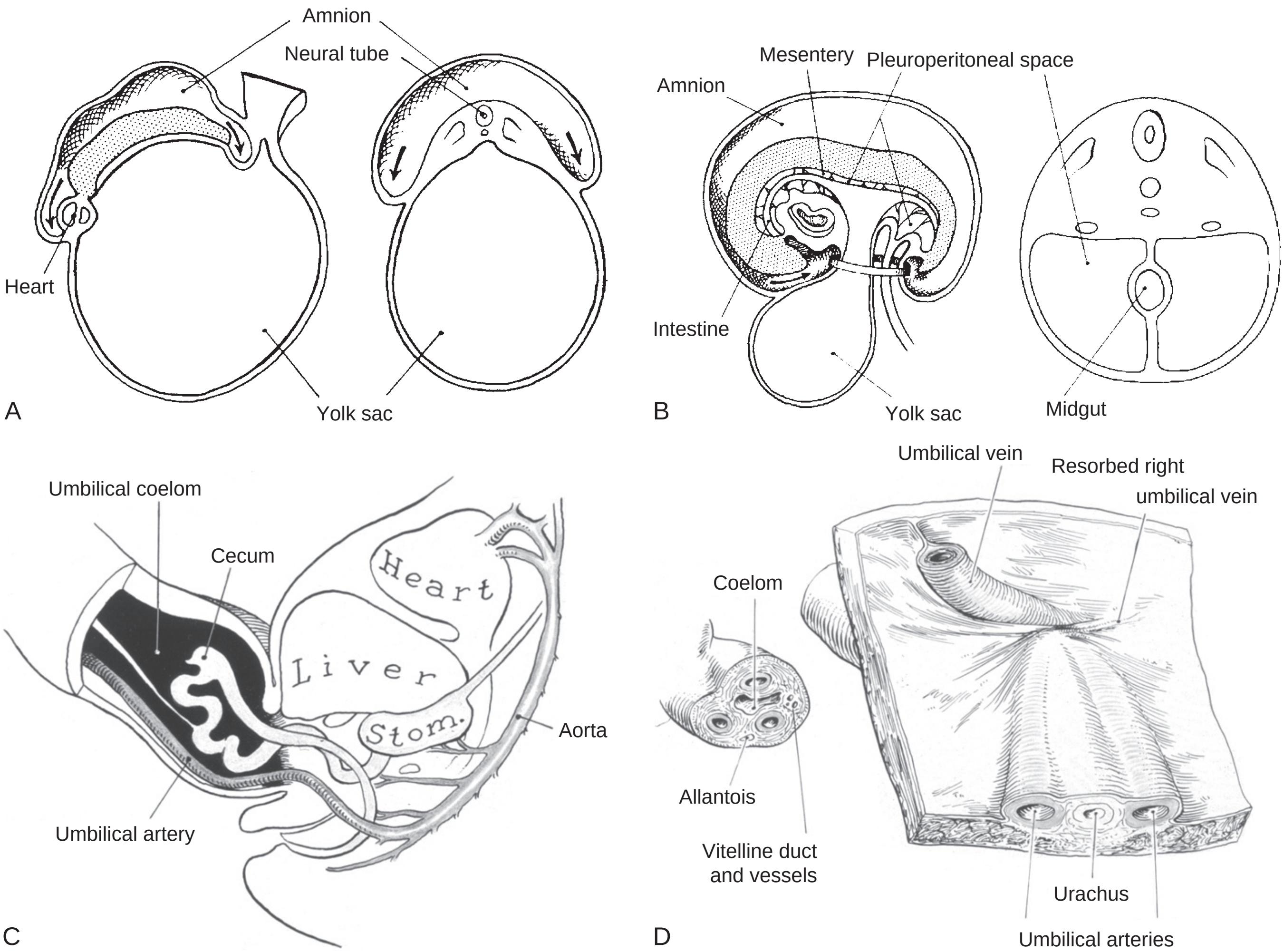


**FIGURE 75-5** Embryology of the abdominal wall. **A,** Two-week embryo as a flat disk before folding to form the body cavities. **B,** At 4 weeks the folding is complete. The gut tube is about to be pinched off the yolk sac. **C,** At 6 weeks the elongating midgut enters the umbilical coelom. **D,** A view from inside the abdominal cavity showing the relatively unsupported right side of the umbilicus as a result of resorption of the right umbilical vein.

brought entirely together in a repair. Whatever the insult may be that causes it, this aberration occurs early in embryogenesis and is thus likely to affect other organ systems as well, so children with omphalocele frequently have associated anomalies. Cephalic fold defects result in ectopia cordis or the pentalogy of Cantrell, whereas caudal fold defects cause bladder and cloacal exstrophy. Gastroschisis, antenatal exposure of the viscera, is probably caused by failure of the umbilical coelom to develop.[50] The elongating intestine then has no space in which to expand and ruptures out the body wall just to the right of the umbilicus, possibly because the right side of the umbilicus is relatively unsupported as a result of resorption of the right umbilical vein at about 4 weeks' gestation (Fig. 75-5, *D*).[51] An alternate explanation that the yolk sac and associated vitelline structures fail to incorporate into the umbilical cord, thus allowing the midgut to exit the abdomen at the point they exit, is also reasonable.[52] Thus gastroschisis has no covering membrane. In gastroschisis the bowel is usually thickened, matted, edematous, and covered with a fibrinous peel. Some have explained the latter appearance on the basis of the change in amniotic fluid electrolyte composition with the onset of fetal kidney function.[53–56] Evidence from studies in animals indicates that the peel forms in utero[57–59] and that it is a postnatal event.[60] Some investigators have related the condition of the bowel to the presence of meconium from the fetus in the amniotic fluid.[19,61] In a recent clinical study, neonates delivered with meconium staining had a fibrinous peel, whereas those without staining had none.[55] Our clinical observation of more than 50 deliveries indicates that the appearance of the bowel is most often a postnatal event (Fig. 75-6). At the moment of birth, the bowel in gastroschisis is usually quite normal. Twenty minutes later it begins to acquire the characteristic changes. These changes may be due to exposure to air, but more likely they are related to mesenteric venous occlusion at the level of the abdominal wall defect with resultant edema and transudation of proteinaceous fluid.

Umbilical cord hernia is a simple failure of the midgut to return to the peritoneal cavity at 10 to 12 weeks. Thus this defect contains only midgut and is covered by a membrane. Such hernias are much smaller than omphaloceles and have a better outlook. Distinguishing umbilical cord hernia from omphalocele both embryologically and clinically is important in managing patients and reporting results. Margulies[61] first translated the embryologic work of Pernkopf[62] and Politzer and Sternberg[63] into English, which permitted Benson, Penberthy, and Hill[64] to recognize it as a separate clinical entity.

**FIGURE 75-6** Gastroschisis at delivery. The bowel does not appear matted, edematous, and coated with a fibrinous peel.

Alternative explanations for these various defects, especially gastroschisis, have been presented, but none have been generally accepted. Some have thought that gastroschisis must represent "failure of mesodermalization" with actual absence of abdominal wall components.[65,66] Although such anomalies have been reported, they are usually stillborn monstrosities. Nearly all live-born children with abdominal wall defects have intact abdominal walls with normal muscle layers. More recently there has been speculation that decreased blood flow in the omphalomesenteric artery might be a cause.[67] This has resulted in many studies on the use of vasoconstrictive agents in the first trimester. Because the omphalomesenteric artery supplies intestine and not the abdominal wall, it is difficult to see how this has gained such credence.

There are many reports of abdominal wall defects induced in animals by exogenous agents. In a comprehensive review of the literature gastroschisis was induced by 22 teratogens, omphalocele by 9, and umbilical cord hernia by 8.[68] Such studies raise the issue of whether the apparent increase in incidence of gastroschisis since 1970 might be due to new environmental teratogens. Studies of abdominal wall defects in animals might not necessarily be relevant. One recent example is the superb work of Brewer and colleagues on the mouse knockout model of congenital abdominal wall defects.[69,70] These investigators demonstrate that the AP-2a transcription factor is important for the normal development of the mouse abdominal wall. They provide beautiful illustrations of the development of the normal abdominal wall and its abnormal development in the knockout model. Yet their careful description allows the clinician to conclude that the defect presented does not represent any of the clinical defects pediatric surgeons see.

Possible causes of abdominal wall defects have also been investigated in clinical material that has recently been reviewed.[71] For gastroschisis, demographic risk factors for which there is more than isolated evidence include young maternal age, low socioeconomic status, absence of the maternal father, poor maternal prenatal care, and primigravida status. Nutritional factors are low levels of glutathione and α-carotene, high levels of nitrosamines, absence of supplemental vitamin intake during pregnancy, folic acid fortification, and general, poor nutrition. Maternal obesity was actually found to be protective. Most, but not all, studies show no familial or genetic risk factors. There is little evidence that living near chemical plants, farms, landfills, or other specific sites is a risk factor. Vasoconstrictive agents are repeatedly reported as related risk factors. Many studies confirmed that use of illegal drugs including cocaine, methamphetamine, and marijuana during pregnancy was a risk factor. Risk factors for omphalocele are different from those for gastroschisis. Demographic factors include both advanced and very young maternal age and maternal obesity. Nutritional factors are failure to use multivitamins during pregnancy (especially Vitamin B 12), lack of folic acid fortification, and alterations in glycemic control. No strong evidence is found for medication, illegal drug, or lifestyle factors, although maternal history of febrile illness and in vitro fertilization do appear to be risk factors.

### GENETICS AND FAMILIAL OCCURRENCE

Although rare, reports of abdominal wall defects, mainly omphaloceles, occurring in families and even in twins have occurred.[72–74] No specific genes have been identified with gastroschisis, but omphalocele is associated with chromosomal anomalies (especially Trisomy 18), and candidates have been reported for specific genes including PITX2, CDKN1C, MTHFR, and 677C-T (folate). OEIS is closely related to caudal fold omphalocele and may be related to a specific gene.[72] Many syndromes include abdominal wall defects. Beckwith-Wiedemann syndrome (congenital abdominal wall defect, macroglossia, and hypoglycemia with a propensity for the development of abdominal tumors later in life) is the most common.[73,74] It is remarkable that the abdominal wall defect in Beckwith-Wiedemann syndrome can be any of the three aforementioned entities, and yet we presume that they all have a different embryogenesis. This syndrome also appears to be associated with assisted reproductive technologies.[75] Other syndromes that include omphalocele are displayed in Table 75-2.

## Antenatal Considerations

### ULTRASOUND

Today, the diagnosis is usually made antenatally by ultrasound (US).[76] Omphalocele can be distinguished from gastroschisis by the presence of a sac and from umbilical cord hernia by the presence of the liver in the defect. The diagnosis allows for antenatal counseling, which given the generally good prognosis, can be reassuring. In a report from 11 European antenatal US registries in 2001, the sensitivity for detecting omphalocele was 75% (range, 25% to 100%), and that for gastroschisis was 83% (18% to 100%).[77] The first age at which omphalocele was detected was 18 ± 6 weeks, and gastroschisis, 20 ± 7 weeks. Only 41% of fetuses with omphaloceles detected antenatally were live-born. Twenty-two percent were fetal deaths, and in 37% the pregnancies were terminated. Fifty-nine percent of fetuses with gastroschisis were live-born, with 12% being fetal deaths and 29% terminations. Recent reports show no significant changes.[78,79]

**TABLE 75-2**
**Omphalocele Syndromes**

| *Name* | *Description* | *Inheritance* | *OMIM #* |
|---|---|---|---|
| Shprintzen omphalocele syndrome | Malformation syndrome that includes mildly dysmorphic facies, omphalocele, scoliosis, learning disabilities, and pharyngeal and laryngeal hypoplasia | Autosomal dominant | 182210 |
| Omphalocele–cleft palate syndrome | Lethal syndrome associated with uterus bicornis in one case, uvula duplex and hydrocephalus internus in another, omphalocele, and cleft palate | | 258320 |
| Beckwith-Wiedemann syndrome (also known as exomphalos-macroglossia-gigantism syndrome [EMG syndrome] and Wiedemann-Beckwith syndrome [WBS]) | Pediatric overgrowth disorder involving a predisposition to tumor development. The clinical presentation is highly variable; some cases lack the hallmark features of exomphalos, macroglossia, and gigantism. Abdominal wall defects common, as well as visceromegaly including liver, spleen, pancreas, kidneys, and adrenals | Inheritance of BWS is complex. Possible patterns include autosomal dominant inheritance with variable expressivity, contiguous gene duplication at 11p15, and genomic imprinting resulting from a defective or absent copy of the maternally derived gene | 130650 |
| Gershoni-Baruch syndrome | Large/giant omphalocele containing liver and intestines. Also associated with diaphragmatic hernia and radial ray defects | Autosomal recessive hypothesis in one case | 609545 |
| C syndrome (Opitz trigonocephaly syndrome, Trigonocephaly syndrome) | Unusual facies, polydactyly, cardiac abnormality, large omphalocele in a few cases | Autosomal recessive mostly, autosomal dominant in a few cases; disruption of the CD96 gene involved with encoding a member of the immunoglobulin family | 211750 |
| Donnai-Barrow syndrome (Faciooculoacousticorenal syndrome) | Facial anomalies, ocular anomalies, sensorineural hearing loss, and proteinuria. Some cases include omphalocele as an associated anomaly | Autosomal recessive; mutation in the LRP2 gene | 222448 |
| Thoracoabdominal syndrome (THAS) | Diaphragmatic and ventral hernias, hypoplastic lung, cardiac anomalies, cleft palate, omphalocele, sporadic pentalogy of Cantrell | X-linked dominant | 313850 |
| Manitoba oculotrichoanal syndrome (MOTA) (Marles syndrome) | Hypertelorism, unilateral eye malformations, aberrant anterolateral scalp hairline, nasal and anal anomalies. Omphalocele noted in several cases | Autosomal recessive | 248450 |
| Craniosynostosis–mental retardation syndrome of Lin and Gettig | Midline craniosynostosis, agenesis of the corpus callosum, severe mental retardation, unusual face, contractures, camptodactyly, hypospadias, hypogonadism, small omphalocele, and multiple small bowel atresias | | 218649 |

*Continued*

**TABLE 75-2**
**Omphalocele Syndromes—cont'd**

| *Name* | *Description* | *Inheritance* | *OMIM #* |
|---|---|---|---|
| Chromosome 9p deletion syndrome | Trigonocephaly, flattened occiput, prominent forehead, broad flat nasal bridge, anteverted nares, malformed external ears, hypertelorism, hypertonia. Omphalocele rare anomaly | | 158170 |
| PAGOD syndrome (agonadism with multiple internal malformations) | Agonadism, hypoplasia of the right pulmonary artery, hypoplasia of the right lung, isolated dextrocardia with complex cardiac malformations, and diaphragm hernia or omphalocele | | 202660 |
| Acrocephalopolydactylous dysplasia (Elejalde syndrome) | Excessive birth weight, swollen globular body with a thick neck, apparently short limbs, polydactyly, craniosynostosis with acrocephaly, omphalocele, and abnormal face | Most likely autosomal recessive | 200995 |
| Popliteal pterygium syndrome (lethal type) (Bartsocas-Papas syndrome) | Popliteal pterygium with a cord containing nerves and vessels, synostosis of hand and foot bones with digital hypoplasia and syndactyly, facial clefts, ankyloblepharon and filiform bands between the jaws, omphalocele, aplasia of the urethra | | 263650 |
| Malpuech facial clefting syndrome (Facial clefting syndrome, gypsy type) | Mental and physical growth retardation, hypertelorism, facial clefting, urogenital abnormalities, eye abnormalities, hearing loss, omphalocele, caudal appendage, umbilical hernia | Autosomal recessive (kindred highly inbred) | 248340 |
| Cerebrocostomandibular syndrome | Severe micrognathia, rib defects, mental retardation, microcephaly, histologic anomalies, omphalocele | Both autosomal dominant and autosomal recessive have been described | 117650 |
| Fryns syndrome | Diaphragmatic hernia, abnormal face, distal limb anomalies* | Autosomal recessive | 229850 |
| OEIS complex | Omphalocele, bladder exstrophy, imperforate anus, and spinal defects | | 258040 |

Data from references 194–198.
*Omphalocele is not reported in OMIM but is noted in several case reports. The first reference also points to other syndromes not noted by OMIM.

Antenatal US also detects associated anomalies.[80] In gastroschisis these anomalies are usually intestinal atresias.[81,82] In omphalocele one study reports a 25% incidence of the detection of major associated anomalies.[83] The frequency of associated cardiac anomalies in omphalocele makes antenatal echocardiography helpful.[84]

Given the poor outcome of all forms of ectopia cordis, termination could be a reasonable alternative when US demonstrates the heart outside the chest. Some ultrasonographers have attempted to correlate the bowel problems of gastroschisis with the antenatal appearance on US,[85,86,90] but this has not been successful in all centers including more recent experience.[82,91,92]

Routine use of antenatal US has not been definitively shown to improve perinatal morbidity or maternal outcome, although there may be some survival benefit for a fetus with a life-threatening anomaly. There may, however, be a cost savings, if the mother chooses termination of pregnancy. Such has not been the case for either omphalocele or gastroschisis,[93] although termination rates for these treatable anomalies can be high (63% in one study).[94] A recent report demonstrated that multidisciplinary prenatal care for mothers carrying pregnancies with gastroschisis produced infants with higher birthweights and greater gestational age, although there was no difference in the outcome for gastroschisis or the likelihood for a successful vaginal delivery.[95]

### AMNIOTIC FLUID AND SERUM TESTS

Elevated alpha fetoprotein (AFP) in both maternal serum and amniotic fluid and elevated amniotic fluid acetylcholinesterase (AChE) have been correlated with abdominal wall defects when there is no myelomeningocele.[96] In a study of 23 pregnancies with gastroschisis and 17 with omphalocele, second-trimester serum AFP was 9.42 times greater than normal in gastroschisis and 4.18 times normal in omphalocele.[97] Another study found elevated amniotic fluid AFP in 100% of pregnancies with gastroschisis and in only 20% of those with omphalocele. AChE was elevated in 80% of pregnancies with gastroschisis and 27% of those with omphaloceles.[98]

## Obstetric Delivery

Intuitively, it may seem appropriate to deliver these patients by cesarean section to avoid injury to the bowel or tearing of the omphalocele sac, and some reports claim a benefit for cesarean section.[99–101] There is also, however, a report of two patients with gastroschisis whose bowel was injured during cesarean section delivery.[102] The more recent obstetric literature finds no benefit of cesarean section.[103–110] Some reports even show no benefit with referral of the mother for delivery in a pediatric surgery center.[111,112] One must conclude that the mode of delivery is a decision to be made by

the obstetrician on the basis of obstetric indications, not on the presence of an abdominal wall defect.

The belief that the condition of the bowel in gastroschisis is due to a relatively late (33 weeks) intrauterine event has led some to recommend preterm delivery.[113] Because we think that the condition of the bowel is a postnatal event, we do not believe that it is worth the risks of prematurity. It seems most likely that the good results observed with preterm delivery by planned cesarean section are related to the fact that it allows for immediate repair and avoids the venous congestion of the mesentery and its effect on the intestine. Others have also found no benefit of preterm delivery,[99] and a recent study shows increased morbidity with preterm delivery.[114]

Antenatal counseling and coordination with the obstetric team are essential. Because the condition of the bowel in gastroschisis and distention of the bowel and size of the liver in omphalocele are often related to the time between delivery and repair, it is important to make arrangements for repair as soon as possible after delivery.[72]

# Clinical Features

## INCIDENCE AND ASSOCIATED CONDITIONS

### Omphalocele

Before 1970, omphalocele was the most common of the abdominal wall defects; it is now the second after gastroschisis. The overall incidence is 1 to 2.5 per 5000 live births[8] with a male preponderance.[115]

Conditions associated with omphalocele are listed in Table 75-3. Up to 45% of patients with omphalocele have been reported to have a cardiac abnormality including ventricular septal defect, atrial septal defect, ectopia cordis, tricuspid atresia, coarctation of the aorta, and persistent pulmonary hypertension of the newborn.[116] Chromosomal abnormalities can be found in up to 20%, and an association with Down syndrome has also been reported.[117] Patients with omphalocele are more likely to be large for gestational age (macrosomia or > 4 kg in birth weight).[118] Musculoskeletal and neural tube defects are also reported in greater than expected incidence.[119,120] Gastroesophageal reflux is more likely, with 43% being affected in one study.[121]

### Gastroschisis

Gastroschisis has become the most common of the abdominal wall defects over the past 30 years.[122–124] This may be related to the increased incidence of prematurity and the increased survival of premature infants in general, or to the fact that it was not until the 1970s that the distinction between gastroschisis and omphalocele was regularly made.[44] The incidence is about 2 to 4.9 per 10,000 live births,[122,125–127] with a male preponderance.[28,115]

The anomalies associated with gastroschisis are usually related to the midgut, with the most common being intestinal atresia (see Table 75-3).[128] In the first year of life infants with gastroschisis are likely to have gastroesophageal reflux (16%)[72] and undescended testicle (15%), although the latter often corrects spontaneously.[129,130] Many reports recognize congenitally short or dysmotile bowel with gastroschisis.[131] Although neither condition has been quantified in terms of severity or incidence, they are certainly lower than the incidence of atresia (<5%).

**TABLE 75-3**
**Associated Conditions**

| *System* | *Gastroschisis (%)* | *Omphalocele (%)* |
|---|---|---|
| Cardiac | 2-12 | 7-47 |
| Respiratory | <1 | 1-4 |
| Central nervous system | 2-10 | 4-30 |
| Musculoskeletal | <1-10 | 4-25 |
| Gastrointestinal | 5-40 | 3-20 |
| Genitourinary | 3-10 | 6-20 |
| Facial | 1-3 | 1-14 |
| Chromosomal | <1-3 | 3-20 |

### Omphalocele

***Initial Care*** Although the bowel in omphalocele is protected by the sac, operation is still urgently needed to increase the chance for primary closure. A nasogastric (NG) tube should be placed early to decompress the intestines. A rectal examination aids this with evacuation of meconium. Maintenance of body temperature is especially important. Ventilator support and supplemental oxygen should be supplied as needed.

Because of the frequency of associated heart defects, cardiology evaluation and echocardiography are in order, although the results will not delay repair.[132] Intravenous fluids are provided at maintenance rates, best through an upper extremity. If not done at birth, 1 mg of vitamin K should be administered, as well as prophylactic antibiotics

The value of primary closure has been debated. Some believe that staged closure is so successful that it is preferable to avoid the possible complications of increased abdominal pressure, which include respiratory compromise, decreased venous return with decreased urine output and cardiac output, compromise of the blood supply to the intestine, and acidosis related to kinking of the hepatic veins as the liver is reduced. Nonoperative initial treatment (painting the sac with an antiseptic) is still useful when operative closure is not possible.[133]

***Operative Closure*** In the operating room the sac and abdomen are prepared with an antiseptic and excess cord is removed. If the patient is hypoxic or unstable, we cannulate and preserve the umbilical artery or vein (or both) for transplantation to the lateral abdominal wall for postoperative monitoring, but this is rarely necessary.[134] We always use plastic adhesive edge drapes to preserve heat. We first attempt to reduce the abdominal contents with the sac intact, as a number of reports suggest.[135–137] Such reduction is often impossible either because the abdominal cavity is too small or because the sac is adherent to the liver and falciform ligament. We then incise the skin a few millimeters from the sac circumferentially around the defect and elevate skin flaps until the rectus muscles can be identified. At this point the sac is excised with ligation of the umbilical vessels and urachus. Any sac adherent to the liver is divided such that some remnants are left on the liver.

If the viscera cannot be reduced, it is helpful to stretch the abdominal wall manually in a posterior-to-anterior direction. The intestine is replaced first and then the liver. The liver

effectively holds the intestine in place, and if skin flap closure should be necessary, the secondary operation will be much safer. For primary closure, mattress sutures are placed through all layers of the abdominal wall except the skin. It is important to place these sutures through the rectus abdominis muscles and not just through the midline fascia, which may result in a postoperative hernia. It will not be possible to appose the rectus muscles in the upper portion of the incision because they insert broadly on the costal margin. It is also not necessary because the liver fills this space. Turning anterior rectus fascial flaps to cover this defect has been suggested, but we have not found this to be necessary. It is best to place the abdominal sutures without tying them and then pull alternate sutures to either side to see how the patient will tolerate fascial closure. If the anesthesiologist can ventilate the patient with peak inspiratory pressures of less than 25 cm $H_2O$, closure is safe. The skin is closed with a running suture, and in most patients this makes a scar that looks like an umbilicus. Several methods have been described for performing a cosmetic umbilicoplasty at the initial operation.[138–141] It often suffices to close the skin incision in a subcuticular purse-string fashion with absorbable suture material while taking every second or third bite to the fascia. However, frequently not enough skin is available for these procedures. In many cases the skin will have a tenuous vascular supply and appear blanched. Adhesive tape should not be used for a wound dressing.

Other methods have been suggested to determine whether the fascial closure is too tight: a saphenous vein intravenous line that will not drip by gravity or intravesical or NG tube pressure greater than 20 cm $H_2O$.[32,142] Splanchnic perfusion pressure (calculated as mean arterial pressure minus intra-abdominal pressure measured either intragastric or intravesical) has been suggested as being an even better predictor.[143] If the fascial closure is judged to be too tight, one can consider only skin closure, but in our experience, if the closure is still too tight after the maneuvers suggested, the skin closure will also probably be too tight. In this case the viscera can be covered with a prosthetic silo that will allow slow reduction of the abdominal viscera over a 1-week period. The simplest of these devices is the preformed Silastic chimney with a spring-loaded ring at the bottom, which is placed though the defect beneath the edges of the abdominal wall (Fig. 75-7).[144] The surgeon can suture this ring to the abdominal wall to prevent the ring from extruding as pressure is applied to reduce the viscera. Antibiotic ointment is applied around the edges as a dressing. If this device is not available, one can use 0.007-inch-thick Dacron-reinforced Silastic. We suture one piece to each side of the abdominal wall so that the knots are on the outside and the edges of both the fascia and Silastic face out. We then separately suture up the inferior and superior edges and over the top (Fig. 75-8).

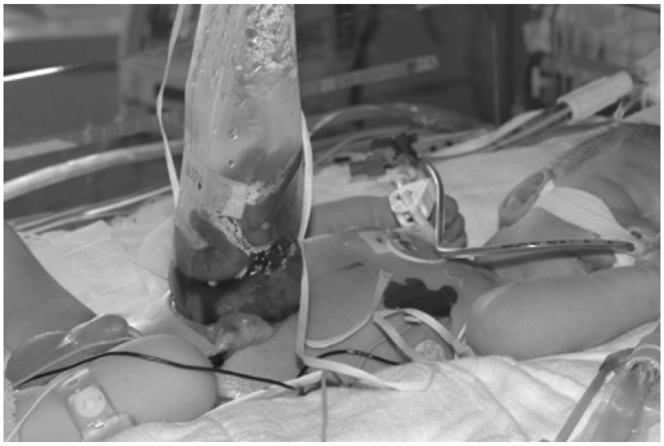

FIGURE 75-7 Gastroschisis with bowel contained in a preformed Silastic silo.

FIGURE 75-8 Gastroschisis with bowel contained in a hand-sewn Silastic silo.

We do not perform a Ladd procedure or appendectomy. If a testicle is present in the sac, it can be placed in the abdominal cavity because in most cases it will be in the scrotum in a year. If an obvious atresia is present, we may bring out a single stoma through normal abdominal wall or simply leave the atresia in the abdomen and wait at least 6 weeks before reoperating.

Most pediatric surgeons agree that giant omphalocele is a separate category of defect that is particularly difficult to treat and which has a much poorer outcome than the usual lateral fold defect.[145] As eloquently described by Campos and colleagues, there is no standard definition of this entity in terms of size or amount of herniated viscera.[146] It simply consists of a degree of visceroabdominal disproportion that defies treatment with fascial or even skin closure whether applied primarily or after a staged closure. A recent report from the Children's Hospital of Philadelphia[147] defines both in utero and newborn giant omphalocele as one with 75% or more of the liver in the sac. Unfortunately they did not present a technique for determining the volume of the liver, so this may also be open to individual interpretation. It is often accompanied by respiratory symptoms.[148] The Philadelphia series is valuable in documenting 31 patients in a 6-year period with 25 survivors. Seventy-one percent required intubation in the first hour of life, and 40% of survivors had chronic lung disease. More than half of the survivors had associated anomalies, more than half had neurodevelopmental disability at 1 year of age, and three fourths had feeding problems.

Giant omphalocele requires some imagination and creativity to treat.[149] Suggestions have included painting the sac with antiseptic,[150] the use of skin flaps with grafting to the open areas remaining,[151] use of tissue expander,[152] and split-thickness skin grafting.[153] We have tried on several occasions to use Gore-Tex and then place skin flaps or grafts over the Gore-Tex, with failure on each occasion as a result of

sepsis and sloughing. However, it has been possible to use flaps or grafts on the granulating surface that occurs after removing the Gore-Tex, and the underlying pseudocapsule seems to stabilize the abdominal wall. Using an absorbable material covered by a VAC sponge dressing is an appealing alternative.[154,155] The use of tissue expanders to either expand the abdominal cavity or obtain more skin in older infants is also an option.[28,156]

***Postoperative Care*** With primary closure, most patients require assisted ventilation initially, but over a period of several days the abdominal wall accommodates the abdominal contents. Intravenous fluids are administered at 150 mL/kg/hr or more to maintain urine output at 1 mL/kg/hr. A central intravenous line is placed for parenteral nutrition. Short-term antibiotics are administered if primary closure has been performed, but antibiotics are continued until completion of staged closure with a prosthesis. The wound is managed with antibiotic ointment, and the sutures are removed at 3 weeks. We keep a 10-French sump NG tube on low intermittent suction until there is evidence of bowel function including stooling, decreased distention, and reduced NG tube output. The tube is then removed, and 12 hours later feedings are begun gradually. It is not unusual for the appearance of bowel function to be delayed. If intestinal function has not resumed in 3 weeks, a small bowel contrast study may be indicated.

If a prosthesis has been used, it is usually appropriate to initiate reduction of the abdominal contents on postoperative day 1. Reduction is accomplished simply by manual manipulation, which can then be secured in many ways: applying long clamps suspended by umbilical tape to the overhead warmer, applying a TIA 90 stapler, running a suture back and forth, or using umbilical cord clamps (Fig. 75-9). A particularly ingenious method is a ringer mechanism,[157] but it is not commercially available. Simply tying the prosthetic sac with umbilical tape leaves a larger circular defect than closing it side to side does. One might consider adding several sutures to each side outside the prosthesis when it is applied. These sutures can then be tied once the prosthesis is flat to further appose the edges.

**FIGURE 75-9** Reduction of intestine contained in a preformed Silastic silo.

Despite Schuster's original hypothesis, it is unlikely that the abdominal wall grows during reduction.[23] It is more likely that the edema of the bowel wall resolves and the intestinal contents are emptied while the abdominal wall is simply stretched.

The several methods of measuring intra-abdominal pressure discussed earlier were originally used to monitor primary closure and then reduction of a prosthesis. The most important lesson learned from these studies is that we had been reducing the abdominal contents too slowly, usually every other day. It is important to be aggressive. Most often the prosthesis can be removed and the abdominal wall closed in 7 days. If it is not performed by 14 days, the prosthesis may begin to separate from the abdominal wall. Recently, Jona suggested that active reduction may not be necessary.[158] In his small series no pressure was applied to the silo, and the abdominal contents spontaneous reduced by day 8.

If skin flaps have been used, the definitive repair can be done at any time, depending on the patient's general condition. If the intestine begins to grow into a large skin sac instead of stretching the abdominal cavity, an abdominal binder can be used to direct forces inward. When it is time to bring the fascia together, the skin can be dissected off the liver with little trauma other than some mild bleeding that will stop with pressure. If the edges of the muscular abdominal wall cannot be brought together, a prosthetic mesh patch can be used as long as it can be entirely covered by healthy skin. If a part of it must be left exposed, it is unlikely to be incorporated and will become infected or extruded. If one can predict that skin flap closure will not be possible initially, it is probably best to avoid dissecting flaps so that that tissue will be healthier when it is time for the final repair.

If a postoperative hernia occurs, it can usually be repaired at 1 year of age without the use of a prosthetic patch. In occasional patients the hernia resolves spontaneously.

## Ectopia Cordis Thoracis and Cephalic Fold Defect

Operative repair of ectopia cordis thoracis and cephalic fold defects is especially challenging. It is difficult to replace the heart in the thoracic cavity without kinking the great vessels or the pulmonary veins. Coverage with soft tissue to gain time can result in cardiac tamponade, so wide intrathoracic dissection around the heart and great vessels has been advocated to increase the space within the chest. The fascia of the abdominal wall is closed once cardiorespiratory stability has been achieved. In ectopia cordis thoracis, it is also important to provide a rigid covering for the heart. This has been performed with rib struts between the sternal halves and with prosthetic material. Reported repairs of these difficult clinical problems emphasize creative use of available tissue and individual anatomic features.[159–162] In the cephalic fold defect (pentalogy of Cantrell), the sternal cleft and pericardial defect need no special treatment. We have used immediate skin closure of the omphalocele and allowed the patient to grow and have the intracardiac defect treated later. A Gore-Tex patch can then be used to close the central tendon of the diaphragm with no tension so that the heart can extend somewhat into the abdomen. With growth the patch becomes taut and elevates the heart slowly into the chest, which can grow to receive it. A valuable recent review of the literature has been published.[163]

### Caudal Fold Defect

This complex problem is more completely dealt with in Chapter 120. Initial management might consist of closure of the omphalocele and creation of a colostomy. Preservation of intestinal length including salvage of any colon that might be attached to the bladder plate before creating a colostomy is especially important. Lund and Woo have reviewed this topic well.[164,165]

### Gastroschisis

***Initial Care*** Two features of gastroschisis make initial care somewhat different from that of omphalocele. The patient is frequently premature, and closer attention must be paid to heat preservation, respiratory support, and the large surface area of exposed intestine. The latter is also responsible for increased fluid needs and heat loss. Perhaps the best way to control this problem is to place most of the infant immediately in a plastic drawstring bowel bag to control evaporative heat and fluid loss.[166] Because in most cases the intestine will be perfectly normal immediately after delivery whether the delivery is vaginal or cesarean, the faster the bowel can be reduced, the more likely primary closure can be achieved and the less bowel wall edema and fibrinous coating will accumulate.

Previously we chose to deal with this issue by operating immediately after delivery[167] because our obstetricians preferred cesarean delivery for all children with abdominal wall defects. As more obstetricians become convinced by the literature that the route of delivery does not affect outcome in gastroschisis, fewer cesarean sections are scheduled. A review of our more recent data indicates that rapid transfer from the delivery room to the operating room (<1 hour) will also lead to a greater likelihood of primary closure.[167a] When the delivery room and the pediatric operating room are in the same hospital, this is much easier to arrange.

***Operative Technique*** Time is taken to wipe the vernix caseosa carefully from most of the baby to facilitate many of the subsequent maneuvers. If there is no immediate respiratory distress, an intravenous line is started, monitoring equipment is applied, and the patient is intubated. It is helpful to evacuate meconium from the rectum by anal dilatation. It has generally been assumed that patients with gastroschisis will have a volume deficit because of the large surface area of the mass of eviscerated intestine. Yet a recent Canadian study suggests that limiting preoperative fluid resuscitation will improve outcomes.[168] While the anesthesiologist is involved with these activities, the surgeon holds the umbilical cord up and, loop by loop, reduces the intestine. In most cases, by the time that the patient is ready for skin preparation, the bowel has been totally reduced. Other operative maneuvers and postoperative care are similar to that described for omphalocele. A satisfactory cosmetic closure can be obtained for gastroschisis by leaving the entire umbilicus intact during the initial stages of the procedure (Fig. 75-10). The vessels and urachus can be divided at the level of the peritoneum after trimming the cord. A subcuticular skin closure is then performed with the umbilicus being the left edge of the midportion of the incision, or often the entire incision, because the defect can often be quite small with gastroschisis or umbilical cord hernia.

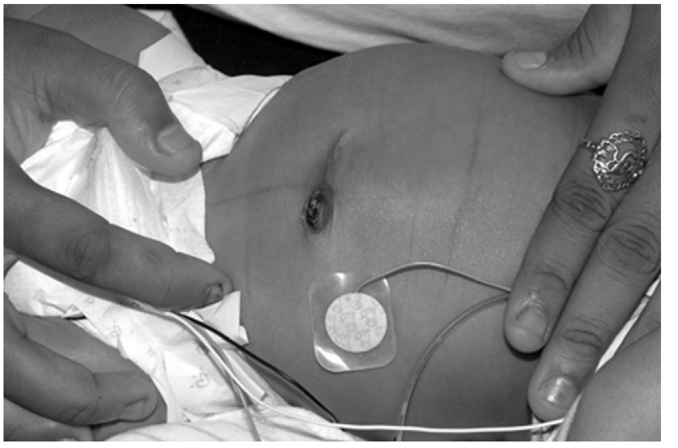

**FIGURE 75-10** Gastroschisis with cosmetic closure obtained by preserving the umbilicus.

In several centers the spring-loaded preformed Silastic pouch (Bentec bag) is frequently placed at the bedside on arrival of the patient.[169,170] Reduction can then be performed also at the bedside, and the patient is taken to the operating room only for final closure. Kidd and colleagues have found that with this technique, they perform fewer primary closures (34% vs. 84%) and have a somewhat longer length of stay (38 days vs. 30 days), but the mortality (3% excluding those with lethal associated anomalies) and time until full feeding are no different.[171] They did, however, report fewer ventilator days, infections, strictures, reoperations, and episodes of necrotizing enterocolitis. Bianchi and colleagues have also shown that waiting several hours to reduce the intestinal mass may not be as deleterious as has been supposed.[172,173] In a 2008 multicenter prospective trial comparing bedside placement of the silo to primary closure, there was a trend to fewer days on the ventilator for the bedside silo group, but no difference in days on TPN, length of stay, incidence of sepsis, or incidence of necrotizing enterocolitis.[174] A study from Stanford showed good results with sutureless closure, which is performed either initially with reduction of the bowel or secondarily after reduction of the Bentec bag.[175] The umbilical cord is laid over the small residual defect and held in place with an adhesive, microporous dressing.

Management of complicated gastroschisis must be individualized.[128] Often an atresia can simply be placed in the abdominal cavity and repaired 6 weeks after the abdomen has been closed with native tissue, whether skin or fascia. A stoma can also be brought out through normal abdominal wall lateral to a prosthesis. This usually requires sewing on Silastic sheets because the spring-loaded ring of the Bentec bag will interfere with stoma placement. The most shrunken nubbins of bowel can be surprisingly useful 2 to 3 months after residence in the abdominal cavity.[176] If they cannot be exteriorized, perforations and other complex wounds can be treated with a VAC sponge dressing.[177]

### Umbilical Cord Hernia

This defect is easily reduced by holding the sac upward and gently massaging the bowel into the peritoneal cavity. The fascia can always be closed primarily, and a cosmetic umbilicoplasty is nearly always feasible.

# Complications

Complications may be related to prematurity (in gastroschisis), associated anomalies (in omphalocele), gastrointestinal tract anomalies (in gastroschisis), and a closure that is too tight. Mention has already been made of the increased fluid needs and delayed recovery of bowel function. It is important to be prepared to treat the problems of prematurity including heat loss, respiratory failure, hyperbilirubinemia, hypoglycemia and hyperglycemia, and hypocalcemia. In managing respiratory distress it is important to obtain blood for capillary blood gas analysis from the upper extremities because the lower extremities are likely to be edematous and congested. Patients with gastroschisis and ruptured omphalocele are frequently hypovolemic. Philippart and colleagues studied fluid resuscitation in patients with both gastroschisis and omphalocele by using muscle pH as an indication of adequate perfusion and resuscitation.[178] They found that all infants needed at least 25% of estimated blood volume during surgery (17 to 80 mL/kg in 45 to 120 minutes) and required 82 to 312 mL/kg in the first 24 hours of life. Urine output is a good monitor of volume in neonates. Treatment of most of the gastrointestinal tract anomalies can be delayed. In omphalocele, the bowel may be normal enough to sustain an anastomosis, but edema accumulates in all tissues and the liver expands with the length of the operation.

A closure that is too tight can lead to ventilatory compromise, decreased venous return and low cardiac output, and oliguria. The remedy is to return the patient to the operating room to remove the fascial sutures and perform skin closure only. One may need to add a prosthesis. If a prosthesis has been used initially, it may be possible to open it at the bedside and reclose it more loosely. In omphalocele, postoperative metabolic acidosis can develop as a result of kinking of the hepatic veins from reduction of the liver. In this case, removal and refashioning of the prosthesis may be necessary.

All these patients tend to have a slow onset of bowel function, no matter how quickly the defect is reduced or how normal the bowel appears. Bowel function seems to return faster in patients with omphalocele than in those with gastroschisis.[179]

# Outcome

## SHORT TERM

The survival rate for gastroschisis is 90% in most series.[121,180] In a registry study in Texas, the survival rate of infants with gastroschisis was 93% in 1995-1997.[181] In a study from Manchester, United Kingdom, a 94% gastroschisis survival rate was obtained.[182] Of the seven patients who died, five died of overwhelming sepsis. Primary fascial closure was achieved in 80%. The median time to feeding was 30 days (range, 5 to 60 days), and the median length of stay was 42 days (range, 11 to 183 days). Those who required a silo or had associated intestinal atresia (8 of 91 patients) required more time until feeding and had a greater length of stay, but no increased mortality. In a 2010 report based on 2490 patients in the Pediatric Health Information System (PHIS) database created by the Child Health Corporation of America (Kansas City, Mo.) the overall survival was 96.4%. Associated conditions included cardiovascular 15%, intestinal resection 12.5%, intestinal atresia 11%, ostomy formation 8.3%, and pulmonary 5%.

Survival rates for omphalocele range from 70% to 95%, with most of the mortality being related to the associated cardiac and chromosomal anomalies.[180] In a report from Los Angeles, there was no difference in mortality from omphalocele for birth weight, size of the defect, or type of initial closure.[183] They also reported no significant change in mortality from 1960-1970 (23%) to 1970-1980, when it was 19%. Mortality was mainly related to associated anomalies. For their patients with gastroschisis, survival rates did increase in the more recent decade to 91%, and mortality was attributed to prematurity, bowel complications, and *Candida* sepsis associated with total parenteral nutrition.

Few patients survive any form of ectopia cordis,[184,185] but Groner does report one normally active 12-year-old who wears a plastic shield to cover the as yet unreconstructed bony defect.[186] O'Gorman and colleagues reported seven patients with pentalogy of Cantrell, of whom four survived and three were free of a ventilator.[187] Nearly all patients with caudal fold defects survive, although bowel and urinary tract function vary.[165]

## LONG TERM

In a report from The Netherlands in 2009 on 111 patients with omphalocele treated between 1971 and 2004, 20% of the patients died, almost all related to associated congenital anomalies.[188] Readmission was required at some time in 70%. The most frequent later operations were inguinal hernia, tonsillectomy, adenoidectomy, myringotomy tubes, fundoplication, bowel obstruction, malrotation, orchidopexy, and cosmetic revision of abdominal scars. Thirty percent of patients were still taking medication of some sort. Only 3 patients ever had the feeling that omphalocele interfered with their choices of activities or professions, and 10 reported that omphalocele did affect some social relationships (teasing).

Davies and Stringer interviewed 25 of 35 patients who underwent surgery for gastroschisis between 1972 and 1984 and survived longer than 1 year.[44] Their median age was 16 years. Ninety-six percent were in good health and experienced normal growth, and 35% required further surgery related to gastroschisis, two for small bowel obstruction and three for scar revision. Fifty-seven percent reported that absence of an umbilicus caused them some distress during childhood. In 25 school-aged children with gastroschisis reported from Oregon, 7 were held back a grade or enrolled in special classes, but all participated in normal physical activities.[180] Eighty-four percent of these patients reported normal bowel movements. Those with abdominal complaints were usually evaluated as nonspecific or functional. Of 22 patients who required bowel resection at the initial operation, 10 had bowel complications, whereas only 2 of the 68 without a bowel resection had such complications. Ten percent of all patients underwent further surgery for abdominal wall hernia, scar revision, or undescended testis. In 2009 the Canadian Paediatric Surgical Network reported a contemporary survival of 95%.[109]

In a combined series of omphalocele and gastroschisis reported from Oklahoma City, 94 patients had an 88% survival rate.[189] There was long-term follow-up in 61 patients for a mean of 14.2 years. Nineteen needed 31 reoperations, mainly for abdominal wall hernia and intestinal atresia. Eighty percent described their quality of life as good, but 40% were

concerned about their height and felt inadequate in sports and social activities. Many also expressed concern about the absence of an umbilicus. Another combined series with a mean age at follow-up of 8.8 years was reported by Lindham from Sweden.[190] He noted several episodes of bowel obstruction in the first year of life, recurrent abdominal pain without a specific abnormality, and some concern in girls about the scar and absence of an umbilicus. Growth and development, however, were normal.

In a study from the United Kingdom, patients with gastroschisis averaged the 32nd percentile for weight at 5 years of age and the 52nd percentile after that.[191] With complicated gastroschisis (such as gastroschisis associated with intestinal atresia), they reached only the 25th percentile. The group from Stanford[192] found that most survivors of omphalocele and gastroschisis had poor weight gain. None had gastrointestinal or metabolic problems at 3 years of age on the basis of imaging studies, fecal fat excretion, and serum chemistry. One third had IQ lower than 90, and this was related to the length of hospitalization and nongastrointestinal anomalies.

Koivusalo and colleagues from Finland sent detailed questionnaires to 75 patients older than 17 years with congenital abdominal wall defects (16 with omphalocele, 11 with gastroschisis) and received a response from 76%.[193] The only illness found more frequently than in the general population was rheumatoid arthritis in 7%. Thirty-seven percent reported some morbidity related to the scar and absence of the umbilicus, 51% had functional gastrointestinal disorders, and 12% had low self-esteem. Still, 88% reported that they were in good health, and their quality of life and educational levels were no different from that of the general population.

Adverse late cardiorespiratory and pulmonary effects are seldom found in patients with either omphalocele or gastroschisis.[179] Many children do express concern later in life about the absence of an umbilicus. Although both the short-term and long-term outlook for patients with ectopia cordis and both cephalic fold and caudal fold omphaloceles is guarded, patients with lateral fold omphalocele, umbilical cord hernia, and gastroschisis have an excellent survival rate and long-term prognosis. Most problems are related to associated conditions, not to the abdominal wall defect or its repair.

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 76

# Inguinal Hernias and Hydroceles

Philip L. Glick and Scott C. Boulanger

## History

Inguinal hernias have been recognized at least as far back as 1500 BC. What appears to be an inguinal hernia has been found on an ancient Greek statuette, and Egyptian writings describe groin bulges elicited by coughing (the Papyrus of Ebers, ca 1552 BC).[1] There is also evidence to suggest that surgery for hernias had been performed as early as 1200 BC. The Roman physician Celsus is credited with some of the earliest surgery for inguinal hernia, circa 50 AD.[1] About that same time Galen described the anatomy of the processus vaginalis; however, he believed that hernias were the result of "rupture" of the peritoneum with stretching of overlying muscle and fascia.[1] This is where the slang term for hernia, "rupture," may have had its derivation.

Modern hernia surgery began in the nineteenth century when an accurate understanding of the anatomy of the inguinal canal became available.[1] Richter, Camper, and Scarpa, among others, contributed to the field during this period. Cooper in 1804 described the transversalis fascia and pectineal ligament, or Cooper ligament. In 1811 Colles described the reflection of the inguinal ligament, and in 1817 Cloquet described the processus vaginalis and noted that it was rarely closed at birth. With a thorough understanding of inguinal anatomy, modern hernia surgery had only to await the development of aseptic techniques of surgery.

In 1870 Lister introduced the concept of antisepsis in surgery, and in 1896 Halstead began operating with gloves.[1] In 1904 Von Mickulicz took aseptic surgery one step further. These developments allowed rapid progress to be made in hernia surgery. In 1871 Marcy described an operation still in use by pediatric surgeons to this day: high ligation of an unopened sac through the external ring and tightening of the internal ring. This technique, however, had an unacceptably high recurrence rate in adults.[2] In 1887 Bassini reported his results using a technique involving opening the external oblique, high ligation of the sac, tightening of the external ring, and reconstruction of the posterior inguinal floor.[2] Along with Halsted, Bassini is credited with the development of the modern hernia repair.

## Incidence

Inguinal hernia repair remains the most common operation performed by pediatric surgeons. The reported incidence of inguinal hernia in children ranges from 0.8% to 4.4%.[3]

### AGE

Inguinal hernia most commonly presents during the first year of life with a peak during the first few months. Approximately one third of children are younger than 6 months of age at the time of operation.[3] The highest incidence of hernia is found in premature infants, 16% to 25%.[4,5] This correlates fairly well with the patency rates of the processus vaginalis. At birth 80% are patent and the rates decrease dramatically by the first 6 months of age.[6] However, all indirect hernias, regardless of age at presentation, are likely secondary to failure of the processus vaginalis to close completely during fetal and newborn development.

### SEX

Males are much more likely to have hernias, with the reported male-to-female ratios between 3:1 and 10:1.[3] Although premature infants have a higher incidence of hernia, there does not appear to be a significant gender difference at this age.[7–9]

### SIDE

Approximately 60% of hernias are right sided.[10] This is true for both males and females. In males, this is possibly the result of later descent of the right testicle than the left, but this does not explain the observation in females. Bilateral hernias are present approximately 10% of the time.[10] It has been suggested that patients with left-sided hernias are more likely to develop a right-sided hernia than vice versa.[11,12] More recent data, however, suggest that this may not be true.[13–15]

### FAMILY HISTORY

Approx 11.5% of patients have a family history.[3] There is an increased incidence in twins as well, about 10.6% in males and 4.1% in female twins.[16]

## Embryology

Indirect inguinal hernias are fundamentally the result of failure of closure of the processus vaginalis (Fig. 76-1). The processus vaginalis is an evagination of the peritoneum through the internal ring, which can first be identified during the third month of fetal life.[17] Some have suggested that formation of the processus vaginalis is a result of intra-abdominal pressure,[18] whereas others believe this to be an active process.[19,20] The intra-abdominal testis passes through the processus during the seventh to ninth months of gestation. During this time the processus elongates. Following this, the portion of the processus vaginalis lying above the testicle obliterates, closing the internal inguinal ring, while the distal portion persists as the tunica vaginalis. Failure of this to occur results in patency of the processus vaginalis and potentially an indirect inguinal hernia (if bowel or other organs can enter the processus) or a hydrocele (peritoneal fluid only). In females the canal of Nuck corresponds to the processus vaginalis and communicates with the labia majora, the female homologue of the scrotum. The canal of Nuck normally closes around the seventh month of gestation, earlier than in males.

The exact timing of closure is uncertain. Studies have suggested that up to 80% to 100% of infants are born with a patent processus vaginalis and that closure, if it occurs, is most likely to happen within the first 6 months of life.[6,21] After 6 months of age, patency rates fall more gradually and plateau generally around age 3 to 5. It also appears that the left side closes earlier than the right. Where in the processus closure begins (i.e., proximal, middle, or distal) is unknown. After closure of the processus, it persists as a cord, which subsequently disappears and becomes incorporated into the external spermatic fascia. The high rate of patency associated with undescended testis suggests that closure most commonly occurs only after descent of the testicle or that these processes are linked.

The biologic mechanisms that signal and induce descent of the testicle through the inguinal canal and obliterate the processus are for the most part unknown. Androgens appear to play a role because patency of the processus is common in androgen insensitivity syndrome. However, the processus itself has no androgen receptors. Work from Hutson and colleagues has implicated the genitofemoral nerve (GFN) and calcitonin gene–related protein (CGRP) in both testicular descent and obliteration of the processus vaginalis.[17] They have suggested that reduced CGRP release from the GFN prenatally may result in undescended testis, whereas reduced CGRP postnatally may lead to hernias and hydroceles.

Although it is clear that a patent processus vaginalis is a prerequisite for an inguinal hernia, it is not sufficient and other factors are involved. Table 76-1 provides a list of other contributing factors that have been identified.

## Clinical Features

Inguinal hernias (unless otherwise indicated in this chapter, inguinal hernia refers to an indirect inguinal hernia) are generally found by parents at bath time or during well-child examinations by their pediatricians. There is typically a history of intermittent bulge in the groin, labia, or scrotum. It is most often apparent when there is increased intra-abdominal pressure such as during episodes of crying or straining. When taking the history of present illness, it is important to sort out inguinal hernias from communicating hydroceles, undescended testis, and inguinal adenopathy. Hernias may present at birth or not until days, weeks, months or even years later, but the defect to a variable extent has been there since birth. This point becomes important to remember when asymptomatic hernias are found, in terms of the timing of surgery (i.e., not an emergency) and the activities children should be allowed to participate in while awaiting repair (i.e., no restrictions if asymptomatic).

**TABLE 76-1**
**Factors Contributing to the Development of an Indirect Inguinal Hernia**

| |
|---|
| Urogenital |
| Undescended testis |
| Exstrophy of bladder |
| Increased peritoneal fluid |
| Ascites |
| Ventriculoperitoneal shunt |
| Peritoneal dialysis |
| Increased intra-abdominal pressure |
| Repair of exomphalos or gastroschisis |
| Severe ascites (e.g., chylous) |
| Meconium peritonitis |
| Chronic respiratory disease |
| Cystic fibrosis |
| Connective tissue disorders |
| Ehlers-Danlos syndrome |
| Hunter-Hurler syndrome |
| Marfan syndrome |
| Mucopolysaccharidosis |

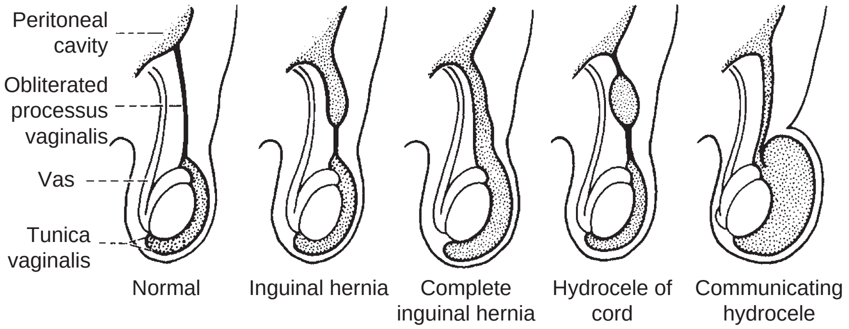



**FIGURE 76-1** The most common variants of hernias and hydroceles arising from failure of complete obliteration of the processus vaginalis.

Hernias are usually asymptomatic. Because hernias often appear during episodes of infant distress, parents often feel the hernia is the cause of these symptoms. Unfortunately, many of these perceived symptoms persist after the repair. Older children often complain of groin or inguinal "pain" during exercise.

Incarcerated hernias result from entrapment of bowel or other viscera within the hernia sac. Debate has continued as to whether "entrapment" occurs at the internal or external ring. The answer is that it can occur at both, but predominately at the level of the internal ring. This can cause intermittent pain and irritability. Subsequently, signs of bowel obstruction result, such as distension, vomiting, and obstipation. If the hernia is not reduced, blood supply to the incarcerated organ may be compromised to the point of infarction, "a strangulated inguinal hernia." The patient may present with peritonitis at this point. This process can occur in as little as 2 hours. Incarceration occurs most commonly in the first 6 months of life and after age 5 is relatively rare.

The concern in this younger population is that they are preverbal and their caretakers may not recognize the signs and symptoms of an incarceration in a timely manner. We instruct our families of preverbal infants with hernias waiting for elective surgery that the differential diagnosis of a crying baby includes (1) needs to be fed, (2) needs a diaper change, (3) needs a nap, and (4) "needs an operation" (may have an incarcerated hernia). We also instruct the families of the signs and symptoms to be aware of.

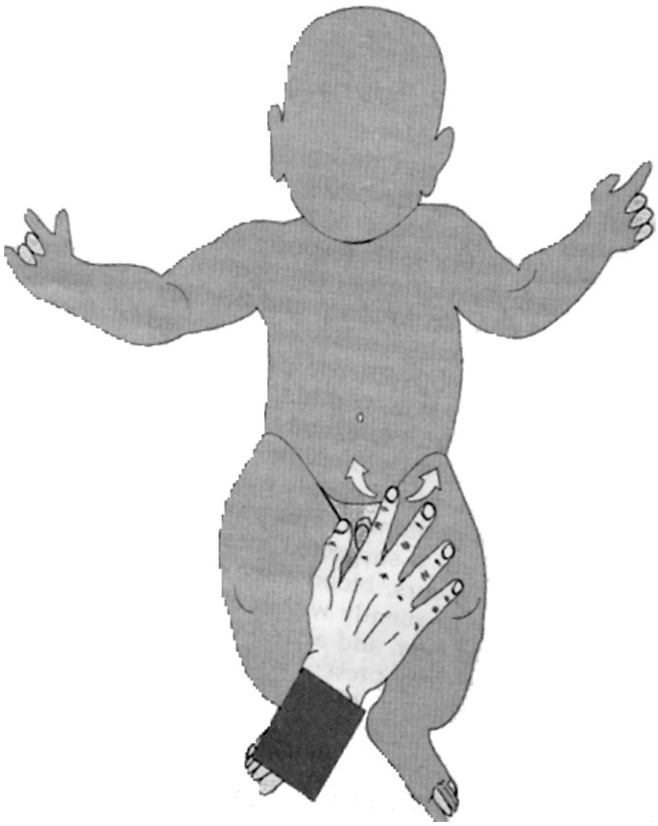


**FIGURE 76-2** Examination for an inguinal hernia. A single finger is laid over and parallel to the inguinal structures, and the finger is rubbed across the cord from side to side at the level of the pubic tubercle.

## Examination

To examine for an inguinal hernia, the patient is placed supine and undressed on an examining table in a warm room. The examiner first observes for an inguinal mass or asymmetry of the groins. The testis should be "trapped in the scrotum" with a finger across the top of the scrotum to account for both testes and to sort out true inguinal bulges from retractile testis. If no mass can be identified, the older child should stand and perform a Valsalva maneuver. An infant may be allowed to strain or cry to provoke an inguinal bulge to appear. If a mass is still not present, the spermatic cord can be palpated to determine thickening (the silk glove sign).[22] This is performed by laying a single finger over the spermatic cord at the level of the pubic tubercle. The finger is lightly rubbed over the cord from side to side over the pubic tubercle (Fig. 76-2). A positive silk glove sign indicates that the cord structures within the inguinal canal are thickened compared with the normal side. The examination imparts to the examiner the sensation of rubbing two pieces of silk together or the sensation of feeling a plastic bag with a few drops of water in it ("plastic baggy sign"), but these signs are not completely accurate and are subjective.

If a hernia is not demonstrable on physical examination, some surgeons will still operate if the hernia has been seen previously by a physician or if the parents give a thorough history.[23] However, with parental education, follow-up examinations, or modern radiologic techniques, unnecessary surgery can be avoided in equivocal cases. Additionally, advantage can be taken of photographic documentation by the parents. Kawaguchi and Shaul (2009)[24] found that they could accurately diagnose an inguinal hernia in equivocal cases using parents' digital images.

## Radiologic Investigations

In most cases the diagnosis of an inguinal hernia can be made by history and physical examination alone. However, in a small subset of patients radiologic testing may be of value. Previously, the technique most commonly used had been contrast herniography, but this has now been replaced by inguinal ultrasonography (US).

Herniography is performed by injecting water-soluble contrast material into the peritoneal cavity via an infraumbilical fluoroscopic-guided injection.[25] Gravity will allow the contrast material to pool into the hernia sac, which is identified by plain radiographs taken at 5, 10, and 45 minutes apart. Hydroceles can be identified by this technique, and femoral hernias can be differentiated from inguinal hernias. This test is also useful for detecting contralateral hernias or in postoperative patients with recurrent ipsilateral groin symptoms. It has no value, however, for incarcerated hernias because the neck of the sac is occluded in those cases. Complication rates for this technique are rare and include intestinal perforation, intramural intestinal hematoma, and allergic reactions to the contrast media.[25,26] Despite this, herniography had not found widespread use.

US has gained some popularity as an adjunct to the physical examination. It has the advantage of being rapid,

noninvasive, and complication free. Chen and colleagues[27] performed US on 244 boys presenting with either unilateral or bilateral hernias. US was performed on both groins. They noted an accuracy of 97% when using 4 mm as the upper limit of the normal diameter of the inguinal canal. In a series of 642 children, Erez and colleagues[28] noted that a preoperative measurement of the inguinal canal of $3.6 \pm 0.8$ mm was associated with normal findings at surgery, whereas $4.9 \text{ mm} \pm 1.1$ mm was associated with a patent processus vaginalis and $7.2 \pm 2$ mm or greater was associated with a true hernia.[28] Therefore using appropriate measurements, US is a reliable tool for diagnosing hernias when a good history is present, but the examination is equivocal and is potentially useful for preoperative evaluation of the contralateral groin in patients presenting with unilateral hernias (Fig. 76-3).

# Management

An inguinal hernia will not resolve spontaneously, so surgical closure is always indicated. Because of the high risk of incarceration, particularly in young infants, repair should be performed expeditiously. Some reports suggest 90% of complications can be avoided if repair is undertaken within 1 month of diagnosis.[29,30] More recently Langer and colleagues found that repair undertaken within 2 weeks decreased the rate of incarceration by half compared with a 30-day wait. Furthermore, most patients can be done safely in an ambulatory setting. Exceptions include premature infants and older children with significant risk factors such as cardiac or respiratory problems. Choice of anesthetic type varies with the patient. Although most patients are treated under general anesthesia with endotracheal intubation or laryngeal mask, several other options exist and the choice of technique depends on several factors including age and significant comorbidities.

## ANESTHESIA

As mentioned earlier, numerous techniques exist for patients undergoing inguinal hernia repair. They can be classified as general, regional, or local techniques. Healthy full-term infants and older patients are generally treated under general endotracheal anesthesia, and this has been found to be extremely safe. However, others, particularly premature infants (>36 weeks gestational age and gestational age plus chronologic age younger than 60 weeks) (see later), require a more varied approach. Regional techniques (spinal, epidural, or caudal anesthesia) are often chosen in these situations. Although each has its proponents, none has been shown to be definitively superior. A recent review of the Cochrane database found several small trials comparing regional versus general anesthesia. No statistical difference was demonstrable in the proportion of premature infants having postoperative apnea/bradycardia, respiratory rate, or postoperative oxygen desaturations. However, the total enrolled number of patients in the trials was only 108.[31]

Postoperative pain control has also been a matter of some debate. Caudal blocks are routinely performed in some centers, whereas other centers use instilled local anesthetic. A recent randomized prospective trial comparing instillation of 0.25% bupivacaine without epinephrine (2.5 mg/kg) versus caudal block found no difference in the level of postoperative

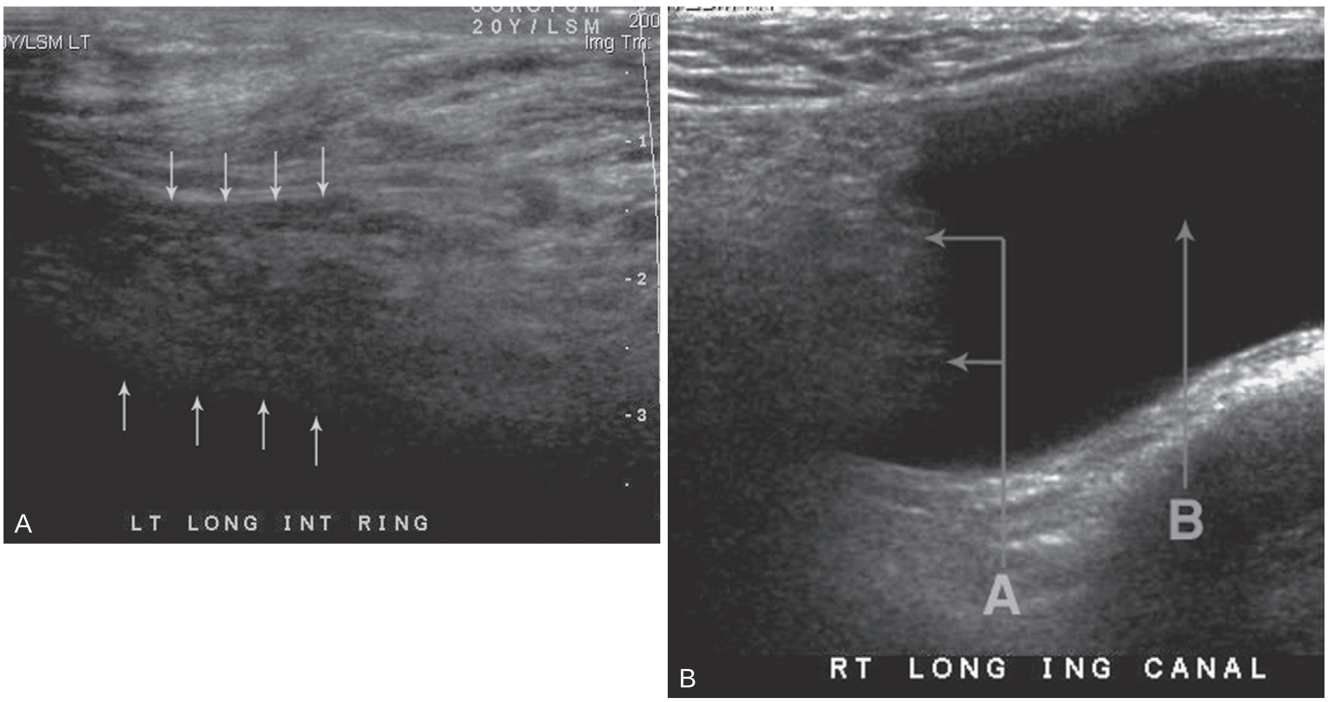



**FIGURE 76-3** Ultrasound examination of the inguinal canal. **A,** No hernia. The arrows outline the normal inguinal canal. The strands are the vas deferens and cord structures. Using Doppler imaging, signals to the scrotum and venous signals to the IVC would be seen. **B,** Inguinal hernia. The double arrow points to the leading edge of incarcerated viscera. If it were bowel, peristalsis would be evident; if it were omentum, it would not. The single arrow is fluid in the hernia sac.

pain.[32] Additionally, instillation of local anesthetic (so-called *splash technique*) is as effective as injection into the wound.

Recently concerns have been raised about the effect of anesthesia in the developing brain. Most research has been in animal models and has clearly shown the anesthetics can induce brain cell apoptosis. However, conclusions about effects on humans have been mixed. In 2009 Wilder and colleagues[33] looked at a population of children and identified that learning disabilities were more common in children younger than age 4 who had undergone general anesthesia. Similar results were found the same year by DiMaggio and colleagues[34] in children younger than age 3 undergoing inguinal hernia. This will likely remain an active area of debate for some time and affect the timing of surgery, particularly hernia repair, which is the most common general surgical procedure in this age group.

## AGE FOR OVERNIGHT STAY

Most full-term infants and older children undergo same-day hernia surgery. The age at which an ex-premature infant can safely have same-day hernia surgery is debatable. One study showed preterm infants younger than 41 to 46 weeks postconceptual age and with a history of neonatal apnea were at greater risk of postoperative apnea.[35] Another large study, using sophisticated monitoring techniques for monitoring postoperative breathing disturbances, found that infants younger than 44 postconceptual age were at increased risk of clinically significant episodes of postoperative apnea.[36] In 1995 a combined analysis from eight prospective studies was performed and concluded that the incidence of postoperative apnea was not less than 1%, with 95% statistical confidence, until 56 weeks for a 32-week premature infant and 54 weeks for a 34-week premature infant.[37] In our center we routinely use 60 weeks' postconceptual age as the cutoff (gestational age in weeks plus chronologic age in weeks). We prefer to err on the side of caution because studies to date do not allow a sufficiently accurate prediction of risk.

## TIMING OF SURGERY

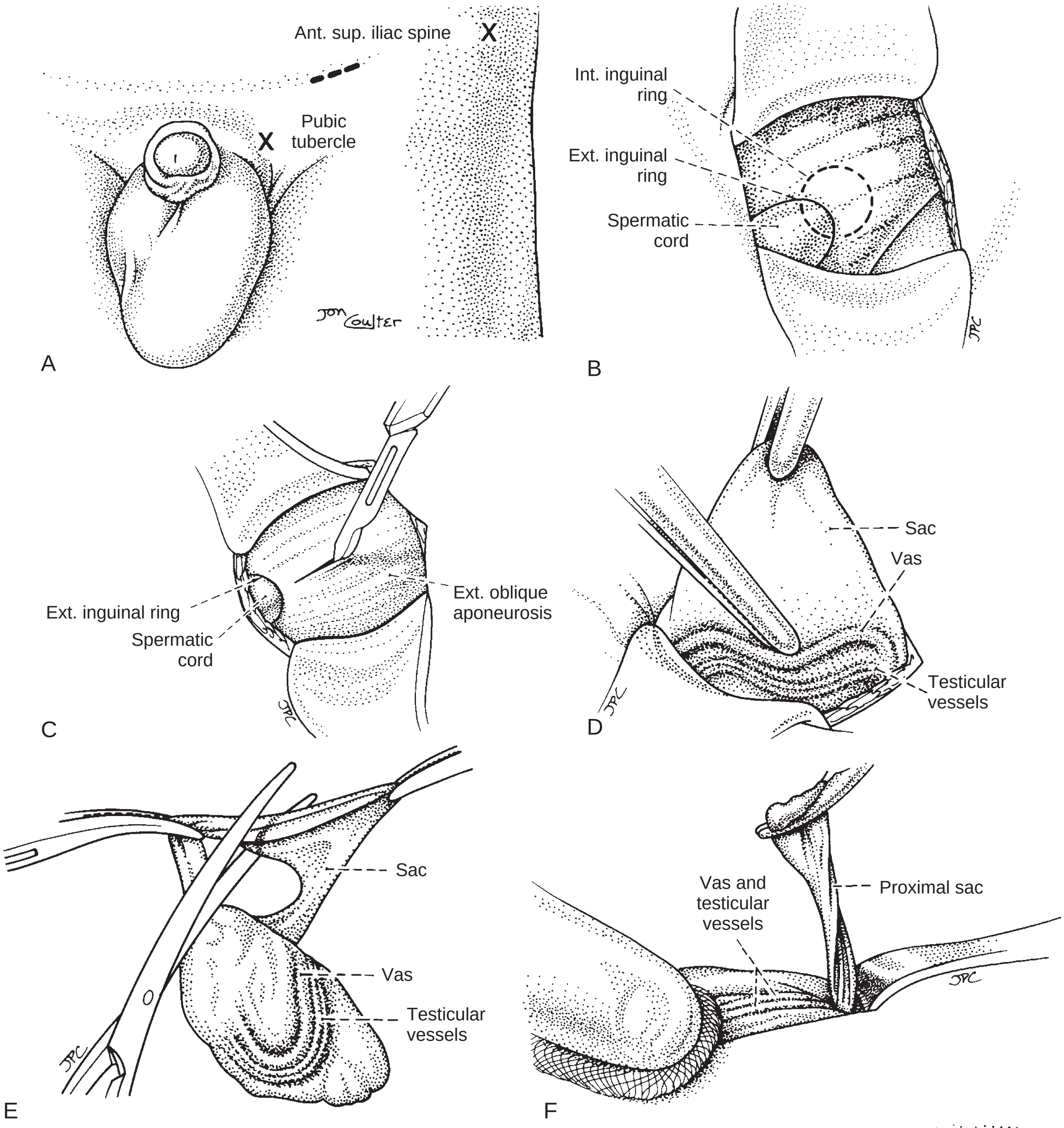
Most surgeons currently recommend repair of the hernia soon after diagnosis.[38] This practice can result in a significant reduction of complications from the hernia and is practicable because of the safety of modern anesthesia. Regarding premature infants, most surgeons recommend repair before discharge after the child has attained a weight of about 2 kg.[38] This is in contradistinction to surgical practice up to 1996, in which only 33% of surgeons polled would operate on a premature infant.[30] Langer and colleagues reviewed a series of infants and young children undergoing inguinal hernia repair. In infants younger than 1 year of age, the risk of incarceration doubled with surgical wait times of more than 30 days compared with fewer than 14.

## TECHNIQUE

The fundamental principle guiding pediatric inguinal hernia repair is high ligation of the hernia sac. A modified Ferguson repair was the procedure of choice for William Ladd and Robert Gross.[22] They preferred this type of repair to the Mitchell-Bank repair popular in Great Britain, which was a simple high ligation of the sac without opening the external oblique and exposing the internal ring. In Ferguson's repair the external oblique is opened and reconstruction of the inguinal canal is performed without altering the relation between the spermatic cord and the inguinal anatomy. In this text we describe our technique for inguinal hernia repair and highlight significant variations in the technique (Fig. 76-4).

With the patient in the supine position the midline, pubic tubercle, and anterior superior iliac spine are marked out. The pubic tubercle is a particularly important landmark because the external ring lies inferior and lateral to it. An incision is made in a skin line with the medial end of the incision just superior and lateral to the pubic tubercle. As children age, the internal ring becomes more lateral, so in infants the internal ring and external ring overlap, whereas in older children the distance between the two increases, necessitating a more laterally placed incision in the older child. Making the incision too medial in a child of any age runs the risk of dissection injury to the cord structures as they exit the external ring before finding the inguinal ligament.

The incision is carried down through the dermis to expose the subcutaneous fat, the Camper fascia. The Camper fascia is spread with scissors to expose the Scarpa fascia. Care is taken not to injure the inferior epigastric vein, which lies above the Scarpa fascia. The Scarpa fascia is then grasped and cut and then spread with scissors to expose the external oblique muscle. Once the external oblique is identified, the inguinal ligament is cleared from lateral to medial by gentle spreading down to the level of the external ring. Care should be taken to stay above the inguinal ligament to avoid injury to the femoral structures. An incision is made in the external oblique along the line of its fibers and extended by spreading with scissors. Straight snaps can be applied to the cut ends of the external oblique, near the external ring, to assist their subsequent identification and closure. The undersurface of the external oblique, superiorly and inferiorly, is then cleared off with forceps and a wet drawn-out sponge to identify the transversalis fascia, iliofemoral and ilioinguinal, nerves and cremasteric fibers. A small incision is made in the cremasterics and then they are spread apart, revealing the hernia sac. The hernia sac is grasped, taking a large gentle bite of tissue and elevating the cord structures into the wound until a clear inverted V-shaped opening underneath the sac is seen. DeBakey forceps are placed through this opening. The spermatic fascia is then bluntly opened, and the vas deferens and vessels are dissected away from the sac. The sac is then checked for contents, and the vas and vessels are then reidentified. Two clamps are then placed across the sac closely together, and the sac is divided. The proximal sac is then cleaned to the level of the internal ring, twisted on itself, and ligated at the level of the internal ring with monofilament absorbable suture. Ladd and Gross[22] had used silk suture to ligate the sac, but we have seen these silks "spit" out of the wound years after the original repair and have now switched to an absorbable suture to avoid this problem. The distal sac is not dissected because this may result in ischemic orchitis or postoperative hematomas. Noncommunicating hydroceles may be windowed open but should not be completely removed for the same reasons. Inspection of the testicle is also not mandatory. If done, care must be taken not to damage the normal insertion of the gubernaculum onto the Dartos fascia. The testis is then returned to the normal scrotal position by pulling on the scrotal skin and the Dartos fascia. The wound



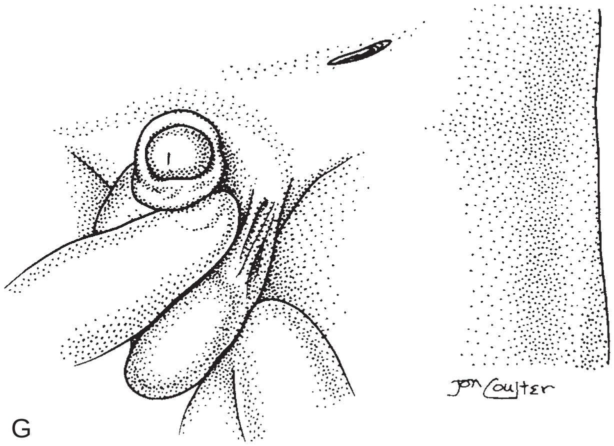




**FIGURE 76-4** Technique of inguinal hernia repair in male children. **A,** The pubic tubercle and anterior superior iliac spine are used as landmarks to place the inguinal incision over the internal ring *(dashes)*. **B,** In infants younger than a year of age the internal and external rings overlap and the inguinal canal is short. Often an incision in the external oblique is not necessary to access the internal ring. **C,** In older children the external oblique aponeurosis is incised lateral to the external ring and over the internal ring. The undersurface of the external oblique is cleared of cremasteric fibers. **D,** The cremasteric muscle is then incised and spread with scissors to expose the spermatic cord, which is then grasped and elevated. The vas and spermatic vessels are then gently separated from the white hernia sac without touching them. **E,** The hernia sac is then inspected for contents. The empty hernia sac is then sharply divided between clamps. The edges of the distal sac are cauterized, and the distal sac is dropped back into the wound. **F,** The proximal sac is then gently dissected to the level of the internal ring where the preperitoneal fat will be seen. The sac is then twisted on itself, taking care not to incorporate the vas deferens and vessels, and doubly ligated. **G,** The testis is then pulled back into position in the scrotum and the spermatid cord is straightened. A standard layered closure is then performed with absorbable suture.

is then closed in layers. The Scarpa fascia is closed with interrupted absorbable suture. We prefer a running subcuticular skin closure, but an interrupted closure is equally effective. Sterile adhesive strips (Steri-Strips, 3M, St. Paul, Minn.) are applied, and an impermeable plastic dressing is placed over the wound to protect it from stool or urine (in children wearing diapers). We have abandoned the use of collodion because of the Occupational and Safety Health Administration's issue with the ether.

## PROCEDURE IN FEMALES

The surgical repair of hernias in females is somewhat simpler than in males because there is no need to identify and preserve a spermatic cord. The surgical approach to the inguinal canal is the same in both males and females. The hernia sac is identified and inspected for contents. Often the ovary, tube, or mesosalpinx is contained within the sac (Fig. 76-5). If the sac is empty, it is divided between clamps. The distal sac is dropped back into the wound after the edges have been cauterized. The proximal sac is dissected out to the level of the internal ring, twisted, and doubly ligated. We then close the internal ring with one or two sutures by approximating the transversalis fascia to the shelving edge of the inguinal ligament and then close in standard fashion.

Before twisting and ligation, we routinely open the sac because up to 40% of indirect inguinal hernias in females have a sliding component. It is not uncommon for the ovary, fallopian tube, and/or uterus to lie within the wall of the sac and not reduce into the abdominal cavity. If the fallopian tube is not readily visibly, some surgeons will place traction on the round ligament in order to identify the fallopian tube before ligation of the sac. We also do not routinely attach the sac and the round ligament to the conjoint tendon in order to reestablish the normal support for the uterus (the Bastianelli maneuver).

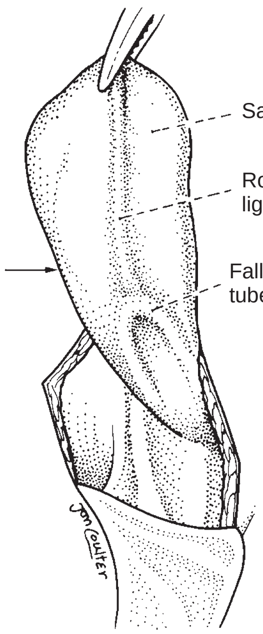



**FIGURE 76-5** Hernia sac in a female. The fallopian tube is often found in the wall of the hernias sac as a sliding hernia and must be identified. If necessary, the hernia sac is opened and the round ligament is followed to the fallopian tube.

If the fallopian tube is identified in the wall of the sac as a sliding hernia, we make no attempt to dissect it off the sac. Rather, we close the sac above the fallopian tube with a purse-string stitch, reduce the sac into the internal ring, and close the internal ring with one or two sutures, known as the Bevan repair.[39]

## LAPAROSCOPIC REPAIR

Laparoscopic repair of inguinal hernias has been fairly commonplace in adults for a number of years. Stated advantages have included less pain, earlier return to work, repair of bilateral hernias though the same ports, and easier repair of recurrent hernias. Disadvantages have included increased cost, longer OR times, and a prolonged learning curve. In addition, multiple techniques have been proposed such as transabdominal repairs and extraperitoneal repairs. For these reasons, most pediatric surgeons have considered laparoscopy for hernia repair unnecessary in children because of the small incisions already used and relative ease of repair compared with adults, as well as the minimal pain patients experience in the postoperative period with the open procedure and rapid return to normal activities. Only recently has laparoscopic repair of inguinal hernias in children become an alternative.

In 1997 El-Gohary reported a series of laparoscopic hernia repairs in 28 females.[40] In his series, the hernia sac was inverted into the abdominal cavity and endoscopic loop tries were placed at the base of the inverted sac. Because this technique does not allow exclusion of the cord structures, the authors recommended this procedure be used only in females. In 1998 Schier reported a series of laparoscopic hernia repairs in 14 females.[41] In his technique 2 to 3 intracorporeally placed Z-stitches were used to close the processus vaginalis.

Montupet and Esposito reported the first successful use of laparoscopic hernia repair in boys.[42] A laparoscopically placed purse-string stitch was placed around the neck of the sac. Care was taken to deliberately exclude the vas deferens and spermatic vessels. There were no surgical complications in 45 males, but there were two early recurrences requiring a second laparoscopic repair. In 2003 Schier[43] updated his series using the Z-stitch and included males. This procedure was performed on 279 patients with 403 hernias. He noted a 2.7% recurrence rate.

Other groups have made use of specially designed devices to pass suture extraperitoneally around the neck of the sac. Lee and Liang[44] reported 450 patients using such a device and found a recurrence rate of 0.88%, which is comparable with open repairs.[44] Prasad and colleagues reported a small series in which a commercially available curved steel awl was used to assist passage of the suture.[45]

More recent variations include the so-called SEAL (subcutaneous endoscopically assisted ligation of the hernia sac) technique in which a percutaneously placed purse-string stitch is placed under laparoscopic guidance to ensure avoidance of the cord structures.[46] In addition, single-site techniques have been used to perform laparoscopic repairs. At present no single technique has been shown to be superior to the others.

The SEAL technique at our center is performed under general anesthesia with the patient supine and a nasogastric tube and Foley catheter (or straight catheterization) in place. A 5-mm trocar

is placed transumbilically and pneumoperitoneum established. A laparoscopic inspection is then performed. Bilaterality, as well as unusual hernias such as femoral and direct hernias, are easily identified. The level of the internal ring on the abdominal wall is then identified with a finder needle. A small nick is made in the skin with a knife, and a 2-0 Ethibond suture is placed through the incision to purse-string the internal ring, taking care to exclude the cord structures. This is done either by skipping over them or dissecting them away from the peritoneum with the needle tip. The dissection of the cord structures from the peritoneum can also be accomplished by hydro-dissection by inserting a hypodermic needle retroperitoneally lateral to the cord and injecting bupivacaine hydrochloride (Marcaine). This elevates the sac completely off the cord. Dissection can also be performed with the tip of the suture needle when passing over the cord. The needle is then brought out to the skin at a separate point and tracked back subcutaneously to the original skin nick. The stitch is then tied down to close the ring. A 3-mm instrument can be placed through a small trocarless incision to assist exclusion of the cord structures if necessary. Published recurrence rates with this technique are between 1.5 and 4%.[47,48]

As mentioned earlier, several alternative techniques are available. One of the most straightforward may be that reported by Prasad and colleagues in 2003.[45] In their technique an umbilical port is placed for the camera and is the only port used. The level of the internal ring on the abdominal wall skin is determined by palpation, and a small skin nick is made with a knife. Under direct laparoscopic guidance a purse-string suture is placed halfway around the internal ring using an extracorporeal needle driver, and the needle is left in the abdomen. A curved, steel awl is used to come around the other half of the ring through the same skin nick, taking care to avoid injury to the cord structures. The awl is used to grasp the needle and pull it back out, completing the purse-string. The knot is tied extracorporeally, and closure of the internal ring is confirmed by the laparoscope.

In one of the largest laparoscopic series, Endo and colleagues[49] in 2009 reported retrospective outcomes on 1257 children using an extroperitoneal technique similar to the awl technique described earlier. Their follow-up ranged from 1 month to 11 years, and recurrence rate was 0.2%. Lower recurrence rates seem to be a consistent feature of extraperitoneal techniques as compared with intraperitoneal ones.

We tend to favor extraperitoneal techniques as described earlier for reasons of cosmesis (no or few port sites needed) and safety (ability to identify and exclude cord structures), as well as possible lower recurrence rates compared with both laparoscopic intraperitoneal approaches and open hernia repair. Moreover, these extraperitoneal techniques are not technically demanding and can be performed by surgeons unaccustomed to laparoscopy. Numerous variations exist and are beyond the scope of this chapter to review. But it appears that the evolution of laparoscopic hernia repair in children is tending toward extraperitoneal repairs and away from intra-abdominal approaches, as well as to fewer and fewer port sites.

Despite the growing number of reported series of laparoscopic repair, there are only two randomized prospective studies comparing laparoscopic repair with open repair, both of which have small patient numbers and limited follow-up. Chan and colleagues[50] randomly assigned 83 patients to open versus laparoscopic repair in 2005. They scored pain and parent assessment of recovery and cosmesis, both of which favored the laparoscopic repair. Their technique uses a transcutaneously placed suture similar to the SEAL technique described earlier. The other study randomized 89 patients to open versus intraperitoneal laparoscopic technique based on the technique of Schier. This study found no significant differences in outcome and recovery or cosmesis. They did not report that the laparoscopic repair was associated with longer operating room times and increased pain.[51]

In females we prefer to use a laparoscopic inversion ligation technique, "LIL repair," because there is no need to be concerned about cord structures. Ports sites are chosen as for males.[52] A bowel grasping or Maryland clamp is placed into the hernia sac, and the apex is grasped and inverted into the abdominal cavity (Fig. 76-6). The sac is twisted on itself, and two ligatures (Endoloops, Ethicon Endo-Surgery, Cincinnati) are placed at the base to ligate the sac. Care needs to be taken when twisting the sac so that adnexal structures are not caught up in the high ligation. We have noted no recurrences in our series, and surgical complications are

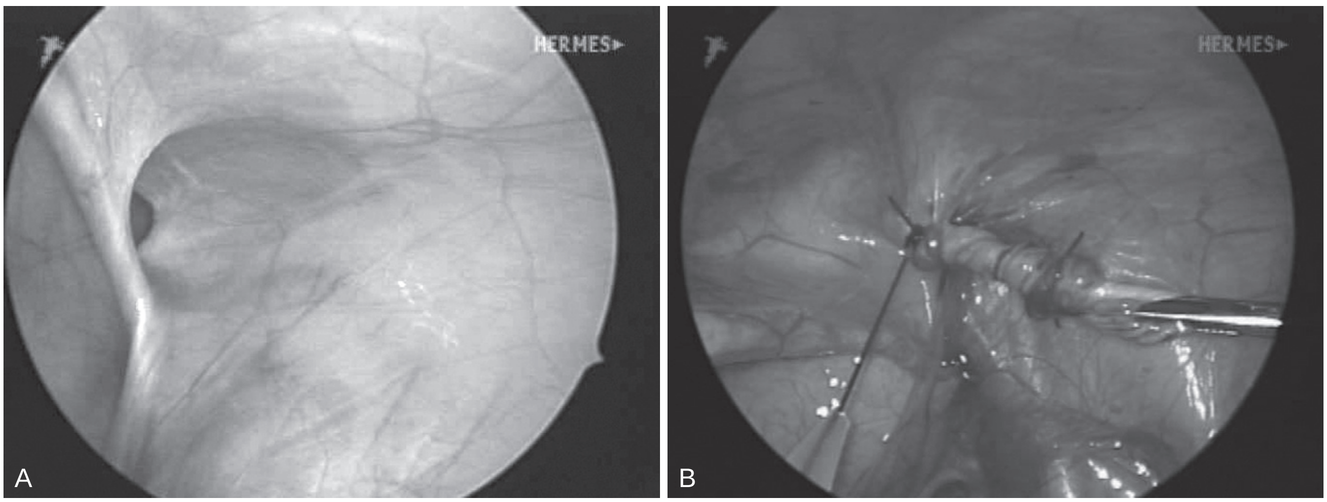



FIGURE 76-6 Laparoscopic view of the processus vaginalis. **A,** Open processus. **B,** Processus inverted into peritoneal cavity and ligated with Endoloops.

quite low. Another simple variation of this involves the use of electrocautery to destroy the inverted sac (personal communication).

## Contralateral Exploration

In 1955 Rothenburg and Barnet[21] reported that 100% of infants younger than 1 year of age and 68.5% of children older than the age of 1 year had bilateral inguinal hernias.[21] Since this report, routine bilateral exploration has been one of the most contentiously debated issues in pediatric hernia surgery. The application of laparoscopy to the diagnosis of bilaterality has recently added to the debate.

Because of the high rate of contralateral hernias, Rothenberg and Barnet recommended routine exploration of the contralateral hernia. What they were seeing, however, was clearly not a contralateral hernia, but rather a patent processus vaginalis. Although many surgeons have supported routine exploration, others have noted that there is a high negative exploration rate because not every patent processus will develop into a clinical hernia. In addition, routine exploration puts both testicles and both vas deferens at risk. Even so, Rowe and Marchildon,[23] in a survey of pediatric surgeons in 1981, found that 80% of surgeons routinely performed contralateral exploration in boys, and 90% did so in females younger than 1 year of age.[23] However, a more recent survey suggests a trend away from routine contralateral exploration. Only 40% of recently surveyed pediatric surgeons routinely explore males younger than 2 years of age and only 13% routinely explore boys between the ages of 2 and 5. Thirty-nine percent routinely explored females, and 51% routinely explored premature infants. This survey also highlighted another trend reporting that 24% of surgeons use laparoscopy to investigate the contralateral side.

We believe that routine exploration of the contralateral side results in a large number of unnecessary procedures, needlessly places the contralateral vas and testicle at risk, and is an unwarranted expense. We base that judgment on the fact that while up to 60% to 80% of infants younger than age 1 and 40% of older children will have a patent processus, only about 20% of patients presenting with a unilateral hernia will develop a clinical hernia on the other side.[6,10,29] Therefore one would need to perform approximately 10 operations to prevent two future hernias. Because of this fact, many surgeons have abandoned routine contralateral exploration on the basis of age of the patient, sex of the patient, or side of the hernia.

### SEX

Historically, many surgeons have performed bilateral exploration on females, primarily on the premise that routine bilateral exploration poses little risk to the patients because of the relative rarity of finding reproductive structures in the sac. In a survey of surgeons in 1981, Rowe and Marchilidon reported that 90% of surgeons routinely explored the contralateral groin in girls younger than 1 year of age.[23] Weiner and colleagues[30] surveyed surgeons in 1996 and found that 84% performed routine exploration in females younger than age 4.[30] It appears that this trend is decreasing because Levitt and colleagues[38] 2002 found that only 39% of surgeons performed bilateral exploration in females younger than age 5. Despite the rare findings of reproductive structures in the hernia sac, damage to the inguinal floor and to the ilioinguinal and iliofemoral nerves still exists and is generally ignored in arguments for contralateral exploration. Because little follow-up data exist in the literature, it is difficult to quantify these risks. It is evident that only about 20% of females with a unilateral hernia will develop a contralateral hernia. Thus a large number of explorations would be necessary to prevent a few hernias from developing. Puri and colleagues recently reviewed 300 females undergoing unilateral hernia repair.[53] In a follow-up ranging from 1 to 4 years, only 8% developed a contralateral hernia and this was not influenced by age at operation of side of initial hernia.

### AGE

On the basis of the findings of Rothenberg and Barnet[21] that 100% of infants younger than 1 year of age will have bilateral patent processus vaginalis, many surgeons routinely perform contralateral exploration in infants. In the most recent survey, 51% of surgeons routinely perform contralateral exploration in premature infants and 40% perform contralateral exploration in boys younger than 2 years of age.[38] This is considerably less than reported from the 1981 survey in which 80% routinely explored the contralateral side in boys.[23] In a large series of 1052 patients followed up to 11 years, contralateral hernias appeared in 13.1% of boys younger than 1 year of age and 13.7% younger than 2 years of age. In females contralateral hernias appeared in 9.6% of patients younger than 1 year of age and 13.9% of patients younger than 5 years of age. Another recent series looked at 181 infants younger than 1 year of age undergoing unilateral repair. Contralateral hernias developed in 7.7% in follow-up ranging from 5 to 10 years. On the basis of these results, it is not completely clear that younger children have a significantly higher chance of developing a contralateral inguinal hernia.

### SIDE AND SIZE

It is speculated that right-sided hernias are more common than left because the right processus vaginalis closes later than the left side. Therefore patients presenting initially with a left-sided hernia would seem to be more likely to have bilateral hernias than those patients initially presenting with a right-sided hernia. As a result, many surgeons recommended routine exploration in patients presenting with left-sided hernias. McGregor and colleagues[12] reviewed a 20-year experience and found that 41% of patients having an initial left inguinal hernia presented with a right hernia, whereas only 14% of patients developed a left inguinal hernia after the right side was repaired.[12] Other series, however, have reported much lower rates of contralateral occurrence after left-sided repair. For example, Kemmotsu and colleagues[54] reviewed 1052 patients who had undergone unilateral repair and found that the side of initial repair did not influence contralateral recurrence.[54] Miltenburg and colleagues[55] found in a meta-analysis that the risk of contralateral hernia repair was 11% (50%) higher than if the initial hernia had been on the right.[55] Overall, it appears that the side of the initial hernia has no bearing on the risk of developing a contralateral hernia.

## LAPAROSCOPY

In an effort to limit the number of negative contralateral explorations, alternative techniques have been used to determine the patency of the contralateral processus. These have included diagnostic pneumoperitoneum (the Goldstein test) in which the abdomen is insufflated via the hernia sac and the contralateral groin is palpated for crepitance, indicating a patent processus vaginalis. A recent study by our group of 62 patients found 11% had a positive study (7 patients).[56] Each underwent exploration and was found to indeed have a contralateral patent processus vaginalis. Of the 55 patients with a negative Goldstein test, only 3 (5%) have subsequently developed a clinical hernia. In our opinion this technique is both safe and reliable. However, others have found that this test is unreliable and often misses patent processes. Bakes dilators have been used to probe the contralateral groin, but this technique is often difficult and unreliable. Herniography has been discussed previously and is rarely used today. Ultrasound has also been discussed previously and found to be fairly sensitive for the presence of patent processes vaginalis when appropriate-size criterion are used.

In the early 1990s laparoscopy was introduced as a means of assessing the contralateral inguinal canal. Laparoscopy has the advantage of being technically easy and allows direct visualization of the contralateral internal ring. And with the increasing popularity of laparoscopy, the equipment is widely available.

Laparoscopy can be performed in a variety of ways. Perhaps the most common technique is to place a port through the ipsilateral hernia sac to insufflate the abdomen and introduce the camera. Evaluation of the contralateral side is made easier by the use of an angled scope (e.g., 70 degrees). Others have introduced the camera via an umbilical port or placed the small cameras through an angiocatheter placed through the abdominal wall to give in-line visualization. Also, both flexible and rigid scopes have been used.[57]

Yerkes and colleagues[58] evaluated 627 patients younger than age 10 with unilateral hernias during a 5-year period for the presence of a contralateral patent processus vaginalis (CPPV) with laparoscopy. Of the patients younger than age 1, 46% were diagnosed with a patent contralateral processus, while 39% older than age 1 had a CPPV. Geisler and colleagues[59] evaluated 358 patients ages 1 month to about 13 years and determined an overall incidence of CPPV of 33%.[58,59] Positive findings were in 50% of patients younger than age 1, 45% younger than age 2, 37% younger than age 5, and 15% older than age 5. Pellegrin and colleagues[60] studied 50 patients and found an overall incidence of CPPV of 31%, while Rescorla and West[61] reported a 48% overall incidence of CPPV. Overall laparoscopy has shown a fairly consistent rate of CPPV, approximately 30% to 45%.

The question becomes, which of these CPPVs will become clinical hernias? The answer, of course, is not known and would most likely require a randomized prospective trial with essentially life-long follow-up, a practical impossibility. However, Kiesewetter and Parenzan[62] performed routine contralateral exploration of 100 infants younger than 2 years and found a 61% incidence of CPPV. Next, they closely followed 231 patients after unilateral repair only and found that 31% went on to develop a hernia, approximately half of what would be expected. On the basis of this information and data from Rowe and Clatworthy, one would expect that laparoscopy would decrease the number of unnecessary procedures from about 1 in 8 to 10 for routine exploration to 1 in 2 for laparoscopic cases, a significant improvement.[63]

Opponents of laparoscopy will point out that at least half the patients will receive a procedure they do not need (not counting any patients with false-negative laparoscopy). Moreover, when factoring in time and equipment, there is a significant increase in cost. With the increasing use of reusable equipment and the decreasing use of disposables, this cost and time factor has been shown, however, not to be as significant as previously thought.

As children age, the rate of CPPV clearly decreases. Is there, then, an age after which laparoscopy is no longer valuable? Bhatia and colleagues[64] studied 101 children between ages 2 and 8 compared with 171 younger than age 2. Thirty-eight percent younger than age 2 had a CPPV, while 20% older than age 2 were positive. In a group of 12 patients older than age 8, only 1 was positive. The authors concluded that laparoscopy is justified in children older than age 2 but could make no conclusion about children older than age 8 because of a small sample size. In the Geisler and colleagues[59] study, CPPV was reported in 15% of patients older than age 5. It seems likely that somewhere in the age 5 to 8 range there will be a significant decrease in return for laparoscopy.

# Nonreducible Hernia

Most inguinal hernias are readily reducible into the abdominal cavity. Those that are difficult to reduce are "incarcerated." A strangulated hernia occurs when there is vascular compromise of the entrapped viscera. This results from constriction by a tight internal or external ring. Most children will progress rapidly to strangulation if the hernia is not reduced. This process can take as little as 2 hours. Initially, constriction by the ring leads to venous and lymphatic obstruction and subsequent swelling of the viscera. Arterial compromise then occurs, and, if the process is unchecked, will lead to gangrene and perforation of the bowel or other viscera. Incarceration and strangulation can also damage the testicle by compromising the blood supply to the testis. Patients with incarcerated hernias are more likely to have testicular atrophy after hernia repair.

Various series have reported the incidence of incarceration to be in the range of 12% to 17% and seem to be similar in boys and girls.[63,65] Incarceration is most likely to occur in the first year of life and then falls off thereafter (Fig. 76-7). Interestingly, the data in premature infants suggest that they are less likely than full-term infants to have an incarceration, even though the incidence of hernia is higher in this subgroup. Full-term infants younger than age 2 to 3 months were found to have a rate of incarceration of 28% to 31%[63,66] and 24% in infants younger than 6 weeks of age.[67] Interestingly, premature infants were found to have a lower incidence of incarceration compared with full-term infants (13% to 18%). This may be a result of larger rings and, therefore, less chance of viscera becoming entrapped. Also, many of these infants are in neonatal intensive care units under constant surveillance; incarcerated hernias may be prevented by early reduction or may simply be underreported as caretakers in the nursery reduce them.

## DIAGNOSIS

If a loop of bowel becomes entrapped in a hernia, the patient often becomes extremely irritable and develops intense pain followed by signs of obstruction (e.g., abdominal distension, vomiting, absence of flatus/stool). A tense, nonfluctuant mass will be found in the groin, possibly extending into the scrotum. As the viscera strangulate, the mass becomes more and more tender. Occasionally the mass will transilluminate and be confused with a hydrocele. Under no circumstances should the mass be aspirated in an attempt to diagnose and treat a supposed hydrocele.

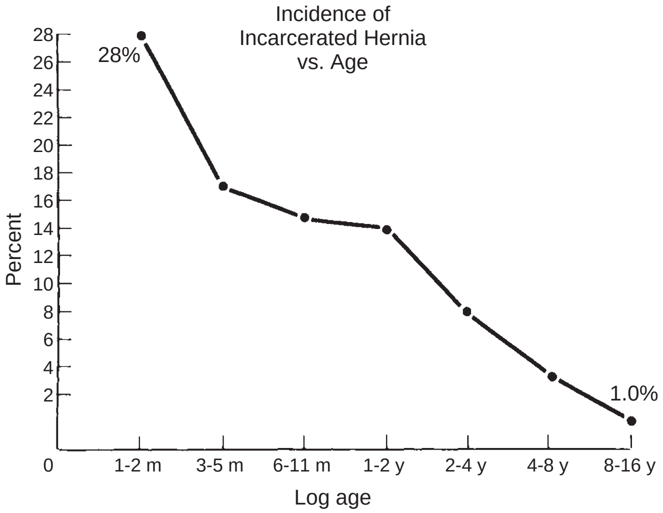



**FIGURE 76-7** Incidence of incarcerated hernias versus age. Incarceration is most common within the first year of life and then drastically decreases.

Late signs of a patient with a strangulated hernia are those of shock, blood in the stool, and peritonitis. The testes are usually palpable, but occasionally they can be large and firm and difficult to distinguish from a testicular torsion. Abdominal radiographs reveal a partial or complete bowel obstruction. Bowel gas may also be seen in the scrotum. In uncertain cases ultrasound can be useful to distinguish bowel from hydrocele fluid or a testicular torsion.

## NONOPERATIVE MANAGEMENT

In patients without obvious signs of shock or peritonitis, nonoperative management is first attempted. We prefer the following technique (Fig. 76-8). Lay the child down and try to calm him or her without feeding with the feet elevated if possible. Standing on the ipsilateral side of the child, or at the feet of an infant, place the left index and middle finger on the ipsilateral anterior superior iliac crest and sweep the fingers down along the inguinal canal toward the ipsilateral scrotum, keeping tension on the testicle in the male child, inguinal mass, or scrotal

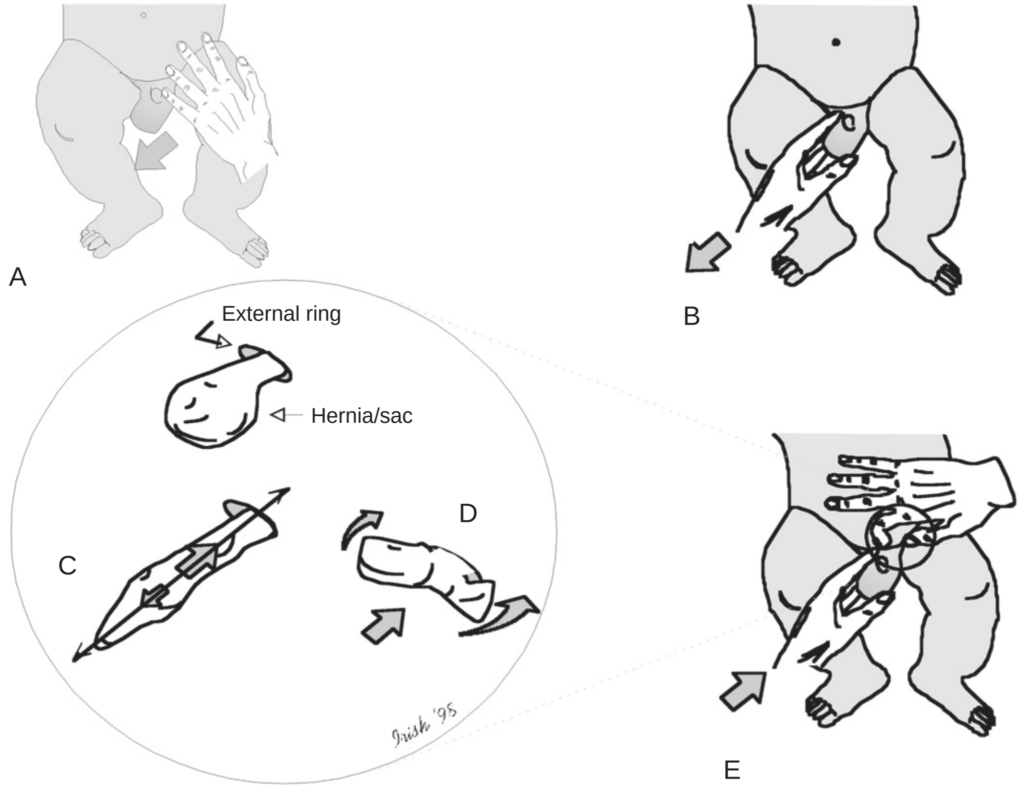



**FIGURE 76-8** Suggested method of reduction of an incarcerated inguinal hernia. **A,** Standing on the ipsilateral side of the child or at the feet of an infant, place the left middle and index finger on the ipsilateral (left in this example) anterior superior iliac spine and sweep your fingers down along the inguinal canal, toward the ipsilateral scrotum. **B,** Keep tension on the testicle, hernia mass, or scrotal skin with the right hand. **C,** Constant, gentle traction on the scrotum helps align the long axis of the hernia with the axis of the inguinal canal. Next, apply pressure with the right index finger and thumb on either side of the hernia neck. **D,** This, along with traction on the scrotum, helps to keep open the external and internal rings and prevents the hernia sac from overlapping or being caught on these potential barriers during reduction. **E,** Finally, with the left hand at the apex of the mass, and with constant pressure on the inguinal canal from your right index finger and thumb, walk your fingers slowly up the groin toward the internal ring, keeping constant pressure on the bottom of the hernia contents.

skin with the left hand. Constant gentle traction on the scrotum or labia majora helps align the long axis of the hernia sac with the axis of the inguinal canal. Next, at the level of the ipsilateral internal ring, apply pressure with the right index finger and thumb on either side of the hernia neck. This, along with traction on the scrotum, helps to align and to keep open the external and internal rings. It also prevents the hernia sac from overlapping or being caught on these potential barriers during reduction. Finally, with the left hand at the apex of the mass, and with constant pressure at the level of the internal ring from the right index finger and thumb, walk your left fingers slowly up the groin toward the internal ring, keeping constant pressure on the bottom of the hernia contents. This may take several minutes. If successful, the hernia contents will gradually disappear into the internal ring. To be certain it is reduced; compare it with the contralateral side. Use a mirror image technique for the right side. If this technique is unsuccessful or the child has a difficult time tolerating it, sedation may be used. We do not recommend reduction of the bowel under general anesthesia because injury to the bowel may occur or gangrenous bowel may be placed back into the peritoneal cavity and be unrecognized. Often sedation alone may be sufficient to promote spontaneous reduction. Reduction of gangrenous bowel has been reported, so we recommend watching the child in the hospital for 24 hours after a difficult reduction.[68] We delay definitive repair of the hernia for at least 24 to 48 hours to let the edema resolve.

## OPERATIVE MANAGEMENT

In those situations where nonoperative management fails or the patient has signs of shock or peritonitis, surgery is indicated. The patient is prepared for surgery in the standard way. Intravenous fluids are initiated, and urine output is monitored. Broad-spectrum antibiotics are given, and if signs of obstruction are present a nasogastric tube is placed. When the patient is adequately resuscitated, the patient is taken to the operating room. If the hernia reduces after the general anesthetic is induced, but before surgery, the operation should still proceed. Several operative approaches have been advocated for incarcerated hernias including inguinal approaches and preperitoneal approaches. The use of laparoscopy can also be valuable in the management of incarcerated hernias.

### Inguinal Approach

The approach is that of a standard inguinal hernia repair, except that the incision is somewhat longer. The external ring is opened, and the hernia sac is identified. If the hernia contents are still present, they are inspected. If viable, the contents are reduced back into the peritoneal cavity and the hernia is repaired in a standard fashion. If the intestine cannot be reduced, then the inferior epigastric vessels are ligated and the floor of the inguinal canal is taken down to enlarge the internal ring. After repairing an indirect inguinal hernia, a formal floor repair will be required in these instances.

If the bowel in the hernia sac is of questionable viability, then it can be covered with a warm moist sponge and reinspected in a few minutes. Again, if the internal ring is constricting, it can be enlarged, taking care not to let the bowel slip back into the peritoneal cavity. If the bowel is determined to be nonviable, it can be resected and primarily reanastamosed through the inguinal incision, through a counter incision through the transversalis fascia (La Roque incision), or through a separate abdominal incision.[69] If the bowel is viable, it is replaced into the peritoneal cavity and the hernia repair proceeds.

Difficulty arises if the hernia contents reduce before they can be inspected. In this instance the hernia sac is inspected and opened. If no evidence of bowel infarction such as bowel contents or foul-smelling or blood-stained fluid is identified, many surgeons proceed with repair. Laparoscopy can be used in these instances to determine bowel viability, with the camera placed either in the umbilical position or through the hernia sac. In fact, a camera can be placed at the beginning of the procedure and the hernia contents reduced under laparoscopic visualization.[70] If the contents are viable, then a standard hernia repair is performed. If the bowel is questionable, it can be laparoscopically reinspected after the hernia repair. If it is clearly nonviable, then the intestine can be brought out through the umbilical port site and resection performed.

### Preperitoneal Approach

Some surgeons prefer a preperitoneal approach to incarcerated hernias. This approach, described for adults by Cheatle in 1921, has been used successfully in children.[71] A recent series of 24 patients described by Kamaladeen and Shanbhogue and another of 12 patients described by Turnock, Jones, and Lloyd found the preperitoneal approach to be easier in terms of reducing the hernia contents and performing the herniotomy.[72,73] If necessary, the peritoneum could be opened to determine bowel viability.

The preperitoneal approach is performed through a skinfold incision at the level of the anterior superior iliac spine, and a standard grid-iron approach is used to reach the preperitoneal plane. The internal ring and hernia sac are identified lateral to the inferior epigastric vessels. The peritoneum is then opened at the base of the hernia sac, and the contents are inspected. Nonviable bowel can be readily dealt with through this incision. Otherwise, the bowel contents are reduced back into the peritoneal cavity and the herniorrhaphy is performed. Should the external ring prevent reduction, one can simply dissect superficially to the external oblique down to the external ring and enlarge it. Once the herniorrhaphy is performed, the wound is closed in the standard fashion. This incision resembles an appendectomy scar on the right side, so the parents should be warned of this.

### Pfannenstiel Approach

Koga and colleagues have recently proposed a Pfannenstiel[74] approach to incarcerated hernias. They perform a Pfannenstiel skin incision followed by a midline fasciotomy. The bowel is reduced and inspected through the fasciotomy, and if resection is necessary, there is excellent exposure through this incision. The hernia sac can also be easily repaired through this incision. The authors also suggest that this approach leaves a cosmetically acceptable scar.

Our preferred approach is to perform laparoscopy through an umbilical port, reduce the hernia contents under laparoscopic visualization, and perform subsequent herniotomy through a standard inguinal incision. There are no reports to date of a complete laparoscopic approach to incarcerated hernias in children.

Special mention must be made of the female patient with an asymptomatic incarcerated ovary in her hernia. Historically

many believed that this incarcerated, mobile, nontender ovary was of long-standing duration and was not at risk for strangulation. Subsequent reports have challenged this idea.[75] The consensus is that these hernias should be done urgently in the next 12 to 24 hours after discovery.[38]

# Postoperative Complications

## SCROTAL SWELLING

After hernia repair and particularly communicating hydrocele repair, fluid may accumulate in the distal sac, forming a noncommunicating hydrocele. Usually this resolves spontaneously: rarely, aspiration or secondary scrotal hydrocele repair may be necessary. Scrotal hematoma may follow excision of the distal sac.

## IATROGENIC UNDESCENDED TESTICLE

Iatrogenic undescended testis after hernia repair is an uncommon but possibly underreported complication. Kiesewetter[76] reported 2 patients with this abnormality in a series of 248 patients, and Hecker and Ring-Mrozik[77] reported 5 patients in a series of 1957 patients, an incidence of 0.2%. Except in the case of congenital undescended testicle, this abnormality results from failure to replace the testis back in the scrotum at the conclusion of the procedure or the testis subsequently trapped in a retracted location. Secondary orchidopexy is required to correct this problem.

## RECURRENCE

It is difficult to determine the precise incidence of recurrence after indirect inguinal hernia repair because factors such as sex and incarceration are not always clearly defined in reported series. In general, the reported recurrence rate for uncomplicated hernia repair is 0% to 0.8%; this rises to about 15% for preemies and about 20% after operation for incarcerated hernias. In many series, patients were not contacted for long-term follow-up; therefore the true incidence is not known and is probably higher than stated. Reports on patients with incarcerated inguinal hernias do not state whether the initial management was operative or nonoperative.

Many factors associated with the development of primary hernias may also predispose to recurrence. For instance, Grosfeld and Cooney, in a series of 25 patients with ventriculoperitoneal shunts, identified three recurrent inguinal hernias (12%).[78] Incarceration is also an important risk factor for recurrence. Steinau and colleagues[79] found that in 24% of 29 patients (25 boys, 4 girls) with a recurrent inguinal hernia, the primary hernia had been incarcerated compared with 7.6% incidence of recurrence in 2754 patients without incarceration. Other risk factors in their study were postoperative complications (9.4% recurrence rate) and concomitant diseases and abnormalities.[80] Interestingly, Harvey, Johnstone, and Fossard found that the level of experience of the surgeon was not a factor, although technical inadequacies contributed to recurrence.[81] Most recurrent inguinal hernias are indirect and probably result from tearing of a friable sac, failure to dissect the complete sac, a slipped ligature at the neck of the sac, or failure to ligate the sac high at the internal ring. Another risk factor for recurrence is prematurity. Several series of inguinal hernia repairs in premature infants have reported increased recurrence rate ranging from 2% to about 15%. Large hernias and inadvertent opening of the hernia sac during surgery have also been noted to increase recurrence.[82] Interestingly, in 2006, Ein and colleagues[83] did not note significantly increased recurrence rates in premature infants, but rather in teenagers.

Less frequently, a "recurrence" presents as a direct inguinal hernia or a femoral hernia missed and not properly diagnosed and repaired at the first operation. Of the 34 recurrences reported by Steinau and colleagues,[80] 4 were direct and one was femoral. In the Fonkalsrud, Delorimier,[84] and Clatworthy series of 14 direct inguinal hernias, 4 (31%) followed repair of an indirect hernia. A direct hernia following repair of an indirect hernia is either a concomitant hernia not recognized at the initial operation or new pathology caused by damage to the posterior wall of the inguinal canal during the initial dissection. A recurrent hernia in the femoral area is also likely to have been a missed hernia rather than a true recurrence.

Several large series now exist of laparoscopic inguinal hernia repair in children. Schier reported 403 inguinal hernia repairs on 279 patients and had a recurrence rate of 2.3%.[85] The technique of laparoscopic inguinal hernia repair varies from surgeon to surgeon and is still in evolution. Moreover, there is likely to be a learning curve with the laparoscopic techniques, such that recurrences are more likely to be higher earlier in one's experience. In our early experience with laparoscopic hernia repair in males, we found recurrences to be quite high and subsequently abandoned the intraperitoneal technique and adopted an extraperitoneal technique. However, in females, using the previously described LIL repair, we have had no recurrences.

## INJURY TO THE VAS DEFERENS

Although vas transection may be obvious interoperatively, accidental operative crush injury to the vas deferens is unlikely to be recognized until adulthood and possibly then only if the injury is bilateral. Vas transections should be immediately repaired with two to three simple monofilament 8-0 absorbable sutures placed with the aid of interoperative magnification. Sparkman[86] reported an incidence of proven injury to the vas deferens of 1.6% on the basis of finding "segments of the vas deferens" in 5 of 313 hernia sacs from children who had undergone hernia repair. Details of the five cases were not published, however, and no histologic or clinical information is available. Walker and Mills found small glandular inclusions in approximately 6% of hernia sacs from prepubertal boys, which they believe to be müllerian duct remnants and not segments of the vas deferens.[87] They emphasized that these structures were of no clinical significance. It is likely that similar structures accounted for some of the findings reported by Sparkman. Perhaps a better estimate is provided by Steigman, Sotel-Avila, and Weber,[88] who reviewed the histology of hernias sacs submitted from 7314 males undergoing hernia repair over a 14.5-year period. Seventeen cases contained vas deferens (0.23%); 22 had epididymis (0.3%), and 30 had embryonal rests (0.4%). Three sacs contained coexisting vas deferens and epididymis. Either vas or epididymis was found in 0.53% of sacs. Also, Patrick and colleagues[89] found a rather low incidence of 0.13% of vas injury in an analysis of

1494 sacs. They also argued that the incidence is so low that routine histologic evaluation of the sac is not warranted.

Shandling and Janick demonstrated the vulnerability of the vas during hernia repair.[90] In their experiments, the vas deferens of rats were exposed and grasped with fingers, nontoothed forceps, bulldog vascular clamps, or mosquito hemostats. Serial studies of the vas were done over 6 months, and damage to the vas was found in all manipulations except digital handling. Ceylan and colleagues[91] demonstrated that stretching of the spermatic cord might also damage the vas and testicle. They applied horizontal stretch force of varying amounts to the spermatic cord of rats. Significant thinning of the smooth muscle layer of the vas was noted with all degrees of stretching, as was testicular atrophy.

The relationship between male fertility and previous inguinal hernia repair is not well defined. Hommonnai and colleagues[92] reported findings on 131 men referred to an infertility clinic who had undergone inguinal hernia repair between the ages of 2 and 35 years. Although 14% of these men had testicular atrophy or abnormal sperm findings that could be related to the hernia operation, clinical details such as the incidence of incarceration and experience of the surgeon were not reported. Yavetz and colleagues reviewed 8500 patients referred to an infertility clinic. Of these, 565 (6.65%) reported inguinal hernia repair with or without testicular atrophy.[93] No correlation was found between age of hernia repair and semen quality following operation.

Operative injury to the vas deferens may result in obstruction of the vas with diversion of spermatozoa to the testicular lymphatics, and this breach of the blood-testis barrier produces an antigenic challenge with formation of spermatic autoagglutinating antibodies. In a review of 76 infertile men with spermatic autoagglutinating antibodies, 12 (16%) had unilateral inguinal hernia repair during childhood.[94] In 10 of these men the site of the inguinal hernia repair was explored, and in 5 patients an obstruction of the vas deferens was identified. The authors concluded that accidental transection or ligation of the vas could and does occur during inguinal hernia repair in a child and may be a reason for infertility in men. Parkhouse and Hendry reported similar findings.[95] Thus although these reports do not indicate the incidence of infertility of men after inguinal hernia repair, they do suggest that an association exists.

## TESTICULAR ATROPHY

The testicular vessels are vulnerable to operative injury, particularly in small infants, but reports of testicular atrophy after routine hernia repair are rare. Fischer and Mumenthaler[97] and Fahlstrom, Holmberg, and Johansson[96] each reported an incidence of testicular atrophy of 1%. In these studies the operative technique varied, and the number of incarcerated hernias was not reported; therefore this may not indicate the true incidence of testicular atrophy when hernia repair is performed by an experienced surgeon using a simple high ligation to obliterate the open sac.

With incarcerated hernia, the blood supply to the testis may be impaired by compression of the testicular vessels by the incarcerated viscus. The incidence of testicular compromise in association with incarcerated inguinal hernia ranges from 2.6% to 5%. The finding of a cyanotic testicle at emergency operation is common, reportedly 11% to 29%. The actual incidence of testicular atrophy as indicated by histologic examination or diminished size at follow-up is much lower, varying from 0% to 19%. Unfortunately, reported series of patients treated with emergency operation consist of small numbers of patients and the length of follow-up and the criteria for evaluation of the testis vary considerably. Puri, Guiney, and O'Donnell,[98] in an analysis of 87 boys with incarcerated hernia treated by nonoperative reduction, found unilateral testicular atrophy in 2 patients or 2.3%. From the available data, we conclude that vascular compromise is common but the risk of actual infarction is low. Therefore unless the testis is frankly necrotic, it should not be removed.

The herniated ovary and fallopian tube are also susceptible to vascular compromise, either as a result of incarceration or, perhaps more likely, torsion of the ovary within the hernia sac. The reported incidence of strangulation of irreducible ovaries is as high as 32%. Boley and colleagues[99] reported a 27% strangulation rate in 15 females presenting with incarceration. In addition, several case reports have demonstrated injury to the fallopian tubes from bilateral hernia repair, resulting in female infertility.

## INTESTINAL INJURY

With incarcerated hernias, the incidence of intestinal infarction is remarkably low. Between 1960 and 1965, the incidence of intestinal resection in the report by Rowe and Clatworthy[63] of 351 patients with incarcerated hernias was 1.4%. A review of three series published since 1978 shows no resections in 221 patients with incarcerated hernia.

## LOSS OF ABDOMINAL DOMAIN

A complication of hernia surgery that is rarely discussed is postoperative respiratory failure as a result of lost abdominal domain. The right of domain is the concept that each organ occupies a space within the body that it has a right to fill. In giant inguinal hernias, particularly bilateral giant hernias, the majority of the intestine can lie within the hernia sac and outside of the peritoneal cavity. If this occurs for some time, the intestine can lose its right of abdominal domain. During repair, the intestine is returned to the abdominal cavity, resulting in increased intra-abdominal pressure and respiratory failure. Bascombe, Caty, and Glick[100] reported an ex-premature infant with large bilateral inguinal hernias who required 41 days of mechanical ventilation after repair.

Respiratory failure after inguinal hernia repair is common, especially in premature infants. Gollin and colleagues[101,102] found 34% of premature infants required mechanical ventilation after herniorrhaphy. It is possible that increased intra-abdominal pressure as a result of loss of domain may be an unrecognized contributor to this problem. As a result of their experience, Glick and colleagues[101] have recommended staged repair of large bilateral hernias in the elective setting, especially because the risk of a second anesthesia is so low using modern technique. In an emergency setting (e.g., repair of giant incarcerated hernias), a silo such as that used for abdominal wall defects may be considered to alleviate abdominal compartment pressures and allow the intestine to be slowly returned to the abdomen.

### CHRONIC PAIN

Chronic pain after adult hernia repair is found in about 10% of patients. This incidence is unknown in patients undergoing hernia repair in childhood. In 2007 Aasvang and Kehlet[103] surveyed adults who had undergone hernia repair younger than the age of 5. Although 13.5% reported some pain from the operated groin (usually associated with physical activity), only 2% reported this pain to be severe.

This issue may be of greater relevance in the older teenager in whom mesh is used. Although mesh repair is not our practice, it is for other surgeons. In fact, there seems to be no general consensus as to the age when mesh repair may be appropriate and the older teenager may receive a different operation if corrected by an adult surgeon versus a pediatric surgeon.

Inguinodynia can be effectively improved in the great majority of patents by combined neurectomy and mesh removal. As noted previously, Ein[83] found in his personal series that teenagers had a significantly higher recurrence rate than other age groups. Interestingly, there are no published studies comparing mesh versus standard repair in adolescents. Clearly, this is an issue that is best addressed with a randomized, prospective trial.

Mesh has also been implicated in male infertility as a result of vasal obstruction. The mechanism appears to be related to the foreign body response to the mesh, leading to dense inflammation and scarring, which can trap or obliterate the vas. This scarring also makes surgical reconstruction of the vas difficult.

## Mortality

Mortality associated with inguinal hernia is related to complications of the hernia or to coexisting risk factors such as prematurity or cardiac disease. In 1938 Thorndike and Ferguson[102] reported an overall mortality of 2.8% for incarcerated hernias treated between 1927 and 1936. In 1954 Clatworthy and Thompson[104] reported one death in 135 patients treated for incarcerated hernia (0.9%), and in a report from the same institution in 1970 of 351 patients treated with incarcerated hernia, there were no deaths.[63] Since then, death from incarcerated hernia has become a rarity. The risk is higher when the hernia is strangulated. In the United Kingdom in 1989, five deaths from infants with strangulated hernia were reported. The risk factors identified include age younger than 6 months and lack of experience in pediatric surgery on the part of the surgeon and the anesthesiologist.

Operative mortality in premature infants is now only rarely seen. In two of the most recently reported series of premature infants undergoing hernia repair, no deaths were reported in a total of 303 patients.[67,105]

## Special Considerations

### PREMATURITY

It is well established that premature infants have a higher incidence of inguinal hernias and are likely to have a bilateral presentation. Moreover, the more premature the infant, the higher is the incidence of inguinal hernia. In a review of 82 infants weighing less than 2000 g, Walsh found a 13% incidence of inguinal hernia. Of 28 infants less than 1500 g, 7 (25%) had an inguinal hernia compared with 4 (7%) infants greater than 1500 g.[5] Rescorla and Grosfeld reviewed 100 infants younger than 2 months of age who required inguinal hernia repair; 30% of these infants were premature and 44% had bilateral hernias.[66] Of 1391 very-low-birth-weight infants (weight $<$ 1500 g) reported by Rajput and colleagues,[4] 222 (16%) developed an inguinal hernia between 28 days and 20 months of corrected age. Peevy, Speed, and Hoff studied 397 newborn infants and found a 9% incidence of inguinal hernias in infants weighing between 1000 g and 1500 g and 30% in those weighing 500 g to 1000 g.[8] In a small series of 37 premature infants weighing less than 1000 g, Harper and colleagues[106] reported that 11 (30%) developed an inguinal hernia. Two of these 11 were incarcerated (18%). Although the incidence of incarceration is increased in infants and may be as high as 28%, it appears to be lower in premature infants, with reported incidences of 13% to 18%, compared with mature infants.

### VENTRICULOPERITONEAL SHUNTS/ PERITONEAL DIALYSIS

A significant factor in the development of an inguinal hernia is excess fluid in the peritoneal cavity, and in patients with a patent processus vaginalis, procedures that introduce fluid into the peritoneal cavity may induce a hernia or hydrocele. Whether hernia is due to the physical presence of the fluid or is secondary to increased intra-abdominal pressure is unknown. Abnormal neuromuscular function may also be a factor. Moazam and colleagues[107] reviewed 134 patients who had ventriculoperitoneal shunt procedures; inguinal hernias developed in 19.5% of patients with meningomyelocele and 47% of those with intraventricular hemorrhage. All of the latter were premature, however. Grosfeld and Cooney[78] found a 14% incidence of inguinal hernia after insertion of ventriculoperitoneal shunts; 20% developed an incarceration and the hernia recurred in 16%. On the basis of this study the authors recommended that (1) after ventriculoperitoneal shunts, infants should be closely watched for the development of a clinical inguinal hernia, (2) operation should be done promptly after diagnosis of a hernia because of the increased risk of incarceration, and (3) in these patients the contralateral side should be explored in the case of a clinical unilateral hernia. Clarnette and colleagues[108] evaluated 430 patients who underwent ventriculoperitoneal shunt placement. In their series, 15% developed an inguinal hernia and a hydrocele developed in another 6% of boys. Hernias were bilateral in 47% of boys and 27% of girls. The incidence of subsequent inguinal hernia development closely paralleled the age at which the shunt was performed. In the last 8 weeks of gestation or in the first few months of life the incidence was 30%, then falling sharply to 10% at age 1 year. They argue that raised intra-abdominal pressure is the likely etiology of these hernias. They also conclude that patency of the processus vaginalis is 30% in the first few months of life and supports the possibility that a patent processus vaginalis can close in the first year of life.

There is a well-established risk of inguinal hernia developing in patients on long-term ambulatory peritoneal dialysis,

ranging from 7% to 15%. In such cases the patent processus vaginalis is likely to develop into a frank hernia. Intraoperative herniography is recommended when the peritoneal dialysis catheter is inserted. Water-soluble contrast is infused through the catheter, and the patient is placed in a head-up position for 15 minutes. If a patent processus vaginalis is identified, repair is in order. Alternatively, direct laparoscopic visualization of the internal ring can be performed at the time of catheter placement, particularly if the catheter placement itself is performed laparoscopically. Repair can then be performed open or laparoscopically.

## SLIDING HERNIA

The fallopian tube or mesosalpinx is frequently found in the wall of the hernia sac in girls and is at risk of injury. The operative management has already been discussed.

The appendix may also be found in the wall of a sliding hernia sac. Appendectomy, if it can be done safely, permits high ligation of the sac in the usual way. Alternatively, the sac is ligated distal to the appendix, and the proximal sac, with the appendix, is reduced into the abdominal cavity, with or without purse-string closure as for a sliding hernia in girls. In the infant, the bladder may lie beneath the internal ring and may be pulled down with the hernia sac during dissection. If this is not recognized, high ligation of the hernia sac may include the bladder wall, leading to hematuria, possible necrosis of the bladder wall, and extravasation of urine. This situation can be avoided by careful inspection of the neck of the sac at the time of transfixion. When there is any question about this possibility, the sac should be opened and the contents inspected. Occasionally, the bladder may extend down the medial wall of the sac as a true sliding hernia. Shaw and Santulli recommend a flap operation, as in the Goldstein-Potts repair in females,[109] but we simply ligate and divide the sac distal to the bladder, invert the stump, and narrow the internal ring (Bevan repair).[39]

## DIRECT INGUINAL HERNIA

A direct inguinal hernia in children had been thought to be extremely rare, but the increasing use of laparoscopy has shown them to be somewhat more common than thought. Previously, the most common presentation was as a recurrence after repair of indirect inguinal hernia repair. This is probably due to the direct hernia being missed at the initial operation or as a result of damage to the floor of the inguinal canal during the first operation. Wright encountered only 19 direct hernias in more than 1600 inguinal hernia operations (1.2%).[110] However, Gorsler and Schier[43] found an incidence of 3.9% direct hernias in 403 inguinal hernias. The diagnosis should be suspected if, when operating on an indirect hernia, a typical sac cannot be found and a fascial defect is found medial to the inferior epigastric vessels. Management is by repair of the transversal fascia such as a Bassini repair or by a Cooper ligament repair when sufficiently developed.

## FEMORAL HERNIAS

Femoral hernias are also rare in children and are often misdiagnosed clinically on examination or at the time of indirect inguinal hernia repair.

Fonkalsrud and colleagues[84] reviewed 5452 patients with inguinal hernias, and Burke[111] reviewed 4567 patients, a total of 10,019 infants and children, and found there were 21 patients with femoral hernia (0.2%). Their ages ranged from 6 weeks to 13 years. There were 18 girls and 10 boys, almost a 2:1 ratio. The correct preoperative diagnosis was made in 8 of 21 patients (38%). Four had bilateral femoral hernias, and in five patients the hernias were incarcerated. De Caluwe and colleagues[112] described 38 patients with femoral hernia over a 20-year period. Four patients had bilateral femoral hernias. Correct preoperative diagnosis was made in 53%. Of the 18 patients with misdiagnosis, seven required a second operation. Whenever intraoperative findings (i.e., failure to find a significant indirect inguinal hernia) do not correlate with the preoperative diagnosis (i.e., indirect inguinal hernia), consideration of a direct inguinal hernia or femoral hernia should be given. Before the availability of pediatric laparoscopy, taking down the inguinal floor and inspecting the inguinal canal were justified in these circumstances. However, with the nearly universal availability of laparoscopic equipment in the pediatric surgical operating room, Lee and Dubois[113] advocate diagnostic laparoscopy as an adjunct to hernia repair particularly in recurrence. They described four patients with presumed recurrence of an indirect inguinal hernia who underwent diagnostic laparoscopy at the second surgery. Three of these patients had femoral hernias. They also identified three contralateral femoral hernias as well. Wright[114] reported 16 patients with femoral hernia and advocated repair through a femoral (infrainguinal) approach, suturing the inguinal ligament to the pectineal ligament and pectineal fascia. Ceran and colleagues[115] have used a mesh-plug successfully in four children, as have Lee and Dubose.[113] We prefer a standard Cooper ligament repair for first-time explorations and find the mesh-plug useful for previously operated groins with ipsilateral femoral hernias. In addition, several different techniques for laparoscopic repair in children have now been reported. Small patient numbers and limited follow-up make conclusions about the effectiveness of these procedures premature.

## INHERITED DISORDERS OF CONNECTIVE TISSUE

Patients with Hunter-Hurler, Ehlers-Danlos, and Marfan syndromes frequently have inguinal hernias and are prone to recurrence unless the floor of the inguinal canal is repaired in addition to the usual high ligation of the sac. Coran and Eraklis[116] found 36% of 50 patients followed with Hunter-Hurler syndrome developed inguinal hernia. The recurrence rate with high ligation alone was 56%, and formal herniorrhaphy was recommended. In adolescents we recommend high ligation of the indirect sac, followed by tensionless floor repair with mesh.

## CYSTIC FIBROSIS

The incidence of inguinal hernia in cystic fibrosis is increased, 6% and 15%.[117] The incidence of absent vas deferens in the general population is 0.5% to 1% on the basis of vasectomy studies.[118,119] In cystic fibrosis, abnormalities of the vas deferens ranging from obstruction to complete absence are invariably present and are usually bilateral. Failure to identify the vas

should, therefore, lead to an evaluation for cystic fibrosis. Agenesis of the vas deferens is found in association with renal dysgenesis in patients who do not have cystic fibrosis, so evaluation of the upper urinary tract is recommended in these situations.

## INTERSEX

Rarely a phenotypic female with a palpable gonad in the labia may be a genetic male with androgen insensitivity syndrome, or a true hermaphrodite. If an ovary is encountered in the hernia sac of a female patient, it should be carefully examined for evidence of testicular tissue ("the ovotestis"). Males with androgen insensitivity syndrome do not have fallopian tubes and a uterus but do have a small testis. Hermaphrodites may have a fallopian tube in the hernia sac, and examination of the gonad reveals an asymmetric ovotestis. In both situations, if an abnormal gonad should be encountered, it should not be removed. Small wedge sections are taken from each pole, the gonad is replaced, and the hernia is repaired. This condition is further discussed in Chapter 123.

## SPLENOGONADAL FUSION

Splenic tissue may be fused to an otherwise normal testis (splenotesticular fusion). Presentation is with a scrotal mass, and the usual preoperative diagnosis is a testicular tumor. Orchidectomy is not necessary; intraoperative frozen section provides the diagnosis and allows preservation of the testis. Spleno-ovarian fusion may also be encountered. Splenogonadal fusion may also present as an undescended testis or intra-abdominal mass. Laparoscopy is useful to both diagnose and treat this condition.

## ADRENAL RESTS

Ectopic adrenal tissue appearing as a small mass of yellowish tissue in the apex of the hernia sac is not rare and has been found in 10 of 385 operations for inguinal hernia (2.6%), an incidental finding in each case.[120] In another series, however, the incidence was 0.2% in 1077 sacs analyzed.[89] The adrenal tissue at this site is likely the result of attachment of developing adrenal cells to the testis before descent from the retroperitoneum to the scrotum during fetal development. Excision of the adrenal tissue is not necessary.

## CONGENITAL HYDROCELE

A hydrocele is a collection of fluid in the space surrounding the testicle between the layers of the tunica vaginalis. Hydroceles may be communicating (patent processus vaginalis with free flow of fluid) or noncommunicating (usually scrotal in males, and may extend to the external inguinal ring). Hydroceles are common in infants and children, and in many cases they are associated with an indirect inguinal hernia. Hydroceles are often bilateral and have a higher rate of occurrence on the right side. If communicating, they can vary in size and will often increase in size during the day while the child is upright and decrease in size overnight when the child is supine and gravity drains the hydrocele. Occasionally, a hydrocele may extend through the inguinal canal into the retroperitoneum as an abdomino-scrotal hydrocele. These are frequently confused with an indirect inguinal hernia. Children may also present with a roundish, tense, but painless mass in the upper scrotum or inguinal canal; this is a hydrocele of the cord. Daily fluctuation in the size, progressive increase in size, or intermittent inguinal bulging is indicative of a communicating hydrocele. An acute hydrocele may be secondary to an acute process within the tunica vaginalis or torsion of the testis, or its appendages. These are associated with considerable pain and tenderness. Alternatively, an acute hydrocele may be seen concurrently with or following an acute upper respiratory infection, or a diarrheal illness when coughing and straining forces fluid into a previously undetected patent processus vaginalis.

Usually a hydrocele can be distinguished from an inguinal hernia on physical examination. Typically a nontender cystic swelling of the scrotum that surrounds the testicle and transilluminates is evident. Simple transillumination does not guarantee the diagnosis of a hydrocele. Incarcerated gas-filled intestine will also transilluminate. Therefore aspiration should never be attempted for diagnosis. It is usually possible to palpate a thin spermatic cord above the hydrocele. However, this may be difficult in a large hydrocele of the cord or an abdomino-scrotal hydrocele.

In the majority of children with congenital hydrocele, the processus vaginalis closes behind the hydrocele (noncommunicating hydrocele) and the hydrocele typically resolves by age 2. Therefore operation is not recommended in the first 2 years of life unless the hydrocele is communicating or a hernia cannot be ruled out. An exception is a large tense hydrocele associated with discomfort. Hydroceles that persist beyond 2 years of age or those that arise in an older child require operation. The operation performed is high ligation of the patent processus vaginalis. The distal hydrocele sac is opened and drained. The open sac is left in place and the edges do not require suturing as in adult hydrocele operations. Reaccumulation of fluid in the sac is uncommon and generally resolves spontaneously.

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 77

# Undescended Testis, Torsion, and Varicocele

John M. Hutson

## Undescended Testis

### HISTORY

The importance of a descended testis has been known since ancient times, but the mechanism of descent remained obscure until 1786 when Hunter dissected the human fetus. He found the intra-abdominal testis connected to the inguinal abdominal wall by a ligament called the “gubernaculum testis” because it appeared to guide the testis to the scrotum.

### EMBRYOLOGY

Testicular descent into the low-temperature environment of the scrotum in mammals is a complex multiple-stage process.[1] Up to the time of sexual differentiation in the human fetus at 7 to 8 weeks’ gestation, the fetal testis and ovary occupy similar positions and are held by the cranial suspensory ligament (upper pole) and the gubernaculum (lower pole). The gonadal positions then diverge; the testis remains close to the future inguinal canal, whereas the ovary moves away from the groin.

The cranial suspensory ligament, which persists in girls, regresses in boys while the gubernaculum enlarges, especially at its distal end where it is embedded in the inguinal abdominal wall. The inguinal canal forms by condensation of mesenchyme around the gubernaculum to form the inguinal musculature. The mesenchyme of the gubernaculum persists to form a solid cord, which later becomes hollowed out by a diverticulum of peritoneum, the processus vaginalis.[5] The proximal gubernaculum, which is initially attached to the gonad, becomes expanded by growth of the caudal epididymis. The processus vaginalis grows caudad into the gubernacular mesenchyme, partly hollowing out the gubernaculum. The caudal end of the gubernaculum remains solid, but the proximal part is divided into a central column attached to the epididymis and an annular parietal layer within which the cremaster muscle develops. At the start of the third trimester, the caudal end of the gubernaculum bulges beyond the inguinal abdominal wall (Fig. 77-1) and migrates across the pubic region to the scrotum.[2] The processus vaginalis elongates proportionally inside the gubernaculum so that the testis can leave the peritoneal cavity within it (see Fig. 77-1). Migration of the gubernaculum and the testis to the scrotum is complete by 35 weeks.[2,3] During migration, the gubernaculum is loose within the inguinoscrotal mesenchyme, suggesting enzymatic digestion of the adjacent tissues. After migration is complete, the processus vaginalis becomes secondarily attached to the bottom of the scrotum (see Fig. 77-1).

The different phases of testicular descent are hormonally regulated.[4] The hormones controlling descent and their mechanism of action remain controversial.[3] The early phase of abdominal testicular descent is regulated separately from the migratory inguinoscrotal phase.[5,6] Androgen controls regression of the cranial suspensory ligament of the testis, but regression of this ligament is not essential for testicular descent.[7] Enlargement of the gubernaculum testis is primarily controlled by insulin-like factor 3 (Insl3),[8] which is an analogue of insulin and relaxin produced by Leydig cells.[9,10]

Insl3 is made up of two peptide chains linked by a disulfide bond, with homology to relaxin, and is a member of the insulin family of growth factors.[8] Knockout mice with mutated Insl3 have high intra-abdominal testes and an abnormal gubernaculum, consistent with a role of Insl3 in stimulating the “swelling reaction” of the gubernaculum to initiate transabdominal testicular descent.[11,12] Studies both in vivo and in vitro show a primary role for Insl3 in stimulating early gubernacular growth, with secondary roles for testosterone and müllerian-inhibiting substance.[11,12]

Migration of the testis and gubernaculum from the inguinal region to the scrotum is under androgenic control. In instances of complete androgen resistance or gonadotropin deficiency, inguinoscrotal migration is absent.[13] The mechanism of androgenic control of gubernacular migration is unknown, but there is substantial evidence implicating the genitofemoral nerve. The signals initiating migration of the gubernaculum out from the abdominal wall have many characteristics of an embryonic limb bud.[14] In addition, the mammary line may be important in triggering this dramatic change in the gubernaculum.[15,16] It has been postulated that the sensory branches of the genitofemoral nerve release calcitonin gene-related peptide (CGRP), which may then indirectly control gubernacular migration by stimulation of growth of the gubernacular tip,[17] as well as provide a chemical gradient to allow

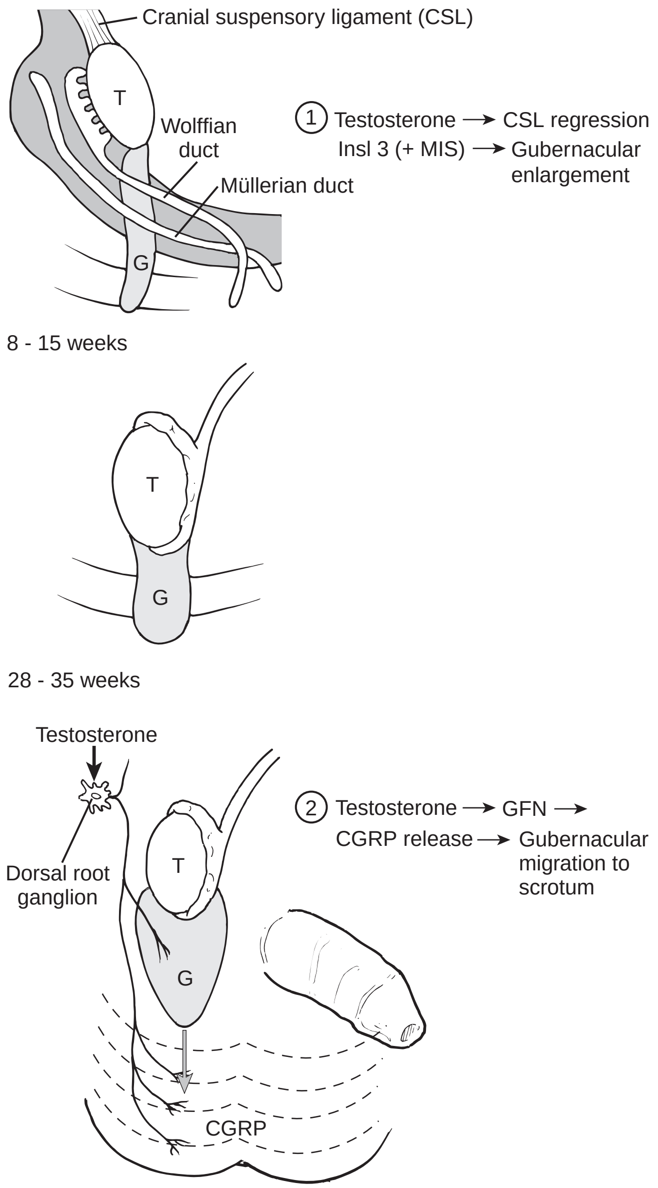


**FIGURE 77-1** Schema showing gubernacular development in the two phases of testicular descent in the human fetus. In the first ("transabdominal") phase at 8 to 15 weeks the testis *(T)* is held near the inguinal abdominal wall during embryonic growth by enlargement of the gubernaculum *(G)*. This relative change in testicular position compared with the ovary is controlled by testicular hormones, with insulin-like factor 3 the primary hormone possibly augmented by müllerian-inhibiting substance *(MIS)*/antimüllerian hormone. The cranial ligament regresses under the action of testosterone. In the second ("inguinoscrotal") phase at 28 to 35 weeks, the gubernaculum migrates by elongation toward the scrotum. This is controlled indirectly by testosterone acting on the genitofemoral nerve *(GFN)* in the dorsal root ganglia to differentiate the sensory fibers to release calcitonin gene-related peptide *(CGRP)*. CGRP controls growth and direction of migration of the rat gubernaculum, and it is hypothesized that it does the same in humans. CSL, cranial suspensory ligament.

migration in the correct direction toward the scrotum. The physical force for migration of the testis is probably provided by intra-abdominal pressure acting through the patent processus vaginalis. Recent work also implicated the propulsive force of the developing cremaster muscle in the wall of the gubernaculum and its sympathetic nerve supply,[18] although this has not been substantiated.[19]

Any anomaly disrupting normal testicular descent leads to cryptorchidism.[20] The complexity of the process suggests that causative factors for nondescent are multifactorial. Most undescended testes are located outside the inguinal canal because the migratory inguinoscrotal phase of testicular descent is deranged more commonly. In contrast, the passive anchoring by the gubernaculum in the transabdominal phase is infrequently disrupted, so the intra-abdominal testes are relatively uncommon, occurring in 5% to 10% of cryptorchid boys.[21] In most cases, the undescended testis is located near the neck of the scrotum, just outside or a little lateral to the external inguinal ring, in the "superficial inguinal pouch," which is the misplaced tunica vaginalis. Abnormalities of gubernacular migration may be related to defects in the migratory mechanism itself or failure of genitofemoral nerve function.[6,22] Defects in the nerve may be caused by deficiency of androgen secretion during the second and third trimester as a result of deficiency of gonadotropin production by the pituitary or the placenta. Recognizable endocrine disorders such as müllerian-inhibiting substance deficiency or decreased testosterone synthesis or receptor function also cause failure of testicular descent but are rare. Since the discovery of Insl3 and its role in transabdominal descent, a search has been made for mutations of the Insl3 gene in undescended testes, but only relatively rare cases have been described.[23–25]

Undescended testes lying well outside the normal line of descent such as in the perineum or femoral region are rare, and their cause is unknown. It has been suggested that this may be the result of an abnormal location of the genitofemoral nerve with consequent abnormal migration of the gubernaculum to the wrong site.[6] The cause of transverse testicular ectopia is also unknown, but in animal models transverse ectopia can be induced readily by cutting the gubernacular attachment to the testes so that the gonad is no longer required to exit the abdominal cavity through the ipsilateral inguinal canal. Increased gonadal mobility may permit accidental descent through the contralateral inguinal canal.[26] The latter also occurs in boys with persisting müllerian duct syndrome, where the elongated gubernacular cord predisposes to accidental descent down the contralateral inguinal canal.

A number of inherited syndromes are associated with undescended testes. The underlying cause is not known, although many are associated with microcephaly, suggesting the possibility of pituitary hormone or gonadotropin deficiency.[27] Some multiple malformation syndromes are also associated with neurogenic and mechanical anomalies, for example, arthrogryposis multiplex congenita.[28] These disorders may cause cryptorchidism either by external compression of the deformed fetus or by intrinsic neurologic anomalies. Experimental inguinoscrotal compression during testicular descent is associated with undescended testes.[29] Intra-abdominal testes are characteristic of the prune-belly syndrome. The cause of the cryptorchidism is controversial, with thoughts ranging from a mesodermal defect to transient prenatal urinary obstruction.[30–33] The absence of a processus vaginalis within the inguinal canal and the position of the testes on the posterior surface of the bladder are consistent with an obstructive cause. Ten percent of infants with posterior urethral valves also have cryptorchidism.[34]

Cryptorchidism is common in infants with abdominal wall defects such as gastroschisis (where the gubernaculum may be ruptured), exomphalos (omphalocele), and exstrophy of the bladder.[35] Undescended testes occur in more than 15% of

infants with gastroschisis and at least a third of children with exomphalos or omphalocele.[27,35] Whether this is caused by decreased abdominal pressure or other mechanical effects is not certain, although a role for abdominal pressure has been determined in experimental animals.[36]

Neural tube defects have a high incidence of undescended testes.[37] When there is a myelomeningocele affecting the upper lumbar spinal cord, the incidence of undescended testes is greater than one third. This could be caused either by abdominal wall paralysis and lower-than-normal abdominal pressure or by dysplasia of the genitofemoral nerve sensory nucleus at the site of the myelomeningocele.[38]

Separation of the body of the epididymis from the undescended testis is frequently observed.[39–41] This is more common in intra-abdominal and high inguinal cryptorchid testis. Whether this is the cause of the cryptorchidism or merely secondary to decreased androgen production in utero occurring simultaneously is not known. Experimental evidence in rodents treated with antiandrogens suggests that in-utero androgen deficiency causes epididymal deficiency.[42] Abnormalities of the vas deferens occur commonly in boys with cryptorchid testes. The impalpable intracanalicular testis may have a vas deferens forming a loop, which protrudes distally through the external inguinal ring. On the basis of an examination of the blood supply of such a long-loop vas, Fowler and Stephens proposed transection of the main testicular vessels to the high undescended testis to permit orchidopexy with testis viability maintained by the redundant vas deferens with its collateral blood supply.[43] Although this operation is less commonly performed as an open one-stage procedure because of the high incidence of atrophy, it is now commonly performed laparoscopically as a one- or two-stage procedure.[44]

## CLASSIFICATION OF UNDESCENDED TESTES

Classification of gonadal position in undescended testes is complicated by the mobility of the testis inside its tunica vaginalis. Undescended testis is best defined as a testis that cannot be manipulated to the bottom of the scrotum without undue tension on the spermatic cord. A normally descended testis resides spontaneously in the lower scrotum even if it was retracted when the patient was first examined. The positions of undescended testes can be divided into those arrested in the line of normal descent and those in truly ectopic positions (Fig. 77-2). The intra-abdominal testis is usually located within a few centimeters of the internal inguinal ring, with the vas deferens and the testicular vessels traveling extraperitoneally and then entering the testis through a short mesorchium. Such intra-abdominal testes were often difficult to find through extraperitoneal exploration through the inguinal canal but are now relatively easy to identify at laparoscopy.

A canalicular testis is one that lies within the inguinal canal but may be difficult or impossible to palpate because of the overlying musculature. Such gonads may be squeezed out of the inguinal canal and become palpable at the external inguinal ring, so-called *emergent testes.*

Undescended testes beyond the external ring may lie near the neck of the scrotum or may be lateral and a little above the external inguinal ring in the superficial inguinal pouch, originally described by Browne (see Fig. 77-2).[45] The latter location is rarely an indication of aberrant gubernacular migration because at surgery the gubernacular attachment is nearly always at or near the neck of the scrotum.[39,46] Essentially, the superficial inguinal pouch is the space created by the tunica vaginalis in the groin and is limited superficially by Scarpa's fascia and its deep attachment to the fascia lata just

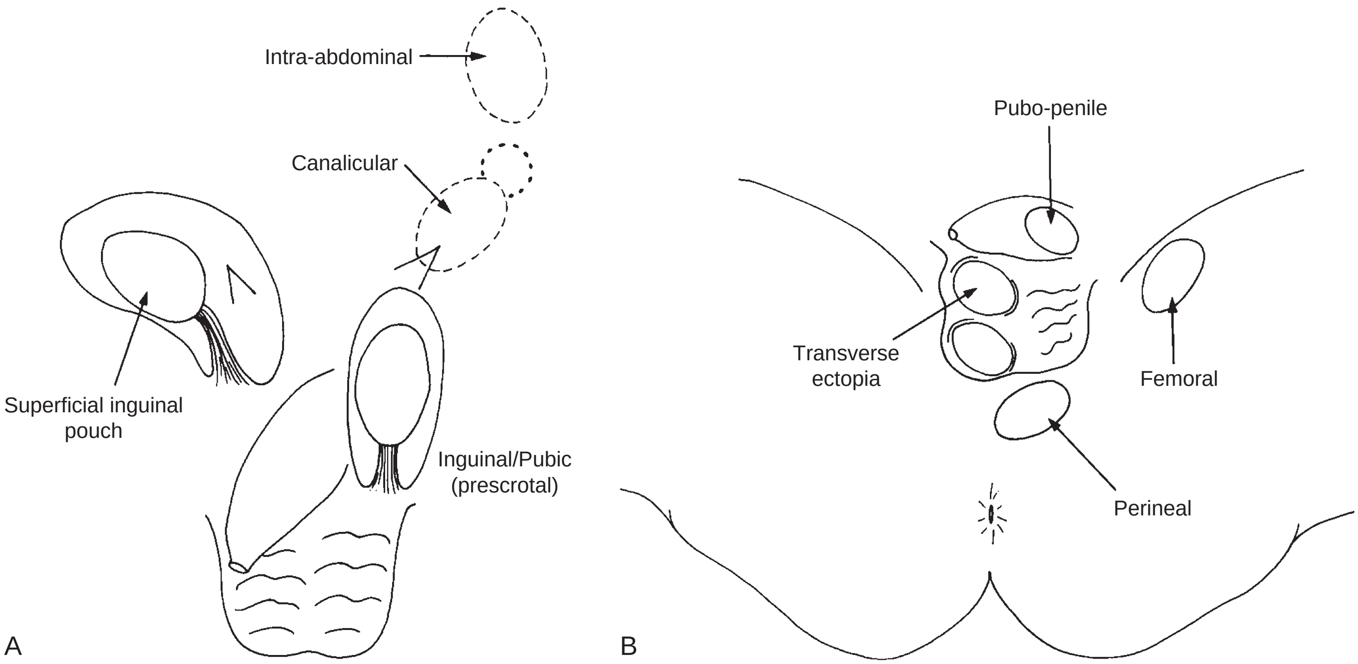


FIGURE 77-2 The range of positions that may be adopted by undescended testes. **A,** In the line of normal descent (including the controversial superficial inguinal pouch, note that the gubernaculum is attached near the neck of the scrotum in most instances). **B,** True ectopic sites, which are rare. (From Hutson JM, Beasley SW: Descent of the Testis. London, Edward Arnold, 1992.)

caudad to the inguinal ligament. Whether testes in the superficial inguinal pouch should be labeled as ectopic is controversial, but because the gubernaculum is attached at or near the neck of the scrotum, they seem to be better classified as testes arrested in the line of normal descent.[47] Truly ectopic testes may be located in the perineum, femoral region, pubopenile region, or contralateral hemiscrotum secondary to transverse ectopia.

## RETRACTILE TESTES

Transient retraction of the testis out of the scrotum is a normal reflex caused by contraction of the cremaster muscle. This muscle functions to regulate the temperature of the testis and to protect it from extrinsic trauma.[48] Retraction occurs as a result of low temperature or stimulation of the cutaneous branch of the genitofemoral nerve (inner thigh).

The normal retractile reflex is weak or absent at birth, and the scrotum is often pendulous. Later in childhood, when androgen levels are low, cremasteric contractility is significantly increased and the cremasteric reflex more pronounced. After 10 years of age, the reflex becomes less pronounced as androgen levels rise with the onset of puberty. The cremasteric reflex and normal retractile testis have been studied by Farrington, who found a high incidence of retractility in the middle of childhood.[49]

At present, there is no consensus about what constitutes a retractile testis.[50] Most clinicians agree that a retractile testis is a descended testis, although careful follow-up is required because it does not always remain descended. The retractile testis probably reflects a normal physiologic response to contraction of the cremaster muscle related to age. Goh and Hutson suggest that so-called retractile testes are, in fact, testes with acquired maldescent.[51] As the distance between the external inguinal ring and the bottom of the scrotum increases with age (from 5 cm in an infant to 10 cm by 10 years of age), it is necessary for the spermatic cord to lengthen for the testis to remain located in the scrotum. Retractile testes may represent acquired maldescent secondary to failure of the spermatic cord to elongate with age, which may be a sequel of excessive contractility of the cremaster muscle in some boys, as in those with cerebral palsy and spastic diplegia.[52]

## ASCENDING TESTES

A newly described variant of the retractile testis is the ascending testis.[50,53,54] In many of these children, long-term follow-up studies have demonstrated that subsequent ascent out of the scrotum later in childhood is often related to delayed descent into the scrotum within the first 3 months after birth. Ascending testes are now being documented by a number of authors.[50,55] The difference between ascending and retractile testes is otherwise not clear, and it may be that they are different names for developing acquired cryptorchidism.

## ACQUIRED UNDESCENDED TESTES

Not all undescended testes are present from birth. Many children with cryptorchidism present later in childhood despite attempts at screening in infancy.[56] In addition, on careful questioning of such families, there is often no history of an anomaly at birth or in early childhood.[57]

Acquired cryptorchidism is caused by failure of the spermatic cord to elongate in proportion to body growth. Such testes appear to ascend out of the scrotum with increasing age, but measurements of the cord length suggest that this ascent is more apparent than real because the scrotum is farther from the groin in older boys. This is certainly true in patients with cerebral palsy, in whom acquired cryptorchidism approaches 50% in postpubertal boys with severe spastic diplegia.[52]

Ascending testes may be caused by persistence of the processus vaginalis either as a patent hernia or an obliterated remnant, which is likely to inhibit elongation of the adjacent vas deferens and testicular vessels.[55,58] In cases in which the testis migrated to the scrotum prenatally and was present within the scrotum in infancy, but the position is too high later in childhood, orchidopexy is often successful through a scrotal approach.[59,60]

## INCIDENCE OF UNDESCENDED TESTES

In 1964 Scorer found the incidence of undescended testes was 4.3% in infants,[61] but by 1 year of age, the incidence had fallen to 0.96%. In 1986 the incidence of cryptorchidism at 1 year of age was 1.58% in British children. The John Radcliffe Hospital Cryptorchidism Study Group found that spontaneous descent occurred postnatally in the first 3 months; beyond that time, it was rare.[53,62] The rate for orchidopexy in England and Wales effectively doubled over several decades.[63] Although this difference between the incidence of cryptorchidism and frequency of orchidopexy suggested that some orchidopexies may be unnecessary, it has been suggested that the apparent doubling of orchidopexy rates may be related to acquired ascending or retractile testes.[50] Because the recommended age for surgery for congenital undescended testes has decreased to 6 months of age, those children with acquired undescended testes are now more readily distinguishable from those children with congenital failure of gubernacular migration.[56]

The frequency of undescended testes is significantly increased in premature infants.[64] When birth weight is less than 1500 g, the incidence of cryptorchidism reaches 60% to 70%.[65] The cause of this high frequency of cryptorchidism is that normal descent is not completed until about 35 weeks' gestation. Most undescended testes in premature infants continue to descend postnatally, so if such children are examined at 12 weeks beyond their expected normal delivery date, the incidence of cryptorchidism has fallen to more normal levels.

## COMPLICATIONS OF CRYPTORCHIDISM

Controversy persists about whether the testis is primarily abnormal, leading to maldescent, or alternatively is undescended, leading to a secondary abnormality. Evidence now suggests that abnormalities seen postnatally in undescended testes are secondary. Occasional primary abnormalities in the hypothalamic-pituitary-gonadal axis, however, lead to inadequate hormone secretion, maldescent, and primary testicular abnormalities.

Species differences have made investigative studies regarding the effects of undescended testes difficult to evaluate. Many studies concerning cryptorchidism have been carried out on rodents, in which the important developmental aspects

of gubernacular migration are complete by the 10th day after birth. The testis, however, does not descend into the scrotum until 2 to 3 weeks in mice or 3 to 4 weeks in rats, at the time of pubertal sexual maturation.[66] Human gubernacular migration and testicular descent occur simultaneously and are normally complete before birth. The effects of undescended testes in the rat, therefore, do not become evident until after puberty.

### Temperature Effects

The scrotal testis resides in a specialized low-temperature environment with the pampiniform plexus, scrotal pigmentation, absence of subcutaneous fat, and regulation by temperature-sensitive muscles such as the cremaster and dartos muscle, all ensuring decreased temperature of the epididymis and gonad. The scrotal testis in the human is maintained at 33°C compared with 34°C to 35°C in the inguinal region and 37°C intra-abdominally (Fig. 77-3).[67,68] The physiology of the testis is well adapted to this lower temperature; therefore in the undescended testis where the ambient temperature is increased, the testis undergoes progressive alteration.[1]

### Endocrine Effects

Steroid pathways in rat testes made cryptorchid by surgical fixation before puberty show no gross abnormalities, indicating that Leydig cells are still functional with cryptorchidism in this model. Measurement of testicular testosterone content in rats made cryptorchid at birth shows no abnormality up to 2 to 3 weeks of age but decreased testosterone production compared with controls after puberty.[69] Gonadotropic regulation of both Leydig and Sertoli cells is abnormal after puberty.[70] The number of Sertoli and Leydig cells, however, remains relatively normal.[71] Functional derangements in Sertoli cells with cryptorchidism have been well documented by de Kretser and Risbridger.[72]

Plasma gonadotropin and testosterone levels have been measured in infants with undescended testes, and the normal postnatal rise in plasma luteinizing hormone (LH) levels and testosterone were found to be significantly lower than normal.[73,74] It is difficult to determine conclusively whether this postnatal androgen deficiency is a primary abnormality or secondary to nondescent.

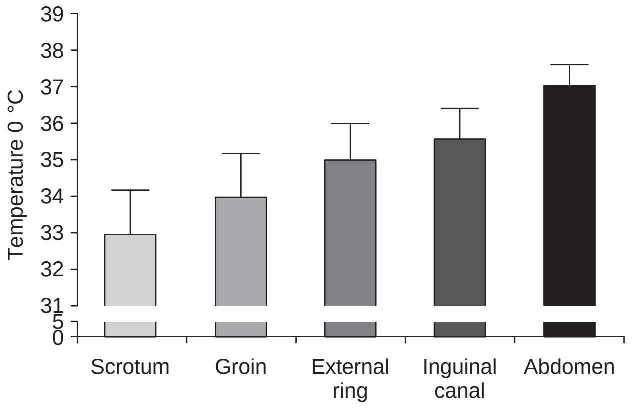


FIGURE 77-3 The temperature (mean ± standard deviation) of the testis at different levels. (From Hutson JM, Beasley SW: Descent of the Testis. London, Edward Arnold, 1992.)

In a study of premature infants born with a mean gestational age of 30 weeks, there was a persistently high incidence (19%) of undescended testes at 18 months despite some testes descending postnatally.[75] The normal rise in testosterone seen in the second and third month postnatally failed to develop in these premature infants with cryptorchidism. The authors concluded that inadequate stimulation of testosterone by human chorionic gonadotropin (hCG) in utero may contribute to the pathogenesis of undescended testes in this special group. Both plasma testosterone and LH levels were decreased in cryptorchid infants between 1 and 4 months of age.[40] Although androgen levels may be deficient, androgen receptor levels in scrotal skin fibroblasts and testicular biopsy specimens taken at orchidopexy are normal in infants with bilateral cryptorchidism.[76] Serum levels of müllerian-inhibiting substance are normally elevated between 4 and 12 months of age, but in children with cryptorchidism this postnatal rise was inhibited.[77]

### Germ Cell Development

Germ cell deficiency in cryptorchidism was previously regarded as congenital.[48] It has been observed, however, that the histology of the testes is initially normal and becomes progressively abnormal with age.[78] Leydig cell development is impaired in undescended testes in the first 2 to 6 months, whereas the Sertoli and germ cells appeared normal.[79,80] By the end of the second year of life, nearly 40% of undescended testes have completely lost their germ cells.[81] It is now well established that the transformation of neonatal gonocytes to type A spermatogonia, an early postnatal step in development of the germ cells, is deficient in infants with cryptorchidism.[82–84]

Moreover, there is now good evidence that type A spermatogonia are the stem cells for subsequent spermatogenesis.[85] Some authors have proposed that these early stages in germ cell development are controlled by androgens and are hence deficient because of postnatal androgen deficiency.[82] There is some contrary evidence to suggest, however, that müllerian-inhibiting substance may be controlling early postnatal germ cell development.[86,87] Certainly, androgen blockade or deficiency does not prevent gonocytes transforming to type A spermatogonia in neonatal rodents.[88]

### Fertility

Fertility is lower in men with a past history of cryptorchidism. In previous generations, it was believed that the undescended testis suffered no adverse changes until after puberty and surgical intervention was not necessary until 12 to 15 years of age.[48] The evidence that germ cell maturation is already abnormal after 6 months of age has led clinicians to appreciate that not only is postnatal degeneration an important issue but also that early intervention may prevent it. In animal studies, it is relatively easy to demonstrate that surgically induced or congenital cryptorchidism causes decreased fertility because of germ cell deficiency after puberty.[89] Paternity rates are not deficient in unilateral cryptorchidism in both animals and humans; but with bilateral cryptorchidism, fertility is significantly impaired.[7,90] Data attempting to correlate fertility rates with timing of surgery are not yet available because there are no long-term studies of children undergoing orchidopexy in the first year of life. Fertility in men with a history of retractile testes remains quite controversial, with some authors describing abnormalities on sperm counts that are not reflected in paternity rates.[91–93] In a recent prospective,

randomized trial, children had orchidopexy at 9 months or 3 years, with follow-up to 4 years of age with testicular ultrasound. Those having earlier surgery had significantly greater testicular volumes at 4 years old, which is promising for improved fertility in the future.[94]

### Malignancy

The risk of a testis tumor occurring in men with a past history of cryptorchidism was at one time believed to be 35 to 50 times greater than normal.[95] By using different methods of calculating the relative risk, Woodhouse[96] suggested the actual risk is 5- to 10-fold. When looking at all men with testis tumors, a relative risk for those with a history of unilateral cryptorchidism is 15-fold or 33-fold for bilateral undescended testes, with the risk of cancer being highest with intra-abdominal testes.[97–99]

The progressive degeneration of germ cells and dysplasia seen in cryptorchid testes is thought to be related to an increased risk of malignancy.[100] Testis tumors are not common in childhood, and they usually occur at the same age as testis tumors in normally descended testes (i.e., 20 to 40 years). Giwercman and colleagues[101] have speculated that testis tumors may be caused by an intrinsic abnormality in the testis rather than secondary dysplasia. They suggest that carcinoma in situ germ cells are the forerunner of invasive tumors and are, in fact, malignant gonocytes. Such germ cells displaying histologic characteristics of carcinoma in situ can be identified in neonates with dysgenetic testes and ambiguous genitalia. Skakkabaek and colleagues[102] have described the histologic features of carcinoma in situ and provided strong evidence that these abnormal cells are a prerequisite to invasive testis tumors. They recommend that young men with a past history of cryptorchidism should be offered testicular biopsy to exclude this condition before malignancy occurs.

### Inguinal Hernia

The processus vaginalis normally obliterates after descent of the testis in the perinatal period. Undescended testes are associated with a higher incidence of patent processus vaginalis and inguinal hernia, in many cases leading to early surgical intervention because of the risk of incarcerated hernia. A clinically evident hernia present with a cryptorchid testis is an indication for immediate intervention. Most surgeons elect to perform a hernia repair and orchidopexy simultaneously.

### Torsion of a Cryptorchid Testis

There is a high incidence of up to 20% for torsion in unoperated undescended testes[48]; however, the trend to early orchidopexy has meant that most pediatric surgeons rarely see torsion in an undescended testis. The mobility of a testis within the tunica vaginalis in the superficial inguinal pouch may predispose to torsion, but the exact frequency is now difficult to determine.[103]

### Trauma

Inguinal testes are at a slightly increased risk of direct trauma, although as with testicular torsion, early surgical intervention has made this a less common problem.[65] The most common clinical cause of trauma in an undescended testis I have seen is in children with cerebral palsy requiring wheelchair restraint. In these children, an inguinal testis may be compressed by the straps of the wheelchair.

### Psychologic Factors

Cryptorchidism is a major psychologic problem because the obvious physical abnormality of the genitalia promotes parental anxiety about subsequent fertility.

### Testicular-Epididymal Fusion Abnormality

Abnormal connection between the testis and the epididymis is common in cryptorchidism.[40,41] The risk of abnormal fusion is greater with testes inside the canal or the abdomen than in inguinal testes or those lying at the neck of the scrotum. These abnormalities may be related to underlying androgen deficiency in utero, and in a percentage of these the abnormality may be sufficient to interfere with fertility.

## DIAGNOSIS

The aim of the clinical examination is to identify the presence or absence of a palpable gonad and to determine the lowest position that it will sit comfortably without undue tension.[104] The lowest limit of testicular position without tension probably corresponds to the caudal limit of the tunica vaginalis. Examination should be conducted in warm surroundings and with the child relaxed. With the child recumbent on the examination table, the genitalia should be inspected for the appearance of the scrotum and any inguinal swelling suggesting a high testis or an associated hernia. It is important to observe the scrotum before palpation because the testis may be seen in the scrotum only to retract briskly into the inguinal space on palpation, which may prove difficult to bring down into the scrotum, confusing the diagnosis. Cranial traction on the suprapubic skin to expose the scrotum often makes testes that are retracted to the upper part of the scrotum conspicuous. The appearance of the scrotum varies dramatically with age, with the neonatal scrotum being thin, pendulous, and flabby compared with the middle of childhood, when the scrotum is small and puckered. If the testis is lying within the scrotum, it is usually visible through the thin scrotal skin. Hypoplasia of the hemiscrotum suggests that the testis has never been within it. A hemiscrotum of normal size is more likely if the testis is retractile or ascending.

The key to locating a suprascrotal testis is to remember that the testis is contained within the tunica vaginalis and is therefore mobile. In addition, the bony landmarks of the inguinal ligament should be identified. It is helpful to begin the examination by blocking the internal inguinal ring with one hand and milk down toward the external ring to prevent the testis from being displaced cephalad into the inguinal canal on palpation. To locate a testis in the superficial inguinal pouch, light palpation with the flat of the hand is most effective. If palpation is too hard, this often displaces the testis from under the fingers, so it may be missed. At least 80% to 90% of testes are palpable in the inguinal region or can be squeezed out of the inguinal canal and felt at the external ring by pressing firmly on the abdominal wall laterally near the anterosuperior iliac spine and pressing downward and medially toward the scrotum. Intra-abdominal or intracanalicular testes that cannot be delivered outside the external ring are uncommon. Once the mobile testis has been identified in the groin, one hand of the examiner attempts to push the testis toward the

scrotum while the other hand attempts to grasp it through the thin scrotal skin. The aim of this maneuver is to determine the lowest level to which the testis can be manipulated without undue tension. A normally retractile testis should be able to be brought right to the bottom of the scrotum and remain there. The position of the testis at physical examination can be documented by measurement from the pubic tubercle as described by Scorer,[61] although this degree of documentation is usually unnecessary.

The most useful clinical observation is whether the testis can reside in the scrotum spontaneously. Examination of the scrotum in the newborn is easy because the testes are readily visible and palpable when in the scrotum. If the testes can be felt above the scrotum, the child should be reexamined at 3 months of age to see whether there has been delayed descent. If the testis remains out of the scrotum at age 3 months, a confident diagnosis of congenital undescended testis can now be made. If the testis has descended within the first 12 weeks, there is a risk that it may reascend out of the scrotum later in childhood, and such children are best kept under close observation.

Determining the exact testicular position may be difficult if there is an associated incarcerated inguinal hernia. Once the hernia has been reduced by manual compression, the position of the testis can usually be identified.

The clinical distinction between a normally retractile testis and an undescended testis can be difficult. Useful criteria for distinguishing normally retractile testes are as follows:

1. The testis can be brought fully to the bottom of the scrotum without difficulty.
2. The testis remains in the scrotum after manipulation without immediate retraction.
3. The testis is normal in size.
4. There is a history that the testis resides spontaneously in the scrotum some of the time.

If the testis cannot be palpated in the usual position in the groin near the external inguinal ring, the sites for an ectopic testis should be examined, such as the femoral region and perineum. Truly impalpable testes are relatively uncommon, being variously reported in 5% to 28% of boys with undescended testes.[105–108] If the testis cannot be palpated, this implies that it is either intra-abdominal (45%) or within the inguinal canal (up to 25%), which is likely if the external ring is palpably open (personal observation). Alternatively, it may be absent (45%). This is known as the vanishing testis and is likely the result of intrauterine torsion of the spermatic cord during migration of the gubernaculum to the scrotum.[84,109,110] This leads to secondary atrophy of the testis, and the contralateral testis is commonly enlarged, which is a useful physical sign.[83,111]

Blind inguinal exploration for the impalpable undescended testis is unlikely to be successful. Numerous imaging techniques have been recommended to identify the position of such a testis.[112] These include abdominal and inguinal ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and spermatic venography and arteriography. Laparoscopy recently has become the most common way to identify the position of an intra-abdominal testis and to exclude the possibility of secondary atrophy.[113–115] Laparoscopy offers the additional benefit of ligation of the testicular vessels should a two-stage Fowler-Stephens operation be contemplated.[113]

## TREATMENT

### Hormone Treatment

Hormone therapy is based on the premise that the undescended testis is caused by deficiency of the hypothalamic-pituitary-gonadal axis and that postnatal treatment can induce the required migration of the gubernaculum.[116] Therapy has been tried with testosterone, hCG, and luteinizing hormone-releasing hormone (LHRH). Direct androgen therapy was abandoned many years ago because excessive doses caused precocious puberty. In the past 10 to 20 years, hCG has been used commonly in Europe but less commonly elsewhere. More recently, LHRH has been tried.

The results of hormone therapy have been mixed and depend on a number of factors. Success rates for treatment range from 10% to 50%.[117–119] Children older than 4 years and those with bilateral undescended testes near the scrotal entrance or retractile testes respond most favorably to hCG. Testes in the superficial inguinal pouch, the most common variant of the anomaly, have a low success rate. It has been suggested that the successful cases are due to the fact that most were retractile testes.[119] In unilateral undescended testis, which is statistically much more likely to be of congenital origin, only 14% of boys have successful hormonal therapy.

In a randomized, double-blind study comparing hCG and LHRH, Rajfer and colleagues found 6% of boys treated with hCG responded with testicular descent compared with a 19% success rate for LHRH.[119] They concluded that neither hCG nor LHRH was effective in promoting descent of truly undescended testes. A double-blind, placebo-controlled study of LHRH nasal spray in boys with cryptorchid testis showed a 9% success rate with LHRH compared with 8% with placebo treatment.[117,120] A second course of LHRH therapy increased the descent rate to 18%. Young children had the lowest response rate, and LHRH was not useful for impalpable testes. There have been recent suggestions that hormone therapy may be useful for germ cell development as an adjunct to surgery,[121] but this remains extremely controversial.[122]

Some clinicians suggest that hormone therapy diagnoses a retractile testis (which has a high success rate) and thereby avoids surgery. Acquired undescended testes with severe retraction or secondary ascent may respond to hCG treatment at levels of 100 IU/kg intramuscularly twice a week for 3 to 4 weeks. Alternatively, LHRH can be given as a nasal spray at 100 mg in each nostril six times a day for 3 to 4 weeks. In my surgical department, hormonal therapy is used rarely, and nearly all children with congenital or acquired cryptorchidism are offered orchidopexy.

### Surgical Treatment

Treatment of cryptorchidism is based on the assumption that early intervention will prevent secondary degeneration of the testes caused by high temperature.[1] The scrotal testis is 3°C to 4°C cooler than the intra-abdominal core temperature, which is essential for normal postnatal testicular development.[67] The timing of surgery remains controversial, with some studies suggesting that delayed orchidopexy late in childhood is associated with good results, whereas others show poor results. Studies showing early degeneration of the germ cells in the first 6 to 12 months through to macroscopic atrophy in school-age children all suggest that undescended testes

undergo progressive degeneration after birth.[82,123] Although the evidence that early surgery prevents this degeneration sequence is not yet available in humans, it is shown in all animal studies.[124]

Orchidopexy is recommended at 6 to 9 months. This is because the first signs of damage to the testes are identified at about 6 months of age.[82] Orchidopexy in such young children, however, can be challenging. In pediatric surgical centers, orchidopexy is safe in the second 6 months of life; however, in centers with less experience in small children, surgery between 12 and 18 months may be safer. When orchidopexy is done in a pediatric surgical center, a younger age does not increase the risk of complications.[125]

Routine examination of all boys should be done at birth with repeat examination at 3 months in those children in whom one or both testes were not descended at birth. If the testis remains undescended at 3 months, the child is best referred for orchidopexy around 6 months of life. When the testis has descended spontaneously in the first 12 weeks, such children are best observed every few years to ensure that they do not develop acquired undescended testes later in childhood. Children presenting with a concomitant inguinal hernia should have the orchidopexy done together with the inguinal herniotomy. This is much safer than delaying the orchidopexy after the herniotomy because reexploration has a higher risk of damage to the vas and vessels. In older boys presenting with acquired maldescent, I recommend surgery once the testis no longer resides spontaneously in the scrotum. This is a controversial recommendation to some.

Orchidopexy is performed as an ambulatory procedure with the child entering the hospital or clinic an hour or so before operation and discharged a few hours later.[126] Topical anesthetic cream is applied to the back of the hand so that induction of anesthesia by injection is not painful. Under general anesthesia, a regional or local anesthetic block is performed to provide pain relief for the first few hours postoperatively.

For inguinal undescended testes, a skin crease incision is made over the external ring and extending a little laterally (Fig. 77-4, *A*). The remaining details are shown in Figure 77-4, *B* to *N*.

A widely patent processus vaginalis is common (up to 70%) and needs to be separated from the vas deferens and the testicular vessels (see Fig. 77-4, *D*). The hernia sac is wrapped around the vessels anteriorly with the vas deferens posteromedial and the vessels posterolateral. In high undescended testes, particularly those found in the inguinal canal, the hernia sac completely envelops the testis so that the vas and vessels are inside the sac within a mesorchium. The method of separation of the hernia sac is that used during routine hernia repair: the sac is stretched over the index finger while round-ended, nontoothed dissecting forceps gently sweep off the other cord structures, taking care not to damage the testicular vessels and vas deferens. En masse separation of the vas deferens and vessels is easier if the sac remains intact. If an opening is made inadvertently, the edges of the peritoneum should be picked up with forceps to maintain extensile exposure. The vas deferens is adherent to the back of the hernia sac, so it must be positively identified before the sac is divided. It is important to remember that the processus vaginalis may encompass the entire spermatic cord because its lateral edges can be fused posteriorly by the external spermatic fascia.

Once the cord structures have been separated from the sac, safely identified, and protected, the sac is divided (see Fig. 77-4, *E*). Dissection is continued proximally up to the internal ring, where external peritoneal fat and divergence of the testicular vessels laterally from the vas medially indicates the retroperitoneum (see Fig. 77-4, *F*). The processus vaginalis is then transfixed and ligated at the internal inguinal ring (see Fig. 77-4, *G*).

Further mobilization of the testicular vessels in the retroperitoneal space may be achieved by dividing small fibrous bands laterally that hold the testicular vessels and prevent them from being gently stretched to allow the testis to reach the scrotum (see Fig. 77-4, *H*). In older children, straightening the curved path taken by the testicular vessels may effectively lengthen the spermatic cord (see Fig. 77-4, *I*), but this advantage is much less evident in small children. Since the advent of laparoscopy, it can be seen that the testicular vessels actually take a straight path from the abdominal aorta toward the internal inguinal ring and that retroperitoneal dissection is more likely to gain length by allowing greater traction and stretching of the testicular artery rather than by straightening the path taken.

The vas deferens usually has sufficient length to reach the scrotum without any special maneuvers. In difficult cases, however, the inferior epigastric vessels can be divided or the posterior wall of the inguinal canal can be opened medial to the inferior epigastric vessels and the testis taken medially to them (Prentiss maneuver). This may give an extra centimeter or so of length to the vas deferens. The method of fixation of the testis in the scrotum is shown in Figure 77-4, *J* to *N*.

An alternative operation, which is particularly suitable for boys with acquired maldescent, is the transscrotal operation described by Bianchi and Squire[59] and Russinko and colleagues.[60] A transverse incision is made at the neck of scrotum, and the tunica vaginalis is exposed, delivered through the wound, and placed under tension. Loose connective tissue attachments to the spermatic cord are divided to expose the spermatic cord itself. Commonly, there is a residual fibrous strand of the processus vaginalis that has not disappeared. Once this fibrous strand has been divided, the vas and vessels stretch out to reach the bottom of the scrotum without difficulty.[58] The testis can be anchored by closing the neck of the scrotum or by suture of the testis to the scrotal septum.

When the testis is located within the inguinal canal or the abdomen, the spermatic cord may have insufficient length to reach the scrotum despite the maneuvers described previously. In this circumstance the surgeon has a number of choices available. If there is necessary expertise and backup support, microvascular anastomosis can be performed, with transection of the testicular vessels and reanastomosis to the inferior epigastric artery and vein.[127] This technique requires a high level of experience and skill with the operating microscope, so it is not often used. More commonly, if the testis has been dissected but does not reach the scrotum, it can be sutured in the groin at the lowermost point where it reaches comfortably as a first-stage procedure, and a second attempt is made 6 to 12 months later. Success rates for this two-stage orchidopexy have been quoted to be 70% to 90%.[128]

An alternative approach is the Fowler-Stephens procedure in which the testicular vessels are ligated intra-abdominally and the testis swung down on a long-loop vas supplied by collateral circulation from the artery to the vas and some

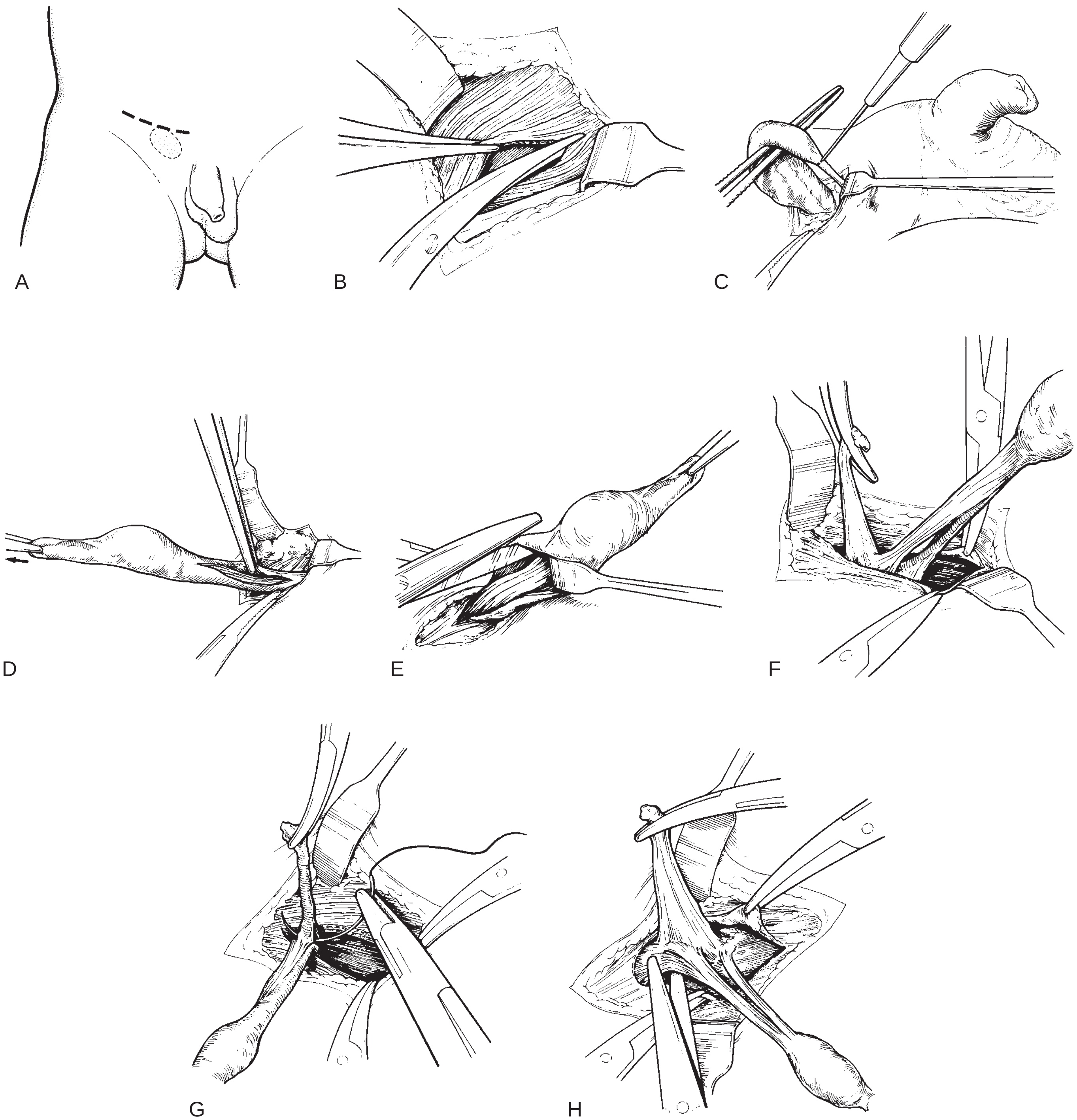


FIGURE 77-4 **A,** Skin crease incision over external ring and extending laterally. **B,** After dividing the Scarpa fascia, the external oblique aponeurosis is exposed and opened with a scalpel and extended medially toward the external inguinal ring with scissors. Application of mosquito forceps to the edges may facilitate subsequent identification and closure. **C,** A testis in the superficial inguinal pouch or pubic region is easily seen at this point, and it can be picked up so that traction on the spermatic cord can permit the distal attachment of the gubernaculum to be identified and divided. In most instances the gubernaculum is attached just lateral or above the neck of the scrotum. **D,** With traction on the tunica vaginalis, the cremaster muscle fibers are stripped off and any residual processus vaginalis is dissected off the vas and vessels, beginning posteriorly where the free edges of the sac are found. **E,** The vas and vessels are identified separate from the hernial sac and are protected by a small retractor while the sac is clamped and divided. **F,** The anteromedial processus vaginalis is dissected from the posterolateral gonadal vessels up to the internal inguinal ring, where the vas deferens diverges medially. **G,** Transfixion and ligation of the processus vaginalis at the internal ring. Twisting the sac first ensures that the needle does not catch any intraperitoneal structures inadvertently. **H,** Extra length may be achieved by freeing up the lateral side of the gonadal vessels in the retroperitoneal space.

*Continued*

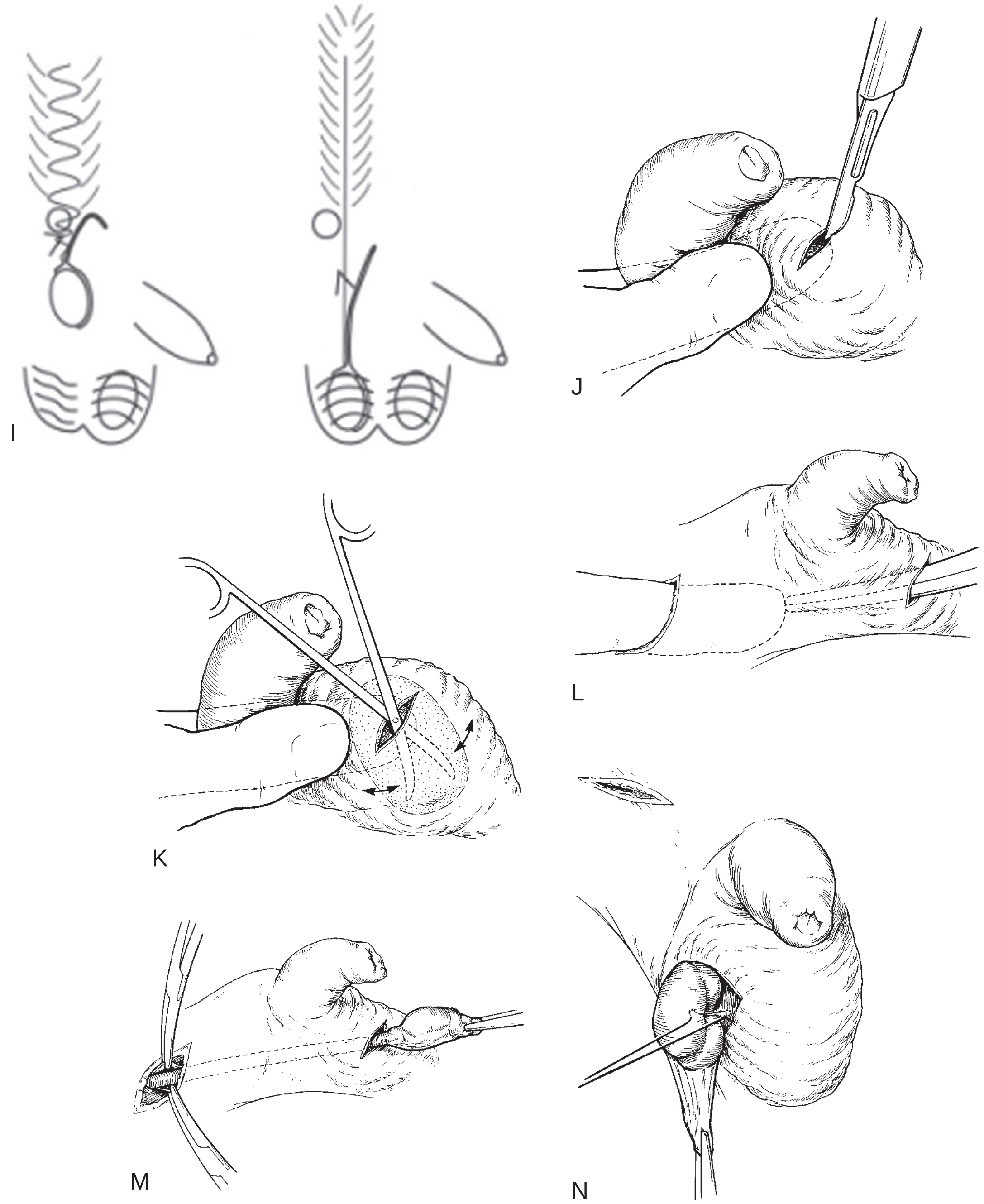


**FIGURE 77-4, CONT'D** **I,** Straightening of the path taken by the gonadal vessels may allow the testis to reach the scrotum. **J,** Incising the scrotal skin after blunt finger dissection has created a path to the scrotum from the inguinal incision. Either midline or transverse incisions may be used to gain entrance to the subdartos space; I prefer the latter because there is less bleeding. **K,** A subcutaneous pouch is made in the scrotum by undermining the incision with scissors or artery forceps. Careful attention must be given to hemostasis to avoid a postoperative hematoma. **L,** A fine artery forceps is pushed through the inguinoscrotal fascia, guided by the retreating finger, to connect the two incisions by a small buttonhole. **M,** The forceps grasps the testis, being careful not to twist the cord structures and pulls the testis down to the scrotal incision through the fascial buttonhole into the subdartos pouch. **N,** There may not be tension on the testis, and anchoring is optional. The testis may be sutured to the scrotal septum by a fine suture through the tunica albuginea, or alternatively the opening in the fascial buttonhole can be narrowed with one or two sutures, particularly if there is any tension on the cord structures, so the testis does not retract upward. The scrotal and inguinal incisions are closed in routine fashion. (From Spitz L, Coran AG: Pediatric surgery. In Rob and Smith's Operative Surgery, 5th ed. London, Chapman & Hall, 1995.)

cremasteric vessels (see Fig. 77-7, *A* and *B*).[43] Radical dissection of the inguinal canal before making the decision to perform a Fowler-Stephens operation may jeopardize its success by damaging the collateral blood supply. This complication can be overcome by performing the Fowler-Stephens operation as a two-stage procedure with initial ligation of the testicular vessels without disturbance to the collateral blood supply; the subsequent second-stage operation then allows the testis to be mobilized on the enlarged collateral vessels from the vas deferens, which then usually reach the

scrotum. In follow-up studies of this two-stage procedure, researchers report 70% to 90% scrotal position without atrophy.[129,130]

Many surgeons now use laparoscopy for impalpable testes in the inguinal canal and abdomen.[106,115] An immediate orchidopexy should be successful if the testis can be pulled to the opposite internal inguinal ring. A staged Fowler-Stephens operation is also relatively straightforward, and results are promising. In the first stage, laparoscopic localization of the testis allows a decision to be made about orchidopexy versus orchidectomy, which should be considered if the testis is small or dysgenetic. If orchidopexy is believed warranted, simple ligation of the testicular vessels above the testes can be performed with an endosurgical tie or a clip.[113] Six months later, the testis can then be mobilized on a flap of peritoneum containing the collateral blood supply and swung down through the medial edge of inguinal canal to reach the scrotum. At present, I perform both stages laparoscopically.[103]

## Complications of Surgery

In the hands of experienced surgeons and particularly with the routine use of magnification, the risk of complications after orchidopexy should be less than 5% (Table 77-1).[20] Damage to the testicular vessels leading to atrophy is the most feared complication, but this is relatively rare. More subtle damage to the vas deferens leading to occlusion of its lumen and subsequent interference with fertility is a theoretic problem, but its exact frequency is difficult to determine. Hemorrhage in the wound secondary to poor hemostasis occurs occasionally.

The most common complication after orchidopexy, particularly now that many are done in infants, is wound infection. Both the inguinal and scrotal incisions are at risk for infection at any age, but, in my experience, scrotal infection is more common in infants. Usually this is of no serious consequence and responds to simple antibiotic treatment or drainage. Secondary ascent of the testis after orchidopexy is an uncommon but important complication caused by inadequate mobilization of the cord or inadequate fixation of the testis within the scrotal pouch. Postoperative lymphedema and vascular congestion of the testis after orchidopexy is a common finding that resolves spontaneously over the first month or two.

After orchidopexy, the child is usually reexamined 1 to 2 weeks later to remove the dressing and assess the short-term outcome. A further follow-up examination is performed 6 to 12 months later to determine whether there has been any significant atrophy or secondary malposition of the testis. The end result and appearance are satisfactory in the majority of instances.

Success rates are higher for those testes that have passed through the external inguinal ring, whereas intracanalicular or abdominal testes have a higher incidence of persisting abnormality after orchidopexy. The intra-abdominal testis may fail to reach the scrotum, at least after a single-stage procedure, or it may be an inadequate gonad subsequently and atrophy. Total infarction of the testis is rare and is reported in 3% of patients with an impalpable testis. A further 15% to 20% have some atrophy after orchidopexy.[131] The risk of atrophy is probably increased if a second operation is required to bring the testis to the scrotum. Exact figures in this subgroup, however, are not available.

The risk of atrophy after orchidopexy is increased if a simultaneous inguinal hernia is performed for incarcerated or strangulated hernia. It is difficult to determine whether the increased rate of atrophy is secondary to compromise of the testicular vessels caused by compression or to the greater dissection required with a large hernia sac. The timing for orchidopexy has therefore been a compromise between the potentially increasing risk of testicular dysplasia with age compared with the potentially increased risk of postoperative atrophy in younger children. Wilson-Storey and colleagues[125] compared 100 infants younger than 2 years of age with 100 toddlers or older children undergoing orchidopexy after age 2 years. They found an incidence of testicular atrophy of 5% in both groups, suggesting that the risk of postoperative atrophy is not directly related to age in pediatric surgical centers.

**TABLE 77-1**

**Complications of Orchidopexy**

| |
|---|
| Failure of testis to reach scrotum |
| Secondary atrophy of the testis |
| Retraction of testis out of scrotum |
| Occlusion of vas deferens |
| Hemorrhage |
| Wound infection |

## Fertility

A significant number of studies have evaluated fertility in men after orchidopexy (Table 77-2).[7,132–137] Testes initially located beyond the inguinal canal have a good prognosis for fertility, although location does not change outcome for unilateral cases.[90] Interpretation of results is difficult, however, because in most current fertility studies of men the operations were

**TABLE 77-2**

**Fertility After Orchidopexy**

| | | | | Fertility | |
|---|---|---|---|---|---|
| *Authors* | *No. of Patients* | *Average Age at Operation* | *Fertility Tests* | *Unilateral* | *Bilateral* |
| Puri et al., 1985 | 142 | 7-13 | Semen analysis | 74 | 30 |
| Singer et al., 1988 | 25 | 6.2 | Semen analysis | 70 | 40 |
| Cendron et al., 1989 | 40 | 7.0 | Paternity | 87 | 33 |
| Kumar et al., 1989 | 56 | 7-18+ | Paternity | 84 | 60 |
| Okuyama et al., 1989 | 167 | 2-5 | Semen analysis | 95 | 24 |
| Mandat et al., 1994 | 135 | 8.9 | Semen analysis | 53 | 26 |
| Lee et al., 2001 | 51 | 7.1 | Paternity | 90 | — |

between 6 and 13 of years of age, suggesting that this group includes many acquired variants such as ascending and retractile testes. These latter patients are far less likely to have abnormal fertility because early germ cell maturation would have occurred normally when the testis was in the scrotum during infancy. The histology of ascending testis is reported to be similar to congenitally cryptorchid testes, and histopathology correlates with future fertility potential.[138,139]

An extensive review of the literature has failed to demonstrate any significant improvement in fertility with early operation within the range of 4 to 14 years.[137] Although 27 papers were reviewed, only four reports were recently published and we can no longer extrapolate data from operations done on adolescent patients before the 1950s and 1960s. With advances in knowledge and changes in clinical management in the past 25 years (i.e., earlier surgical intervention), it is inappropriate to compare these older historical studies with the results of current treatment. Whether orchidopexy in infancy ultimately achieves a significantly improved rate of fertility remains to be seen, but as described earlier, surgery at 9 months shows early promise for improved testicular volume.[94]

### Malignancy

At present, there are no accurate data available as to whether orchidopexy in early infancy reduces the risk of subsequent testicular cancer. However, Cortes reports that the risk of malignancy for acquired undescended testes is low.[140] There will be a lag time between the current trend of orchidopexy in infancy and convincing evidence that this change in the management alters outcome for congenital undescended testes. At this time, all clinicians can do is define those features that appear to affect prognosis. Good prognostic signs include the testis near the neck of the scrotum, ascending or retractile testes, and possibly operation in early infancy. Poor prognosis is associated with primary dysplasia of the testis or epididymis, intra-abdominal or intracanalicular testes, an associated strangulated inguinal hernia, and possibly operation delayed until late childhood or adolescence.

## Torsion of the testis

Torsion of the testis was first described in 1840 by Delasiauve.[141] The condition was first reported in the newborn by Taylor in 1897,[142] and torsion of a testicular appendage was first described by Colt in 1922.[143] Ombredanne,[144] in 1913, described a lesion that was probably a testicular appendage, although he did not recognize its true nature.

Twisting or torsion of the testis results in occlusion of the gonadal blood supply, which, if unrelieved, leads to necrosis. Although it is not the most common cause of the acute scrotum in childhood, it is certainly the most important (Fig. 77-5). Torsion of the testis is a surgical emergency because of the high incidence of gonadal necrosis.

Intratunical or intravaginal torsion occurs most commonly and is predisposed to by an abnormally high investment of the spermatic cord by the tunica vaginalis. The long narrow mesorchium allows the testis to lie horizontally within its peritoneal sac (tunica vaginalis), the so-called *bell-clapper anomaly*. In the normal testis, the short mesorchium attaches to the full length of the epididymis and allows testicular movement

**FIGURE 77-5** Mechanical causes of the acute scrotum present as pain, swelling, and redness confined to the hemiscrotum, as shown in this 1-year-old infant, because the inflammatory reaction is limited by the ipsilateral tunica vaginalis.

within the tunica vaginalis but prevents complete torsion. The pendulous testis associated with a high investment of the cord has a horizontal lie and allows the testis to be readily twisted by leg movement or cremasteric contractions. A rare variant of intratunical torsion is one in which there is separation between the testis and the epididymis, allowing torsion between these structures. This is likely to be more common in undescended testes.

Extratunical or extravaginal torsion is less common and is confined to the perinatal period. During descent of the gubernaculum and testis into the scrotum, there is a loose areolar plane around these moving structures, which allows the entire tunica vaginalis and spermatic cord to twist.

Beyond the newborn period, testicular torsion is almost always associated with the bell-clapper variant. Trauma and physical activity may be important, as may action of the cremaster muscle.[145] Cremasteric contraction may be either the cause or the effect of torsion. The high incidence of testicular torsion at puberty suggests that recent enlargement of the testis associated with increased serum testosterone levels is a predisposing factor.

Torsion of the testis does not always cause necrosis if the number of twists is small or the testis untwists spontaneously. In an experimental dog model, four complete turns of the spermatic cord caused necrosis within 2 hours, whereas one complete turn produced no ischemia in up to 12 hours.[146] In adolescent boys, necrosis is likely after 24 hours of symptoms but may occur after as little as 2 hours.[147,148]

In 1761 Morgagni described the appendix testis, now known as the hydatid of Morgagni.[104] This is believed to be an embryologic remnant of the cranial end of the müllerian or paramesonephric duct. It is present in more than 90% of males and varies in size from 1 to 10 mm in diameter. It is the most frequently twisted of the four testicular appendages. The others are the appendix epididymis, which is a remnant of

the Wolffian duct, the paradidymis, and the vas aberrans. These vestigial structures have a similar histology, being composed of gelatinous and vascular connective tissue covered with a columnar epithelium. The hydatid of Morgagni is usually pedunculated, which predisposes to torsion. The most frequent time for torsion of the testicular appendix is at about 11 years of age. This peak, just before the onset of puberty, may be related to early pubertal stimulation by estrogens.[149–151]

Inflammatory conditions of the scrotum are often called epididymo-orchitis, even though the epididymis alone is usually affected before puberty. Epididymitis is rare after puberty, whereas epididymo-orchitis is more common after puberty. The mumps virus has a predilection for the postpubertal but not the prepubertal testis. Epididymitis is seen between birth and 6 months, and thereafter is rare until after puberty. It is usually caused by infection reaching the epididymis by retrograde spread along the vas deferens from the urinary tract. *Escherichia coli* is the common organism, and infections are predisposed to by urinary tract abnormalities or urethral instrumentation. The most common group now suffering epididymo-orchitis in childhood are boys with spina bifida having intermittent catheterization. This is occasionally seen in infants with imperforate anus and rectourethral fistula or may be seen in the bladder exstrophy population after closure.

Idiopathic scrotal edema is occasionally confused with torsion of the testis or its appendages. In this condition, there is rapidly developing edema of the scrotum with spread to or from the inguinal region, penis, or perineum. The cause of this edema is not always apparent but may be bacterial cellulitis or a topical allergy.

A rare cause of the acute scrotum, which may be confused with testicular torsion, is fat necrosis. It is characterized by the sudden appearance of tender, often bilateral small lumps within the scrotal skin. The affected boys are often obese, and there may be a history of swimming in cold water.

Henoch Schönlein purpura may present with signs of acute scrotal swelling either before or after other systemic signs and symptoms. It is most commonly bilateral and rarely painful.

## CLINICAL FEATURES

Torsion of the testis is common in adolescence, but before puberty torsion of a testicular appendage is more common (Table 77-3). There are two peaks of incidence for torsion of the testis: in the early neonatal period and in adolescent boys aged 13 to 16. In a review of 771 children up to the age of 16 presenting with acute scrotum, 58% had torsion of the testicular appendage and 29% had torsion of the testes. Epididymitis had been diagnosed in 13%, although a significant number of these subsequently turned out to have torsion of a testicular appendage that had not been recognized.[149]

**TABLE 77-3**
**Causes of Acute Scrotum**

| *Pathology* | *Frequency* | *Age at Presentation* |
|---|---|---|
| Extravaginal torsion of testis | Uncommon | Perinatal |
| Intravaginal torsion of testis | Common | Anytime, peak at 13-16 yr |
| Testicular appendage torsion | Very common | Anytime, peak at 11 yr |
| Epididymitis | Rare | 0-6 mo |
| Mumps orchitis | Uncommon | Only after puberty |
| Idiopathic scrotal edema | Uncommon | 0-5 yr |
| Fat necrosis of scrotum | Rare | 5-15 yr |

Clinical presentation of testicular torsion is usually heralded by the sudden onset of pain in the testis, lower abdomen, or groin, associated with nausea and vomiting. Occasionally the onset is more gradual without severe pain, leading to delayed diagnosis. A previous history of short-lived, similar pains suggests prior incomplete torsion with spontaneous resolution. A horizontal lie of the testis when the boy stands indicates a long mesorchium. Unless the testis and the epididymis are necrotic, local palpation is exquisitely painful. The hemiscrotum rapidly becomes red and edematous, and, if untreated, infarction of the testis may give the hemiscrotum a bluish discoloration. The inflammatory signs usually end abruptly at the edge of the hemiscrotum because this coincides with the limits of the peritoneum, tunica vaginalis. A reactive hydrocele from effusion of edema fluid into the tunica may make the physical signs more difficult to interpret (see Fig. 77-5).

Torsion of a testicular appendage presents with an almost similar history, although often the degree of pain is less severe. A bluish black spot (blue-dot) may be seen through the skin at the upper pole of the testis, but this may not be apparent for 24 to 48 hours after the development of symptoms, and palpation of this area causes extreme pain but usually in point tenderness fashion, whereas palpation of the testis itself causes little discomfort. The degree of inflammation of the epididymis is variable with testicular appendage torsion. Once secondary inflammation and edema of the scrotum occur, it may be impossible to distinguish between testicular torsion and torsion of a testicular appendage.

Investigations such as radioisotope scans and Doppler ultrasound have been used to determine whether there is blood flow to the testes in acute scrotum.[152,153] In adolescents beyond pubertal age, such tests may be more useful because the volume of the testis is large enough to allow a reasonably high level of accuracy. Before puberty, however, when the testis is less than 1 or 2 mL in volume, such tests are of lower accuracy and have limited clinical usefulness. I do not usually perform these studies but immediately explore the scrotum through a small midline scrotal incision.

## TREATMENT

Treatment of the acute scrotum and possible torsion of the testis is immediate operative exploration of the scrotum. A midline incision is made in the scrotum, and the hemiscrotum is opened with diathermy. The edema in the scrotal wall may make identification of the tunica vaginalis difficult. It is easy to recognize once this has been opened by the efflux of hydrocele fluid. The testis is delivered through the incision if there is evidence of torsion of the gonad itself. Where the testis appears normally viable, its upper pole is manipulated into the wound and the twisted hydatid is delivered through the incision and excised. Usually this is a black pea after hemorrhagic infarction. A significant number of hydatids, however, undergo torsion without secondary hemorrhage and appear pale at surgery. These should always be excised and sent for pathologic confirmation of necrosis.

If the testis is twisted, this is untwisted and the viability assessed. In a prepubertal child, this maneuver is usually relatively easy and circulation returns within a few minutes. In the postpubertal testis, particularly when there has been some secondary hemorrhage, viability may be difficult to determine. In this circumstance, it may be better to observe the testis for several minutes while exploring the contralateral scrotum. The use of a Doppler probe may be helpful to determine if there is testicular blood flow.

The contralateral hemiscrotum should always be explored when torsion of the testis has been found because the anomaly is usually bilateral. It is not sufficient to place a few absorbable sutures between the testis and the scrotal wall. The best technique is to create a window of tunica vaginalis by excising a segment of the tunica and suturing the edges of the defect to the tunica albuginea with nonabsorbable sutures.[154] This creates permanent fusion of the testicular surface with the connective tissues of the scrotum and creates a second, anterior mesorchium. Inadequate fixation with absorbable sutures may result in recurrent torsion.[155,156]

It is controversial whether testes of doubtful viability should be excised or left in situ to see whether they will recover any hormonal function. There is now good evidence that testicular ischemia damages the blood-testis barrier and exposes the child older than 10 years of age to the potential risk of autoimmunization against his own spermatogonia.[136] This potentially serious complication has been recognized because spermatogenesis later in life is poor in men who underwent fixation of ischemic testes in adolescence. The risk of autoimmunization related to ischemia is low in children younger than age 10 because there is no blood-testis barrier before spermatogenesis commences.[157,158] It is my practice, therefore, to leave doubtful testes in situ in children younger than 10. In children older than 10 with an ischemic gonad, I recommend orchidectomy.

Another controversial issue is whether neonates presenting with a dead testis, apparently caused by perinatal torsion, should have the contralateral testis fixed.[159,160] As mentioned previously, perinatal torsion is usually caused by torsion of the spermatic cord during testicular descent. A significant percentage of such children, however, also have an unfixed or bell-clapper testis and are therefore at risk of having contralateral torsion. A firm recommendation is difficult to give on this issue, but a strong case can be made for exploration of the contralateral testis and fixation as described for adolescent torsion, especially in an infant younger than a few weeks old. After 3 months of age, secondary adherence of the gubernaculum to the scrotum should have occurred and exploration is less useful.

In adolescents presenting with intermittent recurrent testicular pain, bilateral orchidopexy may be justified, especially if there is a horizontal lie of the testes on clinical examination. Almost one third of adolescents who undergo acute torsion have a history of previous intermittent pain.

# Varicocele

Dilation of the testicular veins in the pampiniform venous plexus causes a varicocele.[161] The countercurrent heat exchange mechanism in the spermatic cord vessels is disrupted, which leads to an increased temperature of the testis and scrotum. The abnormally high temperature can be detected by thermography and causes progressive dysfunction of the testis and epididymis.[1,162] This may lead to subsequent testicular atrophy and infertility, as first proposed by Tulloch.[163] Testicular atrophy may be significant in adult life but may become evident quite early in adolescence.[164] The incidence of varicocele is 15% among men in general and rises to 20% to 40% in men presenting to infertility clinics. In children younger than age 10 years, varicocele is rare, but by the end of adolescence the incidence has risen to that seen in the adult population.[165] Varicocele may occur in small children with Wilms tumor, neuroblastoma, or hydronephrotic kidney that causes obstruction of venous return from the testis. Although most cases of varicocele occur on the left, varicocele on the right side is suggestive of a retroperitoneal tumor.

## CLINICAL PRESENTATION

Varicocele presents as a soft, distensible mass in the upper part of the scrotum (Fig. 77-6). In 80% to 90% of cases they present on the left side, with bilateral lesions reported as occurring between 2% and 20% and right-sided lesions between 1% and 7%.[166] In the supine position, a redundant left hemiscrotum and horizontal lie of the left testis may be noted.[167] On standing, the varicocele fills with blood to produce the typical "bag of worms" appearance. The lesion is not usually painful; however, the boy may complain of a dragging sensation.

Varicoceles may be classified by size into grades I to III or small, medium, and large. Small varicocele (grade I) may be evident only during Valsalva maneuver.[168,169] Medium-size

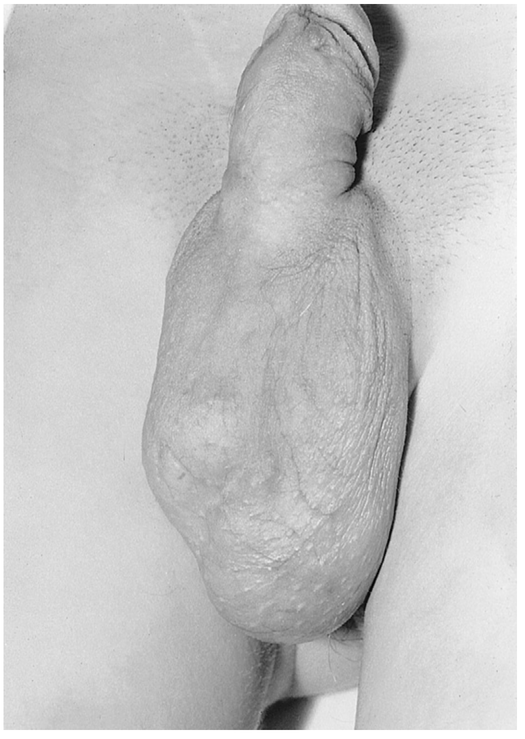

FIGURE 77-6 A grade III varicocele in a 14-year-old boy is visible as a space-occupying lesion of the left hemiscrotum even in the supine position before surgery. On standing, the dilated vessels fill to produce a "bag of worms."

varicoceles (grade II) are palpable without Valsalva maneuver, and large varicoceles are visible as a scrotal space-occupying lesion.[170]

## ETIOLOGY

Lack of valves in the left testicular vein is one of the primary factors in the etiology of varicocele. In postmortem examinations, the left testicular vein contains no valves in 40% of specimens compared with absence of valves in only 23% of right spermatic veins, and the right-angle entry of the left spermatic vein into the high-pressure venous system of the left renal vein may predispose to varicocele.[171] When upright, the long pressure column generated in the pampiniform plexus results in poor venous return and varicose distention of the veins. There are a number of other etiologic theories including disruption of the venous pump created by the coverings of the spermatic cord, compression of the left renal vein between the superior mesenteric artery and the aorta, extrinsic pressure on the left testicular vein by a full sigmoid colon, and vascular spasm at the origin of the left testicular vein caused by adrenaline coming from the left adrenal gland. In a series of 659 patients undergoing spermatic venography, absence of the valves in the left testicular veins was documented in 484 patients.[172] In addition, a further 172 patients with varicocele had valves intact but had reflux of blood into the testicular vein through collaterals draining the left kidney. Renal vein stenosis was identified in 103 patients. The external spermatic vein (cremasteric vein) has also been implicated because it may be dilated in up to 50% of varicoceles.[173]

Because the testis is supplied by three separate arteries, so is the venous drainage formed by more than one set of veins. Blood reaches the testis via the testicular (or internal spermatic) artery from the abdominal aorta, the deferential artery supplying the vas deferens, and the cremasteric (or external spermatic) artery arising from the external iliac artery and inferior epigastric vessels (Fig. 77-7, *A*). These three vessels form an anastomosis around the caudal epididymis. Blood drains from the testis and epididymis into the pampiniform plexus accompanying the testicular artery. Above the internal inguinal ring, the number of venous channels decreases to one or two and finally coalesces into a single testicular vein entering either the inferior vena cava on the right or the left renal vein; the latter join at a right angle. Retrograde flow in the veins is prevented by the presence of valves. Anastomoses with subsidiary veins occur along the vas deferens to the base of the bladder through the cremasteric and scrotal veins to the saphenous vein (see Fig. 77-7, *B*).

## EFFECTS OF VARICOCELE

Varicocele leads to testicular atrophy and subsequent infertility in adult life, probably secondary to abnormally high temperature.[174] How the excessive temperature actually produces testicular dysfunction, however, is not so clear. A number of abnormalities have been documented in hormonal function and other physiologic parameters of the testis, but whether these are primary or secondary abnormalities is uncertain. This is particularly true for a proposed defect in the hypothalamic-pituitary-gonadal axis. Serum testosterone levels are usually normal, although a subclinical defect in the androgen axis is possible.[175] Leydig cell hypoplasia with high serum follicle-stimulating hormone levels has mostly been reported in adults with established testicular atrophy. Inhibited testicular development during puberty is seen in association with histologic changes that are similar to those seen in adults with infertility caused by varicocele.[135,176,177] Where testicular atrophy is recognizable, an abnormal production of pituitary hormones occurs in response to a gonadotropin-releasing hormone stimulation test.

## INDICATIONS FOR TREATMENT

The criteria for treatment are controversial, with common indications including symptoms such as chronic pain or discomfort, demonstrable atrophy of the testis in adolescence, and subfertility in adults. When there is greater than a 10% difference in gonadal volume on orchidometry, Parrott and

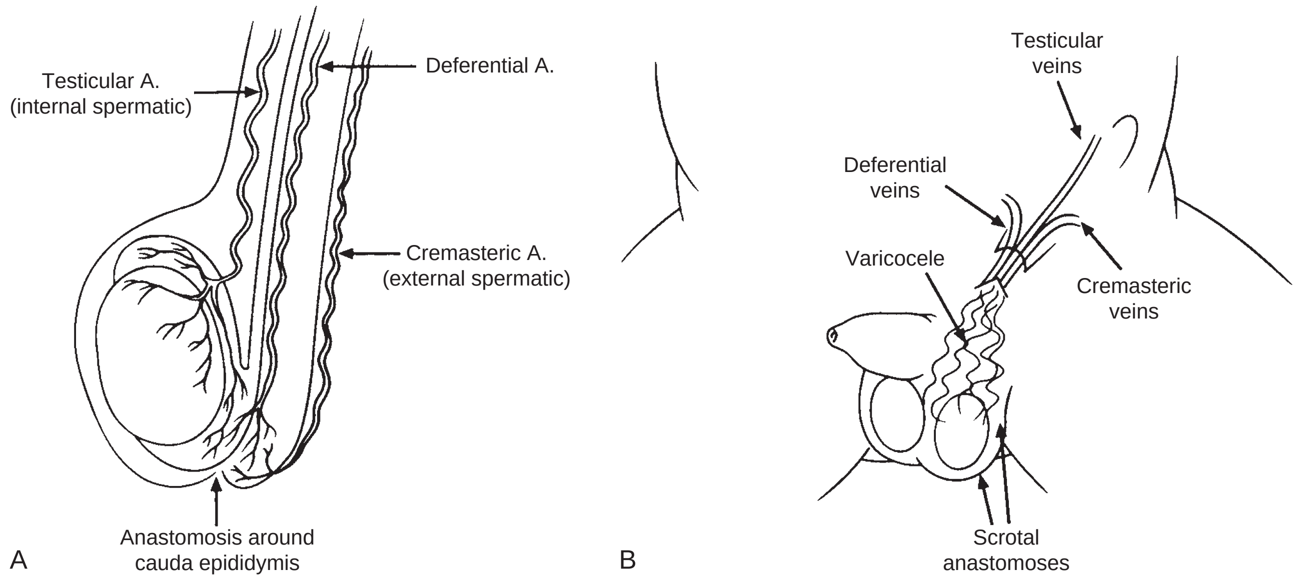


**FIGURE 77-7** **A,** Arterial supply to the testis, epididymis, and vas deferens, with anastomoses around the cauda epididymis. **B,** Venous drainage of the testis, showing the anastomoses with the varicocele. (From Hutson JM: Varicocele and its treatment. Pediatr Surg Int 1995;10:509.)

Hewatt[178] advocate operation. Nagar and Levran[168] have recommended screening of school boys by physical examination to identify varicoceles at any early stage of development and found varicoceles were present but asymptomatic in 10% of nearly 800 boys examined. They propose that screening enabled the diagnosis to be made at an earlier age and a lower stage of disease. They speculated that this should produce improved future fertility in adults, but this will not be proven for some time. Doppler ultrasound is currently a popular test used in adult infertility clinics to identify subclinical varicoceles.[179] In early adolescence, however, when the testicular volume and blood flow is much less than in adults, the role of Doppler ultrasound is less reliable. Diagnostic or therapeutic testicular venography is currently popular for men with a varicocele.[180,181] In young adolescents, general anesthesia is usually required for such a procedure, although a study using therapeutic testicular venography with insertion of spring coils has been described using only local anesthesia.

## OPERATION

The multiple theories of etiology of varicocele have led to a wide range of surgical options (Fig. 77-8). Inguinal exploration has been a standard procedure for many years, with careful ligation of all the venous channels as described by Ivanissevich[182] and by Sayfan and colleagues.[181] Historically, this technique has been associated with a high incidence of secondary hydrocele, accidental ligation of the testicular artery leading to testicular atrophy, and recurrence of the varicocele.[183,184] Poor results in some hands have led to a search for alternative approaches including microsurgical dissection of the testicular veins, preserving the testicular artery and lymphatics within the spermatic cord. Some authors have suggested identifying the artery or veins intraoperatively so that the artery can be preserved. For this purpose, both Doppler ultrasonography and venography have been used, but the role of these intraoperative investigations remains uncertain.[184–186] Antegrade sclerotherapy is also being used in some units.[187]

Shafik and colleagues[188] have suggested plication of the external spermatic fascia to cause external compression of the pampiniform vessels. This is a simple procedure but does not address the persisting problem of retrograde flow of blood within the testicular veins. One might predict a high frequency of recurrence, although this is not currently known.

Laparoscopic ligation of the testicular vein proximal to the internal ring has gained popularity.[115] Some authors have recommended selective ligation of the venous channels preserving the artery, whereas others have recommended mass ligation of the artery and the veins. Many publications attest to the feasibility of laparoscopic ligation, but long-term follow-up is not available.[183,189]

Palomo first proposed mass ligation of the testicular vessels including both artery and veins in the retroperitoneum above the internal inguinal ring.[190] The technique has a high success rate with a surprisingly low risk of testicular atrophy as long as the collateral vessels have been preserved.[178,189,191,192] The operation has been available for a long time but has only recently gained popularity. Fear of devascularizing the testis has made many surgeons cautious. As stated in Palomo's publication, however, the blood supply of the testis should be maintained if any two of the three vessels are preserved. Because the cremasteric and deferential vessels are preserved, the collateral arterial supply of the testis should be intact and no venous channels are accidentally excluded by being mistaken for the testicular artery itself.

Laparoscopic mass ligation as described by Palomo is my personal choice, although I offer the family the option of having the procedure done laparoscopically or by a small open retroperitoneal approach. The laparoscopic method is similar to that described elsewhere in this book, with a 5-mm telescope port through the umbilicus and two 4-mm ports, one in the left abdomen level with the umbilicus and the other in the hypogastrium. With the surgeon standing on the right side of the operating table and the assistant on the left, the video screen is placed near the left foot. The colon can be displaced readily by tilting the patient. The peritoneum is opened several centimeters away from the internal inguinal ring, and the entire vascular pedicle including artery and all venous channels is ligated in continuity with a 3-0 absorbable suture. Lymphatic channels may be preserved if identified.

The open procedure is also straightforward and may be done on an ambulatory basis. Under a short general anesthetic, an incision is made in the left iliac fossa medial and just a little below the left anterosuperior iliac spine. This is usually several centimeters away from the internal inguinal ring. The oblique muscles are divided along the line of their fibers just lateral to the rectus abdominis muscle. Once the peritoneum is visualized, it is mobilized medially by pledget and blunt dissection. Using this site of access, the peritoneal cavity is shallow and medial displacement of the peritoneum immediately exposes the testicular pedicle well below the level of the ureter entering the pelvis. The vascular pedicle is isolated from the overlying peritoneum with a right-angle forceps, and two 3-0 absorbable ligatures are placed in continuity around the pedicle. It is not necessary to divide the testicular pedicle, although this is an option. On removal of the retractors, the peritoneum immediately resumes its normal position and a few tacking sutures can be placed in the muscle layers and the skin closed with subcuticular sutures in the normal manner. Because the Palomo operation does not disturb all the lymphatic drainage of the inguinoscrotal region and leaves collaterals to the cremasteric and deferential vessels intact, the postoperative risk of an acute hydrocele is lower than with other procedures.

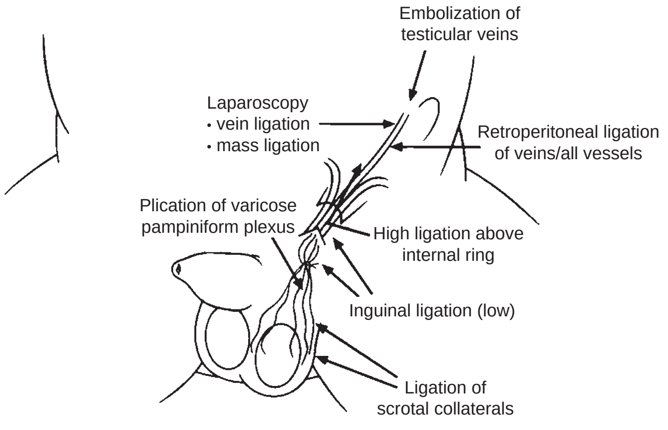


FIGURE 77-8 The large range of approaches to correction of a varicocele. (From Hutson JM: Varicocele and its treatment. Pediatr Surg Int 1995;10:509.)

## RESULTS

The recognized complications of varicocele repair are shown in Table 77-4. The risk of recurrence or persistence of the varicocele is quoted as 5% to 45%.[184] Risk of reactive hydrocele varies between 7% and 39%. The incidence of testicular atrophy, which is one of the most important outcome measures related to this surgery, is rarely reported, so accurate figures are unknown.

**TABLE 77-4**
**Complications of Varicocele Repair**

| | |
|---|---|
| Recurrence/persistence | 5%-45% |
| Reactive hydrocele | 7%-39% |
| Testicular atrophy | Not known |
| Ilioinguinal nerve injury | Not known |
| Injury to vas deferens | Not known |

Ilioinguinal nerve damage has been reported after inguinal approaches, and genitofemoral nerve injuries have been reported after laparoscopy and injury to the vas. Ligation of the veins within the inguinal canal using a modified Ivanissevich procedure has a 16% recurrence, compared with high retroperitoneal selective vein ligation, which has a reported recurrence rate of 11%. In a study of 32 boys treated with mass ligation through the Palomo procedure, no failures and no testicular atrophy were found after any of the operations. I concur from my own experience that the Palomo operation is the preferred technique. The surgical management of varicocele continues to evolve, but at present the laparoscopic Palomo operation holds reasonable promise as having higher success and lower complication rates than previous procedures.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 78

# Hypertrophic Pyloric Stenosis

Marshall Z. Schwartz

## History

The history of what we now refer to as *infantile hypertrophic pyloric stenosis* dates back to the early 1700s. Blair[1] described an infant with postmortem findings consistent with hypertrophic pyloric stenosis in 1717. Hirschsprung, in 1888,[2] provided the first complete description of hypertrophic pyloric stenosis. He believed that this entity was congenital and represented failure of involution of the fetal pylorus and named it *angeborener pylorusstenose* (congenital pyloric stenosis). In a landmark paper in 1908, Dufour and Fredet[3] suggested that surgical correction could be accomplished by splitting the hypertrophied pyloric muscle to the submucosa and closing the muscle transversely. However, in 1912, Ramstedt[4] suggested that closure of the muscle was not necessary, and the current standard operation was established.

Infantile hypertrophic pyloric stenosis (IHPS) is the most common cause of gastric outlet obstruction in infants. The prevalence of IHPS ranges from 1.5 to 4.0 per 1000 live births in Caucasian infants but is less prevalent in African-American and Asian children.[5] Reports have suggested that the incidence is increasing.[6,7] It is well known that it is more common in boys than girls, with a ratio of approximately 2:1 to 5:1.[5] The occurrence of IHPS has been associated with several variables including both environmental and familial factors. IHPS is now thought to be caused by a mechanism other than a developmental defect. Based on considerable evidence, including a study by Wallgren,[8] in which 1000 male infants had a barium swallow immediately after birth, there were no anatomic abnormalities of the pylorus identified. Thus it is generally agreed that IHPS is not a congenital abnormality. Of interest is that subsequently, IHPS developed in five of these infants. In a similar but more recent study, 1400 consecutive newborn infants underwent ultrasound (US) measurements of the pylorus, with no abnormalities seen.[9] In nine of these infants, however, IHPS subsequently developed.

## Anatomy and Histology

The gross appearance of the pylorus in IHPS is that of an enlarged, pale muscle mass usually measuring 2 to 2.5 cm in length and 1 to 1.5 cm in diameter (Fig. 78-1). Histologically, there is marked muscle hypertrophy and hyperplasia[10] primarily involving the circular layer and hypertrophy of the underlying mucosa.[11] Immunohistochemical analysis of the hypertrophic muscle reveals an increase in fibroblasts, fibronectin, proteoglycan chondroitin sulfate,[12] desmin,[13] elastin,[14] and collagen.[15] Confocal microscopy identifies abnormally contorted and thickened nerve fibers.[16] The result of these gross and microscopic changes is either partial or complete obstruction of the pyloric channel.

## Etiology

The etiology of IHPS has eluded investigators for several decades. Despite considerable research attempting to elucidate the etiology of IHPS, no definitive causative factors have been identified. Both genetic and environmental factors seem to play a role in the pathophysiology. Evidence for a genetic predisposition includes variability among races, a clear male preponderance, an increased risk to first-born infants with a positive family history, and certain ABO blood types. Mitchell and Risch studied the familial occurrence patterns of IHPS and noted that it was compatible with either multifactorial threshold inheritance or the effects of multiple interacting loci.[5] Although pyloric stenosis is more common in boys, the risk for IHPS in the offspring of mothers who had pyloric stenosis as infants is greater than if the father had IHPS. Environmental factors associated with IHPS include the method of feeding (breast-feeding versus formula feeding), seasonal variability, erythromycin exposure, and transpyloric feeding of premature infants.[5,17–19]

Another focus has been on alterations in relaxation of the pyloric muscle. One study noted a decrease in ganglion cells in the circular muscle of the pylorus,[20] but a subsequent study found that the ganglion cells were normal in number but appeared to be immature.[21] Zuelzer[22] and Jona[23] did not find any change in number or ultrastructural appearance of the ganglion cells. As new technology and concepts have evolved, additional associations that involve IHPS and gastrointestinal peptides, growth factors, neurotrophins, changes in neural development, and nitric oxide have been described.

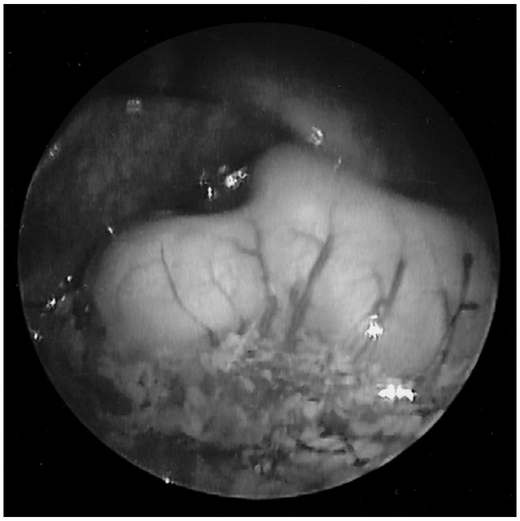

FIGURE 78-1 Laparoscopic view of a hypertrophied pylorus.

## GROWTH FACTORS AND GASTROINTESTINAL PEPTIDES

Over the past several decades numerous gastrointestinal peptides or growth factors have been implicated by direct or indirect methodologies as having a causal relationship including gastrin, substance P, epidermal growth factor (EGF), transforming growth factor-$\alpha$ (TGF-$\alpha$), insulin-like growth factor-I, somatostatin, secretin, enteroglucagon, and neurotensin.[24,25] Other peptides have been evaluated for their potential relationship to IHPS. Substance P, a neurotransmitter responsible for enteric muscle contraction, could produce chronic pylorospasm leading to muscle hypertrophy.[26] This peptide is present in higher concentration in the pyloric muscle of patients with IHPS. Shima and colleagues[27–29] found an increase in the gene expression of EGF, TGF-$\alpha$, and insulin-like growth factor-I and an increase in immunostaining for EGF and TGF-$\alpha$. Somatostatin, secretin, enteroglucagon, and neurotensin have also been implicated.[24,30,31] However, their role has not been substantiated, and no clear etiologic relationship has been identified.

### Neurotrophins, Neural Development, and Nerve Function

Neurotrophins, which are important for nerve differentiation and survival, have been noted to be decreased in IHPS. Further studies have shown that one of the specific receptors for these neurotrophins, the tyrosine kinase A receptor c-kit, is not present in IHPS tissue.[32–34] Investigators also identified that the pylorus in IHPS is deficient in glial-derived growth factors, which may be indicative of immature development of the enteric nervous system.[35]

Other techniques have been applied to the evaluation of pyloric innervation. Okazaki and colleagues[36] used monoclonal antibodies targeted to nerve terminals and neurofilaments. They found a reduced density of both neural elements in patients with IHPS. Kobayashi and colleagues[37] demonstrated a decrease in nerve-supporting cells in both the circular and longitudinal muscle layers in infants with IHPS. Piotrowska and colleagues[38] found that muscle biopsy specimens from IHPS patients have decreased numbers of interstitial cells of Cajal, the pacemaker cells for the gastrointestinal tract, and a lack of heme oxygenase-2, which may play a role in communicating between the interstitial cells of Cajal and smooth muscle cells.

### Nitric Oxide

Nitric oxide can induce smooth muscle relaxation in the esophagus, stomach, and intestine. It was reasoned that a deficiency of nitric oxide in the pyloric muscle might result in failure of relaxation.[39–41] Nicotinamide-adenine dinucleotide phosphate (NADPH) diaphorase (essentially identical to nitric oxide synthase) was measured in biopsy specimens of hypertrophied pyloric muscle wall from IHPS patients. The hypertrophied circular muscle did not demonstrate any NADPH diaphorase activity, but the activity in the longitudinal muscle was normal. The authors concluded that the lack of nitric oxide synthase in pyloric tissue might be responsible for pylorospasm and lead to IHPS.[42]

Thus at present no definitive cause of IHPS has been elucidated. Whatever the mechanism, it must take into account that the process of IHPS generally occurs several weeks after birth and the circular muscle hypertrophy is transient even without myotomy. It is also apparent that whatever triggers IHPS causes a dramatic change in cellular architecture and function through what may be a broad array of pathways.

# Clinical Features and Differential Diagnosis

The typical clinical finding in an infant with IHPS is the onset of nonbilious vomiting at 2 to 8 weeks of age with a peak occurrence at 3 to 5 weeks. Two reports are at variance with traditional concepts: IHPS has been diagnosed at birth[43] and even in utero.[44] Initially, the emesis may not be frequent or forceful, but over a period of several days it progresses to nearly every feeding and becomes forceful (projectile). On occasion, there may be blood in the emesis that gives it a brownish discoloration or a coffee-ground appearance as a result of gastritis or esophagitis. Infants with IHPS remain hungry after emesis and are otherwise not ill appearing or febrile. A significant delay in diagnosis leading to severe dehydration, however, results in a lethargic infant. Some infants have diarrhea (starvation stools) and are thought to have gastroenteritis. Approximately 2% to 5% of infants have jaundice from indirect hyperbilirubinemia, which can reach levels as high as 15 to 20 mg/dL. This is believed to be secondary to glucuronyl transferase deficiency.[45] In premature infants, IHPS is generally diagnosed 2 weeks later than in term infants.[19] The emesis may not be projectile and evolves more slowly, which frequently leads to a delay in diagnosis.

Pylorospasm and gastroesophageal reflux may be difficult to differentiate from IHPS without further imaging evaluation. Other medical causes of nonbilious vomiting include gastroenteritis, increased intracranial pressure, and metabolic disorders. Other surgical causes of nonbilious emesis include antral webs, pyloric atresia, duplication cyst of the antropyloric region, and ectopic pancreatic tissue within the pyloric muscle, all far less common than IHPS.

## Diagnosis

Nonbilious projectile vomiting, visible peristaltic waves in the left upper part of the abdomen, and hypochloremic, hypokalemic metabolic alkalosis are cardinal features of IHPS. A definitive diagnosis can be made in 75% of infants with IHPS by careful physical examination of the upper part of the abdomen. Unfortunately, this is becoming a lost skill. Frequently, imaging procedures are requested by primary care physicians in lieu of a careful physical examination. To be successful in palpating an enlarged pylorus, the infant must be calm, warm, and cooperative. The use of a pacifier or a small feeding (5% dextrose in water) may be helpful. If the stomach is distended, aspiration with a nasogastric tube assists successful palpation of an enlarged pylorus, often referred to as "the olive." With the infant supine and the legs bent to relax the abdominal muscles, the examining hand should be placed on the epigastrium. After the edge of the liver has been identified with the fingertips, gentle pressure deep to the liver and progressing caudally in the midline a third of the distance between the umbilicus and xiphoid should reveal a palpable pylorus if IHPS is present. The examiner should be willing to commit 5 to 15 minutes of uninterrupted time if necessary to obtain an adequate examination. One should be able to roll the hypertrophied pylorus under the fingertips to be convinced of the diagnosis. Failure to palpate the pylorus requires further workup to clarify the cause of vomiting. The differential diagnosis includes gastroenteritis, food allergy, gastroesophageal reflux, pylorospasm, antral web, pyloric duplication, ectopic pancreatic tissue in the wall of the pylorus, and vomiting occasionally accompanying adrenogenital syndrome, metabolic disorders, and increased intracranial pressure.

US has become not only the most common initial imaging technique for the diagnosis of IHPS but also the standard for diagnosing IHPS. Under optimal circumstances, this technique is reliable. However, it is dependent on the level of experience and expertise of the ultrasonographer. The generally accepted criteria for a positive US study are a pyloric muscle thickness of 3.5 (in premature infants) to 4 mm or more and a pyloric channel length of 16 mm or greater (Fig. 78-2).[19] Some centers also determine pyloric diameter and consider more than 14 mm to be abnormal.[46] Lamki and colleagues[47] reviewed their experience with US and concluded that a muscle thickness of 3 mm should be considered a positive finding for IHPS in infants younger than 30 days. US also obviates the need for radiographic contrast studies and the associated radiation exposure.

If US is not available or diagnostic, an upper gastrointestinal (UGI) contrast examination is highly effective in making the diagnosis of IHPS. Barium is generally preferred compared with water-soluble contrast to avoid the chemical pneumonitis should aspiration occur. This study should demonstrate an elongated pyloric channel and indentation on the antral outline, which are indirect findings of pyloric muscle enlargement (Fig. 78-3). If barium does not leave the stomach, it is not possible to confirm the diagnosis of IHPS because pylorospasm can also produce transient complete gastric outlet obstruction. However, if sufficient time is taken with intermittent fluoroscopy, it should be possible to differentiate between the two entities. It is advisable for the radiologist to aspirate the residual barium from the stomach after termination of the radiographic procedure to avoid perioperative aspiration.

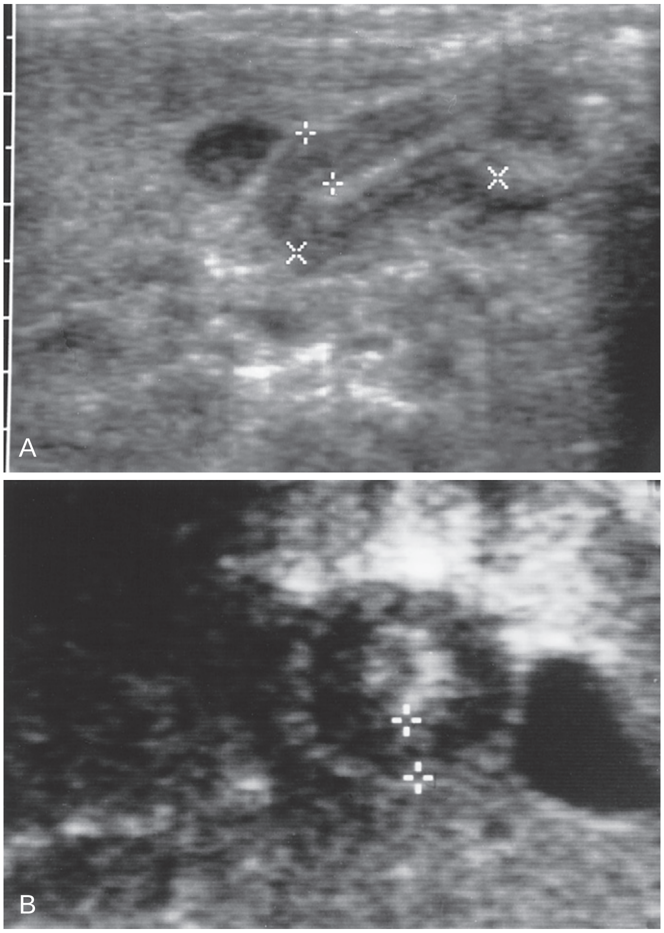


**FIGURE 78-2** Ultrasound images of the hypertrophied pylorus in a 5-week-old infant. **A,** A longitudinal view is shown with pyloric length (X-X) measuring 18 mm and pyloric muscle thickness (+-+) measuring 5.2 mm. **B,** Transverse view illustrating muscle thickness (+-+). (**A,** Courtesy of Dorothy Bulas, MD.)

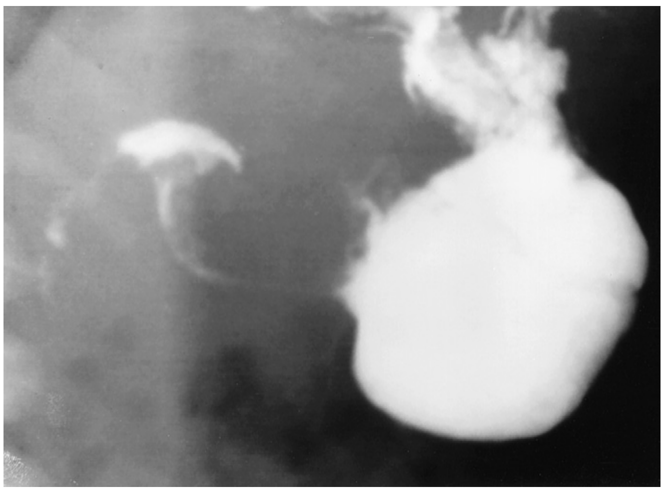

**FIGURE 78-3** Upper gastrointestinal study illustrating an elongated pyloric channel with shoulders proximally as indirect evidence of pyloric muscle hypertrophy. Note the small amount of contrast in the duodenal bulb defining the length of the hypertrophied pylorus.

In 1998 our group conducted a survey of practice patterns for the diagnosis of IHPS among pediatric surgeons in community, university, and children's hospitals.[48] The questionnaire was distributed to 487 board-certified pediatric surgeons, with a 69% response rate. Ninety-one percent of the respondents stated that they would not request a further diagnostic test if a pyloric olive was palpable. US was identified as the diagnostic study of choice for an inconclusive physical examination (86% of the time). Finally, 82% of pediatric surgeons would proceed with an operation with a positive US study even if the results of physical examination under anesthesia were negative. The response to this question indicates that US has essentially supplanted physical examination as the diagnostic test of choice for IHPS.[48]

# Treatment

## PREOPERATIVE PREPARATION

It is most important to prepare the infant adequately for anesthesia and surgical correction of IHPS. The length of preparation depends on the severity of the fluid and electrolyte abnormalities. Benson and Alpern[49] defined three levels of severity primarily on the basis of the serum carbon dioxide content (slight, <25 mEq/L; moderate, 26 to 35 mEq/L; and severe, >35 mEq/L). In addition to the elevated bicarbonate, hypokalemia, hypochloremia, dehydration, and possibly malnutrition may be present.

Most infants with IHPS do not have complete gastric outlet obstruction and can therefore tolerate their gastric secretions. Oral feedings should be discontinued. A nasogastric tube should not be placed routinely because it removes additional fluid and hydrochloric acid from the stomach, which perpetuates the electrolyte and acid-base imbalance.

Fluid resuscitation should be based on the degree of dehydration and the extent of electrolyte abnormalities. Most infants with IHPS should be able to be resuscitated within a 24-hour period. With severe metabolic and fluid abnormalities, however, aggressive resuscitation should be avoided because it can produce rapid fluid and electrolyte shifts, possibly leading to seizures and other complications. Intravenous administration of 5% dextrose in 0.45 normal saline containing 20 mEq/L of potassium chloride is the optimal resuscitation regimen for fluid and electrolyte replacement. Under circumstances of extreme hypokalemia, the concentration of potassium chloride can be increased to 30 mEq/L, but because the intravenous fluid rate likely will be above maintenance rates, the serum potassium level should be carefully monitored. Withholding potassium chloride in the intravenous fluid while awaiting urine output only delays appropriate replacement. The exception (rare) is knowledge of preexisting renal impairment or evidence of acute renal compromise. Hyponatremia is rarely a problem. Nonetheless, it is common to see normal saline given as an initial bolus. However, there is little rationale for the use of normal saline because it enhances the hypokalemia by dilution and provides an excess amount of sodium. Intravenous therapy should be correlated with the level of dehydration. An initial rate for fluid resuscitation is 1.25 to 2 times the normal maintenance rate until adequate fluid resuscitation and urine output are achieved. The concentration of potassium chloride in the intravenous fluid should be based on the level of hypokalemia and the rate of infusion while keeping in mind that a potassium chloride concentration exceeding 30 mEq/L is rarely indicated.

It is necessary to monitor urine output and serum electrolytes. Normalizing the serum bicarbonate level (with the goal of decreasing the level below 30 mEq/dL) usually lags behind normalization of fluid volume and serum potassium and chloride. Administration of ammonium chloride or dilute hydrochloric acid is rarely necessary. As noted previously, indirect hyperbilirubinemia with clinical signs of jaundice occurs in a small percentage of infants with IHPS. It is not usually necessary to evaluate the hyperbilirubinemia further. The hyperbilirubinemia invariably resolves postoperatively.

## OPERATIVE PROCEDURE

Again, it is important to emphasize that fluid and electrolyte abnormalities must be corrected preoperatively including having a serum bicarbonate below 30 mEq/L to avoid respiratory depression and prolonged postoperative intubation.

In the operating room, before the induction of anesthesia, it is important to aspirate the stomach. If a barium UGI study has been performed, it is advisable to remove the residual contrast material by gastric irrigation and suctioning to avoid the risk for perioperative aspiration.

The operative procedure of choice remains the Ramstedt pyloromyotomy. This procedure has stood the test of time because it is straightforward, curative, and associated with remarkably low morbidity. Regardless of abdominal access techniques, the myotomy created is identical.

### Minimal Laparotomy ("Open") Technique

The standard open approach is a right upper quadrant transverse incision of approximately 2.5 to 3 cm made either over or lateral to the right rectus muscle and just superior to the edge of the liver. The fascial layers are divided transversely over the rectus muscle, and it can be either retracted laterally or split longitudinally in the middle. Several other incisions have been described.[3] A commonly used alternative is a supraumbilical curved skin incision followed by division of the midline fascia superiorly for 1 to 2 cm. The edge of the liver is retracted superiorly to expose the greater curvature of the stomach (near the pylorus), which is grasped with a noncrushing forceps or clamp and brought out through the incision. A damp gauze sponge can then be used to grasp the stomach, and with traction inferiorly and laterally to the patient's left, the pylorus can be delivered through the incision. Grasping the duodenum or pylorus directly with forceps can result in injury or perforation of these structures and should therefore be avoided. The pylorus can be stabilized by the index finger of the operating surgeon standing to the right of the patient. The serosa on the anterior wall of the hypertrophied pylorus is incised with a scalpel from the area just proximal to the hypertrophied muscle extending just proximal to the pyloric vein (Fig. 78-4). I and many others prefer to use the back of a scalpel handle to complete the myotomy by bluntly splitting the hypertrophied muscle down to the submucosa (see Fig. 78-4). Other surgeons prefer the use of a pyloric spreading clamp such as that described by Benson.[50] It is appropriate to leave a few pyloric muscle fibers intact at the duodenal end to reduce the risk for duodenal

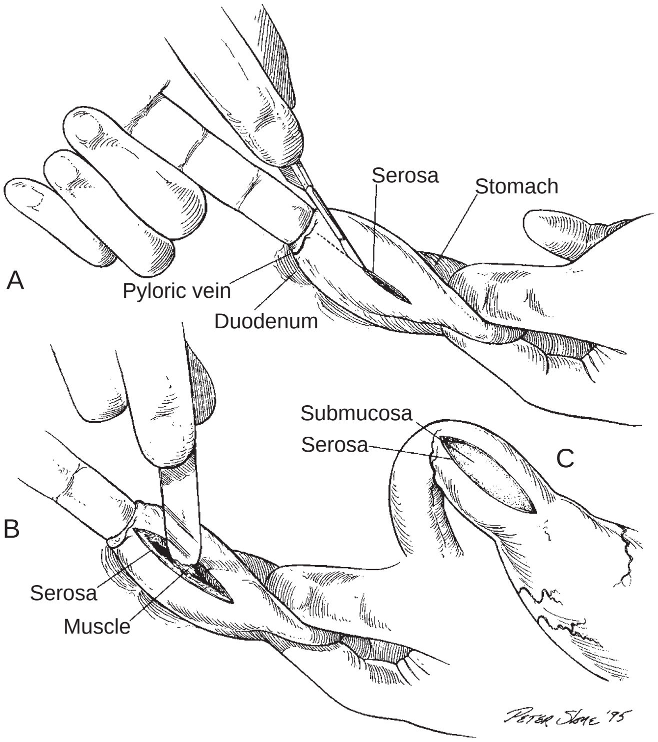


**FIGURE 78-4** Pyloric stenosis, operative technique. **A,** Pylorus delivered from the peritoneal cavity and stabilized between the surgeon's index finger at the duodenal end with the stomach grasped proximally by the assistant. The serosal incision is outlined and begun. **B,** Back of a scalpel handle being used to split the hypertrophied muscle down to the submucosa. **C,** Completed myotomy showing submucosa bulging through the divided muscle.

perforation. Most incomplete myotomies are a result of failure to extend it far enough proximally onto the antrum. A careful check for a leak from the stomach or duodenum should be made before returning the pylorus to the peritoneal cavity. Bleeding from the pyloric muscle edges or submucosal surface is generally venous and almost always stops after returning the stomach and pylorus to the peritoneal cavity.

Entrance into the lumen during pyloromyotomy should be a rare event. If it occurs, the submucosa should be approximated with interrupted fine absorbable suture and a portion of omentum placed over this site. An infrequently needed alternative is to reapproximate the myotomy site, rotate the pylorus 180 degrees, and perform a myotomy on the posterior wall of the pylorus. The fascial layers of the abdominal wall are closed with running absorbable suture. The skin is closed with subcuticular suture and Steri-Strips and covered with a dressing.

### Laparoscopic Procedure

The first description of a laparoscopic pyloromyotomy was by Alain and colleagues[51] in 1991. Since that time, numerous publications have supported this approach. As the procedure is currently performed in most centers, the infant is placed supine at the end of the operating table (Fig. 78-5). A 5-mm port is placed through a small vertical incision in the umbilicus, and the abdomen is insufflated with $CO_2$ to a pressure of 6 to 8 cm $H_2O$. Two additional access sites are chosen (under direct vision with the camera) in the left and right upper quadrants—ports are not usually required (Fig. 78-6). After

**FIGURE 78-5** Position of the infant on the operating room table for laparoscopic pyloromyotomy.

infiltration with a local anesthetic, a No. 11 scalpel blade is used to make a small (2- to 3-mm) skin incision and extended through the abdominal wall. Until recently an arthrotomy knife was used to begin the myotomy: This instrument is no longer available. The extended cautery blade has served as an adequate substitute. A grasper is placed directly through the left upper quadrant incision and used to grasp the antrum just proximal to the pylorus. After the right upper quadrant 2- to 3-mm incision is accomplished, the extended cautery blade is passed directly into the peritoneal cavity. The grasper stabilizes the pylorus, and the cautery blade is used to score the serosa of the hypertrophied pylorus with a low electrical current at the site of the myotomy in a fashion similar to what is done during the "open" technique (Fig. 78-7). The cautery blade (without electrical current) is used to initiate splitting of the hypertrophied muscle and removed. A pyloric spreader designed for laparoscopic procedures is placed through the right upper quadrant incision. This instrument is used to complete the myotomy (Fig. 78-8). At the completion of the myotomy, each side of the divided muscle is grasped and moved in opposite directions to ensure that a complete myotomy has been achieved. Air is then insufflated through a nasogastric tube (typically 60 mL) to check for a leak. If none is seen, the instruments are removed, the $CO_2$ is evacuated, and the umbilical port is removed. The umbilical fascial defect is closed, and the skin at all three sites is closed with subcuticular suture.

## COMPARISON OF THE OPEN VERSUS LAPAROSCOPIC APPROACH

Aesthetics were the initial impetus for developing this procedure; however, proponents of laparoscopic pyloromyotomy now cite many other benefits including faster recovery time with quicker return to full feeding, earlier postoperative discharge, a decrease in postoperative emesis, and a decrease in pain.[52] However, advocates of open pyloromyotomy state that recovery time is similar and that the laparoscopic approach has a greater complication rate including perforation,[8,52–55] missed perforation,[54] incomplete myotomy,[54,56] an increase in operative time, and increased expense.[53] All

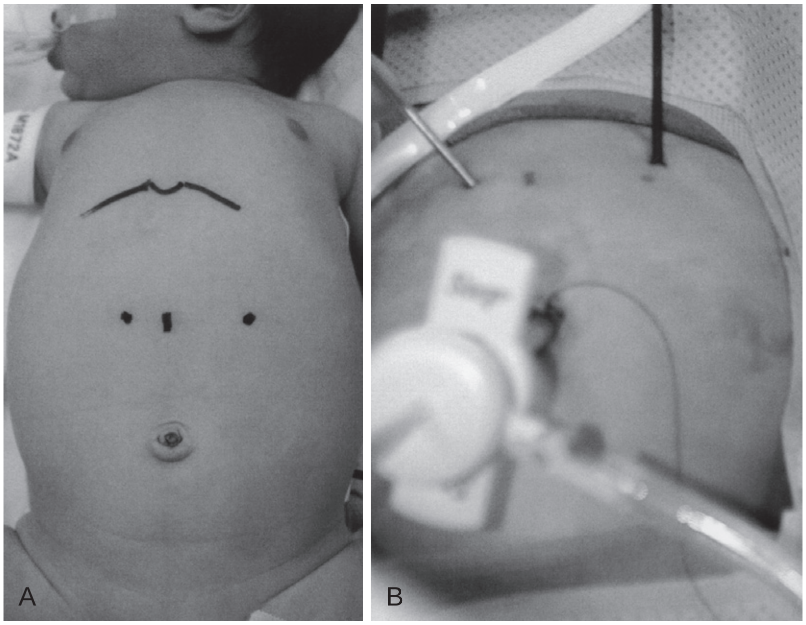


**FIGURE 78-6** Location of "ports" **(A)** and after the instruments and telescope are in place **(B).**


**FIGURE 78-7** View through the laparoscope with the arthrotomy knife being used to incise the serosa over the hypertrophied pylorus.

the published studies to date have been retrospective and demonstrate a marked degree of variability.

The range for the average time to discharge in the published literature for laparoscopy is similar to that for open procedures. Of the four publications that compare time to discharge between the open procedure and laparoscopy, only one group found statistical significance and the difference in discharge time was only 4 hours (Table 78-1).[53,55,57–61]

There is wide variation in the incidence of postoperative emesis. The range for laparoscopy was 1% to 68%, whereas for the open procedure it was 25% to 65%, with no statistical significance observed between the open and laparoscopic groups.[52,53,57,58,62]

The average time to establish full feeding in the laparoscopic group ranged from 16 to 32 hours versus 20 to 61 hours for the open procedure (Table 78-2).[52–54,57,62] The results are no different if the Fujimoto outlier study is eliminated.[52]

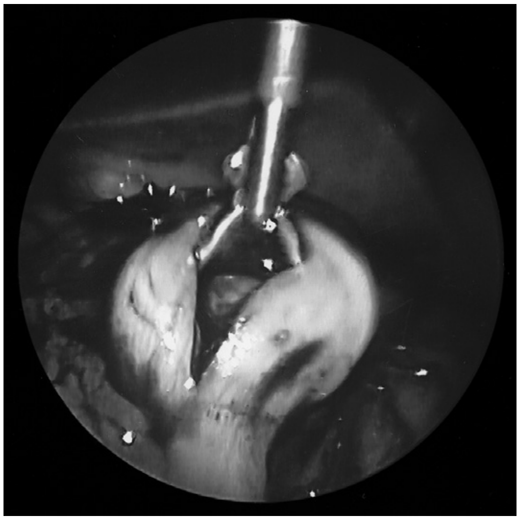

**FIGURE 78-8** Hypertrophied pyloric muscle after being split with the spreader.

Over the past decade, considerable additional experience has occurred and laparoscopic pyloromyotomy has become the standard at the training sites and children's hospitals in the United States with low morbidity and short hospital stays.

The wound infection rate for both groups was similar and ranged from 0% to 6% in the laparoscopic groups and from 0% to 7% in the open groups. None of these studies identified a significant difference between the groups (Table 78-3).[52,54,55,57–59,63]

The operative time was similar for both groups, with laparoscopy taking from 24.3 to 41 minutes and the open procedure taking from 18.9 to 32.5 minutes. Yagmurlu and colleagues[56] (the largest study) showed that laparoscopy was faster by 4.7 minutes on average. Sitsen and colleagues[55] and Scorpio and colleagues[60] found that laparoscopy was slower by 14.3

**TABLE 78-1**
**Average Length of Stay (Hours)**

| *Author* | N | *Laparoscopic* | *Open* |
|---|---|---|---|
| Kramer WL, et al. | 133 | 61.6 | |
| Caceres M, Liu D | 56 | 60 | 61.5 |
| Campbell BT, et al. | 117 | 31 | 28 |
| Shankar KR, et al.* | 86 | | 58 |
| Sitsen E, Bax NM, van der Zee DC | 72 | 70 | 74† |
| Najmaldin A, et al. | 37 | 28 | |
| Scorpio RJ, et al. | 63 | 44 | 63 |
| Range | | 28-70 | 28-74 |

*Umbilical approach only.
†$P < .05$.

**TABLE 78-2**
**Average Time to Full Feeding (Hours)**

| *Author* | N | *Laparoscopic* | *Open* |
|---|---|---|---|
| Caceres M, Liu D | 56 | 24.1 | 27 |
| Campbell BT, et al. | 117 | 19 | 20 |
| Fujimoto T, et al.* | 60 | 34.8 | 61.2† |
| Ford WD, Crameri JA, Holland AJ | 84 | 32 | 41 |
| Greason KL, et al. | 25 | 19 | 23 |
| Range | | 19-35 | 20-61 |

*Umbilical approach only.
†$P < .01$.

**TABLE 78-3**
**Average Wound Infection Rate**

| *Author* | N | *Laparoscopic* | *Open* |
|---|---|---|---|
| Kramer WL, et al. | 133 | 3% | |
| Caceres M, Liu D | 56 | 0% | 3% |
| Fujimoto T, et al.* | 60 | 0% | 7% |
| Sitsen E, Bax NM, van der Zee DC | 72 | 6% | 3% |
| Ford WD, Crameri JA, Holland AJ | 84 | 3% | 2% |
| Najmaldin A, et al. | 37 | 0% | |
| Scorpio RJ, et al. | 63 | 0% | 5% |
| Range | | 0%-6% | 0%-7% |

*Umbilical approach only.

**TABLE 78-4**
**Average Operative Time (Minutes)**

| *Author* | N | *Laparoscopic* | *Open* |
|---|---|---|---|
| Yagmurlu A, et al. | 457 | 24.3* | 29 |
| Kramer WL, et al. | 133 | 29 | |
| Caceres M, Liu D | 56 | 36.1 | 32.5 |
| Campbell BT, et al. | 117 | 38 | 33 |
| Shankar KR, et al.† | 86 | | 30 |
| Fujimoto T, et al.† | 60 | 27.4 | 31.9 |
| Sitsen E, Bax NM, van der Zee DC | 72 | 33.2 | 18.9* |
| Ford WD, Crameri JA, Holland AJ | 84 | 41 | 28 |
| Greason KL, et al. | 25 | 25.4 | 26.1 |
| Najmaldin A, et al. | 37 | 29 | |
| Scorpio RJ, et al. | 63 | 40.2‡ | 27.3 |
| Range | | 24-41 | 19-33 |

*$P < .01$.
†Umbilical approach only.
‡$P < .05$.

**TABLE 78-5**
**Average Perforation Rate**

| *Author* | N | *Laparoscopic* | *Open* |
|---|---|---|---|
| Yagmurlu A, et al. | 457 | 0.40% | 3.6%* |
| Kramer WL, et al. | 133 | 3% | |
| Campbell BT, et al. | 117 | 8% | 4% |
| Fujimoto T, et al.† | 60 | 3% | 0% |
| Sitsen E, Bax NM, van der Zee DC | 72 | 9% | 6% |
| Ford WD, Crameri JA, Holland AJ | 84 | 10% | 6% |
| Range | | 0.4%-10% | 0%-6% |

*$P < .05$.
†Umbilical approach only.

minutes and 13 minutes, respectively, but in each series the smaller number of patients probably indicates less operative experience at the time of the study. The other five comparative studies failed to reach statistical significance (Table 78-4).[53–62]

The perforation rate, which includes both duodenal and pyloric injuries, had ranges of 0.4% to 10% for laparoscopic pyloromyotomy and 0% to 6% for the open procedure. Four comparative studies found that laparoscopy had a slightly higher perforation rate, but the differences were not statistically significant (Table 78-5).[52–56,58]

Other factors that have been analyzed include the abdominal wall hernia rate, which in some laparoscopic groups ranged from 4% to 7%,[55,60] interleukin-6, and heat loss. Fujimoto and colleagues[52] found that interleukin-6 peak levels were significantly lower in the laparoscopy group 24 hours after surgery. They hypothesized that this could indicate a decreased level of stress on the patient. Holland and colleagues[63] found that laparoscopy tended to decrease the temperature of the infant to a greater degree than the open procedure did, which may have detrimental physiologic effects. These biologic markers indicate subtle differences between the open and laparoscopic procedures, but they may not be clinically significant.

As experience with laparoscopy has increased, the learning curve for the surgeon has become shorter, and technology has continued to improve, application of this technique has become commonplace. The larger laparoscopic studies demonstrate a comparable complication rate, and there may be a decrease in subjective factors such as pain and earlier feeding. Ultimately, the main difference may be the increased cost of laparoscopy. However, for surgeons who have limited exposure or access to laparoscopic techniques and equipment, the "open" Ramstedt pyloromyotomy remains the gold standard with which all other methods should be compared.

## POSTOPERATIVE MANAGEMENT

In the majority of infants, feeding can be started within 4 hours after the surgical procedure. Infants with hematemesis from gastritis may benefit by delaying feeding for an additional

**TABLE 78-6**

| Postpyloromyotomy Feeding Schedule* |
|---|
| Pedialyte, 30 mL orally every 3 hr × 1 |
| Full-strength formula, 30 mL orally every 3 hr × 1 |
| Full-strength formula, 45 mL orally every 3 hr × 2 |
| Full-strength formula, 60 mL orally every 3 hr × 1 |
| Full-strength formula, 75 mL orally every 3 hr × 1 |
| Full-strength formula as desired |

*Begin 4 to 6 hours after surgery. For very small infants, the starting feeding volume may be reduced to 15 mL and the schedule stopped at volumes of 60 to 75 mL, which provide an adequate calorie supply. Breast milk can be substituted for formula if appropriate.

6 to 12 hours after the procedure. A typical feeding schedule is shown in Table 78-6. It is clear that the more aggressive the feeding schedule, the greater the incidence of emesis in the initial postoperative period, but this approach is usually successful and generally allows for earlier hospital discharge.[64] The feeding schedule shown in Table 78-6 is moderately aggressive and allows for hospital discharge approximately 24 hours after the feedings are initiated. In the future, infants may be discharged within 3 or 4 hours after pyloromyotomy, in which case resumption of feeding will be undertaken by the family at home.

### NONOPERATIVE TREATMENT

This approach never gained acceptance in North America but was practiced in the past in some European countries. Although infants with IHPS can be managed with frequent small feedings, this practice necessitates either a prolonged hospital stay or an attentive caregiver at home and may lead to aspiration and malnutrition. It may take months for the hypertrophied muscle to resolve. The occasional mortality and the prolonged interval from diagnosis to resolution led to abandonment of this type of management.

## Complications

Complications after pyloromyotomy should be minimal if performed by experienced surgeons. Vomiting, frequent in the early postoperative period, is thought to be secondary to gastroesophageal reflux, discoordination of gastric peristalsis, or gastric atony and should not be considered a complication. Frequent vomiting persisting beyond 3 to 4 days may suggest an incomplete myotomy or an unsuspected perforation. A postoperative contrast study may demonstrate a leak but is not helpful in evaluating the completeness of the myotomy. It takes several weeks for the radiographic appearance of the pylorus to improve.[65] Persistent and frequent vomiting 1 week beyond the pyloromyotomy may require reexploration.

## Outcome

After pyloromyotomy, mortality should be a rare occurrence and morbidity should be low. In a large series of infants undergoing open pyloromyotomy, the incidence of perforation was 2.3%, wound-related complications occurred in 1%, and there was one death.[50] More recent series have reported even lower morbidity and mortality.[66]

As experience with laparoscopic pyloromyotomy has increased, outcomes have become similar to those after the open approach. With a somewhat aggressive postoperative feeding schedule, infants should be able to be discharged within 24 hours of pyloromyotomy.

The long-term sequelae from pyloromyotomy are minimal. Ludtke and colleagues[67] evaluated the presence of gastrointestinal symptoms, measured scintigraphic gastric emptying, and determined pyloric measurements by US in 36 adults 17 to 27 years after pyloromyotomy. Their results were compared with those of age-matched and gender-matched controls. They identified no differences between the postpyloromyotomy group and the control group for the parameters measured.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 79

# Peptic Ulcer and Other Conditions of the Stomach

L. R. Scherer III

## Acute and Chronic Peptic Ulcer

Reports of peptic ulcer disease in infants and children date back to 1826. A collective literature review on peptic ulcers in 243 children was published by Bird and colleagues in 1941.[1] The series consisted of 119 patients who required surgical treatment for peptic ulcer. Ulcers in infants aged 1 to 15 days of age characteristically presented acutely with hemorrhage or perforation without premonitory signs or symptoms. Preschool-aged children, on the other hand, frequently had a prodromal illness before the onset of hemorrhage or perforation. The heterogeneity of the cause of the ulcers was apparently not recognized, and these differences were ascribed to age.

The theories and etiology of peptic ulcer disease remained consistent for the next 45 years. Careful historical information regarding ulcer-like symptoms in children with no other identified causes and eliciting a family history of peptic ulcer disease were common in instances of primary gastroduodenal ulceration.[2,3] In 1984 Marshall and Warren[4] reported a possible bacteriologic cause for primary ulcers. Secondary ulcers were defined as those caused by severe stress or critical illness. This classification of peptic ulcer is used in this chapter in discussing cause, diagnosis, and treatment (Table 79-1).

## Epidemiology

### PRIMARY PEPTIC ULCER DISEASE

The incidence of peptic ulcer in children is approximately 5.4/100,000 new cases per year.[5] Although the incidence in boys is two to three times higher than that in girls, the sex distribution is equivalent in infants and very young children. Several predisposing factors have been implicated in the development of peptic ulcer disease in patients of all ages. Duodenal and prepyloric ulcers behave similarly and are usually associated with higher levels of hydrochloric acid secretion. The ulcer is usually located in the area of the junction of parietal cell mass and the antral mucosa.[6] The question has been raised as to whether peptic ulcer disease in children is the same condition that presents in adults. A strong familial tendency has been noted. Thirty-three to 56 percent of children with ulcer disease have first- and second-degree relatives with peptic ulcer disease.[7–10] Heritability of peptic ulcer disease has been calculated at 0.91 per first-degree relative for children,[8] a rate considerably higher than the heritability calculation of 0.37 derived for adults. A positive family history for peptic ulcer disease is considered an important characteristic of ulcer disease in children.[2,11] There is a link to primary gastritis and peptic ulceration occurring in children in the presence of *Helicobacter pylori* infection clustering among family members of affected individuals.[12–14] *H. pylori* colonizes the gastric antrum and has satisfied Koch's postulates as a human pathogen causing primary ulceration and chronic-active gastritis in children.[15] The incidence of *H. pylori* infection is estimated to be 0.5% per year in industrialized countries[16,17] and 3% to 10% per year in developing countries.[18] The route of transmission of *H. pylori* is postulated to be fecal-oral or oral-oral.[19,20] Risk factors associated with *H. pylori* infection in children include crowded living conditions, endemic country of origin, poor socioeconomic level, immigrant children, children born of recent immigrants, infected family members, and ethnicity.[21] Pathologic conditions associated with *H. pylori* infection include nodular gastritis, primary duodenal ulcer, gastric ulcers, Barrett esophagus, gastric cancer, and MALT lymphoma.[22–25]

### SECONDARY PEPTIC ULCER DISEASE

Secondary ulcers (stress ulcers) are acute ulcers in children usually associated with major physical or thermal trauma, sepsis, shock, or other critical illness (see Table 79-1). Gastric stress ulcers are usually multiple superficial mucosal erosions found primarily in the fundus of the stomach. The cause of these ulcers has been related to one or a combination of three factors: (1) decreased mucosal blood flow, (2) disruption of the protective mucosal barrier, and (3) intraluminal acidity.[26] Stress ulcers account for 80% of the peptic disease seen during infancy and early childhood.[27] Drug- and chemical-induced ulcers resemble stress ulcers in appearance and distribution. The ulcer that occurs from intracranial disorders, however, is usually a single, deep ulcer and prone to perforation

**TABLE 79-1**
**Classification and Causes of Gastritis and Ulcers in Children**

| *Classification/ Category* | *Etiology* |
|---|---|
| Primary | *Helicobacter pylori* |
| Secondary | |
| Excessive acid production | Zollinger-Ellison syndrome |
| | Antral G-cell hyperplasia |
| | Antral G-cell hyperfunction |
| | Systemic mastocytosis |
| | Renal failure, hyperparathyroidism |
| Stress | Infants: traumatic delivery, neonatal sepsis, perinatal asphyxia |
| | Children: shock, trauma, sepsis, head injury, burns |
| Other conditions | Eosinophilic gastroenteritis |
| | Ménétrier disease, hypertrophic gastritis |
| | Lymphocytic (varioliform) gastritis |
| | Autoimmune (atrophic) gastritis |
| | Gastroduodenal Crohn disease |
| Drug-related | Nonsteroidal antiinflammatory drugs, with or without *H. pylori* |
| | Aspirin |
| | Ethanol (alcohol) |

(Cushing ulcer). Studies in adults indicate that gastric hypersecretion is not associated with stress ulcers or ulcers resulting from drug ingestion.[28,29] Most Cushing ulcers, on the other hand, are associated with an increased acid output.[16,30] Secondary ulcers in older children are frequently single and deep (similar to Cushing ulcer). No detailed studies have been done to determine whether gastric hypersecretion is present in children with stress ulcers.

With the development of pediatric endoscopes, the location of stress ulcers in children was found to be similar to that in adults, mostly occurring in the stomach; other investigators have observed an equal distribution in the stomach and duodenum.[31] Reported series by Williams,[32] Grosfeld,[33] and Deckelbaum[34] of 194, 29, and 25 patients, respectively, found equal distribution of Curling-type single ulcers in the stomach and duodenum. The single gastric ulcers in these studies were usually located in the prepyloric region and behaved similarly to duodenal ulcers. Endoscopy has refined the approach to diagnosis and has led to a better understanding of the presentation and course of ulcer disease in children. Currently, more than two thirds of the patients receiving treatment with corticosteroids or nonsteroidal antiinflammatory drugs (NSAIDs) developed secondary peptic ulcer disease presenting as acute epigastric pain.[35]

## GASTRIC PHYSIOLOGY AND PATHOPHYSIOLOGY

### Aggressive Factors

Acid secretion has been identified in the fetal stomach as early as the nineteenth week of gestation, and pepsin secretion is present by the thirty-fourth week. Term infants can secrete both acid and pepsin.[36] Gastric hyposecretion occurs during the first 5 hours after birth and increases during the next 48 hours when the pH stabilizes to a value of approximately 3.[37] The premature infant can secrete acid and pepsin but in diminished quantities compared with the term infant. Thirty-three percent of premature infants have an alkaline gastric pH, and 20% do not produce acid for 10 days. Many premature infants will maximally produce gastric acid by 4 days. In neonates, the parietal cell mass per unit area is two to three times that found in adults.[38] Infants have a relatively high acid secretion during the first week to 10 days of life (Table 79-2).[37] Maternal gastrin secretion may be responsible for both the increased parietal cell mass and the high acid secretion rate. Acid secretion rapidly decreases after about 10 days of age.[39] During the next 4 months, acid and pepsin secretion increase, paralleling weight instead of age throughout childhood.

**TABLE 79-2**
**Aggressive and Defensive Factors Involved in the Gastroduodenal Mucosal Balance**

| *Aggressive Factors* | *Mucosal Defense Factors* |
|---|---|
| Vascular injury: decreased microcirculation | Mucosal circulation: adequate microcirculation |
| Cancer chemotherapeutic agents | Epithelial cell turnover |
| Aspirin | Increased bicarbonate secretion |
| Nonsteroidal | Inhibit gastric acid secretion antiinflammatory drugs |
| Infectious agents: cytomegalovirus herpesvirus | Preserve vascular cytomegalovirus, flow/microcirculation |
| Systemic stress: increased | Restore epithelial cell surface catecholamines |
| Increased pepsin secretion | Mucous layer: glycoproteins, glycocalyx |
| *Helicobacter pylori* | Bicarbonate layer: pH gradient |
| | Immunoglobulins: IgG, IgA |

Elevated levels of gastric acid secretion have been reported in children with peptic ulcer disease. Similar to adult studies, elevated acid secretion is not necessarily useful in identifying the child with peptic ulcer disease. For example, Ghai[40] used the augmented histamine test to study 18 children with peptic ulcer disease and 16 control children. He found no significant increase in basal acid output in patients with an ulcer. The mean maximal and peak acid output increased, but the two groups overlapped; maximal and peak values increased with the patient's age and weight. Robb[10] noted a similar relationship of age, weight, and acid secretion but did not observe any difference between the acid secretion in 49 children with duodenal ulcers compared with 30 children with dyspepsia and no ulcer. Nagita[41] and colleagues measured the diurnal variation of intragastric pH in children with primary peptic ulcer and healthy children. They found that gastric acidity increased with age and approached adult levels by age 14 years. In children with gastric ulcers, the mean pH for all ages was higher than that for the age-matched controls; in children with duodenal ulcers, the mean time during which the pH was less than 2 was greater than in an age-adjusted comparison group.[41]

In 1984 Marshall and Warren[4] reported the successful culture, under microaerophilic conditions, of a novel gram-negative bacterium *(H. pylori)* from the antral mucosa of humans (see Table 79-2). Recurrent peptic ulcers in adults

may be associated with gastritis that primarily involves the antrum. The accumulation of clinical and laboratory studies provides strong evidence that *H. pylori* fulfills each of Koch's postulates as a cause of chronic active gastritis in humans.[15] The flagella-bearing *H. pylori* organisms require a microaerobic environment for culture, reflecting their environmental niche to navigate through the thick and viscous mucus layer to reach the apical layer of the gastric epithelium.[42] All children infected with *H. pylori* appear to develop chronic-active gastritis. Most have asymptomatic infections that may never lead to clinically evident disease. Theories concerning the mechanism that causes inflammation include the bacterial production of urease and vacuolating cytotoxin. Urease hydrolyzes urea to ammonia and bicarbonate at the gastric mucosal surface. Ammonia can be directly toxic to epithelial cells, and the concomitant increase in the mucosal surface pH may interfere with gastric epithelial function such as production of mucus.[43] This cytotoxin produces vacuoles in the cytoplasm of eukaryotic cells in vitro. The gene *(vacA)* of this cytotoxin has two alleles and is variably expressed among isolates.[44] CagA, a cytotoxic protein, has been isolated in approximately 60% of *H. pylori* isolates, and its presence correlates strongly with the expression of the vacuolating cytotoxin.[45] *H. pylori* that is present in a majority of patients with nodular gastritis, gastric or duodenal ulcer, or in situ expression of cagA is higher in duodenal ulcers ($<0.05$).[46]

Cellular injury in the gastric and duodenal epithelium initiates the inflammatory infiltrate (see Table 79-2) in the gastric mucosa and includes monocytes, macrophages, and polymorphonuclear and plasma cells.[47,48] These inflammatory changes may be due to cagA expression and tumor necrosis factor promoter,[49] which may induce other cytokines including interferon-γ, interleukin-1 (IL-1), IL-2, IL-6, and IL-8.[50]

## Defensive Factors

The presence of hydrochloric acid is required for ulcer formation even though hypersecretion is not usually present (except with Cushing ulcer). Most of the factors contributing to the development of stress ulcers reduce the ability of the stomach mucosa to protect itself against acid injury.[51] Investigators generally agree that mucosal ischemia is also implicated in the pathogenesis of stress ulcers (see Table 79-2).[52] Normally, small amounts of hydrogen ions diffuse into the mucosa but are rapidly cleared or neutralized if mucosal blood flow is adequate. Ischemia reduces production of mucus and the capacity for neutralization of acid entering the tissues, leading to an accumulation of hydrogen ions and subsequent mucosal ulceration. The adverse effect of ischemia on energy metabolism may be an additional factor that reduces the ability of the mucosa to defend itself against injury.[53] Intravenous infusion of sodium bicarbonate administered during the experimental production of mucosal injury by hemorrhagic shock has a protective effect.[54] These findings suggest that ischemia, energy deficits, and systemic acidosis are important factors in the pathogenesis of stress ulcers. In instances of medication-induced ulcers, the drug disrupts the mucosal permeability barrier.[29] A thick mucous gel is secreted from the superficial epithelial cells and mucus cells throughout the stomach. The release of mucus is stimulated by cholinergic agonists, prostaglandins, and inflammatory or immune cytokines. The layer of mucus in the stomach is approximately 20 times the thickness of the surface epithelial cells and is full of charged protein particles. In the normal setting, this mucus provides an effective barrier to the deleterious effects of acid.

Prostaglandins protect against the development of experimentally induced stress ulcers.[55] The mechanism is uncertain but may be related to prostaglandin's stimulation of chloride ion transport out of the cell in exchange for bicarbonate ion, which blocks cyclic adenosine monophosphate (AMP) generation. The available intracellular bicarbonate increases the ability of the cell to buffer acid. Endogenous prostaglandins also have a role in maintaining adequate blood flow to the gastric mucosa and stimulate production of mucus, improving the ability of the mucosa to withstand acid destruction.[56] Corticosteroids and NSAIDs have been implicated as causative agents in peptic ulcer disease. Studies have shown the cytoprotective effect of prostaglandins, the development of ulcers during treatment with NSAIDs and corticosteroids, and a decreased level of prostaglandins in the stomach during treatment.[35,57] Drugs can cause secondary ulcers by damaging the mucosa and thereby allowing acid-peptic digestion. Aspirin is a common agent associated with medication-induced secondary ulcers. In general, drug-induced ulcers should respond to cessation of the medication and conservative supportive treatment, unless complications develop.

## Clinical Presentation

The clinical features of primary peptic ulcer disease in children can easily be confused with those of many other disorders; this similarity may inflate the actual incidence of ulcer disease in children (Table 79-3). Clinical symptoms in the

**TABLE 79-3**
**Clinical Findings in Primary and Secondary Gastritis and Peptic Ulcer Disease**

| *Disease Entity* | *Signs and Symptoms* |
|---|---|
| Primary gastritis | Asymptomatic (most common) |
| | Recurrent abdominal pain (any location) |
| | Epigastric pain |
| | Water brash, heartburn (gastroesophageal reflux disease symptoms) |
| | Vomiting, nausea, anorexia |
| | Iron deficiency anemia |
| | Short stature, growth failure (?) |
| Secondary gastritis | Abdominal pain |
| | Upper gastrointestinal blood loss—hematemesis, melena |
| | Epigastric pain localization ("crampy") |
| | Irritability, change in feeding patterns |
| | Fatigue |
| | Iron deficiency anemia |
| Primary peptic ulcer disease | Chronic, recurrent abdominal pain |
| | Episodic epigastric pain |
| | Vomiting, particularly recurrent |
| | Nocturnal awakening |
| | Anemia |
| Secondary peptic ulcer disease | Life-threatening gastrointestinal bleeding |
| | Gastric or duodenal perforation |
| | Shock |
| | Abdominal pain (rare) |

infant include refusal of feedings, persistent crying, and vomiting.[6] The risk of a child developing an ulcer may be higher with a positive family history. Several studies present evidence that in an endemic population of infected parents, mothers in particular may play a key role in transmission of *H. pylori* to the child.[11] The diagnosis is often elusive until such complications as perforation or bleeding occur. Vomiting is common in preschool-aged and school-aged children with peptic ulcers. Abdominal pain is recognized with increasing frequency as the child becomes older. The pain is often vague and difficult to describe and may be related to meals or relieved by eating, as is seen in adults.[34,58] In older children and adolescents, the clinical presentation and natural history of peptic ulcers are more comparable with those observed in adults.[59–61] The ulcers present with epigastric and nocturnal abdominal pain in teenagers with a positive family history of peptic ulceration. In this setting, despite healing of the acute ulceration, the natural history of this disease process is for the ulcer to recur. It is now clear that such ulcers are not related to a genetic predisposition to hyperpepsinogenemia but are associated with *H. pylori* infection.[14] Almost all patients with primary peptic ulcer disease present with abdominal pain. Unfortunately, psychogenic, recurrent abdominal pain of childhood, the most common pediatric intestinal disorder, causes nearly identical symptoms.[62] Nocturnal awakening caused by episodes of abdominal pain may differentiate organic from psychogenic origin. Gremse and Shakoor[63] evaluated the predictive values of signs and symptoms of acid-peptic disease in children in whom endoscopy confirmed the diagnosis. Six symptoms correlated significantly with acid-peptic disease: epigastric pain, nocturnal pain, postprandial pain, water brash, weight loss, and a family history of peptic ulcer disease. Only 7% of children with psychogenic recurrent abdominal pain report pain occurring at night compared with 60% of children with peptic ulcer disease. In a study of 110 children with duodenal ulcers, the mean age at diagnosis was 11.3 years; in 46% of children, some symptom of peptic ulcer disease manifested before 10 years of age.[2]

Secondary ulcers are acute. Although the age of patients with secondary ulcers ranges from 1 day to 18 years, most patients are younger than 6 years of age. Secondary peptic ulcers are usually due to noxious agents (e.g., corticosteroids and NSAIDs) or after major stresses (e.g., burns, head injury, systemic illness).[21] In these settings, upper gastrointestinal tract hemorrhage, vomiting, and perforation are frequent presenting features. Diagnosis is therefore more difficult and usually made when a catastrophic event such as hemorrhage or perforation occurs. Gastrointestinal bleeding, the predominant presenting symptom of secondary ulcers, occurs in 92% of patients younger than 6 years of age.[64] The ulcers tend not to recur after healing if either the offending agent or underlying disease predisposing to mucosal ulceration is successfully treated.

## Diagnosis

Endoscopic diagnosis followed by treatment with histamine-2 ($H_2$)-receptor antagonists has changed the presentation and course of acute ulcer disease in children. Before the use of endoscopy in children, patients with peptic ulcer disease frequently presented with an acute surgical abdomen, massive hemorrhage, or perforation; the diagnosis was made at the time of operation or autopsy. The present indications for the early diagnosis of acid-peptic disease are gastrointestinal bleeding, dysphagia, persistent vomiting, and the abdominal pain characterized earlier.[65] Gastric analysis is not a useful diagnostic test. Secondary ulcer was previously diagnosed by contrast radiologic studies, angiography, laparotomy, and autopsy. The known occurrence of secondary ulcers in association with physiologic stress should lead to the diagnosis before signs and symptoms become catastrophic. Radiologic diagnosis can be difficult in the presence of hemorrhage because blood clots can mask the ulcer; therefore endoscopy has become the standard for the diagnosis of the acute bleeding ulcer. In one report, endoscopy provided a diagnosis in 85% of children with upper gastrointestinal bleeding compared with 62% using radiologic studies.[66] Angiography can be useful in locating a bleeding ulcer if the rate of bleeding is at least 0.5 mL/min.[67,68]

***H. pylori*** *Invasive Methods:* Endoscopy is the method of choice to accurately diagnose peptic ulceration in children. Nodularity in the antrum of the stomach is a specific (but not sensitive) feature indicative of active *H. pylori* infection in children. Biopsy specimens should be taken from the stomach and tested for the presence of *H. pylori* by a variety of techniques including staining of biopsy sections (silver, Giemsa, Genta, acridine orange) and microscopic evaluation, culture, and testing for the presence of urease activity. In children and teenagers receiving concurrent therapy with a proton pump inhibitor, biopsies should be performed on the body and cardia (and, possibly, transition zones) of the stomach, as well as from the antrum to reduce the chances of false-negative results.[69] Follow-up endoscopy is rarely necessary in pediatric populations, except in the setting of peptic ulceration associated with complications (e.g., massive hemorrhage or perforation).

*Noninvasive Methods:* Infection with *H. pylori* induces a vigorous immune response resulting in the presence of local and systemic antibodies. *H. pylori*-specific IgG antibodies are present in serum, plasma, whole blood, saliva, gastric juice, and urine. The humoral immune response is less vigorous in children. Therefore the cutoff values established for use in adults to determine the presence or absence of *H. pylori* infection are not appropriate in young children. Increasing concerns have been raised about the utility of testing for antibodies in low-prevalence settings, such as is the case for children and adolescents living in developed nations. Although immunoassays are relatively inexpensive and technically easy to perform, those used in children must first be validated in each country or region, using serum samples obtained from relevant populations.[12] Breath testing using the stable isotope $^{13}$C- or radiolabeled $^{14}$C-urea as substrate shows great promise as an alternative approach to noninvasively diagnose *H. pylori* infection in adults. However, $^{14}$C-labeled substrates should not be used in children and women during their reproductive years. Urea breath testing is accurate in children older than 2 years of age.[70,71] A commercially available stool antigen test has been reported to be highly accurate as a diagnostic test in adults. In contrast to serology, in which antibody titers may remain elevated for months after successful eradication of the organism, the stool antigen test is reported to turn negative within a week after elimination of *H. pylori*. The accuracy of the stool antigen test when used in pediatric populations in a variety of clinical settings validates its usefulness.[71,72]

## Treatment

The treatment of peptic ulcer disease in children is similar to that used in adults. Antacids and $H_2$ receptor antagonists (e.g., cimetidine) are the mainstays of medical therapy. Other therapeutic agents include selective anticholinergic agents, proton-pump inhibitors, cytoprotective agents, and anti-infective agents (Table 79-4).

Omeprazole and lansoprazole, proton-pump inhibitors, inhibit the stimulation of gastric acid secretion at the final common pathway (cyclic AMP-adenylate cyclase, $H^+$-$K^+$ adenosine triphosphatase inhibition). Therefore all forms of secretion (histaminergic, gastrinergic, and cholinergic) are blocked. A pediatric dosage of omeprazole, 1 mg/kg/day up to 20 mg/day; or lansoprazole, 0.5 mg/kg/day up to 30 kg and then 30 mg daily in children greater than 30 kg, is effective in 95% of patients within 4 weeks.[21,73] Although omeprazole is well tolerated, side effects include headache, nausea, and abdominal pain.

In children with documented *H. pylori* gastritis or duodenal ulcer, eradication of this microorganism requires the use of standard antimicrobial agents and bismuth preparations (see Table 79-4). The current standard treatment consists of two antibiotics (choosing two of the following): amoxicillin (50 mg/kg/day), clarithromycin (15 mg/kg/day), or metronidazole (20 mg/kg/day) and a proton pump inhibitor. Treatment regimens include twice-daily dosing of antibiotics for 2 weeks and a proton-pump inhibitor for 4 weeks. The use of this triple therapy results in eradication of the infection in more than 80% to 90% of patients.[21,73]

Antacids effectively neutralize acid secretion and heal peptic ulcer disease compared with placebo (75% compared with 40%). Unfortunately, compliance is disappointing, and the complications of the medications including diarrhea and constipation are bothersome. Therapy requires antacid administration (0.5 mL/kg) 1 hour before meals, 3 hours after meals, and at bedtime.

Histamine is a stimulant of gastric secretion. $H_2$ receptors are present on the gastric acid–producing parietal cells of the stomach; $H_2$ receptor antagonists inhibit responses to all secretagogues and thus are effective in suppressing gastric acid secretion. Cimetidine (20 to 40 mg/kg/day) was the first commercially available antagonist. The antiandrogen side effects and the effects on the central nervous system are likely due to the imidazole ring of the compound, which inhibits the cytochrome P450 system of the liver. Ranitidine (6 to 9 mg/kg/day PO or 2 to 4 mg/kg/day IV), an $H_2$ antagonist that lacks an imidazole ring, is six to eight times more potent and is equally effective (85% to 95%) in healing ulcers in 8 weeks. However, a relapse rate of 20% has been reported. Famotidine and nizatidine are other potent antagonists used in adults, but little information regarding their use in children has been reported.

The cytoprotective effect of sucralfate results from a coating action due to the negative charge of the sulfated disaccharide aluminum salt that adheres to the positive protein charge of the injured mucosa. The compound also seems to stimulate mucus production and prostaglandin synthesis, bind bile salts, and neutralize pepsin and acid. The adult dosage is 1 g (1 g/10 mL slurry) four times per day; the childhood dose is 40 to 80 mg/kg/day. Constipation is the only clinically significant side effect.

The E-type prostaglandins including misoprostol, enprostil, and arbaprostil are cytoprotective.[35] The mechanism of action that provides protection to the mucosa is related to blocking production of cyclic AMP, stimulation of $HCO_3^-$, and an increase in mucosal blood flow. The adult dose is 200 μg four times daily, but there is little documented information concerning experience in children.

**TABLE 79-4**
**Three Recommended Combination Eradication Therapies for *Helicobacter pylori*–associated Disease in Children**

| *Duration of Medications* | *Dose* | *Treatment* |
|---|---|---|
| Amoxicillin | 50 mg/kg/day | 14 days bid |
| Clarithromycin | 15 mg/kg/day | 14 days bid |
| Proton pump inhibitor | 1 mg/kg/day | 1 month bid |
| Amoxicillin | 50 mg/kg/day | 14 days bid |
| Metronidazole | 20 mg/kg/day | 14 days bid |
| Proton pump inhibitor | 1 mg/kg/day | 1 month bid |
| Clarithromycin | 15 mg/kg/day | 14 days bid |
| Metronidazole | 20 mg/kg/day | 14 days bid |
| Proton pump inhibitor | 1 mg/kg/day | 1 month bid |

## Surgical Treatment

Historically and presently, surgical management of peptic ulcer disease has been reserved for complications such as perforation, bleeding, obstruction, and intractable pain.[59–61] Follow-up studies of children with primary ulcer disease treated medically revealed a high rate of recurrence after cessation of treatment throughout childhood and into adult life.[2,74] Increasing numbers of these patients eventually required surgical treatment. Because of the prolonged morbidity reported in medically treated patients, earlier surgical intervention had been recommended.[75] Vagotomy and pyloroplasty rather than gastric resection are recommended as effective treatment, with a minimal effect on subsequent growth and development.[76] In the past decade, highly selective or parietal cell vagotomy has been used extensively in several centers to treat adult patients with peptic disease, but no series has been reported in children. The high recurrence rate observed with this approach (10% to 15%) may be an issue; however, some consider this rate to be acceptable in children because it may cause only minimal disturbance of growth and development while providing a reasonably good long-term outcome.[77]

Bleeding or perforated ulcer that occurs in the first 1 to 2 weeks of life (unassociated with other illness or stress) appears to be an acute ulcer resulting from hypersecretion of acid caused by maternal gastrin. These ulcers are usually complicated by bleeding and often respond to orogastric decompression, accompanied by careful saline lavage to keep blood clots evacuated from the stomach and appropriate volume replacement. Perforation requires prompt surgical intervention with the simplest method (i.e., a Graham patch) to safely close the defect.[60] If the operation is performed for hemorrhage, simple suture ligation of the ulcer bed should suffice.[61] No evidence suggests that these ulcers recur. Although the incidence of bleeding and perforation has diminished over the past 2 decades, the complication of chronic obstruction from peptic ulcer disease is unchanged. In a recent 45-year review, Azarow[78] and colleagues described a persistently high incidence of gastric outlet obstruction requiring surgical intervention. Vagotomy and pyloroplasty or gastroenterostomy were used

to relieve the obstructions. Chronic, partial gastric outlet obstruction secondary to a congenital problem such as a duodenal web[79,80] or hypertrophic pyloric stenosis also can result in peptic ulcers in infants and children. It is important to identify the cause in these instances because the ulcer can be completely eradicated by treatment of the distal obstruction.

## ZOLLINGER-ELLISON SYNDROME

The Zollinger-Ellison syndrome is relatively rare in children.[81] The diagnosis may be suggested by the presence of large gastric rugal folds, duodenal dilatation, and edema of the small-bowel mucosa and can be confirmed by an elevated serum gastrin level. The calcium infusion test, reliable in both adults and children, has been used to confirm the diagnosis of hypergastrinemia. Treatment of the Zollinger-Ellison syndrome has traditionally been total gastrectomy unless the primary pancreatic tumor can be completely resected. Some reports suggest that $H_2$ receptor antagonists or proton-pump inhibitors can eliminate the need for gastrectomy in children.[82] The fact that many of these endocrine tumors may be malignant suggests that a careful evaluation of each case to determine its nature and long-term follow-up after treatment with $H_2$ receptor antagonists or proton-pump inhibitors is necessary before reliable conclusions about management can be drawn. In addition, occasionally the gastrin-producing tumors may occur in the wall of the duodenum and require resection. The multiple endocrine neoplasia type 1 syndrome may be present in 25% of the cases. Somatostatin receptor scintigraphy is useful in detecting primary and metastatic gastrinomas.

## STRESS ULCER

Prevention is the preferred treatment goal for stress ulcers. It has been shown experimentally that, under simulated clinical conditions, development of stress ulcers requires a low gastric pH. The use of prophylactic antacids to maintain the gastric intraluminal pH at a value of 6 or greater is effective. Supportive care with improved ventilatory support, maintenance of vascular volume, correction of acid-base imbalance, and nutritional support may also contribute to the ability of the gastric mucosa to withstand acid-peptic injury.

The effectiveness of $H_2$ receptor antagonists and proton-pump inhibitors for the prevention of stress ulcers is extremely effective.[83,84] An $H_2$ receptor antagonist is probably indicated in the prevention and treatment of Cushing ulcers, which are associated with gastric hypersecretion.

When a secondary ulcer presents as bleeding, immediate supportive treatment with balanced salt solution and blood transfusion is frequently adequate. Children who have experienced a major episode of upper gastrointestinal hemorrhage or recurrent bleeding require endoscopy.[85] Endoscopy for bleeding requires greater skill and greater technical demands than do other endoscopic procedures. The endoscopist should have the knowledge and experience not only to identify the source of bleeding but also to control it. Potential interventions include therapeutic injections (of hypertonic NaCl, epinephrine, or absolute ethanol) and cauterization with heater probe, bipolar coagulation, or laser (Nd:YAG or argon). If the endoscopist is not a surgeon, a pediatric surgeon should evaluate the child before emergency endoscopy. The surgeon may then be available to observe the source of hemorrhage and be immediately available for surgical intervention if necessary.

If massive hemorrhage continues or recurs despite drug and endoscopic therapy, surgical control is indicated. Massive hemorrhage has been defined as blood loss in a 24-hour period equal to the total estimated blood volume in infants younger than 2 years of age and as loss equal to half of the estimated blood volume in older children (with 80 mL/kg used as an estimation of total blood volume). This definition correlates with the report of Williams and colleagues,[32] in which no child recovered without surgical management if the rate of blood loss was more than 60% of the estimated total blood volume in 24 hours. The successful use of selective intraarterial vasopressin to manage bleeding stress ulcer in a child has been reported,[86] but others have not found this to be useful.[33,87] Although bleeding often precedes perforation of a secondary ulcer, perforation can be the initial presentation and requires immediate operation.

The surgical procedures used to treat stress ulcers have ranged from simple closure of a perforation to oversewing of the base of a bleeding ulcer to gastrectomy.[88] As a general rule, these ulcers are not associated with an ulcer diathesis and therefore should respond to the simplest procedure that effectively treats the presenting problem. Because stress ulcers are the result of an underlying disease, recurrence of the ulcer is possible if the underlying problem is unresolved; this fact must therefore be considered when the appropriate operation is being selected. The simplest procedure, plication of the site of perforation or oversewing of the bleeding point, is usually effective. On the other hand, when it is apparent that the underlying problem will remain unresolved for an extended period, a more definitive ulcer procedure may be appropriate. Vagotomy and pyloroplasty are recommended most frequently because they rarely interfere with subsequent growth. Vagotomy and antrectomy may occasionally be necessary to control the bleeding ulcer in patients with extensive burns and intracranial problems.[89] Antrectomy also may be necessary for large perforations that cannot be managed by pyloroplasty, although the possibility of serosal patching to close such large defects should be kept in mind. In adults, even total gastrectomy has been infrequently recommended for treating massive hemorrhage from multiple gastric ulcers. Such a procedure is rarely indicated in children. The surgeon who operates on a child for ulcer disease must remember that the patient must continue to grow and develop; therefore the simplest, least disruptive procedure should be selected. Evidence suggests that these children do have problems such as low hemoglobin levels.[90] Experimental evidence comparing the effects of gastrectomy with vagotomy and pyloroplasty on growth and development in miniature swine[91] suggests that vagotomy with pyloroplasty results in less growth disturbance. Follow-up data indicate that vagotomy with pyloroplasty is an effective method of treatment unassociated with substantial long-term problems.[76] In view of the reports of osteoporosis, iron deficiency, and dumping noted in adults who have had various operations for peptic ulcer disease,[92,93] long-term follow-up is essential. There are rare reports of adenocarcinoma occurring in gastric remnants after subtotal gastrectomy.[94] The risk is higher after a Billroth II (gastrojejunostomy) anastomosis. One of our patients developed cancer in the gastric remnant at age 23 years—12 years after a vagotomy and antrectomy for a chronic obstructing duodenal ulcer. Other tumors may arise

in the stomach and present with bleeding due to erosion. These include rare cases of gastric teratoma and instances of leiomyosarcoma and gastrointestinal stromal tumors (GIST).

# Other Conditions of the Stomach

## CONGENITAL GASTRIC OUTLET OBSTRUCTION

### Pyloric Atresia

***History*** Congenital pyloric atresia (CPA) is a rare condition. It constitutes about 1% of all intestinal atresias. In 1749 Calder reported the first case of CPA, and Touroff performed the first successful operation in 1940. CPA typically occurs in isolation, but associated anomalies are also commonly seen in 40% to 50% of the cases and epidermolysis bullosa (EB) is the commonest. The presence of associated anomalies is a contributing factor for the reported high mortality.

***Embryology and Pathology*** The antral and supraampullary parts of the duodenum develop from the caudal end of the foregut. Atresias in this region occur in the form of webs, membranes, or rarely solid cords (Table 79-5). The cause of antral web and atresia has not been fully elucidated. Skandalakis and Gray[95] have postulated that redundancy and slipping of epithelial lining may initiate the formation of an incomplete diaphragm. Sharma and colleagues[96,97] also hypothesize this etiology on a small series of acquired mucosal obstruction of the pylorus. Although these explanations appear to be a possible cause of membranous webs, it still remains speculative and definite confirmatory evidence is not currently available. The similarities of the clinicopathologic features in related patients and their occurrence in siblings and cousins, in the absence of teratogenic factors, point to a genetic etiology that is similar in pathology to the familial genetic etiology of infants with pyloric atresia[98,99] and epidermolysis bullosa.[100,101] One other cause of gastric outlet obstruction with similar embryology is the pyloroduodenal duplication cyst.[102]

***Clinical Presentation and Pathophysiology*** A maternal history of polyhydramnios is often reported. With the frequent use of prenatal ultrasound, polyhydramnios may be observed and the fetal stomach may be distended during the last trimester.[103] The affected infant presents in the first few days of life with nonbilious vomiting and complete gastric outlet obstruction.[104,105] Examination of the abdomen shows epigastric fullness due to the distended stomach. If diagnosis is delayed, excessive distention of the stomach may lead to perforation. Because the obstruction is proximal to the ampulla of Vater, the passage of a meconium stool may mislead the casual observer.

***Diagnosis*** Abdominal radiography confirms the clinical diagnosis (Fig. 79-1). Abdominal radiography performed in various positions may be required to establish the correct diagnosis. A single gastric bubble is observed with no air visible beyond the pylorus. With symptoms of nonbilious vomiting, a distended stomach, and air noted distal to the stomach, dilute barium or soluble contrast is required for the diagnosis of an incomplete pyloric membrane (Fig. 79-2).

**TABLE 79-5**
**Classification of Antral and Supraampullary Atresias**

I. Pyloric
   A. Membrane
   B. Atresia
II. Antral (1 cm or more proximal to pylorus)
   A. Membrane
   B. Atresia

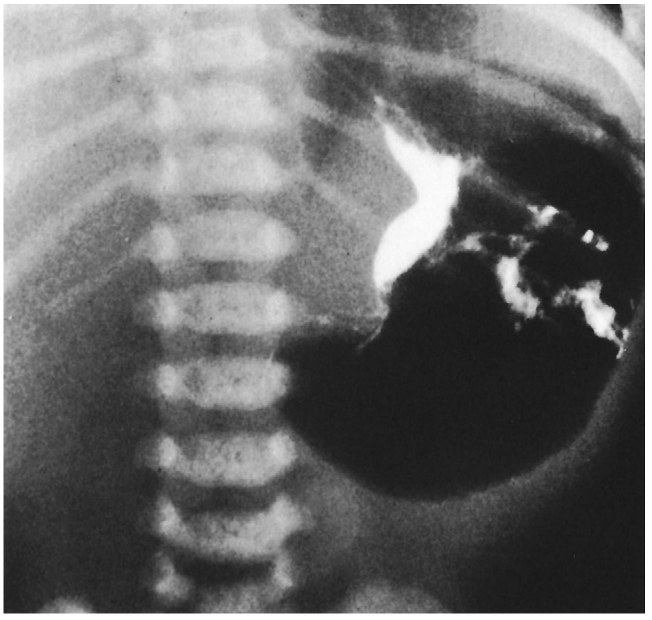

**FIGURE 79-1** Pyloric atresia in a newborn. Air provides excellent contrast. No air extends beyond the pylorus. This child was dehydrated and developed hypochloremic, hypokalemic alkalosis after early postnatal discharge. The anomaly was successfully treated by end-to-end gastroduodenostomy.

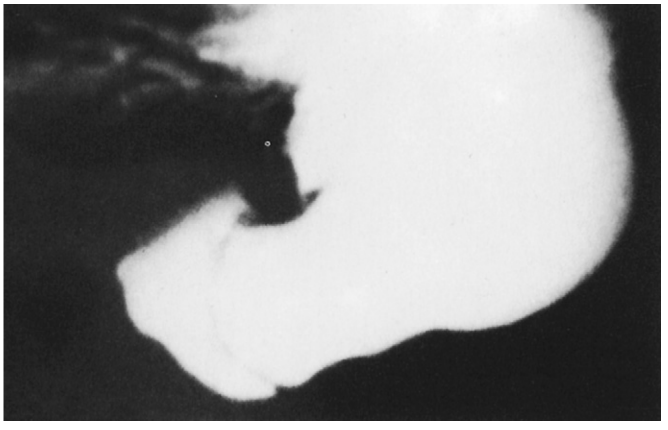

**FIGURE 79-2** Incomplete antral diaphragm in a newborn. This infant had non-bile-stained vomitus shortly after birth. A dilute barium contrast swallow established the diagnosis of an incomplete obstruction. Treatment with a Heineke-Mikulicz pyloroplasty and with excision of the web was successful.

***Treatment*** Pyloric atresia can usually be recognized at the time of operation; a fibrous cord may join two blind ends (Fig. 79-3). Gastrotomy and distal passage of a catheter may be required to detect membranous obstructions (Fig. 79-4). Excision of a complete or partial diaphragm with Heineke-Mikulicz or Finney pyloroplasty is the most straightforward corrective procedure. Haller and Cahill[106] warn against missing a pyloric web in association with a duodenal atresia. They recommend a wide gastrotomy and distal passage of a catheter after excision of the prepyloric diaphragm to identify an associated duodenal diaphragm. In the presence of pyloric atresia with the atretic ends separated by a cordlike or discontinuous segment, gastroduodenostomy is necessary. Dessanti[107] and colleagues described an anatomic pyloric sphincter reconstruction procedure using the atretic cul-de-sac to perform an end-to-end anastomosis. This procedure replaces the resection of the atretic segment and a side-to-side or end-to-oblique anastomosis because of the size disparity between the stomach and duodenum. A temporary decompression gastrostomy and insertion of a transgastric feeding tube may be useful. Recent advances in endoscopy have stimulated development of alternate treatment strategies including balloon dilatation, laser web excision, and laser radial incisions of a type I membrane. The number of these cases is few, and long-term follow-up data are limited.

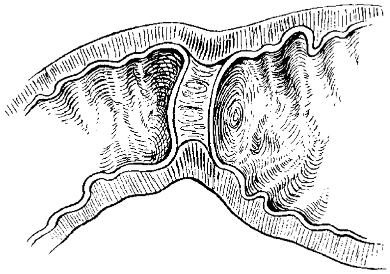

**FIGURE 79-3** Pyloric atresia. The seromuscular layers are uninterrupted. The tissue between the gastric and duodenal mucosa was of two types: fibrous and areolar.

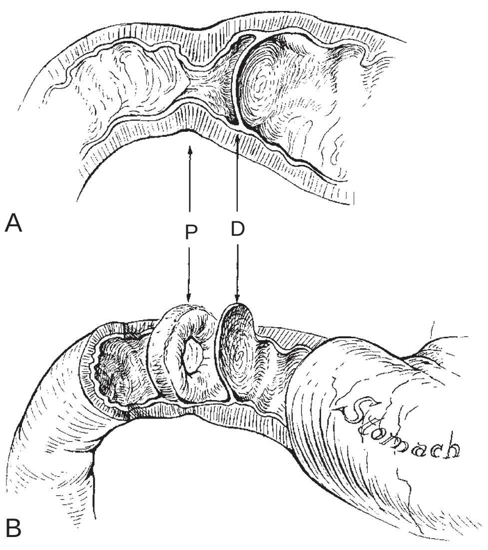


**FIGURE 79-4** Congenital pyloric and prepyloric obstruction. **A,** Prepyloric membrane. **B,** Antral diaphragm. P, Pylorus; D, diaphragm.

***Outcomes*** Survival should be anticipated if diagnosis and surgical intervention occur early and if adequate supportive care is provided. Death has been associated with delayed diagnosis[80,98,108] and associated conditions.[109] Fifty-nine cases of congenital pyloric atresia have been reported. A familial occurrence was described in 13 infants in six families; an unexplained high-mortality rate was seen in this familial group. Some familial cases are associated with epidermolysis bullosa.[98,110] Junctional epidermolysis bullosa/pyloric atresia syndrome is associated with extremely adverse outcomes due to the risk of sepsis, malabsorption, renal disease, and failure to thrive. Of the 70 cases presented in the medical literature, death occurred in 54 patients by 11 months of age. Of the 16 survivors, all are plagued with complications of epidermal disease ranging from 30 days to 16 years.[100] Pyloric atresia associated with junctional epidermolysis bullosa results from mutations in the *PLEC1* gene. The lethal form is associated with intracellular degradation of beta-4 integrin.

### Pyloric Duplication

Duplications of the stomach and pylorus are uncommon, representing less than 3% of alimentary tract duplications. Pyloric duplications are slightly more frequent in girls. They share a common wall with the stomach or pylorus and rarely communicate. Infants present with nonbilious vomiting and weight loss in the first 2 to 3 weeks of life.[111,112] The condition may be mistaken for hypertrophic pyloric stenosis. Occasionally, pyloric duplications present with a palpable mass, further confusing this occurrence with hypertrophic pyloric stenosis. The diagnosis is suggested by ultrasound studies that show a cystic extraluminal mass compressing the gastric outlet.[113] The condition may not be recognized until the time of operation. The procedure of choice is extramucosal excision. Occasionally cyst-gastrostomy may be necessary. Postoperative survival is expected and complications are few. Duplication cysts affecting the stomach usually present later in life. Duplications are covered extensively in Chapter 90.

## VOLVULUS OF THE STOMACH

### History

Gastric volvulus was first reported by Berti in 1886. In 1904 Borchardt described the classic triad of acute or localized distention of the epigastrium associated with pain, inability to pass a nasogastric tube, and nonproductive attempts at vomiting. Gastric volvulus in children is a rare condition; a recent literature review described 581 cases in infants and children.[114] Acute volvulus occurred in 252 children with more than 50% younger than the age of 1 year. Chronic volvulus occurred in 329 children and more than 70% were younger than a year of age. Bautista-Casasnovas[115] and colleagues reported their 25-year experience with children, confirming the early age of diagnosis of acute volvulus in infants.

### Embryology and Classification

Gastric volvulus is rare because the stomach is held securely in place by the gastrophrenic ligaments, esophageal hiatus, retroperitoneal fixation of the duodenum, short gastric vessels, and gastrocolic ligament. Volvulus may occur primarily when these attachments are lax or absent or secondarily when

pathologically associated with eventration of the diaphragm, diaphragmatic hernia, congenital bands, wandering spleen,[116] elongated gastric attachments, or absence of the gastrocolic ligament.[117] They are detailed in Table 79-6. Details of acute volvulus come from case reports. Cribbs[114,118–121] and the largest single-institutional[115] study identify neonates and infants younger than 12 months of age as the most common age group of children with acute volvulus of the stomach. The principal symptoms include cyanosis (11%), acute respiratory distress (10%), abdominal pain (34%), nonbilious emesis (75%), and epigastric distention (47%). In contrast to the acute presentation, 75% of chronic volvulus was of primary etiology. The vast majority of chronic cases are organoaxial (85%). Nonbilious emesis remains the most common symptom. Feeding problems or growth failure (30%) was seen more prominently in chronic cases.

Gastric volvulus is classified according to the plane of rotation (Fig. 79-5). In organoaxial volvulus, the stomach rotates on its long axis; the greater curvature passes anteriorly but may be displaced posteriorly. In the less common mesenteroaxial volvulus, rotation is on an axis from greater to lesser curvature (the pylorus or cardia commonly rotates anteriorly). The opposite rotation may also occur. The torsion may be total, involving the entire stomach, or partial, limited to the pyloric end. The rotating section usually passes anteriorly.

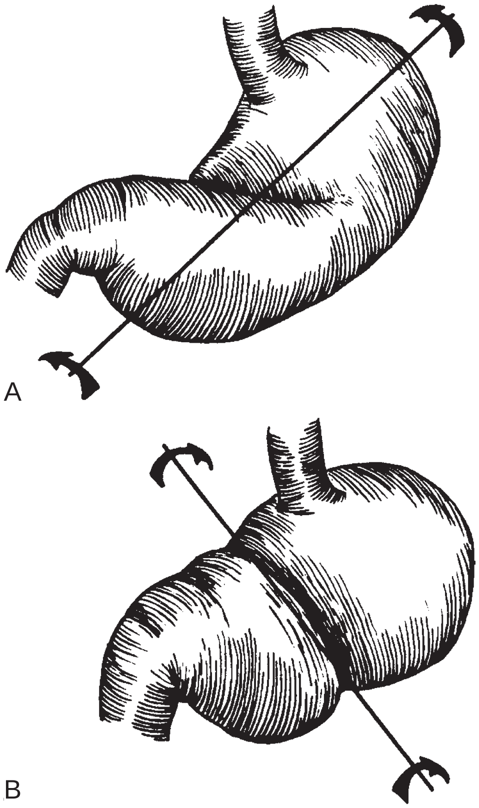

FIGURE 79-5 Gastric volvulus. **A,** Organoaxial. The greater curvature usually passes forward, as depicted, but may rotate posteriorly. **B,** Mesenteroaxial. The pylorus or the cardia commonly rotates anteriorly, but the opposite may occur. (With permission from Cole BC, Dickinson SJ: Acute volvulus of the stomach in infants and children. Surgery 1971;70:707.)

## Radiologic Features

Radiographic examination confirms the diagnosis of gastric volvulus and often identifies underlying associated congenital anomalies or defects. The radiographic features of acute volvulus of the stomach include (1) localized massive distention of the upper abdomen; (2) high greater curvature of the stomach (87%); (3) greater curvature crossing the stomach (83%); (4) fixation of the loop regardless of the position of the patient; (5) delimitation of ingested barium at the tapered extremity of the esophagus, the so-called "bird's beak"; (6) possible evidence of a hiatal sacculation or other diaphragmatic herniation; and (7) deviation of the position of the spleen.

**TABLE 79-6**
**Anatomic Etiology of Gastric Volvulus**

- I. Absence, Failure of Attachment, or Elongation of Gastric Fixation
  - A. Gastrosplenic
  - B. Gastrocolic
  - C. Gastrohepatic
  - D. Greater omentum
- II. Disorders of Gastric Anatomy or Function
  - A. Acute or chronic distention
    1. Gastric outlet obstruction
    2. Gastric hypomotility
    3. Massive aerophagia
  - B. Peptic ulcer disease
  - C. Neoplasm of the stomach
  - D. Hourglass stomach
  - E. Gastric ptosis
- III. Abnormalities of Adjacent Organs
  - A. Diaphragm
    1. Hiatal hernia, sliding or paraesophageal
    2. Bochdalek's hernia or other congenital defect
    3. Diaphragmatic rupture
    4. Eventration of the diaphragm
    5. Phrenic nerve palsy
  - B. Splenomegaly, polysplenia
  - C. Volvulus of transverse colon
  - D. Malrotation and midgut volvulus
  - E. Dislocation or hypoplasia of the left lobe of the liver

## Treatment

Gastric volvulus may present acutely and require acute surgical intervention to prevent or limit vascular compromise. Simple decompression with a nasogastric tube may temporize the situation but is inadequate as a long-term treatment. At operation, gastric decompression facilitates reduction. Once normal anatomic relationships have been restored, the site is carefully inspected to identify possible areas of perforation or gangrene. The remainder of the procedure is focused on preventing a recurrence of volvulus and correcting any diaphragmatic defects (hiatal and Bochdalek hernias). In infants and children, gastrostomy or anterior gastropexy is then performed. Several cases of successful outcomes using each of these techniques by open or endoscopic repair have been reported.[114,115,118,121] Follow-up of these patients ranges from 1 to 10 years without recurrence. Recurrence despite fixation has also been reported.[122] Outside of North America nonoperative treatment strategies are emerging in the management of chronic volvulus. In Africa, Asia, and Europe, 36% to 60% of infants and children are treated successfully

nonoperatively.[114] The management strategy includes positioning the infant on the right side or prone with the head elevated above the torso after feeding. This allowed for the dependent portion of the stomach to remain inferior to the lesser curvature. Such an approach must be tempered by a rapid surgical response to avoid life-threatening complications proven correctable with timely operation.

## GASTRIC PERFORATION IN THE NEWBORN

### History

In 1943 a neonatal gastrointestinal perforation was closed successfully. In 1964 Lloyd and colleagues[123] reported 61 cases of spontaneous perforation of the gastrointestinal tract in the newborn and called attention to the fact that all of these lesions, regardless of location, were the result of ischemic necrosis. The undesirable side effect of an asphyxial defense mechanism, known as selective circulatory ischemia, activated by perinatal stress, hypoxia, or shock, was implicated as the principal factor causing these lesions.[124–126] In 1969 Lloyd[127] reviewed the world literature and found 315 cases of neonatal gastrointestinal perforation qualifying as ischemic lesions. Since then, multiple predisposing factors and causes have been suggested.[128–130]

### Embryology and Pathology

Although ischemia may be the common denominator, a multifactorial cause including congenital muscular defect of the gastric wall,[131] bacterial colonization of the gut with pathogenic organisms,[132] immaturity of the immune system,[133] and endothelial injury related to the use of indomethacin is likely.[130] Gregory[134] and colleagues described the association of perinatal stress in 39 of 42 infants with ischemic necrosis of the gut. The reader is referred to the report of Elsner[125] for details concerning the "diving reflex" theory in mammals and in humans. Asphyxia at birth in infants with low Apgar scores is particularly likely to lead to gastrointestinal perforation. Redistribution of blood flow during hypoxia, hypovolemia, or other stress states[126] with shunting away from mesenteric vascular beds is thought to result in microvascular injury[135,136] and subsequent loss of mucosal integrity.[137] The periods of stress and potential mesenteric ischemia may be temporally remote from the recognition of perforation (intestinal perforation is covered extensively in Chapter 94). Isolated gastric perforation usually occurs along the greater curvature between the smooth muscle layers and, as previously noted, iatrogenic injury due to overzealous resuscitation with an Ambu bag, inadvertent esophageal intubation, or trauma from the passage of an orogastric tube.[133]

### Signs, Symptoms, and Diagnosis

The first indication of spontaneous gastric perforation often occurs at 3 to 5 days of life. Abdominal distention is frequently abrupt and rapidly progressive. Signs of hypovolemia and decreased perfusion are usually present, manifested by tachycardia and lethargy. Respiratory difficulty from massive pneumoperitoneum may be the first sign. Infants born of pregnancies complicated by abruptio placentae, placenta previa, and amnionitis (severe fetal distress) and infants delivered by emergency cesarean section are at increased risk and should be carefully observed.[138] Most infants with gastric perforation have evidence of free air on abdominal radiographs (Fig. 79-6). Further evaluation includes measurement of leukocyte and platelet counts and arterial pH and blood gas analysis.

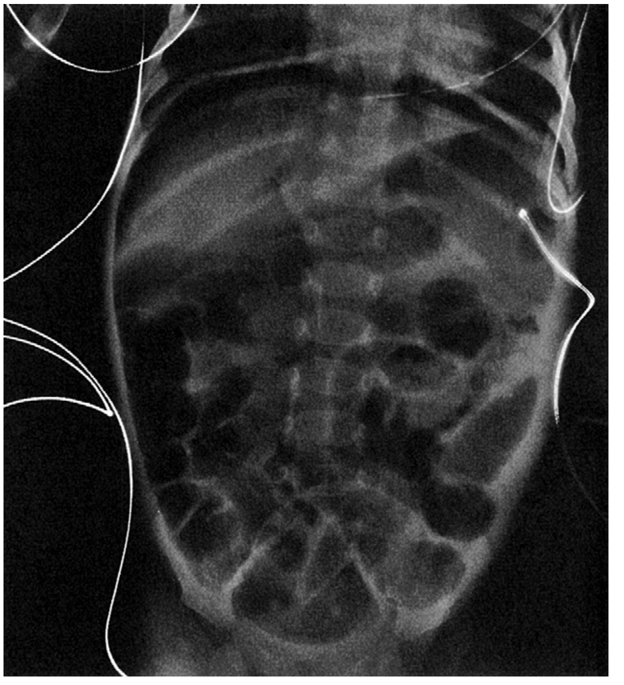

**FIGURE 79-6** Abdominal radiograph in an infant with spontaneous gastric perforation shows free air in the peritoneal cavity.

### Treatment

The condition of an infant with gastric perforation can deteriorate rapidly; therefore early recognition and prompt treatment are essential. This includes rapid fluid resuscitation, blood transfusion, correction of acidosis, administration of antibiotics, orogastric suction, maintenance of body temperature, and performance of only essential diagnostic studies.[139] These infants usually require immediate intubation and ventilatory support. Paracentesis to evacuate the pneumoperitoneum with a blunt needle or plastic catheter may relieve life-threatening respiratory distress due to diaphragmatic elevation during the resuscitation period. Emergency laparotomy through a transverse, supraumbilical abdominal incision is used. The peritoneal contents should be cultured for aerobic and anaerobic bacterial organisms and fungi. Clear gastric contents or slightly bile-tinged fluid often suggests a perforation of the stomach or duodenum. Perforation sites may be occult; after careful examination of the stomach, esophageal hiatus to the lesser omental space may be necessary. Most spontaneous gastric perforations occur along the greater curvature of the stomach distal to the esophagus. Perforation due to a duodenal ulcer in infancy occurs on the anterior wall of the duodenum or near the pyloroduodenal junction, whereas gastric ulcers may perforate along the lesser curvature near the antral-fundic junction. Perforations of the stomach can usually be debrided and closed primarily. If the greater curvature of the stomach is more extensively involved with necrosis, it can be resected. Occasionally when there is extensive necrosis of the gastric antrum, a partial gastrectomy and gastroenterostomy may be required. A Billroth I procedure (gastroduodenostomy) is preferred.

Infants with isolated gastric perforation generally receive antibiotics until the white blood cell count and differential return to normal and there is evidence of bowel function and gastric returns through the orogastric tube are clear and of low volume. Many clinicians obtain a contrast swallow before initiating feedings.

### Outcomes

Current survival for isolated gastric perforation is 75% to 80%: Those infants who succumb often have multiple-organ dysfunction as a result of their initial insult associated with peritonitis, sepsis, and immature immunologic function. Infants with gastric necrosis associated with extensive necrotizing enterocolitis have a high morbidity and mortality.[133,139]

## CONGENITAL MICROGASTRIA

### History

Congenital microgastria is a rare condition first reported in the 1800s.[140] To date, 43 cases have been reported. The malformation has been frequently associated with other congenital anomalies including asplenia, malrotation of the intestines, situs inversus, megaesophagus,[141,142] and upper limb anomalies such as radial, ulnar, and thenar hypoplasia (microgastria-limb reduction association).[140] Increasing regionalization of the care of infants and children in pediatric hospitals has resulted in increased recognition of this condition.[143] Reported therapy for microgastria has ranged from conservative dietary manipulation in patients minimally affected to surgical augmentation of the small stomach.

### Embryology and Pathology

This is a rare congenital anomaly of the caudal part of the embryologic foregut, characterized by a small, tubular stomach, megaesophagus, and incomplete gastric rotation. The esophageal, gastric, small intestinal, and large intestinal mucosae are normal. Many associated conditions of the gastrointestinal tract such as nonrotation of the midgut with duodenal bands and asplenia exist. Situs inversus and asplenia have been reported.[144] Skeletal anomalies including micrognathia, radial and ulnar hypoplasia, vertebral anomalies, oligodactyly, and hypoplastic nails are common. Anophthalmia has also been reported.[145]

Because of the associated anomalies in organogenesis, arrest in development is thought to occur between the fourth and eighth weeks of fetal life. Absence of the gallbladder has also been reported.[146] Massive and persistent reflux into the biliary tract may occur. Patients may have congenital heart disease characterized by a single atrium, a single ventricle, and total anomalous pulmonary venous return into the portal vein.

### Clinical Presentation and Pathophysiology

With the more frequent use of prenatal ultrasound, polyhydramnios and a small stomach may be noted late in a pregnancy. Most patients are beyond the neonatal period at the time of diagnosis, frequently have a dilated esophagus with an ill-defined gastroesophageal junction, and are therefore prone to gastroesophageal reflux. The most frequent presenting signs are vomiting, aspiration and pneumonia, and failure to thrive. Malnutrition and developmental delay may result. Diarrhea is common. An incompetent lower esophageal sphincter has been demonstrated in these cases. When coupled with reduced gastric capacity and a dilated esophagus, vomiting, esophageal erosion, and aspiration are common. Although not well studied, it is postulated that malnutrition and diarrhea may result from a small gastric capacity with rapid emptying of acid content. Bacterial overgrowth and a blind looplike syndrome have been suggested to explain the diarrhea and malnutrition, but results of the Shilling test have been normal.

### Diagnosis

Contrast examination of the upper gastrointestinal tract with barium, usually the first study obtained, demonstrates the features just mentioned. Imaging techniques augment the radiographs.[147] Endoscopy has proved difficult and has yielded confusing results. Appropriate cardiac studies are dictated by the specific findings, and asplenia may be demonstrated by examination of the peripheral erythrocytes for Howell-Jolly bodies and by nuclear imaging. If gastroesophageal reflux disease is a clinical feature, manometry and esophageal pH studies may be appropriate. In patients with diarrhea, malnutrition, or growth retardation, intestinal absorption studies may elucidate the cause.

### Treatment

Medical treatment should be attempted initially. Continuous or nighttime orogastric feedings may allow the patient to grow and the stomach to enlarge so that the patient can then tolerate normal feedings. If gastroesophageal reflux disease develops, prokinetic agents and acid-reducing therapy may improve gastric emptying. Complications of gastroesophageal reflux may require the use of a nasojejunal feeding tube or surgically placed jejunostomy tube. The jejunal feedings supplement the smaller oral feedings, allowing the stomach to enlarge.[148] If the infant's stomach fails to enlarge, several authors have recommended augmenting the stomach capacity by construction of a double-row jejunal reservoir,[149,150] and outcomes from early follow-up are encouraging.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 80

# Bariatric Surgery in Adolescents

Sean Barnett, Victor F. Garcia, and Thomas H. Inge

Obesity is a progressive, chronic, and often fatal disease, refractory to most currently available medical interventions. The definition of overweight and obesity in children is a body mass index (BMI) greater than 85th and 95th percentile (P), respectively, for age and gender. In 2007-2008, 32% of children (2 to 19 years old) were at or above the 85th P, 17% were at or above the 95th P, and 12% were at or above the 97th P of the BMI-for-age. Trend analyses indicated that there was no significant increase in overweight or obesity prevalence between 1999-2000 and 2007-2008. However, prevalence of those at the highest (97th P) levels of obesity among 6- through 19-year-old boys and among non-Hispanic white boys of the same age was increasing. In 2007 the estimated prevalence of extreme pediatric obesity (BMI $>$ 99th P) was 4%.[1] Obesity-related decreases in life expectancy predominantly affect age groups younger than previously thought, especially in young black males.[2]

Childhood and adolescent obesity are independent risk factors for adult morbidity and premature mortality.[3–4] In the extreme form, with BMI for age in the greater than 99th P, obesity is refractory to even the most intensive conventional approaches to weight loss.[5–6] Bariatric surgery is currently the most effective means to achieve durable weight loss and amelioration, if not resolution, of most obesity-related comorbidities in severely obese individuals. It also decreases the long-term mortality of morbidly obese patients.[7–8] The morbidity of surgery varies between 5% and 11%. The mortality was recently estimated by the LABS study group to be 0.3 for gastric bypass procedures[9]; most studies demonstrate even lower mortality risk for adjustable gastric banding (AGB). Experienced centers have shown that weight loss following bariatric surgery in adults can be sustained.[10] Among adults, the nutritional consequences of the most common bariatric surgical procedures are well defined and effectively managed with vitamin and mineral supplementation. Among adolescents, however, it is unknown whether the outcome will be the same as in adults or whether there will be unacceptably high degrees of recidivism and long-term nutritional sequelae related to poor compliance or reduced micronutrient absorption.[11–13] Nonetheless, for the extremely obese adolescent there are currently no effective nonsurgical treatments.[14] As the number of severely obese children increases and the serious health consequences escalate, surgical weight loss is becoming the only effective means to treat severely obese adolescents. On the basis of the best available evidence, this chapter proffers a conceptual framework and clinical guidelines for adolescent bariatric surgery. The approach borrows heavily from the most successful adult bariatric surgical programs and best practice guidelines.

The unique physiologic, cognitive, developmental, and psychosocial needs of the adolescent are best managed with a family-centered, interdisciplinary approach, incorporating behavior modification techniques that have been successful in other chronic health care models. Given the technical difficulty of bariatric surgery, the complexity of the postoperative management of the patient undergoing bariatric surgery, and the extant uncertainty about its long-term outcomes in adolescents, regionalization of care with a focus on prospective clinical data collection will be essential to achieving outcomes commensurate with the best adult series. Further, it will accelerate our understanding of the short- and long-term consequences of bariatric surgery among adolescents.

## History of Bariatric Surgery in Adolescents

The earliest report of pediatric bariatric surgery was Randolph and Weintraub's experience with jejunal ileal bypass.[15] Their reported outcomes were similar to those in adults. More specifically, the weight loss was dramatic and sustained and the improvements in quality of life were viewed as excellent. However, the metabolic complications were significant[15] and considered unacceptable by today's standards. Greenstein[16] reported a largely favorable experience with vertically banded gastroplasty, concluding that adolescents given extensive dietary counseling can experience the same benefits as adults. The subsequent reports of bariatric surgery in pediatrics have consisted of small case series of adolescents largely undergoing open and, more recently, laparoscopic Roux-en-Y gastric bypass surgery (RYGB) or laparoscopic AGB. As summarized in a recent systematic review, the reported outcomes have been good to excellent, with few complications and no procedure-related mortality.[17] As with pediatric laparoscopic cholecystectomy, minimally invasive repair of pectus excavatum, and laparoscopic antireflux procedures, bariatric

operations among adolescents are only now beginning to be studied in a prospective and controlled fashion.[18] None of the adolescents who have undergone AGB have been followed for more than 4 years. The only randomized controlled trial examined AGB compared with lifestyle intervention in a cohort of 50 Australian adolescents. In the gastric banding group ($n = 25$, with 24 completing the 2-year study), a weight loss of 34.6 kg representing a BMI reduction of 28% (excess weight loss of 78.8%) was seen, compared with a 3-kg loss representing a BMI reduction of 3% (excess weight loss of 13.2%) in the lifestyle group. Health and quality of life improvements were also documented.[19] However, eight operations (33%) were required in seven patients for revisional procedures either for proximal pouch dilatation or tubing injury during follow-up. This high rate of surgical complications is of considerable concern and is based primarily on symmetric pouch dilation, a problem infrequently seen in adults. It is likely that maladaptive eating behaviors rather than surgical technique contributed to this problem. Thus programs that focus on banding as a weight loss intervention for adolescents must consider how to best educate patients and families about postoperative dietary behaviors to address preventable complications.

The report with the largest and longest follow-up is that of Sugerman and colleagues.[13] These authors' outcomes reported 33 adolescents (mean preoperative BMI = 52 kg/m$^2$) who underwent various bariatric procedures, primarily gastric bypass. This group had an excess weight loss of 63% (mean BMI = 33 kg/m$^2$) at 5 years and 56% (mean BMI = 34 kg/m$^2$) at 10 years after operation. Only six of nine patients who were 14 years following operation could be found. These six had maintained 33% of their excess weight loss (mean BMI = 38); 15% of the cohort had regained most or all of their overweight, suggesting that recidivism may be just as likely in adolescents as in adults. These data beg several questions—whether adolescents require alternate selection criteria or different postoperative management strategies than adults and whether the long-term nutritional and metabolic outcomes of adolescents will be better or worse than similarly obese adolescents who have undergone bariatric surgery in youth.

In 2001 the first children's hospital–based bariatric surgery program was established at Cincinnati Children's Hospital Medical Center.[18] The bariatric surgery program was integrated into an existing behaviorally based weight management program for children and adolescents. This comprehensive program offers bariatric services to adolescents with intractable clinically severe obesity. Candidates for bariatric surgery are evaluated by pediatric bariatric surgeons, a pediatric psychologist, and other pediatric medical specialists with expertise in pediatric obesity; an advanced practice nurse; dieticians; and an exercise physiologist. Since that time, there have been few dedicated pediatric centers for the treatment of morbid obesity established. The vast majority of these patients are still treated in adult facilities.

Our most recently published data analyzed 61 adolescents with a mean preoperative BMI of 60.2 kg/m$^2$ who underwent laparoscopic Roux-en-Y gastric bypass from August 2002 to January 2007.[20] The mean weight loss for this group was 37.4% one year postoperatively with statistically significant improvements in systolic and diastolic blood pressure, total cholesterol levels, triglyceride levels, and fasting insulin levels.[20] Of the nine patients who were on medications for diabetes preoperatively, only one remained on medication postoperatively.[20]

# Science of Obesity

Obesity research is one of most exciting areas of scientific investigation at the nexus of physiology, genetics, neurobiology, endocrinology, molecular biology, and gastrointestinal surgery. Genes regulate body weight by balancing caloric intake and energy expenditure. Familial aggregation and twin studies have demonstrated that genes contribute to the development of obesity with a heritability index of 0.7 to 0.8, a degree of heritability equivalent to that of height.[21–22] Only about 5% of childhood morbid obesity is a result of a single gene defect, usually in an isoform of the melanocortin receptor, the receptor for melanocyte stimulating hormone.[23] In the remainder of the population, obesity is the result of many genes interacting with environmental factors. Evidence indicates that genes and metabolic processes that predispose to obesity offered our ancestors a survival advantage in times when food was scarce.[24–25] This may explain the highly variable frequency of obesity in different populations (African Americans, Native Americans, and Hispanics) that once lived under adverse conditions.

# Risk Factors for Adolescent Obesity

The risk of obesity accumulates with age and is influenced by genetic, biologic, psychologic, socio-cultural, and environmental factors acting throughout our life span. Recent insights into the fetal, neonatal, and developmental origins of obesity[26] have implications for clinical evaluation of the adolescent candidate for bariatric surgery. There are critical phases in the development of adolescent obesity within the period between preconception and adolescence.[27–31] Epidemiologic evidence has linked birth weight and later body mass index[32] in childhood[33] and adulthood.[34] Lower birth weight elevates the risk for central obesity[33,35] and insulin resistance.[35] Childhood obesity risks are higher for offspring of mothers with diabetes mellitus.[36] Postnatally, longer duration of breastfeeding[37–38] and later onset of adiposity rebound[39] reduce the risk of adolescent overweight. Of all the aforementioned risk factors, low birth weight and high BMI of the adolescent confer the highest risk of chronic obesity.

Obesity in family members is an additional risk factor for adolescent obesity. The odds ratio for persistence of childhood obesity into adulthood is about 3 if one or 10 if two parents are obese.[40] This effect is most pronounced in children younger than 10 years. Puberty is also a critical period for the development of obesity.[41] Earlier menarche is seen in obese children. A BMI greater than the 85th P is associated with a twofold increase in rate of early menarche.[42–43] The risk of obesity persisting into adulthood is far higher among obese adolescents than among overweight younger children.[1,6] Finally, there is a preexisting racial-ethnic disparity in the risk of obesity.[44] Lower socioeconomic groups may be especially vulnerable because of poor diet and limited opportunity for physical activity.[45]

## HEALTH CONSEQUENCES OF ADOLESCENT OBESITY

Adolescent obesity has important health consequences as outlined in Table 80-1. Associated with the rise in the prevalence and severity of pediatric obesity in the United States, there has

**TABLE 80-1**
**Health Consequences of Pediatric Obesity**

| Complications of Adolescent Obesity | |
|---|---|
| Psychosocial | Poor self-esteem[85–87,164] |
| Depression[86–88,165–166] | |
| Eating disorders[167–168] | |
| Attention deficit hyperactivity disorder[169] | |
| Neurologic | Pseudotumor cerebri[170–172] |
| Pulmonary | Sleep apnea[77,173–175] |
| Asthma and exercise intolerance[176–177] | |
| Cardiovascular | Dyslipidemia[61,114,178–179] |
| Hypertension[92,180–182] | |
| Coagulopathy, chronic inflammation[183] | |
| Endothelial dysfunction[184–187] | |
| Gastrointestinal | Gallstones |
| Steatohepatitis[67,72,188] | |
| Gastroesophageal reflux disease[189] | |
| Renal | Glomerulosclerosis[190–191] |
| Endocrine | Type 2 diabetes mellitus,[65,91,192–195] |
| Insulin resistance[33,65,92–93,196–198] | |
| Metabolic syndrome[53,55,93,199–200] | |
| Precocious puberty[50,201] | |
| Polycystic ovary syndrome[95,202] | |
| Musculoskeletal | Slipped capital femoral epiphysis, Blount disease[203] |
| Forearm fractures, flat feet | |

been an emergence of new or newly identifiable health conditions in children[46] with onset at a younger age[47–48] and an increased risk for adult morbidity and mortality.[47] Childhood obesity also has adverse social and economic consequences.[49–50] The persistence of obesity,[51] with approximately 70% to 80% of overweight children becoming obese adults,[1,46] is of particular concern for certain complications. The clustering of hypertension, dyslipidemia, chronic inflammation, hypercoagulability, endothelial dysfunction, and hyperinsulinemia, known as *insulin resistance syndrome* or *metabolic syndrome*,[52] has been identified in children as young as 5 years of age.[53] The Bogalusa Heart Study noted the correlation of cardiovascular disease risk factors with asymptomatic coronary atherosclerosis. The more severely obese individuals had more advanced lesions.[54] The metabolic syndrome is far more common among children and adolescents than previously reported, and its prevalence increases directly with the degree of obesity.[55] Each element of the syndrome worsens with increasing obesity, independent of age, gender, and pubertal status.

A prediabetic state, consisting of glucose intolerance and insulin resistance, is highly prevalent among severely obese children, even before clinical diabetes has been diagnosed.[56] Even though formerly considered an "adult-onset" disease, type 2 diabetes mellitus now accounts for nearly half of all new pediatric diagnoses of diabetes[57–58] and is thought to be largely the result of the pediatric obesity epidemic. Of particular concern are data from the Centers for Disease Control suggesting that 33% of all Americans born in the year 2001 will develop diabetes.[59] For blacks and Hispanics this number rises to nearly 50%.[59] The data suggest that the onset of the beta cell dysfunction associated with diabetes occurs well before the development of hyperglycemia and may commence many years before diagnosis of the disease.[60–63] Other work clearly suggests that type 2 diabetes developing in childhood or early adulthood progresses much more rapidly than in adults[64] and may be more virulent than diabetes that develops later in adulthood. Bariatric surgery in adolescents, particularly gastric bypass, has been shown to completely resolve type 2 diabetes following significant weight loss.[65] Given these findings and the progressive nature of the disease, established type 2 diabetes mellitus is a strong indication for weight loss surgery in adolescents.[66]

Nonalcoholic steatohepatitis is recognized as a common cause of chronic liver disease in children.[67] This condition is frequently associated with obesity, with 25% of overweight children in one report having abnormally elevated liver function tests.[68] It has been suggested that obesity-related pediatric nonalcoholic steatohepatitis[69] may become a major cause of hepatic failure and a leading indication for liver transplantation in decades to come.[67,70–72] Bariatric surgery has been shown to decrease not only the amount of steatosis[73] but also the associated inflammatory markers.[74] Currently weight loss is the only treatment for severe steatosis and is considered a strong indication for bariatric surgery.[66]

Exercise intolerance, sleep-disordered breathing, and asthma are frequent pulmonary complications of adolescent obesity.[75–77] Asthma and exercise intolerance can also limit physical activity and contribute to further increases in weight.[78] Obstructive sleep apnea (OSA), the most severe manifestation of sleep-disordered breathing, can significantly impair the obese adolescent's health-related quality of life,[77,79] result in abnormal left ventricular geometry,[80] and put him or her at increased risk for hyperactivity and learning difficulties.[81] Although up to 20% of adolescents with obesity have moderate to severe OSA, those presenting for bariatric surgery have a prevalence of greater than 50%.[82] Within our institution using polysomnography, OSA significantly improves or resolves completely in adolescents undergoing gastric bypass.[77] Therefore moderate to severe OSA is a strong indication for early bariatric surgery in adolescents.[66]

Pseudotumor cerebri is a process for which the major symptoms include headache, dizziness, nausea, tinnitus, and blurry vision due to increased intracranial pressure caused by morbid obesity. The treatment of choice has long been bariatric surgery,[83] and these symptoms can improve over the course of months following surgery in adolescents.[84]

Arguably the most prevalent and debilitating consequences of adolescent obesity are psychosocial.[85–88] The psychologic stress of social stigmatization imposed on obese children may be as damaging as the medical morbidities.[89] Many obese adolescents have low self-esteem associated with sadness and high-risk behaviors.[85] In a recent inventory of health-related quality of life (QOL) indices, obese adolescents demonstrated significantly lower QOL scores than lean children and scores that were comparable with pediatric cancer patients.[79] Overweight has also been associated with lower levels of socioeconomic attainment. Women who were overweight adolescents

were less likely to marry and had completed fewer years of school.[90] A recent longitudinal prospective study demonstrated a significant improvement in depressive symptoms and quality of life over the first postoperative year following bariatric surgery in adolescents.[87]

The health consequences of childhood obesity are broader in scope, greater in prevalence, and more severe at a given time point in disease progression than previously thought.[91–96] BMI thresholds for obesity do not account for the ethnic disparity of disease burden nor the accelerated progression of disease in certain populations of obese adolescents.[94,97–98] The progressively younger age at which adult diseases are recognized in children;[53,99] the increasing prevalence of impaired glucose tolerance, insulin resistance, metabolic syndrome, and type 2 diabetes mellitus in younger children;[53,56,100–102] and the suggestion that childhood-onset type 2 diabetes mellitus may be more virulent than adult-onset diabetes validates concerns about the clinical relevance of the current definitions of obesity in children and about disease burden over time affecting the ability to control these comorbidities.[103–105] Longitudinal studies performed at our institution assessing the characteristics of 61 adolescents undergoing gastric bypass demonstrated a mean baseline BMI of 60.2 kg/m$^2$. At 1-year follow-up, the cohort had experienced a BMI reduction of 37%, but only 17% achieved a nonobese BMI of less than 30 kg/m$^2$. Of note, those adolescents with a baseline BMI above 65 kg/m$^2$ reached a nadir BMI still in the morbidly obese range (47 kg/m$^2$) at 1 year, suggesting that "late" referral at the highest BMI values all but eliminates the chances of attaining a nonmorbidly obese BMI after the most intensive of treatments.[20] One could argue that earlier referral, with BMI values in the 35 to 50 range should be the goal to optimize treatment outcomes in adolescents.

# Adolescent Cognitive Development: Concepts and Principles Relevant to Adolescent Bariatric Surgery

Cognitive development refers to the development of the ability to think and reason. Around 6 to 12 years of age, children develop the ability to think concretely. Adolescence marks the beginning of more complex thinking. At any given age, adolescents are at varying stages of cognitive and psychosocial development, which more closely correlates with pubertal status than with chronologic age.[106] Additionally, there are gender differences in the attainment of formal operations and identity formation enabling new levels of intellectual functioning, abstract thinking, and cognitive skills, which are critical to providing assent to, and complying with, medical recommendations. Examples of formal operations include thinking about possibilities, hypothetical-deductive reasoning, anticipating events that have not yet happened, thinking about conventional limits, and thinking about thought. Before the attainment of formal operations, the adolescent functions and reasons in concrete operations. At this stage of development, adolescent problem solving is confined to identifiable objects that are either directly perceived or imagined and mental operations are only possible when they are applied to information from the direct experience. In acquiring formal operations, the adolescent has the ability to reason, think abstractly and logically, form hypotheses, and consider various consequences of behavior. The adolescent who has acquired this ability is better able to consider the consequences of taking or not taking nutritional supplements or of following and adhering to the prescribed protein-sparing diet. Adolescence is also generally regarded as a period of social experimentation, limit-testing, risk taking, and egocentrism—all of which predictably add to the challenge of adolescent compliance with desired health behaviors.

The postoperative management of the adolescent bariatric patient requires an assessment of the level of cognitive development and an understanding of the risk-taking propensity of adolescents.[107] It is also important to note that the level of cognitive sophistication differs from adolescent to adolescent and may be independent of chronologic age.[108] The attainment of new mental abilities does not carry with it immediate proficiency in their use, nor does education alone enhance cognitive maturity. Enhanced compliance with a vigorous nutritional and lifestyle regimen requires effective education that applies cognitive development theory and also input from peers and family that helps the adolescent attain a more realistic appreciation of their own vulnerability.

## COMPLIANCE

Long-term therapeutic success with bariatric surgery is dependent on compliance with the prescribed dietary, lifestyle, and nutritional supplement regimen. Adolescence is generally viewed as a time of increased experimentation with a variety of health-related behaviors such as diet and exercise. Expertise with enhancing adherence to preventive health practices and compliance with treatment regimens is critical. Historically, compliance with health recommendations in the adolescent population is disappointingly low, estimated at 40% to 50% for adolescents with chronic medical conditions such as cystic fibrosis, diabetes, and asthma.[109] Rand and McGregor found that after bariatric surgery, less than 20% of adolescents demonstrated perfect compliance with vitamin and mineral supplementation regimens.[11] For adolescents with chronic medical conditions, adherence with rigorous medical and dietary regimens is substantially improved with use of behavioral therapy.[110–115] Unfortunately, there is no clear profile of the psychosocial factors consistently associated with the compliant patient, thus precluding a "cookbook" solution for the prevention and management of poor compliance in the adolescent who has undergone bariatric surgery. To enhance adolescent compliance with a lifelong postoperative dietary and nutritional supplement regimen, an adolescent bariatric surgery program should employ professionals capable of assessing levels of cognitive development, personality characteristics such as self-esteem and locus of control, as well as family variables such as cohesiveness and level of effective communication.[108] Prior knowledge of these factors may enhance the ability of the bariatric team and the primary care physician to offer useful anticipatory guidance postoperatively. For example, it can be useful to know when and with whom most nonnutritive calories are consumed so that the team is aware of the periods/people that may increase the adolescent's vulnerability to maladaptive postoperative eating habits. Adolescent compliance may be enhanced by

**TABLE 80-2**
**Strategies to Improve Postoperative Compliance**

- Dietary regimen rehearsal preoperatively enables problem identification and solving before the surgical intervention.
- Use of actual measuring cups, a food scale, and photographs of specific food items that are recommended enhances the adolescent's ability to follow through with plans.
- Provide the adolescent with a diet diary and exercise diary with form pages for him or her to fill out, and practice this preoperatively.
- Provide a list of acceptable food items for every phase of the postoperative recovery (first week, second through fourth week, second through third month, etc.) including the caloric density and protein, carbohydrate, and fat content of the items to encourage label reading.
- Provide a detailed listing of micronutritional supplements needed postoperatively that includes the reason why the supplement is necessary, as well as the potential consequences of not taking it.

(1) visual aids, (2) focus on immediate benefit from treatment, (3) participation in self-management, (4) self-monitoring, and (5) self-reinforcement.[116] Adolescent self-management and related strategies encourage independence from the family, an important developmental task of adolescence. With the alterations in eating patterns that are required after bariatric surgery, repetitive reinforcement is necessary to facilitate the formation of lifelong health-promoting habits. Patients and their families may require counseling and close follow-up to promote their physical and emotional well-being.

The adolescent bariatric surgery program should build on the best practices of other adolescent disease management programs[111,117–118] and thus be based on the premise that sustained weight control for the adolescent requires structured family involvement and continued support. Specific strategies to increase adolescent compliance include education, treatment regimen modification within the social-cultural context of the patient, and enlisting family and peer support[108] (Table 80-2). Some adolescents respond to formalized modes of reinforcement such as contracting.

# Bariatric Surgery

Bariatric surgery should be viewed as a surgical discipline and not just a technical procedure. Bariatric patients are a distinct and often problematic cohort with serious and often multiple concurrent comorbidities. They have unique postoperative needs and in the event of postoperative complications conventional diagnostic approaches often do not work. They require close long-term follow-up making the transition of the adolescent who undergoes bariatric surgery to adult care an essential component of the clinical care plan.

The majority of bariatric surgery is now performed laparoscopically. Minimally invasive bariatric surgery has significant advantages over open surgery but is one of the most technically difficult operations to perform.[119] The learning curve is steep.[8] Schauer suggests the curve levels off at 100 operations.[120] Laparoscopic skills employed in foregut surgery are not directly transferable to bariatric surgery, and proficiency in minimally invasive surgery may not confer the same level of proficiency in minimally invasive bariatric surgery. Several societies and associations have developed credentialing criteria and guidelines for bariatric surgery, and most recently the American Society for Bariatric Surgery has introduced criteria for Centers of Excellence in Bariatric Surgery. Pediatric surgeons pursuing bariatric surgery should at a minimum take a course in bariatric surgery and have their early experience proctored by an experienced laparoscopic bariatric surgeon. Additionally, they must be cognizant of and take into account, during patient selection, patient characteristics that are recognized as risk factors for perioperative complications and mortality.[121–125] Recent data demonstrate the mean BMI of patients undergoing gastric bypass at our institution is 60.2 kg/m$^2$.[20] Adult studies of patients with BMI greater than 60 kg/m$^2$, coined the super-super obese, have shown longer procedure times and longer hospital stay.[126] The pediatric bariatric surgeon must also be prepared for these more difficult patients early in their learning curve given current referral patterns.

# Surgical Options

There are five bariatric procedures in general use: RYGB; laparoscopic AGB; vertical banded gastroplasty; biliopancreatic diversion (BPD), with or without duodenal switch (DS); and the laparoscopic sleeve gastrectomy. Each has its unique profile of potential complications and nutritional concerns.[127] All of these operations can achieve significant weight loss with improvement or reversal of obesity comorbidities. Each can be performed laparoscopically, which may result in shorter length of hospital stay, shorter convalescence,[122,128–129] and decreased risk of wound complications. Attempts to determine what patient features might predict which particular operation might be best suited to an individual's needs are ongoing, but none have been prospectively evaluated.[130] For the most part, vertical banded gastroplasty is of historical interest and is not addressed further. Table 80-3 outlines the percent of excess weight loss, associated morbidity and mortality, and whether the operations can be revised or reversed.

**TABLE 80-3**
**Comparison of Bariatric Procedures**

| *Procedure* | *Weight Loss % EBW* | *Mortality %* | *Morbidity %* | *Can Be Reversed* | *Can Be Revised* | *Durability of Weight Loss* |
|---|---|---|---|---|---|---|
| RYGBP | 65-70 | 0.5 | 5 | Yes | Yes | ++++ |
| LAGB | 47 | 0.1 | 5 | Yes | Yes | ? |
| LSG | 33-83 | 0.39 | 0-20 | No | Yes | ? |
| BPD ± DS | 70 | 1.5 | 5 | Yes | Yes | ++++ |

BPD ± DS, biliopancreatic diversion with or without duodenal switch; EBW, excess body weight; LAGB, laparoscopic adjustable gastric band; LSG, laparoscopic sleeve gastrectomy; RYGBP, Roux-en-Y gastric bypass.

### Roux-En-Y Gastric Bypass

Gastric bypass is chiefly a restrictive procedure that modifies normal appetite signals and is modestly malabsorptive as well. It is the first of the gastric procedures and the most common bariatric procedure performed in the United States. The restrictive component is a small gastric pouch (15 to 20 mL) with a small gastric outlet (1 to 2 cm) that results in early and sustained satiety. Intestinal continuity is reestablished with a gastrointestinal bypass of varying segments of bowel—standard, 75 cm; long limb, 150 cm; and very long limb or distal gastric bypass, 250 cm.[119] The limb can be positioned retro-colic or ante-colic and the gastrojejunal anastomosis can be fashioned with an end-to-end stapler or linear stapler, or it can be hand sewn.[119] See Figure 80-1. Currently a 25-mm, end-to-end, circularly stapled gastrojejunostomy with an antecolic or retrocolic reconstruction is commonly performed.

In patients with BMI greater than 50 kg/m$^2$ the longer limb bypasses result in weight loss comparable with that of standard gastric bypass in less obese patients. Weight loss (30% to 40% of preoperative weight) occurs over 1 to 2 years, followed by a plateau and then gradual regain of 5% to 10%. Complications include dumping syndrome, gastrojejunal stomal stenosis, marginal ulcers, and internal hernias. This operation has been studied for more than 14 years and results in durable weight loss over this period of time.[10]

## Laparoscopic Adjustable Gastric Banding

The AGB procedure is the least invasive bariatric procedure and the most common procedure performed in Europe, Latin America, and Australia. The U.S. Food and Drug Administration (FDA) approved the Lap Band for use in adults in 2001 and the Realize Band in 2007. Their use and acceptance in this country is increasing. The laparoscopically placed band creates a small pouch and a small stoma high on the stomach. A port for adjustment of the band is placed in the anterior abdominal wall. Periodic adjustments of the band are critical for a successful outcome, requiring from 4 to 10 visits within the first postoperative year. Complications of the Lap Band include gastric prolapse, stomal obstruction, erosion of the band into the stomach, and problems with the access port. The pars flaccida technique has significantly reduced the risk of gastric prolapse.[131] Average weight loss after 3 years is approximately 25% to 30% of the baseline weight.[121] The LAGB is currently being used within the context of an investigational device exemption from the FDA in adolescents younger than 18 years at several U.S. centers. Results of the trial are still pending.

## Biliopancreatic Diversion/ Duodenal Switch

BPD[132] is widely used in Europe. The DS is a modification developed by Hess and colleagues.[133] Both are primarily malabsorptive operations involving the creation of a 100- to 150-mL gastric pouch. By dividing the intestine into a long enteric limb anastomosed to a long biliopancreatic limb, a common channel 50 to 150 cm from the ileocecal valve is created and toxic problems seen with jejuno-ileal bypass are avoided. The weight loss is greater with BPD/DS than with the other weight loss procedures. However, the vitamin, nutrient, and protein deficiencies are more common with these procedures than with the aforementioned bariatric procedures.[134–135] Given the well-described compliance issues among adolescents and the aforementioned protein and vitamin deficiencies, the risks of the surgery outweigh the benefits and are not recommended in adolescents.[66]

### Laparoscopic Sleeve Gastrectomy

Laparoscopic sleeve gastrectomy (LGS) has long been used as part of the larger biliopancreatic diversion/duodenal switch (BPD/DS) or as a bridge to BPD/DS in the super-obese patient. This restrictive procedure involves the longitudinal resection of the stomach along a narrow 32- to 34-Fr bougie, although some have used larger bougie sizes. The resection extends from roughly 6 cm from the pylorus to the angle of His, thus creating a long gastric tube along the lesser curve. The fundus and greater curvature of the stomach are removed. The mechanism of weight loss is not yet understood but may be the result of both restriction and alteration of appetite and satiety signals from the gut to the brain including changes in ghrelin and PYY levels.[136] Excess weight loss ranging from 33% to 83% have been reported with the longest follow-up of only 3 years.[137] Complication rates range from 0% to 24% with an overall reported mortality rate of 0.39%.[137] Long-term data have not been reported for sleeve gastrectomy at this time, and the lack of these data should be discussed with the patient before the operation. Laparoscopic sleeve gastrectomy does involve much less anatomic and physiologic derangement than that of RYGB and is an intriguing alternative in the adolescent patient population. We have currently performed 14 laparoscopic sleeve gastrectomies at our institution and in our early experience have found similar weight loss compared with our patients undergoing RYGB. Long-term data are still necessary to determine whether LGS is a durable alternative or will require conversion to RYGB at a later date in some patients.

## New Procedures

A number of new concepts/procedures are being developed for use in the bariatric arena including the intragastric balloon, vagal and gastric stimulators, greater curve gastric plication, Endosleeve bypass, and new endoscopic techniques.[138] Although none of these is currently FDA approved in the United States, they among others are certainly on the horizon for the surgical treatment of obesity.

## NUTRITIONAL AND METABOLIC CONSEQUENCES

Nutritional and metabolic consequences of bariatric surgery have been well-delineated.[139–144] There is impaired absorption of iron, folate, calcium, and vitamin $B_{12}$ after all procedures that bypass the lower stomach and proximal small intestine. Even with supplementation, iron, vitamin $B_{12}$, folate, and calcium deficiencies may occur. Given the known poor compliance among adolescents,[11] certain factors such as vitamin $B_1$, folate, and calcium warrant special consideration.

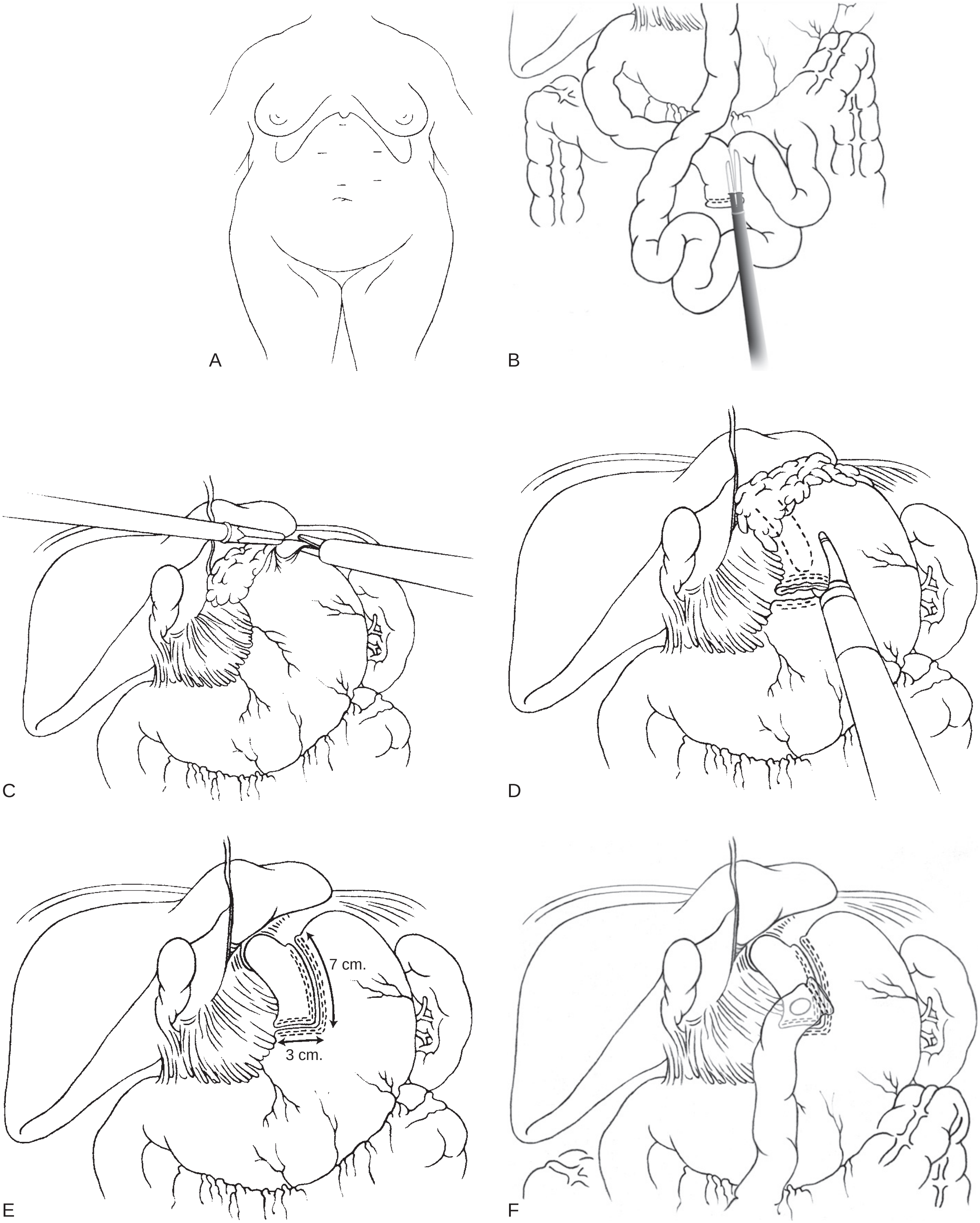


**FIGURE 80-1** Roux-en-Y gastric bypass surgery. **A,** Sites for various laparoscopic ports. **B,** Preparation of the Roux limb. **C,** Mobilization of stomach. **D,** Preparing bypass pouch. **E,** Pouch is 3 cm wide and 7 cm long. **F,** Gastrojejunal anastomosis.

Folate is specifically necessary for the synthesis of DNA and RNA and amino acid interconversion, particularly methylation reactions in the methionine-homocysteine cycle. It is essential for growth, cell differentiation, gene regulation, repair, and host defense.[139,140,145] Folate deficiency is more prevalent in the general population than previously suggested. Adequate maternal periconceptional folic acid consumption during critical periods of organ formation may reduce the likelihood of neural tube defects, conotruncal structural heart defects, obstructive urinary tract abnormalities, limb defects, facial clefts, and congenital hypertrophic pyloric stenosis. Closure of the neural tube occurs between 26 and 28 days after conception (e.g., 1 to 2 weeks after the first missed menstrual period, before pregnancy is recognized). Folic acid supplementation started after this critical period is therefore unlikely to prevent a neural tube defect.

Maternal folic acid deficiency is also associated with perinatal complications such as low birth weight, prematurity, placental abruption, infarction, and the development of neuroectodermal tumors in children. Folic acid deficiency, suggested by elevated plasma homocysteine, is also associated with cardiovascular diseases, increased risk of dysplasias, and the subsequent development of cancer. Given the protean manifestations of folic acid deficiency, the general recommendation is that all women of childbearing age take folic acid supplementation. In the adolescent who undergoes bariatric surgery, folic acid supplemented food items (such as cereals) may be inadequate. Additional supplementation contained in multivitamins is thus critical; measurement of serum folate and homocysteine concentrations may be useful.[142,146–148]

Adolescence is a period of enormous skeletal growth. This period of peak skeletal mineral accretion is a window of opportunity to influence lifelong bone health, both positively and negatively. Variations in calcium nutrition in adolescence may account for as much as 50% of the difference in hip fracture rates in postmenopausal years.[149,150] Though it is generally assumed that the obese adolescent has greater than normal bone mass[151] and is not operating at a disadvantage as it pertains to calcium absorption and risk for fracture or later osteoporosis, some experts disagree.[152] It is not clear whether the decrease in bone density that occurs after surgical weight loss, combined with potential poor compliance with vitamin D and calcium intake, will put the adolescent bariatric patient at greater risk for fractures later in life. Thus we consider it essential to closely monitor bone mineral density of adolescents undergoing bariatric surgery, particularly gastric bypass and biliopancreatic diversion.

## Guidelines for Performing Bariatric Surgery in Adolescence

Severely obese adolescents who have failed nonsurgical attempts at weight loss and have serious comorbidities should be considered candidates for bariatric surgery. Current recommendations for patient selection can be found in Table 80-4. There are others with such extreme obesity that activities of daily living may be severely impaired and in whom the development of health consequences of obesity is inevitable. For adolescents who have failed 6 months of attempts at professionally supervised weight loss, bariatric surgery is a reasonable weight loss option. See Table 80-5. Increasing preoperative weight and male gender are risk factors for procedure-related complications and mortality.[122,153] Given current referral patterns, the mean baseline BMI at our institution is 60.2 kg/m$^2$.[20] It is important for the surgeon to consider the impact of patient size on the potential for increased risks of the procedure. Some authors have suggested that surgeons who are early in the learning curve should avoid these high-risk patients to reduce complications.[153]

Adolescent bariatric surgery should be performed in centers having a multidisciplinary team capable of providing long-term follow-up and managing the unique behavioral challenges posed by the adolescent age group. Consistent with the guidelines established by the American Bariatric Surgical Association and the American College of Surgeons, these teams should include specialists with expertise in adolescent obesity evaluation and management, psychology, nutrition, physical activity instruction, and bariatric surgery. Depending on individual needs, additional expertise in adolescent medicine, endocrinology, pulmonology, gastroenterology, cardiology, orthopedics,

**TABLE 80-4**
**Recommendations for Patient Selection**

| |
|---|
| 1. Psychological maturity |
| Demonstrates understanding of surgery and is compliant with preoperative therapy |
| 2. BMI $\geq$ 35 with major comorbidities |
| Type 2 diabetes mellitus |
| Moderate to severe sleep apnea (AHI>15) |
| Pseudotumor cerebri |
| Severe NASH |
| 3. BMI $\geq$ 40 with other comorbidities |
| Hypertension |
| Insulin resistance |
| Glucose intolerance |
| Impaired quality of life or activities of daily living |
| Dyslipidemia |
| Sleep apnea (AHI >5) |
| 4. Individuals with mental retardation, syndromic obesity, and psychological disorders should be evaluated on a case by case basis |

From Pratt JS, Lenders CM, Dionne EA, et al.: Best practice updates for pediatric/adolescent weight loss surgery. Obesity (Silver Spring) 2009;17:901-910.

**TABLE 80-5**
**Attributes of Adolescent Bariatric Candidate**

- Patient is motivated and has good insight
- Patient has realistic expectations
- Family support and commitment are present
- Patient is compliant with health care commitments
- Family and patient understand that long-term lifestyle changes are necessary
- Agrees to long-term follow-up
- Decisional capacity is present
- Well-documented weight loss attempts
- No major psychiatric disorders that may complicate postoperative regimen adherence
- No major conduct/behavioral problems
- No substance abuse in preceding year
- No plans for pregnancy in upcoming 2 years

and ethics should be readily available. The team approach should include a review process similar to that used in multidisciplinary pediatric oncology and transplant programs. This review should result in culturally sensitive treatment recommendations tailored for the patient and family.

The optimal timing for weight loss surgery for overweight adolescents is unknown and largely influenced by the pressing health needs of the patient. There are growth and maturation factors that need to be considered. Physiologic maturation is generally complete by sexual maturation (Tanner) stage 3 or 4. Skeletal maturation (adult stature) is normally attained by the age of 13 to 14 in girls and 15 to 16 in boys. Overweight children generally experience accelerated onset of puberty. As a result, they are likely to be taller and have advanced bone age compared with age-matched, nonoverweight children. If there is uncertainty about whether adult stature has been attained, skeletal maturation (bone age) can be objectively assessed with a radiograph of the hand and wrist. If an individual has attained greater than 95% of adult stature, it is unlikely that a bariatric procedure would significantly impair completion of linear growth.

In determining patient suitability, all candidates should undergo a comprehensive psychologic evaluation. Goals of this evaluation are (1) to identify psychologic stressors or conflict within the family; (2) to identify past/present psychiatric, emotional, behavioral, or eating disorders; (3) to define potential supports and barriers to patient adherence, as well as family readiness for surgery and the required lifestyle changes (particularly if one or both parents are obese); (4) to assess whether there are reasonable outcome expectations; and most importantly, (5) to determine the level of cognitive and psychosocial development of the adolescent. With the alterations in eating patterns that are required after bariatric surgery, repetitive reinforcement is necessary to facilitate the formation of lifelong health-promoting habits. Bariatric surgical programs for this age group should be based on the premise that sustained weight control for the adolescent requires intensive and regular postoperative psychologic support. The role of the behavioral therapist depends on the level of intellectual function of the adolescent and includes behavioral rehearsal of regimen components before surgery, the use of behavioral contracts to outline regimen requirements and document the patient's agreement to adhere, a plan for patient and parental monitoring of adherence, and contingency reinforcement for adherence. The therapist plays a central role in developing parent-adolescent communication and conflict resolution skills and empirically based behavioral and family interventions, which facilitate the family's management of the patient's new lifestyle. A stable family environment, with full, unconditional support of all family members, is a desirable prerequisite for bariatric surgery in adolescents.

## Clinical Pathway for the Management of the Adolescent Undergoing Bariatric Surgery

The long-term consequences of bariatric surgery performed on adolescents have not been prospectively evaluated. The goals of adolescent bariatric surgery centers and programs should be to not only achieve dramatic and sustained weight loss but also contribute to the understanding of the most effective operations, risk factors for recidivism, and long-term outcome of adolescents undergoing bariatric surgery. Centers performing adolescent bariatric surgery should pay particular attention to bone mineral density and the ramifications of lifelong decreased vitamin and nutrient absorption on the adolescent and, particularly relevant to reproductive females, their offspring. Progress in this regard will require the implementation of broad-based clinical and basic research programs at these centers. The potential benefits of regionalizing selected, complex surgical procedures such as adolescent bariatric surgery have been well documented.[154–159] To this end, adolescent bariatric surgery should be concentrated in centers willing and able to provide comprehensive and extended preoperative and postoperative investigations including laboratory and diagnostic evaluations. Therefore the clinical pathway developed by the Comprehensive Weight Management Center at Cincinnati Children's Hospital Medical Center is designed to better characterize the prevalence and resolution of obesity-related complications among adolescents who undergo bariatric surgery, as well as provide surveillance for the known and potential consequences of the more popular bariatric surgical procedures performed at a comparatively young age.

Our preoperative panel includes a complete chemistry profile, liver function tests, uric acid, transferrin, iron, folate, lipid profile, urinalysis, electrocardiogram, cell blood count, hemoglobin A1C, fasting blood glucose and fasting insulin levels, thyroid stimulating hormone, and a pregnancy test for females. Nondiabetics receive a 2-hour glucose tolerance test. With the exception of the glucose tolerance test, the aforementioned laboratory and diagnostic panels are repeated at 3, 6, 9, and 12 months postoperatively, then yearly. Body composition is assessed with either bioelectrical impedance, for patients weighing in excess of 300 lb, or dual energy x-ray absorptiometry analysis (DEXA), for patients weighing less than 300 lb preoperatively and annually postoperatively. DEXA not only allows for the measurement of rate and relative amounts of fat and lean body mass loss but also provides a quantitative assessment of changes in bone mineral density. This body composition analysis is used to modify dietary plans intended to preserve lean body mass during the period of dramatic weight loss. Evidence suggesting that even as little as a two-standard-deviation change in bone mineral content of the adolescent can significantly increase the risk of osteoporosis and bone fractures in later life underscores the importance of meticulous and extended monitoring of nutrient, vitamin, and mineral absorption.[160] Because of the increased prevalence of abnormal heart geometry[161–163] and sleep disorders[80] among obese adolescents compared with nonobese adolescents, candidates for bariatric surgery undergo echocardiography and pediatric specific polysomnography.

Adolescent obesity may represent a disease that is more serious[2] and more difficult to manage[11,13] compared with this disease in adults. We currently lack an understanding of the long-term outcomes (both positive and negative) of bariatric procedures in this population. Thus centers offering bariatric care to these patients are obligated to critically evaluate outcomes, both positive and potentially negative, by ensuring that a mechanism is in place to carefully collect detailed data regarding comorbidity change and adverse events on all

adolescents who undergo surgery. This will help us to better define the role of bariatric procedures in the management of these patients. Ongoing longitudinal studies such as Teen-LABS (http://www.teen-labs.org) will provide long-term data to allow us to better understand the impact of bariatric surgery on the adolescent.

## Conclusion

The obesity epidemic in this country has generated a population of adolescents with the premature onset of adult disease. Clinical and epidemiologic studies have elucidated some of the life course risk factors for the development of childhood and adolescent obesity. Currently, bariatric surgery is the most effective treatment that achieves sustained weight loss and resolves or ameliorates the majority of the associated comorbidities. Success in adolescent bariatric surgery should be defined not only in terms of weight loss and morbidity resolution but also in terms of normal progression through adolescence and adulthood. Toward this goal adolescent bariatric surgery programs should have expertise that increases the likelihood of lifelong compliance with complex nutritional and lifestyle regimens (i.e., expertise that enables them to assess and meet the unique medical, cognitive, physiologic, and psychosocial needs of the adolescent). The guidelines for bariatric surgery should be conservative, be sensitive to the potential impact on the growth potential of the adolescent, and offer surgery during the time course of the disease that minimizes the risk of procedure-related complications and ensures the greatest likelihood of treating the comorbidities associated with obesity. Adolescent compliance with the strict nutritional and lifestyle regimens required after bariatric surgery may be best managed with a family-centered team that incorporates behavioral strategies to maximize compliance with postoperative dietary and physical activity instructions. Bariatric surgery is an exceedingly complex and technically difficult operation. The relative effects of hospital volume and surgeon volume in terms of procedure-related mortality and outcomes have direct implications for volume-based referral. Given the existent uncertainty about long-term outcomes of bariatric surgery in adolescents, regionalization of care and a national patient database are essential to achieve outcomes commensurate with the best adult series and to accelerate our understanding of the short- and long-term consequences of bariatric surgery among adolescents.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 81

# Duodenal Atresia and Stenosis—Annular Pancreas

Harry Applebaum and Roman Sydorak

## Short Capsule History

The duodenum is one of the most common sites of neonatal intestinal obstruction.[1] Although duodenal atresia, stenosis, and annular pancreas were recognized as disease entities as early as the eighteenth century, successful treatment of congenital high intestinal obstruction was a rare exception well into the twentieth century. The first reported case of duodenal atresia is attributed to Calder, in 1733.[2] Cordes, in 1901,[3] described the typical clinical findings associated with this congenital defect, while Vidal from France and Ernst from the Netherlands are credited with the first successful surgical repairs, in 1905 and 1914, respectively.[4,5] By 1929, Kaldor was able to identify 250 patients with duodenal atresia reported in the literature, although a review by Webb and Wangensteen, in 1931, revealed only nine survivors.[6,7] In stark contrast, modern surgical management has resulted in greater than 95% survival, with the uncommon mortalities usually related to anomalies of other organ systems.[8]

Historically, when duodenal atresia was encountered in association with trisomy 21 (Down syndrome), a finding in nearly one third of patients, the newborn obstruction was often intentionally left untreated. It was not until the1970s that changing societal and medical ethics led to a universal operative approach for infants born with these paired anomalies.[9–11] A gradual decline in the incidence of newborns with duodenal obstruction can be attributed to the increasing ability of perinatologists to determine an abnormal chromosome association early in gestation, leading to elective termination of many of these pregnancies.[12–15]

## Introductory Issues

The incidence of duodenal atresia has been estimated at 1 in 6,000 to 1 in 10,000 births.[16] A recent large review of 18 congenital anomaly registries across Europe identified 64 cases among 670,093 births, or 1 in 10,500.[17] Although no specific genetic abnormality is known to cause duodenal atresia, the number of reports of the anomaly occurring among siblings and among several generations of a family, as well as its frequent association with trisomy 21, suggests that one may be present.[15,18–25]

## Embryology

During the third week of embryonic development, gastrulation occurs. The cellular surface of the embryo facing the yolk sac becomes the endoderm, the surface facing the amniotic sac becomes the ectoderm, and the middle layer becomes the mesoderm. The endoderm gives rise to the gut tube beginning in the fourth week of development. In the sixth week, the gut epithelium proliferates rapidly, resulting in obliteration of the intestinal lumen. The intestine is then gradually recanalized over the next several weeks of development. Errors in recanalization are thought to be the primary cause of duodenal atresia and stenosis.[26–28] This differs from that of intestinal atresias and stenoses in other parts of the bowel, which are thought to result from vascular accidents during the later phases of gestation.[29]

The pancreas begins to develop from the endodermal lining of the duodenum in the fourth week of gestation. Two pouches are formed, which develop into a larger dorsal and a smaller ventral pancreatic primordium. The ventral bud then rotates dorsally to fuse with the dorsal bud during the eighth week. If the ventral bud fails to rotate completely, it remains anterior to the duodenum, and fusion with the dorsal pancreatic primordium results in a ring of pancreatic tissue encircling the duodenum, creating an annular pancreas with concomitant partial or complete obstruction.[26–28,30,31]

Approximately half of all infants with duodenal atresia or stenosis will also have a congenital anomaly of another organ system.[32–39] Sweed[40] collated statistics for associated anomalies from a dozen large series of duodenal obstructions, and found Down syndrome, annular pancreas, congenital heart disease, and malrotation to be the most common (Table 81-1).

**TABLE 81-1**
**Associated Anomalies (Collected Statistics)—after Sweed[40]**

| *Anomaly* | *Percent* |
|---|---|
| Down syndrome | 28.2 |
| Annular pancreas | 23.1 |
| Congenital heart disease | 22.6 |
| Malrotation | 19.7 |
| EA/TEF | 8.5 |
| Genitourinary | 8.0 |
| Anorectal | 4.4 |
| Other bowel atresia | 3.5 |
| Other | 10.9 |
| None | 45.0 |

From Sweed Y: Duodenal obstruction. In Purl P (ed): Newborn Surgery, ed 2. London, Arnold, 2003, p 423.
*EA/TEF*, Esophageal atresia/tracheal esophageal fistula.

## Spectrum of Disorders Involved

Several varieties of intrinsic and extrinsic congenital lesions can cause complete (81%) or partial (19%) obstruction of the duodenum.[1] The spectrum of abnormalities causing intrinsic obstruction includes imperforate and perforate webs of variable thickness within continuous bowel as well as complete or almost complete bowel discontinuity. Abnormalities causing extrinsic obstruction include annular pancreas, preduodenal portal vein, Ladd bands, and volvulus.[20,41–47]

Gray and Skandalakis[48] have grouped the variations of duodenal atresia into three types:

**Type 1** (92% of cases)[49]: There is an obstructing septum (web) formed from mucosa and submucosa with no defect in the muscularis. The mesentery is intact (Fig. 81-1, *A*). A variant of type 1 duodenal atresia, a "windsock deformity," can occur if the membrane is thin and elongated. The base of the membrane usually lies in the second portion of the duodenum, but balloons out distally, distending the third and fourth portions. Thus, externally the obstruction appears considerably more distal than it actually is.[50]

**Type 2** (1% of cases): A short fibrous cord connects the two blind ends of the duodenum. The mesentery is intact (Fig. 81-1, *B*).

**Type 3** (7% of cases): There is no connection between the two blind ends of the duodenum. There is a V-shaped mesenteric defect (Fig. 81-1, *C*).

In type 1 atresia, the obstructing septum may vary in thickness from one to several millimeters. Imperforate septa cause a complete obstruction, whereas those with central perforations cause incomplete obstruction (Fig. 81-2). With perforate septa, the diameter of the opening directly determines the degree of obstruction, and is therefore inversely related to symptoms.[50]

Although intrinsic blockage may occur in almost any portion of the duodenum, it occurs near the junction of the first and second portions in 85% of cases. The distal portion of the

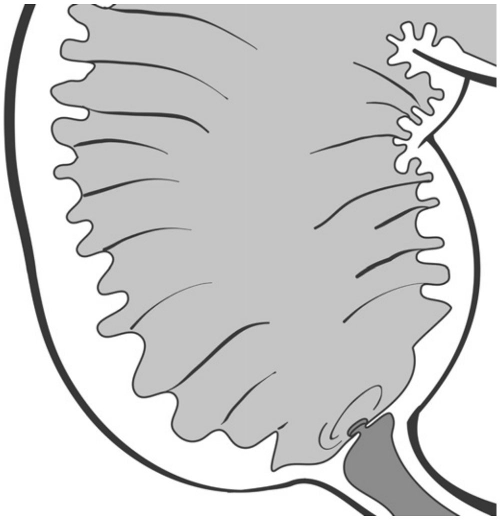

**FIGURE 81-2** Typical duodenal web with central perforation.

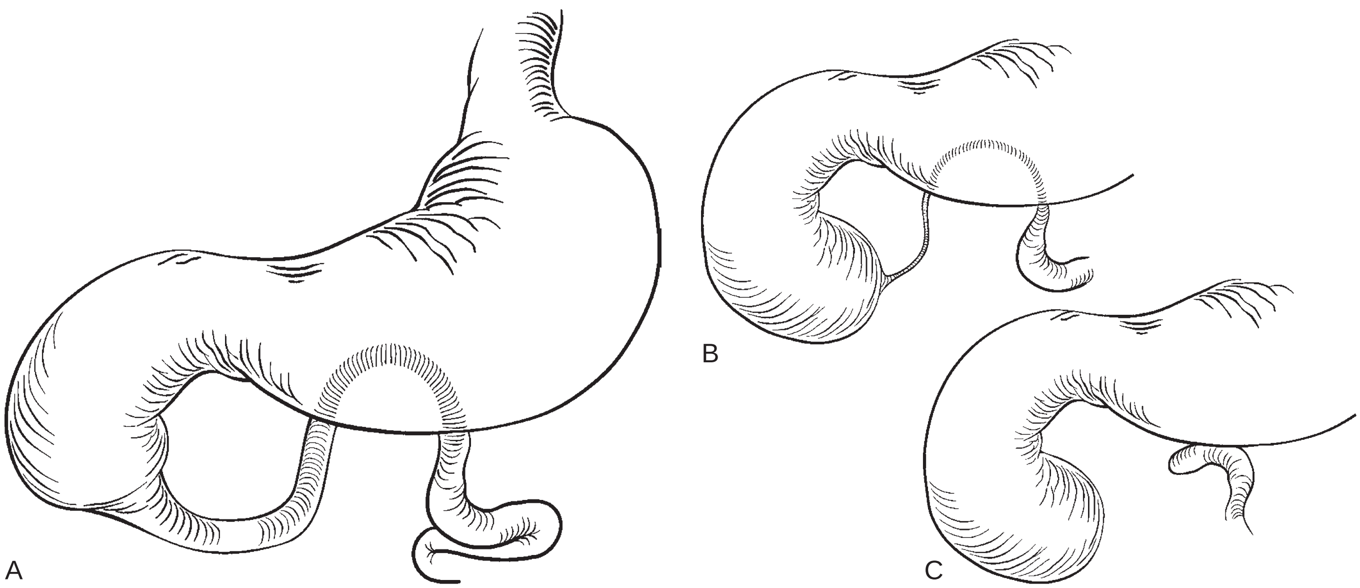


**FIGURE 81-1** **A,** Type I duodenal atresia. **B,** Type II duodenal atresia. **C,** Type III duodenal atresia.

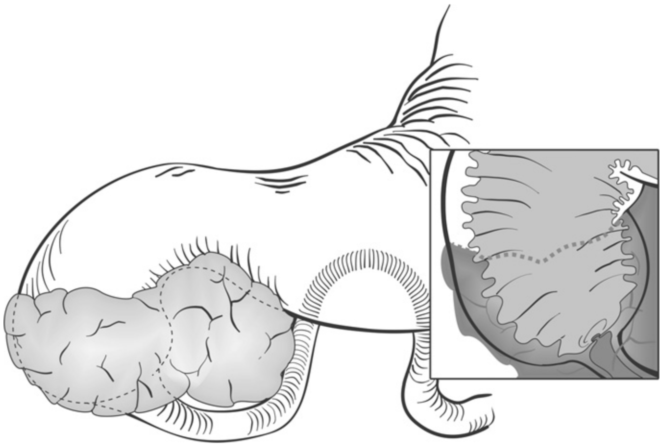

**FIGURE 81-3** Annular pancreas with underlying web causing partial duodenal obstruction.

common bile duct often traverses the medial portion of the septum, with the ampulla commonly located on the proximal surface of the obstruction. In rare instances, the distal portion of the duct is bifid, with proximal and distal openings, giving rise to what at first glance appears to be an impossible situation of air and bile distal to a complete congenital obstruction.[52,53]

With an annular pancreas, the ring of pancreatic tissue encircling the duodenum may itself cause an extrinsic partial obstruction. More often, however, a duodenal atresia or stenotic web underlies the annulus and is the actual cause of blockage (Fig. 81-3).[41,54] A preduodenal portal vein crosses the anterior surface of the second portion of the duodenum, rather than running posterior to it, and may cause incomplete obstruction by compression. This rare cause of extrinsic duodenal compression is usually found in infants with complex congenital heart disease.[8,47] Intestinal malrotation results in Ladd bands that usually give rise to an extrinsic partial obstruction of the second to third portion of the duodenum. Varying degrees of midgut volvulus—acute, intermittent, or chronic—can occur in these infants, also resulting in obstruction.[55]

## Clinical Presentation

Advances in prenatal care have allowed the majority of duodenal obstructions, both complete and incomplete, to be detected before birth.[56] Maternal polyhydramnios, noted in 30% to 65% of cases, is an early clue.[1,46] The classic "double-bubble" obstructive pattern is usually identifiable on fetal ultrasonography (Fig. 81-4). The larger of the twin bubbles juxtaposed in the fetal abdomen is the dilated, fluid-filled stomach, whereas the other is the distended proximal duodenum. An annular pancreas may also be recognizable.[57,58]

Repeated bilious emesis is the characteristic clinical feature of almost all newborns with duodenal obstruction. Because of the proximal level of intestinal blockage, the infant does not appear distended, although a subtle upper abdominal fullness may be noted. In patients with complete or high-grade duodenal obstruction, a plain film of the abdomen will generally confirm the diagnosis, with a finding of the "double-bubble" sign. The lack of more distal intestinal gas is diagnostic of a complete obstruction, whereas the presence of gas indicates

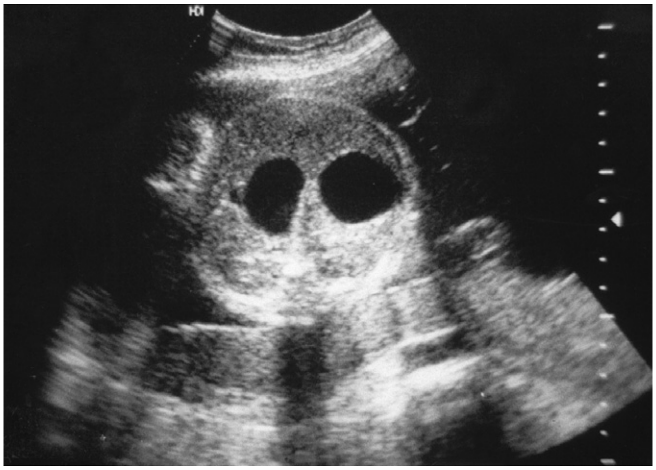

**FIGURE 81-4** Fetal ultrasound with "double-bubble" sign.

a partial obstruction (Fig. 81-5, *A* and *B*). In situations where the diagnosis is suspected but the "double-bubble" sign is not clearly visible, injection of 30 to 60 mL of air through the nasogastric tube may demonstrate this characteristic imaging finding.

The recognition of partial obstructions may be considerably delayed if the obstruction is of a relatively minor degree.[16] In this situation, it is not uncommon for symptoms to first occur when advancing the infant from formula to solid food, or it may only be unmasked much later in infancy, childhood, or, in rare instances, adulthood, when a progressive decrease in

**FIGURE 81-5** Plain abdominal film of newborn with duodenal stenosis (perforated web). Note the small amount of air distal to "double-bubble." The same finding with a lack of distal air would indicate duodenal atresia.

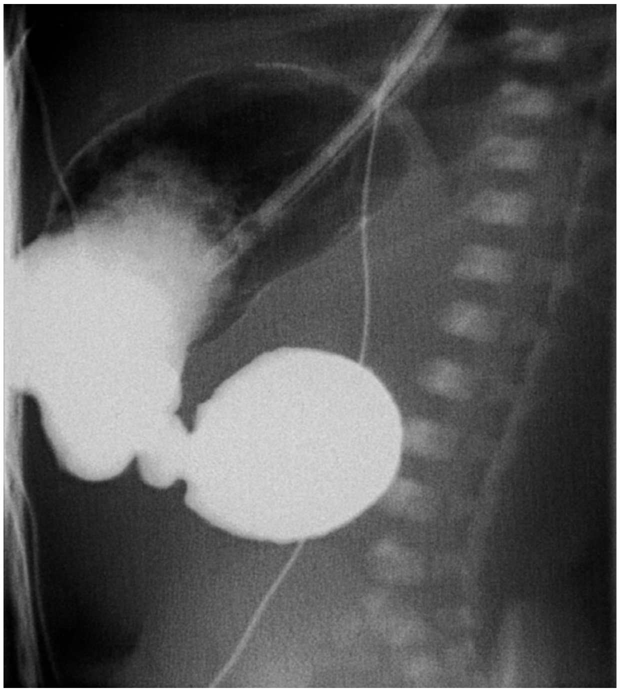

FIGURE 81-6 Upper gastrointestinal (UGI) radiographic contrast study of duodenal atresia.

motility or impaction of food or a foreign body causes more pronounced symptoms.[59–61]

With characteristic findings of duodenal obstruction on plain abdominal radiographs, it is appropriate to proceed directly to operative intervention without obtaining contrast studies. Occasionally, an upper gastrointestinal study (UGI) may be helpful in differentiating intrinsic duodenal obstruction from midgut volvulus (Fig. 81-6). With intrinsic obstruction, a smooth, rounded end will usually be seen at the level of obstruction in the second portion of the duodenum, and a ligament of Treitz may be visible if the obstruction is incomplete. A distal "beaking" effect in the third portion should arouse concern about volvulus and the need for an urgent operation.[62] The UGI is the most useful study for the evaluation of older infants and children with symptoms of chronic partial obstruction.[51] Gastroduodenoscopy may also be a useful diagnostic and sometimes therapeutic tool in these patients.[63,64]

## Treatment

Neonates with duodenal obstruction are initially managed with nasogastric or orogastric tube decompression and intravenous fluids. Gastrointestinal (GI) losses are replaced appropriately, and placement of a peripherally inserted central catheter (PICC) line for parenteral nutrition is recommended, because feeding is commonly delayed for up to several weeks following repair. Assuming that a diagnosis of midgut volvulus has been reasonably excluded, surgical correction of duodenal obstruction is not emergent. It can take place once the infant is optimized and associated anomalies have been appropriately studied.[34] Pulmonary status and size may preclude early operative intervention in very premature infants.

The operation is best accomplished through a right upper quadrant transverse incision halfway between the liver edge and the umbilicus. Following abdominal exploration, the right colon and hepatic flexure are then mobilized medially to allow full exposure of the proximal duodenum. Eviscerating and positioning the small bowel and colon cephalad and to the left of the incision best achieves access to the third and fourth portions of the duodenum. This maneuver will fully expose the root of the mesentery and ligament of Treitz. Although many patients with high-grade duodenal obstruction will have accompanying malrotation, on closer inspection, a number will actually be found to have a pseudomalrotation, because the underlying grossly dilated duodenum may cause abnormal leftward displacement of the right colon and hepatic flexure. Absence of the ligament of Treitz will be noted in patients with true malrotation.

The entire duodenum is inspected, and the probable location and type of the obstruction are noted. In a complete or nearly complete obstruction, the proximal duodenum appears as a large, boggy, thickened sphere. In type 1 cases, diminutive, gasless bowel distal to this point indicates that the obstruction is complete. In type 2 and 3 cases, the discontinuity of the bowel will become evident during dissection. In patients with annular pancreas, pancreatic tissue will be seen extending circumferentially around the second portion of the duodenum.

When there is gross dilatation of the proximal segment, a tapering duodenoplasty, as the initial part of the procedure, may hasten the postoperative return of effective peristalsis.[65–71] This is accomplished by either suture plication or by resection using a gastrointestinal anastomosis (GIA) stapler or needle-tip electrocautery and suture closure. The tapering is positioned on the anterior or anterolateral surface to avoid damage to the common bile duct, pancreas, and ampulla (Fig. 81-7).[72] In addition, division of the ligament of Treitz to help mobilize the distal segment may greatly facilitate an eventual untwisted, tension-free anastomosis.

When there is continuity of the proximal and distal duodenum, it is best to open the distal bowel near the apparent point of obstruction, in a position and direction suitable for a potential bypass. If filmy or thin webs are identified as the cause of

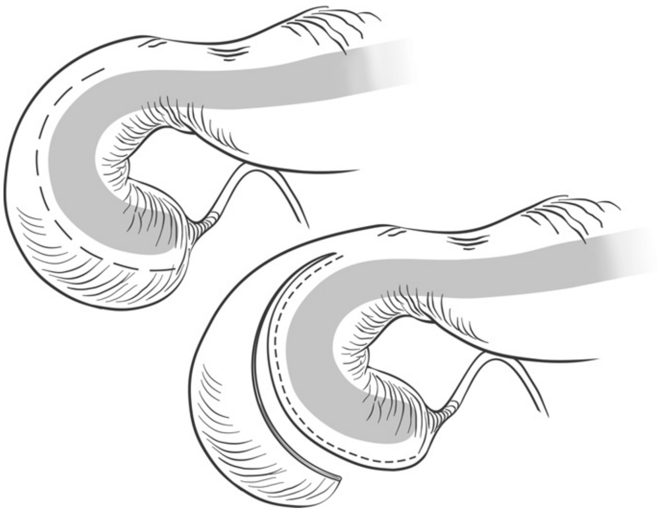

FIGURE 81-7 Tapering of distended proximal duodenum over dilator.

the obstruction, they may sometimes be excised rather than bypassed. In this case, the incision is carried over the web into proximal lumen, and the web is excised with cautery. If the ampulla is on the medial aspect of the web, or is not well visualized, excision should include only the lateral portion of the web. The duodenum is closed as a duodenoplasty in a transverse manner, to shorten and widen the bowel overlying the resection to minimize the risk of stenosis. Web excision should only be attempted when the web is thin, and when it is clearly the only cause of obstruction.

In almost all situations, a duodenoduodenostomy, joining the bowel just proximal and distal to the obstruction, is the best corrective option. It is the most direct, physiologic repair and, of the available options, has the least potential for later complications. When this procedure is difficult because of patient anatomy, particularly in some small, premature infants, duodenojejunostomy is the next best choice. A loop of proximal jejunum is chosen that will comfortably reach the proximal duodenal segment and is brought through the mesentery of the right transverse colon in a retrocolic position (Fig. 81-8). Duodenojejunostomy provides postoperative results that are generally equivalent to those obtained with duodenoduodenostomy. Gastrojejunostomy, the third bypass option, suffers from the frequent late complications of marginal ulceration and blind loop syndrome, and therefore should be avoided.

In a recent series of patients with duodenal obstruction, duodenoduodenostomy was the procedure of choice in the great majority of patients (>80% ), with duodenojejunostomy used in approximately 10% and web excision in 5% to 10%. Gastrojejunostomy was a rarely chosen option.[1,33,49,73]

When performing a bypass anastomosis, a “diamond anastomosis” (proximal transverse and distal longitudinal incisions) (Fig. 81-9, *A*), first described by Kimura, is preferred

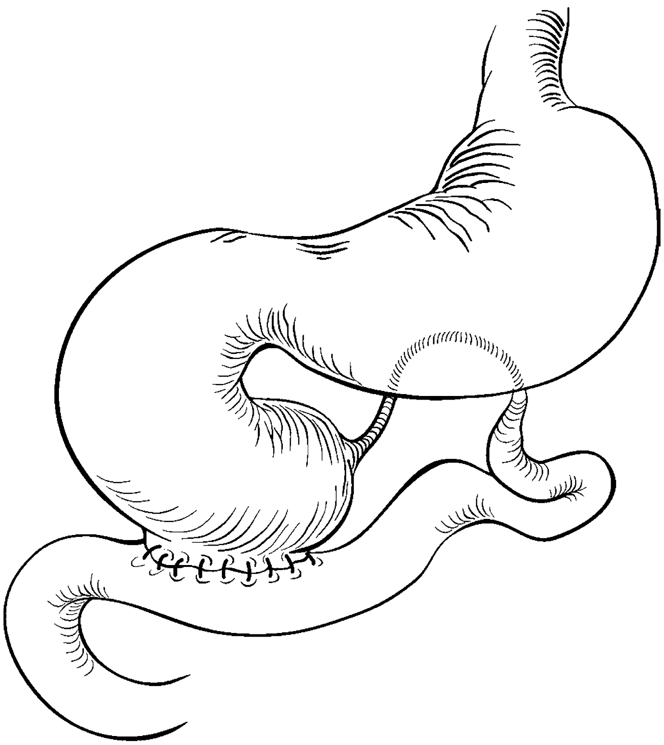

**FIGURE 81-8** Duodenojejunostomy.

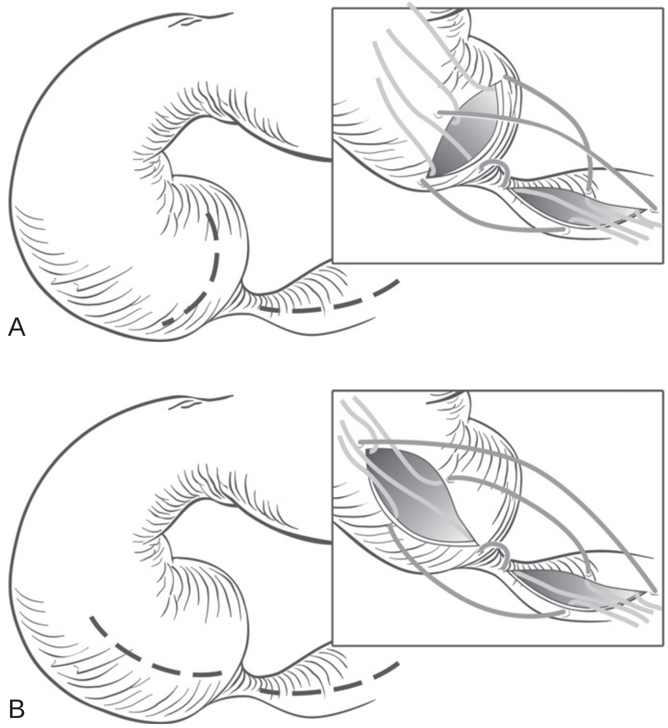


**FIGURE 81-9** **A,** “Diamond” anastomosis. **B,** “Simple” anastomosis.

over the “simple anastomosis” (proximal and distal longitudinal incisions) (Fig. 81-9, *B*).[74–76] This asymmetric anastomosis will maintain itself in a more wide-open position, and permit earlier transit of duodenal contents.

The antimesenteric incisions in each segment should be 1 to 2 cm in length, depending upon the size of the patient, to ensure an adequately patent anastomosis. With type 3 deformities, the end of the distal segment is spatulated appropriately. Before making the incision in the distal segment, it is useful to inject saline into the lumen while occluding the bowel distally to slightly stretch the wall, thus enabling a technically easier anastomosis. In addition, a 10-Fr Foley catheter should be passed proximally into the stomach and distally into the jejunum and pulled back with the balloon inflated, to ensure that no additional web or a windsock deformity is overlooked. Before starting the anastomosis, small retractors can be placed in the duodenum to inspect the point of obstruction and to determine the position of the ampulla of Vater. This anatomic landmark is usually easily visible, and identification can prevent injury to it. In addition, the distal intestine should be examined, because there is an association with additional atresias.

The diamond anastomosis is constructed by placing initial stay sutures joining the midpoints of each incision to the ends of the other. Placement should anticipate a posterior row of knots inside the lumen and an anterior row on the outside. The posterior row of the anastomosis is constructed using a repeating bisecting technique, to ensure even placement of the sutures and good coaptation of the bowel edges. The anterior row of the anastomosis is then completed in a similar fashion. The anastomosis is checked for patency, and the intestine is returned to the abdominal cavity in its usual position. Proper positioning of a nasogastric tube is also confirmed. Although commonly used in the past, gastrostomy tubes are now considered useful only in selected infants

who are not expected to feed orally in the near future. Some surgeons routinely position transanastomotic feeding tubes, although their benefit has not been clearly delineated.[76,77]

Congenital obstruction of the distal duodenum at or near the ligament of Treitz presents an especially difficult problem. The long segment of atonic dilated duodenum is difficult to effectively taper; so, the reconstructed bowel and anastomosis are likely to function poorly for a lengthy time period or not at all. In this situation, subtotal removal of the dilated duodenum with preservation of the ampulla is recommended.[78,79] The anterior wall of the second portion of the duodenum is opened, and the ampulla of Vater is located. The ligament of Treitz is taken down, and the dilated duodenum is dissected from the pancreas in a retrograde fashion to just distal to the ampulla. The first and second portions of the duodenum are then tapered to near the level of the ampulla, with the resected proximal duodenum removed in continuity with the distal duodenum. The end of the normal jejunum distal to the obstruction is spatulated and anastomosed to the tapered proximal segment (Fig. 81-10).

When an annular pancreas is encountered in association with duodenal obstruction, bypass is always the procedure of choice. The ring of pancreatic tissue should never be transected because of the major ductal structures that traverse it. Damage to these structures will lead to leakage of pancreatic fluid and/or pancreatitis. An obstructing preduodenal portal vein is bypassed in a similar manner.

The introduction of advanced laparoscopic techniques in the neonate has more recently led to a new surgical approach, the laparoscopic duodenoduodenostomy.[80–82] Depending on the size of the patient, 3- or 5-mm ports can be used. Three ports are used, one at the umbilicus for the camera and two working ports in the left/right midabdomen for suturing. A fourth port in the left upper or right lower quadrant can aid with retraction of the liver. The technique of repair is the same as the open approach using a diamond-shaped anastomosis. Either running sutures or single interrupted sutures can be used for the anterior and posterior walls. Intracorporeal knot tying is used. The apical stitches can be tied extracorporeally and left on tension through the abdominal wall to help align the enterotomies. Alternatively, U-clips can be used to perform the anastomosis.[81] The approach becomes more difficult in infants weighing less than 2 kg, because there is little working space. As a result, experience with advanced laparoscopy is necessary. It is currently impossible to compare the long-term outcomes of this technique with those of the classic open approach, because of the limited number of selected patients and the lack of prospective randomized results. However, the procedure can be performed with no bleeding, no conversions, no difference in operative times, and no postoperative anastomotic leaks.[81,82]

Postoperatively, total parenteral nutrition (TPN) is continued, and nasogastric tube output is monitored. As with other neonatal intestinal procedures, feedings may be started when the volume of the nasogastric output has diminished and its color has lightened and it becomes clear. This stage is commonly reached within several days to a week, but it may be prolonged. Small feedings are then initiated, with volume and concentration advanced as tolerated. This is a rapid process in most infants, and the majority may be discharged within one to several weeks.

## Complications (Intraoperative and Postoperative)

### INTRAOPERATIVE

Several intraoperative judgmental and technical pitfalls can lead to postoperative difficulties.[83] Incorrect identification of the site of obstruction most commonly occurs when a long, floppy web

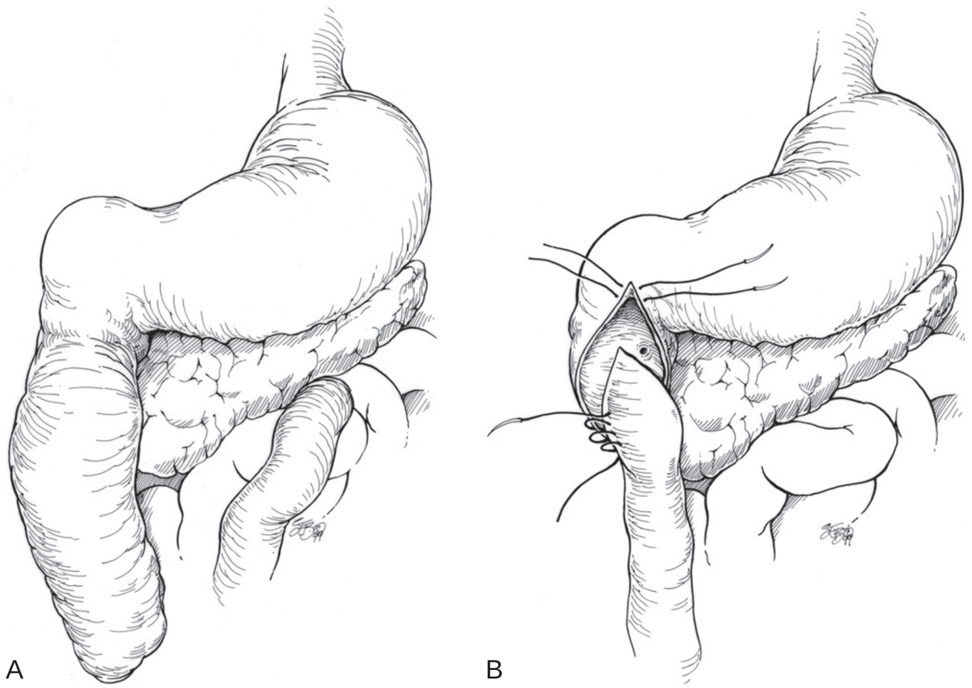


**FIGURE 81-10** Subtotal duodenectomy and jejunal onlay patch procedure.

(windsock deformity) is present. The proximally based web fills with gastrointestinal secretions and balloons out into the distal duodenum, distending it and causing the site of obstruction to appear much more distal than it actually is. The unwary surgeon, not recognizing the true attachment of the web, may then construct a bypass anastomosis entirely distal to it. In addition, on rare occasions, there will be more than one obstruction present. A distal web is easily missed because of the lack of any obvious adjacent proximal dilatation. The careful passage and withdrawal of balloon catheters both proximally into the stomach and distally into the jejunum before starting an anastomosis should prevent both of these situations.[51,84,85]

### POSTOPERATIVE

Prolonged feeding intolerance is the most common complication following surgery to relieve duodenal obstruction. There is a great deal of variability in the time required for a bypass anastomosis or web excision to function adequately. Although a variety of prokinetic agents have been proposed to hasten this process, none have been found to be of any consistent benefit. In general, if no specific difficulties were encountered at the initial procedure, there should be concern if relatively normal function has not been achieved by 3 weeks. At that time, an upper gastrointestinal series is helpful to search for residual anatomic obstruction, anastomotic stenosis, previously unrecognized obstruction at a different location, or poor peristalsis. Any decisions as to further surgical procedures should be based on a combined assessment of both imaging studies and clinical gastrointestinal function. A dilated proximal duodenum may be visualized radiographically for at least several months in the presence of a fully functional bypass anastomosis.[86] If prolonged poor function should occur, the finding of an anatomic obstruction is far less likely than identifying persistently poor peristalsis. Additional simple tapering of the proximal duodenum may suffice to provide adequate additional motility. Once adequate gastrointestinal function has been achieved, further problems may develop but are uncommon.

Late duodenal obstruction may occasionally be noted in older infants and children. This may occur following a seemingly successful neonatal bypass procedure or excision of web, or de novo, when a diagnosis of partial duodenal obstruction was initially missed. In the former, a piece of fibrous food or a foreign body may become impacted at the site of a partially resected web, or when a relatively narrow anastomosis was constructed to an inadequate size, and has become strictured over time or has failed to grow with the child. In the latter, it may occur at the site of a relatively low-grade stenosis that has become progressively symptomatic because of the development of proximal dilatation and ineffective peristalsis. In others, no persistent anatomic obstruction can be demonstrated following initial surgical correction, but poor peristalsis can be demonstrated in an area of persistent, and sometimes increasing, dilatation.[87]

Proximal tapering is often helpful at this time, either in conjunction with correction of an obviously inadequate initial procedure, or by itself, in situations where no distinct anatomic narrowing is found.[88,89] Most of these older infants and children are large enough for full-function upper gastrointestinal endoscopy, which may aid in the diagnosis and may be therapeutic by permitting dilatation of anastomotic strictures or resection of webs.[63,64]

## Outcomes

Survival of infants with duodenal obstruction has increased from 45% to 95% over the past half century.[48,90–92] This dramatic improvement is primarily related to improved diagnosis and surgical and postoperative management, although selective pregnancy termination has likely played a role. Almost all mortality is now related to associated anomalies of other organ systems, primarily those of the heart, lungs, and brain.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 82

# Jejunoileal Atresia and Stenosis

Jason S. Frischer and Richard G. Azizkhan

## History

Jejunoileal atresia and stenosis are the most common congenital anomalies of the small intestine and are a major cause of intestinal obstruction in neonates. Atresia (complete occlusion of the intestinal lumen) accounts for 95% of cases, whereas stenosis (partial intraluminal occlusion) accounts for only 5%. The first description of ileal atresia appeared in 1684 and is attributed to Goeller.[1] Other early commentaries on this anomaly were recorded in the 1770s by Calder[2] and Osiander.[3] By the early 1800s, Voisin had performed an enterostomy for intestinal atresia and Meckel had published a review of this condition and speculated on its etiology. Decades later (1889), Bland-Sutton[4] proposed a classification of the types of intestinal atresia and postulated that these defects occurred at the sites of obliterative embryologic events such as atrophy of the vitelline duct. In 1894 Wanitschek performed the first, though unsuccessful, resection and anastomosis.[3] In 1900 Tandler[5] theorized that intestinal atresia was secondary to a failure of recanalization of the solid-cord stage of bowel development; this concept was reaffirmed a decade later by Johnson's clinical observations.[6] The first successful anastomosis for intestinal atresia was achieved by Fockens in 1911.[7] A year later, Spriggs[8] suggested that causality for intestinal atresia could be attributed to mechanical accidents including vascular occlusions. This concept was later substantiated by the clinical observations of Davis and Poynter (1922)[9] and Webb and Wangensteen (1931).[2] In 1955 a landmark study conducted by Louw and Barnard[10] documented that late intrauterine mesenteric vascular accidents were responsible for most jejunoileal atresias. Their findings laid the foundation for our contemporary understanding of the wide range of intestinal defects seen in clinical practice.

As reported by Evans (1951),[1] the survival of children with intestinal atresia in the first half of the twentieth century was dismal, with only 139 of 1498 cases having a successful outcome. During the past 3 decades, a better understanding of etiologic factors and impaired intestinal function, as well as refinements in pediatric anesthesia, operative techniques, and preoperative and postoperative care (especially in the area of nutritional support), have led to a significant improvement in survival.[11–13]

## Prevalence

Reports of the prevalence of jejunoileal atresia vary significantly across the globe, ranging from as low as 1.3 to 2.25 cases per 10,000 live births in Spain, Latin America, and France to as high as 2.9 cases per 10,000 live births in various regions of the United States.[12–16] Several authors[14–16] have reported a higher prevalence of small-bowel atresia in African-American children and in twins, regardless of race. Consistent with the latter finding, a population-based study conducted in the Netherlands found a higher incidence of jejunal atresia in fraternal twins.[17] A population-based study in Hawaii found a higher incidence of jejunoileal atresia in Far East Asians compared with whites.[16] Factors that increase the risk of developing small intestinal atresias include use of pseudoephedrine alone or in combination with acetaminophen and receiving ergotamine tartrate and caffeine (Cafergot) for the management of migraine headaches during pregnancy.[18–19] Nixon and Tawes[20] reported a 2:1 ratio in the frequency of jejunoileal to duodenal atresias. In contrast, a review of 387 patients with intestinal atresia and stenosis treated over a 32-year period (1972 to 2004) at the Riley Children's Hospital in Indianapolis revealed that 50% of cases involved the jejunoileal region, 44% were duodenal, and the remaining 6% were colonic.[21] In a study of 619 patients representing the combined experience of members of the Surgical Section of the American Academy of Pediatrics, de Lorimier and colleagues[22] noted that boys and girls were equally affected by intestinal atresia. Although the mean birth weight of this cohort was 2.7 kg (range 0.9 to 4.8 kg), 33% of the infants with jejunal atresia, 25% of those with ileal atresia, and more than 50% of those with multiple atresias were infants with low birth weight.[22] Furthermore, infants with intestinal atresia detected on prenatal ultrasound (US) frequently have low birth weight.[23] Although trisomy 21 is seen in 30% of infants with duodenal atresia or stenosis, it is uncommon in those with jejunoileal atresia. More specifically, the previously cited studies conducted by Nixon and Tawes[20] and deLorimier and colleagues[22] noted that only 2 of 127 patients and 5 of 619 patients, respectively, with jejunoileal atresia had trisomy 21. In the study conducted at Riley Children's Hospital only 1 of 194 infants with jejunoileal atresia had this disorder,

and this patient also had duodenal atresia.[21] The incidence of extraintestinal anomalies in patients with intestinal atresia ranges from 25% to 35%, with a higher incidence of anomalies associated with jejunal atresia as compared with ileal atresia.[11,13,24,25] Furthermore, concomitant extraintestinal anomalies more commonly occur (>50%) in patients with duodenal atresia.[11,24,26] Though rarely observed, jejunoileal atresia reportedly coexists with biliary atresia, duodenal atresia, colonic atresia, gastric atresia, Hirschsprung disease, and arthrogryposis, and it also occurs in identical twins.[25,27–32]

# Etiology

The work of Lynn and Espinas (1959)[33] confirmed the earlier observations by Tandler[5] suggesting that epithelial plugging could be a cause of the failure of recanalization, resulting in intestinal atresia. Nevertheless, this etiology is likely to apply to duodenal atresia but not jejunoileal atresia. It is common knowledge that the bowel segments proximal and distal to jejunoileal atresias are separated by either a cordlike structure or a gap between the segments of bowel with an obvious mesenteric defect. The clinical observations of a number of authors[10,34,35] document that bile pigments, squames, and lanugo hairs are often found distal to atretic segments, implicating that events other than epithelial plugging may cause intestinal atresia and that these perturbating events occur later in utero.[36] Moreover, fetal bile secretion and the swallowing of amniotic fluid begin in the eleventh and twelfth weeks of intrauterine life, well after the luminal revacuolization process. The concept of other intrauterine events causing intestinal atresia was proposed by Davis and Poynter[9] in 1922. Since that time, others have maintained that mesenteric defects, volvulus, and infarction or other interruption of local blood supply can and do produce this anomaly in the fetus.[37,38] Endeavoring to understand the etiology of intestinal atresia, Louw and Barnard (1955)[10] subjected dog fetuses to ligation of mesenteric vessels and strangulation obstruction late in the course of gestation. Examination of affected fetal intestine 10 to 14 days later showed a variety of atretic conditions similar to those seen in human neonates. These findings strongly suggest that most jejunoileal atresias are the result of late intrauterine mesenteric vascular occlusions. Additionally, Courtois (1959)[34] observed that fetal rabbits undergoing experimental intrauterine intestinal perforation can manifest intestinal atresia or stenosis or can heal completely (with or without evidence of meconium peritonitis). Further, if an intestinal loop is isolated, resorption of the loop occurs if its blood supply is poor.[38] Later research conducted with fetal rabbits, sheep, dogs, and chick embryos confirms these findings.[35,39–41]

Glüer (1995)[42] reported the occurrence of jejunoileal atresia in four sets of twins after intraamniotic injection of dyes and theorized a teratogenic mechanism. In 2001 Sweeney and colleagues[43] reported that infants with jejunal atresia had a higher incidence of associated anomalies than those with ileal atresia (42% vs. 2%, respectively) and suggested that some cases of jejunal atresia may arise from a broader malformative process. In a rat model using doxorubicin (Adriamycin), Gillick and colleagues (2002)[44] reported that abnormal development of the notochord in the area of the developing midgut was associated with multiple intestinal atresias.

Grosfeld and Clatworthy[45] observed the occurrence of jejunal atresia with infarction of the entire midgut in a tight gastroschisis defect. Intestinal atresias secondary to late intrauterine mesenteric vascular insults are often seen in patients with volvulus, intussusception, internal hernia, and tight anterior abdominal wall defects.[38,45–48,50,51] de Lorimier and colleagues[22] found evidence of bowel infarction in 42% of 619 patients with jejunoileal atresia. Nixon and Tawes[20] observed macroscopic or microscopic intrauterine peritonitis in 48% (61 of 127) of patients with atresia, with an obvious volvulus noted in 35% (44 of 127). Murphy[52] noted that 5% of atresias were related to fetal internal hernias. Other studies[20,35,53] document instances of atresia related to bowel incarceration in an omphalocele. Iatrogenic postpartum ileal atresia as a result of umbilical clamping of an occult omphalocele has also been reported.[54,55] Although results of an American Academy of Pediatrics survey published in 1962 indicate that jejunoileal atresia associated with gastroschisis is observed in 2% of patients,[22] later studies consistently report an increase.[56–58]

Evans' review[1] of 1498 patients with atresia yielded only 9 patients with associated intussusception, whereas Komuro[59] described intrauterine intussusception as a cause of intestinal atresia in 25% of patients with a single mid-small-bowel atresia. In the latter study, intussusception was not detected as a cause of atresia in patients with high-jejunal, *apple-peel,* or multiple atresias. The cause of intrauterine intussusception is as yet unknown[48,50]; however, most of these infants are full term and without associated anomalies or cystic fibrosis.[28,60–63] Postnatal intussusception as a cause of jejunal atresia in a premature infant has also been described.[64] In the previously cited study conducted at Riley Children's Hospital,[21] volvulus was detected in 33% of patients, malrotation in 16%, intussusception in 3%, internal hernia in 1%, and gastroschisis in 14%; evidence of meconium peritonitis was found in 12%.

A study conducted by Komuro and colleagues (2004) clearly documents the association of placental vascular anomalies and the occurrence of complex jejunoileal atresia (multiple atresias, apple-peel deformity).[23,65] All of these patients had low birth weight, consistent with the impact of placental vascular compromise on fetal growth. Multiple atresias have also been noted in patients with congenital and acquired immunodeficiency.[66–69]

The genetic contribution to jejunoileal atresia is unclear. Gross and colleagues[66] reported familial instances of combined duodenal and jejunal atresia. Numerous authors have reported hereditary multiple intestinal atresias.[67,70–72] Furthermore, both autosomal recessive and autosomal dominant transmission has been documented.[73,74] On the basis of a review of the literature, Shorter and colleagues (2006)[36] proposed a novel classification system (Table 82–1) for the five distinct types of familial atresia documented to date (i.e., pyloric atresia, duodenal atresia, hereditary multiple atresia syndrome, apple-peel atresia, and colonic atresia). The basic premise of these authors is that the identification of familial cases of these various forms indicates the existence of specific embryologic pathways; when disrupted, these pathways give rise to intestinal atresias. The authors maintain that nonfamilial cases result from disruption of the same pathways by nongenetic mechanisms. The conceptual difference between

**TABLE 82-1**
**Classification of Familial Cases of Gastrointestinal Atresia***

| *Class* | *Description* | *Genetics* |
|---|---|---|
| 1 | Pyloric atresia (may include antral atresia or atresia of the proximal duodenum) | Autosomal recessive |
| 2 | Duodenal atresia—second or third portion of duodenum, no other atresias | Autosomal recessive |
| 3 | Multiple atresia syndrome, rotation is usually normal | Autosomal recessive, uniformly lethal |
| 4 | Apple-peel atresia, proximal atresia is typically at the duodenojejunal junction, almost always associated with malrotation | Autosomal recessive |
| 5 | Colonic atresia, rarest type, usually in the sigmoid colon | X-linked recessive |

From Shorter NA, Georges A, Perenyyi A, Garrow E: A proposed classification system for familial intestinal atresia and its relevance to the understanding of the etiology of jejunoileal atresia. J Pediatr Surg 2006;41:1822-1825.
*All classes have a nonfamilial counterpart.

this model and the previously discussed vascular accident model is that in the latter, the atresia results from the loss of a preexisting vessel; in the former, however, the vessel fails to develop altogether.

# Diagnosis

## CLINICAL PRESENTATION

A number of key prenatal and postnatal clinical signs should elicit suspicion of jejunoileal atresia. These signs include maternal polyhydramnios, bilious emesis, abdominal distention, jaundice, and failure to pass meconium on the first day of life (Table 82-2).[22,52,75–78] Polyhydramnios is observed in 24% of intestinal atresia cases and is more common in patients with proximal jejunal atresia (38%).[22] Bilious emesis is slightly more common in patients with jejunal atresia (84%), whereas abdominal distention is more common in patients with ileal atresia (98%).[75] Jaundice, which is characteristically associated with an elevation of indirect bilirubin,[79,80] occurs in 32% of infants with jejunal atresia and 20% of those with ileal atresia.[22] Although most infants with jejunoileal atresia fail to pass meconium in the first 24 hours of life, either meconium or necrotic tissue is occasionally passed.[20,47,63,75,77] Upper abdominal distention is often associated with more proximal atresia; more generalized distention usually indicates a more distal obstruction (e.g., distal small bowel or colon) in which many loops of bowel are filled with air proximal to the level of obstruction. Severe distention may be associated with respiratory distress as a result of elevation of the diaphragm. Because the abdomen is thin, the outline of the abdominal loops may be visible through the abdominal wall. Occasionally, peristaltic waves are visible on physical examination. Although distention usually develops 12 to 24 hours after birth, abdominal distention may be noted at birth. This suggests the presence of giant cystic meconium peritonitis.[75,81]

**TABLE 82-2**
**Jejunoileal Atresia: Clinical Presentation**

| | *Jejunal Atresia (%)* | *Ileal Atresia (%)* |
|---|---|---|
| Polyhydramnios | 38 | 15 |
| Bilious vomiting | 84 | 81 |
| Abdominal distention | 78 | 98 |
| Failure to pass meconium | 65 | 71 |
| Jaundice | 32 | 20 |

## PRENATAL IMAGING

Prenatal ultrasonography (US) in mothers with polyhydramnios has identified small-bowel obstruction associated with atresia, volvulus, and meconium peritonitis[23,82–84]; however, it is more reliable in detecting proximal versus distal intestinal atresia. The presence of small-bowel atresia is suspected when US reveals multiple distended loops of proximal bowel with vigorous peristalsis.[85] In these patients, the distal bowel is decompressed. Intestinal atresia is also suspected in fetuses with gastroschisis and marked intestinal dilatation on prenatal US.[57,82]

Phelps and colleagues[86] reported that only 42% of prenatally diagnosed gastrointestinal malformations were confirmed postnatally and only 16% of gastrointestinal anomalies observed at birth had been detected antenatally. Further, although the appearance of echogenic bowel on prenatal US is frequently associated with a gastrointestinal malformation, only 27% of cases were confirmed after delivery. Basu and Burge[23] found that only 31% of patients with small-bowel atresias were diagnosed on antenatal US and noted that the later in gestation the US is performed, the more likely it is to detect the malformation. Studies reported by both Dalla Vecchia and colleagues[87] and Tam and Nicholls[88] corroborate the infrequency of US detection of small bowel atresias. When recognized, the atresia was more often in a proximal location and the infants required prolonged postnatal treatment. Collectively, these studies suggest that antenatal US findings have a relatively poor predictive value for bowel abnormalities and are also unreliable in detecting or excluding fetal gastrointestinal malformations. Moreover, these findings do not affect neonatal outcomes in patients with intestinal atresia.[89]

Over the past decade, studies of the utility of fetal magnetic resonance imaging (MRI) indicate that this modality can identify gastrointestinal abnormalities and suggest that it may be more accurate than US in the prenatal diagnosis of bowel atresia.[90–91] In view of these findings, we recommend that abnormalities or ambiguities on prenatal US be followed up with fetal MRI (Fig. 82-1).[92]

## POSTNATAL RADIOGRAPHIC FINDINGS

In most instances, radiographic examination of the abdomen demonstrates the presence of intestinal obstruction in the neonate. Supine and lateral decubitus abdominal radiographs are obtained in each case. Thumb-sized intestinal loops and air-fluid levels are highly suggestive of intestinal obstruction.[45] Proximal jejunal atresia may present with only a few air-fluid levels and no distal gas beyond the atresia

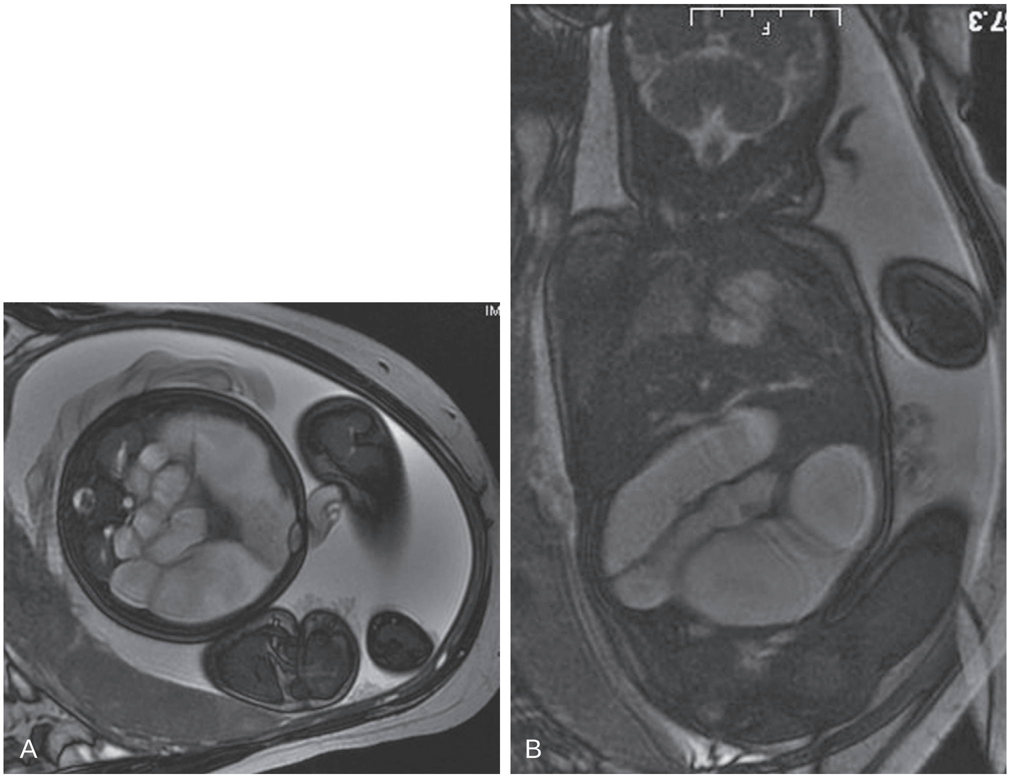


**FIGURE 82-1** Fetal magnetic resonance imaging (MRI). **A,** Axial. **B,** Coronal. Prenatal ultrasound demonstrated a bowel obstruction. MRI shows multiple dilated, fluid-filled bowel loops with no meconium. Findings are suggestive of distal bowel obstruction.

(Fig. 82-2). The more distal the atresia, the more apparent the abdominal distention and the greater the number of distended intestinal loops and air-fluid levels. Just proximal to the atresia, a larger loop with a significant air-fluid level may be seen (Fig. 82-3). Peritoneal calcifications are seen in 12% of cases on plain abdominal radiographs; these calcifications signify the presence of meconium peritonitis, a sign of intrauterine intestinal perforation (Fig. 82-4). In addition, instances of intraluminal calcification may be observed, indicating an antenatal volvulus with partial absorption of necrotic bowel.[93,94] In instances of giant cystic meconium peritonitis, plain radiographs of the abdomen may demonstrate a large air-fluid level in a meconium pseudocyst.[81] This type of occurrence is related to a late intrauterine perforation, resulting in an encapsulated mass (pseudocyst) of perforated bowel and contained meconium.[75,77]

Colonic haustral markings are rarely seen on abdominal radiographs in the newborn. Differentiating between dilated loops of small and large intestine thus becomes difficult. In these patients, a contrast enema can be extremely useful in distinguishing between small- and large-bowel distention; in determining if the colon is used or unused (microcolon); and in locating the position of the cecum in regard to the possible presence of anomalies of intestinal rotation and fixation.[75] The vast majority of infants with jejunoileal atresia demonstrate a microcolon, which is directly related to the fact that little meconium has passed the area of obstruction in the distal fetal small intestine, and the unused colon is therefore not distended.[95] If the intrauterine vascular event leading to atresia occurs extremely late in gestation, the colon may appear of normal caliber. This is particularly true in instances of atresia related to intrauterine intussusception (Fig. 82-5).[47,63,96] Malrotation has been observed in approximately 10% of patients with jejunoileal atresia[20,22] and was noted in 16.5% of patients with jejunoileal atresia at Riley Children's Hospital.[21]

When it is clear on a plain radiograph that there is a complete intestinal obstruction, contrast studies may not be necessary; however, in cases of intestinal stenosis where there is an incomplete obstruction, a small-bowel contrast enteroclysis study has a higher diagnostic yield than a routine small-bowel series.

## DIFFERENTIAL DIAGNOSIS

A neonate with a bowel obstruction from other causes may present with a clinical picture that is similar to that of a neonate with jejunoileal atresia. The differential diagnosis includes malrotation with or without volvulus, meconium ileus, intestinal duplication, internal hernia, colonic atresia, adynamic ileus secondary to sepsis, and total colonic aganglionosis.[10,29,97] The contrast enema yields valuable information that frequently rules out specific causes of obstruction such as colonic atresia. Because of the potential coexistence of jejunoileal atresia and malrotation (10% to 18%), meconium peritonitis (12%), meconium ileus (9% to 12%), total colonic aganglionosis, and rarely, intestinal neuronal dysplasia, a definitive preoperative diagnosis is not always possible.[10,20,29,75,98–101]

Radiographic subtleties may help distinguish uncomplicated meconium ileus from other neonatal intestinal obstructions. Radiographs of meconium ileus often show substantial distension of multiple bowel loops that have few, if any, air-fluid levels. This is related to the fact that the meconium in

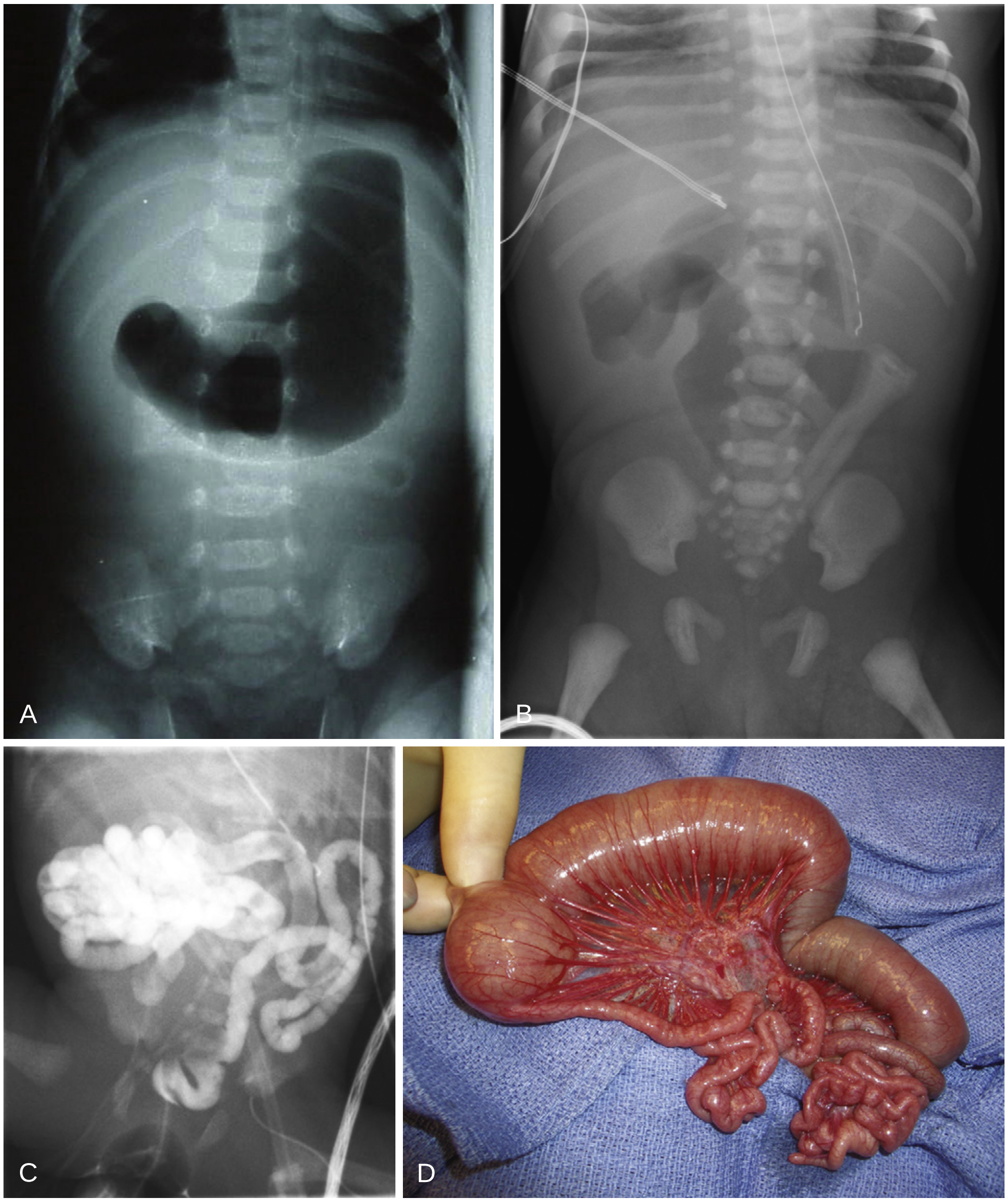


FIGURE 82-2 Jejunal atresia. **A** and **B,** Plain abdominal radiographs demonstrating a proximal small bowel obstruction. **C,** Contrast enema revealing an unused colon (microcolon) with incomplete rotation (cecum in the right upper quadrant). Contrast fills multiple decompressed loops of small intestine hinting at a proximal obstruction. **D,** Type I jejunal atresia seen at laparotomy. The appendix and cecum are seen in the bottom right of the photograph.

these patients is viscous and therefore fails to layer out as an air-fluid interface.[75] Other signs of meconium ileus include the ground-glass appearance (also referred to as Neuhauser sign) or the soap-bubble sign of Singleton, which may be observed in the right lower quadrant and is representative of the viscid meconium mixed with air.[102,103] Separating out patients with uncomplicated meconium ileus can avoid unnecessary operations. In cases where meconium ileus complicates an atresia, surgical intervention is required.

## PATHOLOGIC FINDINGS

Jejunoileal atresias are nearly equally distributed between the jejunum (51%) and the ileum (49%). Most atresias (36%) occur in the distal ileum; 13% occur in the proximal ileum; 31% occur in the proximal jejunum; and 20% occur in the distal jejunum.[22] Intestinal atresias are generally a single event (>90%); however, multiple atresias can occur (6% to 20%)[9,22,27] and most often involve the proximal jejunum.[72,104,105]

Since the observations of Bland-Sutton and Spriggs in the late nineteenth and early twentieth centuries,[4,8] the classification of jejunoileal atresia has changed only slightly. In 1955 Louw and Barnard described three different types of jejunoileal atresia: type I referred to a mucosal (septal) atresia with an intact bowel wall and its mesentery (Fig. 82-2, *D*); type II referred to two atretic blind ends connected by a fibrous cord with an intact mesentery; and type III comprised two separated segments of bowel with a V-shaped gap within the mesentery (Fig. 82-5, *C*).[10] In a study evaluating 559 cases

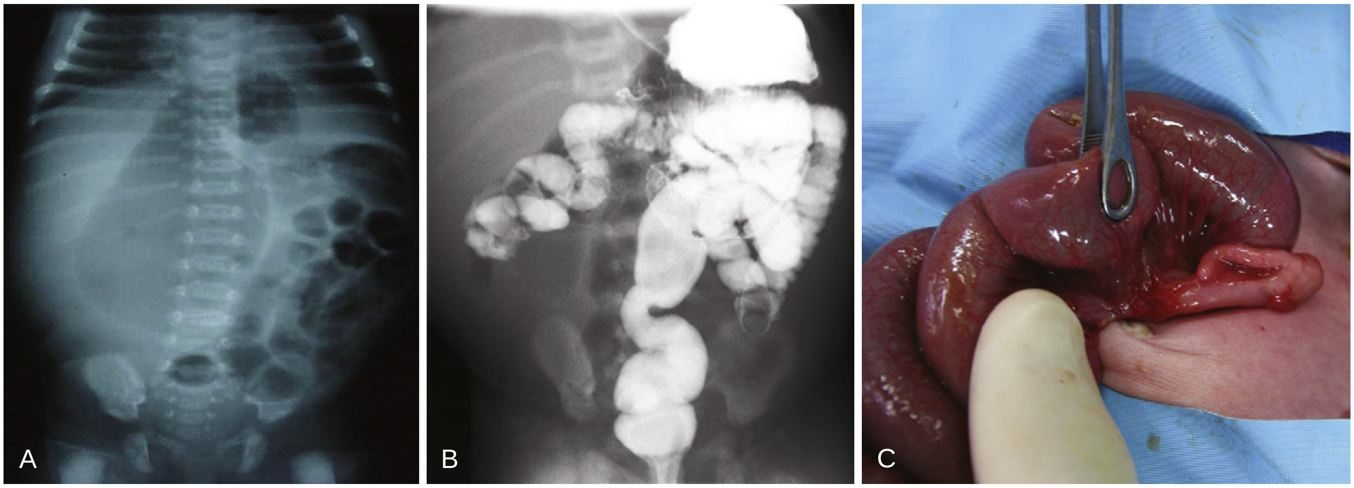


**FIGURE 82-3** Ileal atresia. **A,** Radiograph of the abdomen showing dilated loops of intestine with a very distended loop inhabiting most of the right abdomen. **B,** Contrast enema showing a small colon that does not fill the dilated loops of bowel. **C,** Distal ileal atresia with the terminal ileum and cecum seen on the right side of the photograph.

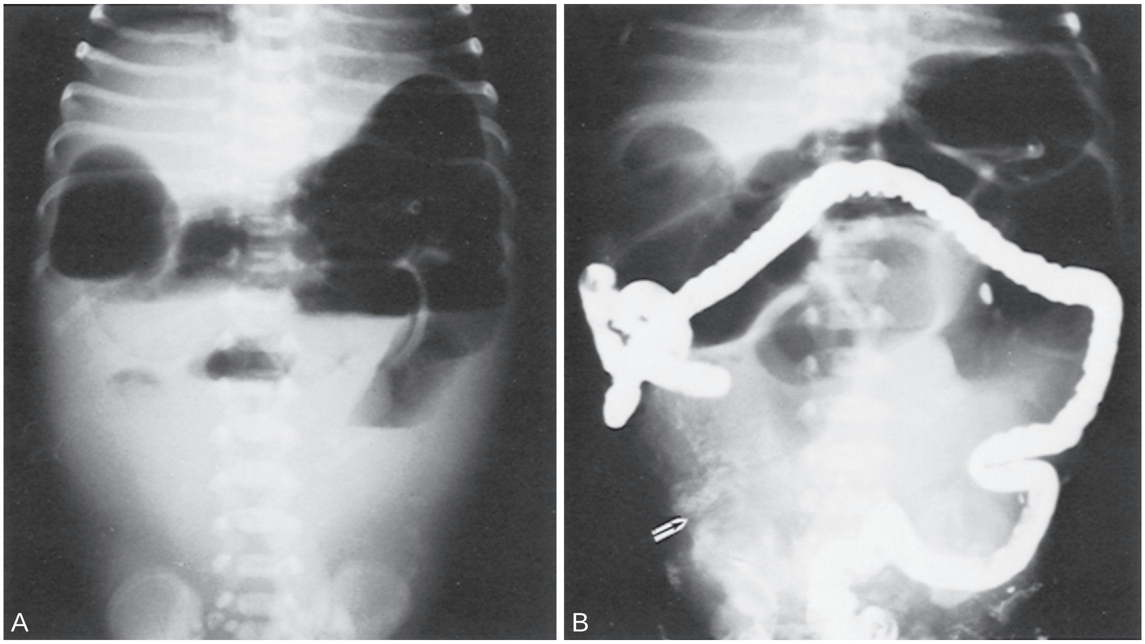


**FIGURE 82-4** Meconium peritonitis. **A,** Erect radiograph of the abdomen demonstrates greater than thumb-sized loops of intestine with multiple air-fluid levels. **B,** Barium enema demonstrates a microcolon with incomplete rotation (cecum in right upper quadrant) and calcification in the right lower quadrant (*arrow*) indicative of meconium peritonitis (From Grosfeld JL: Alimentary tract obstruction in the newborn. Curr Probl Pediatr 1975;5:3).

of jejunoileal atresia, de Lorimier and colleagues[22] reported that 19% were type I, 31% were type II, and 46% were type III. The authors noted that type I and type II atresia typically have a normal length of intestine as compared with the type III lesions, which are associated with a shorter bowel length caused by resorption of the fetal gut after a vascular accident.[22]

Although multiple atresias reportedly occur in 6% to 20% of cases,[9,22,27,106] they are not mentioned in the classification system of Louw and Barnard.[10] These atresias are associated with a foreshortened intestinal length, prematurity, and a high mortality. The appearance of the intestine at operation resembles a string of beads or string of sausages (Fig. 82-6).[106] A diffuse inflammatory process has been proposed as a contributing factor.[107]

Another unusual group of patients are those with apple-peel or *Christmas-tree* deformity, which occurs in 11% to 32.4%[108,109] of jejunoileal atresias. These patients present with proximal atresia near the ligament of Treitz, a large mesenteric defect, and foreshortened bowel. Additionally, the blood supply to the distal bowel is precariously supplied in a retrograde fashion by arcades from the ileocolic, right colic, or inferior mesenteric arteries (Fig. 82-7).[3,109–113]

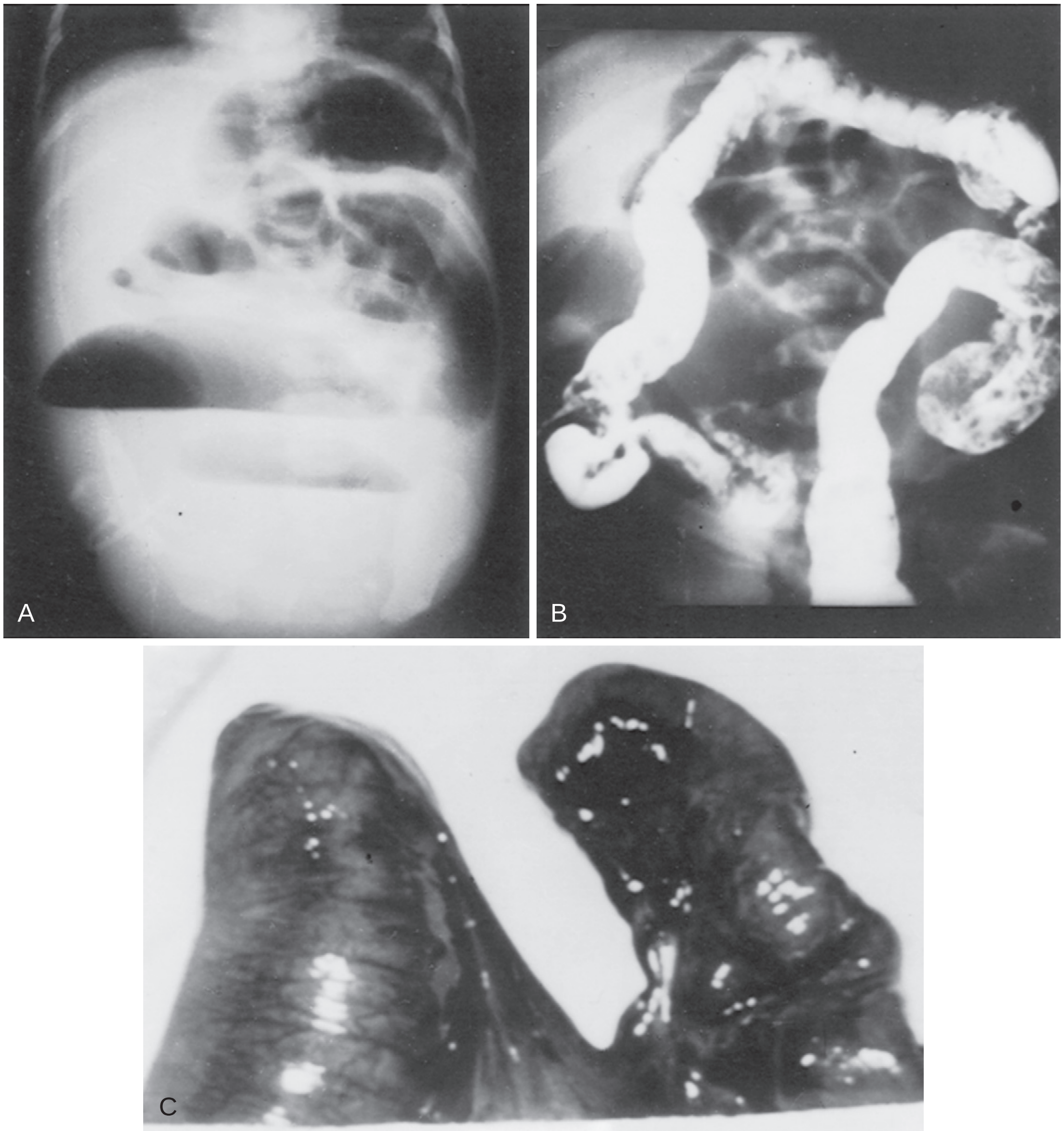


**FIGURE 82-5** Ileal atresia. **A,** Upright radiograph of abdomen showing distended loops of intestine with air fluid levels. **B,** Contrast enema showing normal-caliber colon filled with debris. **C,** At laparotomy, ileal atresia with a V-shaped defect in the mesentery (type IIIa) and evidence of an intrauterine intussusception were found. (From Grosfeld JL: Alimentary tract obstruction in the newborn. Curr Probl Pediatr 1975;5:3).

The apple-peel variant is associated with a familial pattern. Patients with this variant typically are premature (70%), of low birth weight (70%), have a high rate of malrotation (54%), and are associated with an increased number of congenital anomalies.[58,114] Apple-peel deformity has also been seen in siblings with ocular anomalies and microcephaly.[115]

A number of studies have focused on the genetic aspects of multiple atresias. In 1973 Guttman and colleagues[67] reported a familial pattern of multiple atresias affecting the stomach, duodenum, small intestine, and colon occurring in French Canadians near the St. John River in Quebec. Because of the high degree of consanguinity observed in this group, a number of authors[67,116] proposed that extensive multiple atresias are most likely an expression of a rare autosomal recessive gene. A report describing the natural history of the patients reported by Guttman was reported by Bilodeau and colleagues in 2004.[117] These authors found that all of these patients had an IgM deficiency and had died. The etiology remains unclear due to a specific gene mutation not yet elucidated.

The contemporary classification system that incorporates both multiple atresias and the apple-peel variant was first described by Martin in 1976[118] and later revised by Grosfeld and colleagues,[27] who incorporated these lesions into the previous nomenclature of Louw.[10] Type III atresias have been divided into type IIIa, which describes the previously designated type III lesion, and type IIIb, which refers to the apple-peel or Christmas-tree anomaly. Multiple atresias are referred to as type IV lesions (Fig. 82-8).[27]

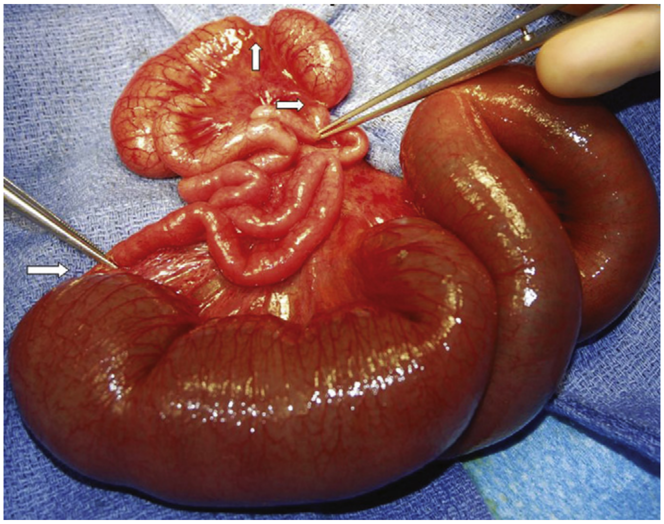

**FIGURE 82-6** Multiple atresias (type IV). Intraoperative photograph demonstrating multiple ileal atresias (*arrows*). This was repaired with a tapering enteroplasty and multiple single-layer anastomoses.

**FIGURE 82-7** *Apple-peel* atresia or *Christmas-tree* deformity (type IIIb). Presents with a proximal jejunal atresia with foreshortened bowel and a large mesenteric defect. The distal bowel has a precarious blood supply delivered in a retrograde fashion.

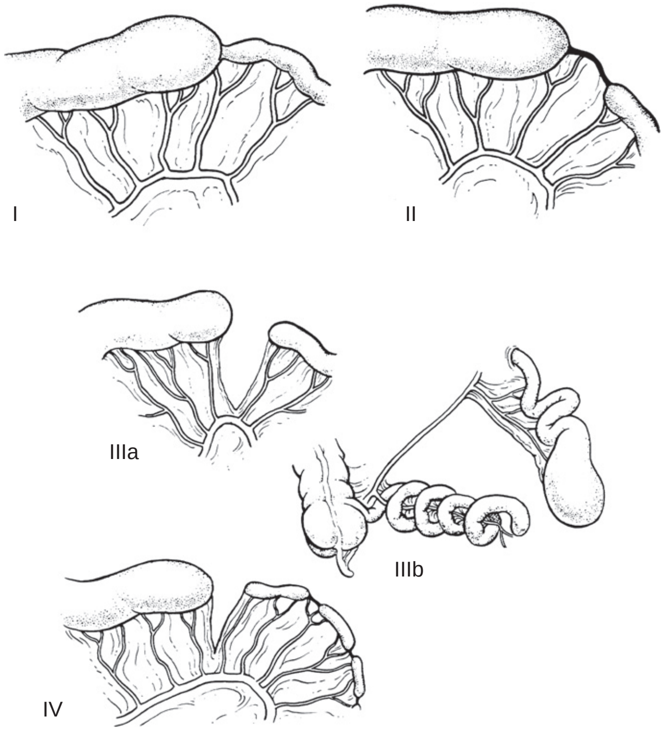


**FIGURE 82-8** Classification of intestinal atresia. Type I, mucosal (membranous) atresia with intact bowel wall and mesentery. Type II, blind ends are separated by a fibrous cord. Type IIIa, blind ends are separated by a V-shaped (gap) mesenteric defect. Type IIIb, apple-peel atresia. Type IV, multiple atresias (string of sausages). (From Grosfeld JL, Ballantine TVN, Shoemaker R: Operative management of intestinal atresia and stenosis based on pathologic findings. J Pediatr Surg 1979;14:368).

# Treatment

Optimally, the newborn is maintained in a warm humidified environment. A 10-Fr orogastric or nasogastric sump tube (Replogle tube) is placed, though smaller tubes may be required for premature infants. The color of the gastric contents is then noted because bile-stained fluid is commonly identified with intestinal obstruction. On suction, the tube allows decompression of the stomach and helps prevent gaseous distention of the bowel from swallowed air. This is helpful in preventing emesis and aspiration, especially during transport of the infant to radiology or another medical facility. Intravenous access is secured, and a laboratory workup is obtained. This workup includes basic electrolytes, a complete blood count, and a type and crossmatch. If a delay in diagnosis occurs or a more extensive workup is required, aggressive fluid resuscitation may be necessary. Close monitoring of the patient's fluid balance, especially urine output, is crucial, and significant fluid loss from the nasogastric tube should be replaced intravenously.

Once resuscitation is adequate, the neonate is taken to the operating room for an abdominal exploration. The entire operating room environment needs to be appropriate for an infant, with special attention paid to ensuring that the infant is kept warm. Abdominal access is typically gained through a right supraumbilical transverse incision that can be extended either medially or laterally as needed. Excellent communication between the surgical and anesthesia teams is vital to the maintenance of electrolyte and glucose homeostasis. This should include precise calculations for fluid and blood loss in order to accurately determine the appropriate replacements.

## OPERATIVE TECHNIQUES

The operative technique used for each patient with jejunoileal atresia is individualized and often depends on the pathologic type of atresia. Associated circumstances such as the presence

of malrotation, volvulus, meconium ileus, or meconium peritonitis may alter the type of operation performed. Additionally, if an abdominal wall defect is present (i.e., gastroschisis or omphalocele), the condition of the bowel and the stability of the patient influence the procedure performed.

Historically, cases in which the very distal segment of the proximal atresia was used to construct the anastomosis often resulted in a functional obstruction. A side-to-side anastomosis was also commonly used in early attempts to surgically correct jejunoileal atresia; however, these patients not only had a functional obstruction but also developed blind loop syndrome.[10,20,95,119] Studying the pathophysiology of the proximal segment of bowel has provided convincing evidence that this segment has ineffective peristalsis and fails to function with lower pressures seen postoperatively. At the microscopic level, Nixon[20,119] noted that the proximal atretic segment of bowel demonstrated significant smooth muscle hypertrophy and enlargement of the bowel diameter. These findings were confirmed by de Lorimier[120] and Cloutier,[121] who suggested that hyperplasia was the primary change occurring to the intestinal smooth muscle proximal to an obstruction. This hyperplasia may become so extreme proximal to a complete obstruction (as seen in an atresia) that the bowel may decompensate to the point that even a strong contraction cannot approximate the intestinal walls sufficiently to adequately generate a luminal pressure that permits efficient propulsion.[121] Several studies have also demonstrated an effect on the enteric nervous system in association with jejunoileal atresia. Investigations looking at chicks with experimentally induced small bowel atresias demonstrated structural changes to the enteric nervous system and attributed these abnormalities to the proximal bowel dilation.[122] In neonatal human specimens of the excised proximal atretic bowel, Masumoto and colleagues demonstrated the presence of hypoplasia of the enteric intramural nerves and C-kit positive pacemaker cells.[123] Elaborating on these findings, Tander and colleagues recently demonstrated a remarkable decrease of interstitial cells of Cajal (pacemaker cells of the gastrointestinal tract) in the wall of the small bowel of patients with intestinal atresia.[124] These investigators were unable to ascertain whether the reduction in these cells is a primary event or is secondary to other possible etiologies such as ischemia. In another relatively recent (2005) study, Ozguner and colleagues[125] observed segmental defects in muscular and neural structures of the intestinal wall on both mesenteric and antimesenteric sides of the atretic small bowel, thus supporting the vascular insult theory. The authors recommend adequate resection rather than tapering enteroplasty to avoid intestinal dysmotility.[125]

When dealing with a proximal jejunal atresia, resection of the proximal dilated atretic segment of bowel up to the ligament of Treitz, followed by an end-to-oblique anastomosis, can be performed if an adequate length of intestine is present. This scenario is typically successful and often avoids the complications of functional anastomotic obstruction and later development of the blind loop syndrome.[21] In the clinical setting of inadequate bowel length that could potentially lead to dependence on parenteral nutrition (short-bowel syndrome), tapering of the dilated bowel on the antimesenteric border should be performed with an end-to-end anastomosis.[126] Numerous authors have reported the applicability of tapering enteroplasty in selected cases.[127–131] de Lorimier and Harrison reported that intestinal imbrication effectively reduces the luminal diameter and restores function while preserving mucosal surface area. Nevertheless, this method tends to break down over 1 to 2 years, resulting in recurrent dilation.[132] Because of this complication, imbrication is no longer favored. For patients with a very proximal jejunal atresia, a lateral duodenectomy with a duodenojejunostomy is occasionally performed.[133]

At the start of the laparotomy, the bowel is gently eviscerated to allow for inspection of the intestine. The entire intestine is visualized, and the proximal and distal ends of the atresia are identified. The inspection process should include the identification of possible malrotation, volvulus, or segments of partially resorbed fetal intestine. If volvulus is identified, this is carefully reduced to ensure a complete evaluation of the pathologic anatomy. The bowel and its mesentery are displayed in their entirety, and the proposed anastomosis is aligned. Next, assessment of the distal segment of bowel is performed by placing a pursestring suture in the distal atretic segment of bowel; this segment is opened to allow for the placement of an 8-Fr red rubber catheter within the lumen of the distal bowel. The bowel is then injected with saline to rule out another atretic segment or distal mucosal membrane or web. If the distal bowel is unobstructed, a short segment of the distal atretic segment is resected at a 45-degree angle (more distal on the antimesenteric side).

A soft, atraumatic infant bowel clamp (Allen clamp) is applied on the proximal bowel at a 90-degree angle. This should be located slightly proximal to the planned resection site. If adequate bowel length is present, the proximal dilated atretic segment is resected back to the level at which the diameter of the intestine approaches 1 to 1.5 cm in circumference for ileal atresias. When the atresia is located in the very proximal jejunum, resection should be taken back toward the ligament of Treitz, but only so far that an anastomosis can be fashioned without difficulty. If a significant size discrepancy exists between the proximal and distal segments, which have been opened at an oblique angle, a Cheatle slit on the distal segment should be considered to alleviate the size discrepancy. A Cheatle slit is a longitudinal incision into the antimesenteric border of the small intestine. This incision ultimately allows for a wide-caliber elliptical anastomosis to be performed (Fig. 82-9).

A one- or two-layer anastomosis is then performed depending on the surgeon's preference. The single-layered anastomosis is typically performed with simple interrupted sutures using any of a number of suture types. For a two-layer anastomosis, the posterior outer layer is initiated with interrupted 5-0 silk sutures. The bowel clamp is removed, and the crushed tissue is trimmed. The inner layer can be approximated with simple interrupted sutures or in Connell fashion (in-out, out-in) with the knots on the inside. Absorbable 5-0 or 6-0 suture (i.e., Vicryl, PDS, or Maxon) can be used for the inner layer. The outer anterior layer is completed with a seromuscular interrupted Lembert closure using 5-0 silk or Vicryl sutures. Differences in the leak and stenosis rates between the two techniques have not been clearly established. The mesenteric defect is carefully approximated, avoiding injury to the mesenteric blood vessels and ensuring that the geometric lie of the anastomosis does not compromise the blood supply or obstruct the lumen of the distal bowel.

In the case of type IV atresias, especially when intestinal length is in question, a concerted effort is made to preserve as much bowel as possible. To accomplish this goal, multiple

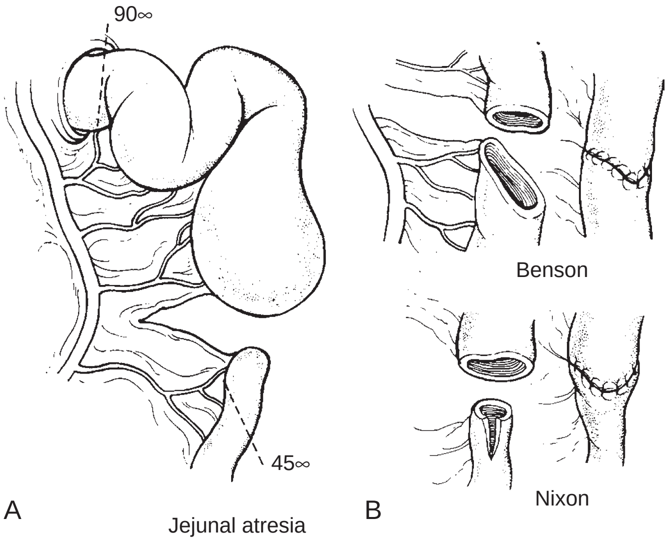


**FIGURE 82-9** Techniques of anastomosis. **A,** The proximal atretic segment is resected at a 90-degree angle and the distal segment at a 45-degree angle. **B,** End-to-oblique anastomosis is carried out by the techniques of Benson (one-layer) or Nixon (two-layer) with fine interrupted sutures. The Nixon anastomosis depicts a Cheatle slit on the antimesenteric border of the distal limb.

anastomoses may be necessary.[134,135] Typically, the distal atretic segments are decompressed, and if the lumina are patent, end-to-end anastomoses can be fashioned (Fig. 82-10). The technique of stenting multiple atresias has been described, with reports of excellent outcomes, albeit in limited patient populations.[136–138]

If the length of bowel is perceived to be inadequate and the proximal segment (typically the jejunum) is significantly dilated, a tapering antimesenteric jejunoplasty is performed. This is accomplished by using either a hand-sewn or stapling enteroplasty. The most bulbous portion of the proximal atretic segment is resected, and the remaining bowel is tapered over a 24- to 26-Fr catheter guide, which is placed within the lumen on the mesenteric side of the intestine. The enteroplasty is then carried out to the ligament of Treitz. If a stapler is used, the staple line is typically oversewn with interrupted 5-0 sutures and the anastomosis is completed in an end-to-oblique fashion in either one or two layers, as previously described (Fig. 82-11). Ismail and colleagues[139] described a new option for a dilated proximal segment in conjunction with short bowel. These authors performed a serial transverse enteroplasty (STEP), which lengthens the bowel and increases the mucosal surface area.

At completion of operation the orogastric or nasogastric tube position is confirmed and secured in place. Alternatively, when there is concern of short gut, gastrostomy tube placement may be beneficial for long-term management.

Although a primary anastomosis is the preferred method of treatment, this method is inadvisable in certain circumstances. In the setting of an atresia with a volvulus when the vascular integrity of the intestine is in question, or in severe cases of meconium peritonitis, the creation of an enterostomy is warranted. The most expeditious procedures are either a side-by-side (modified Mikulicz)[140–143] double-barrel enterostomy brought out through the wound or separate proximal and distal stomas brought out at opposite ends of the wound

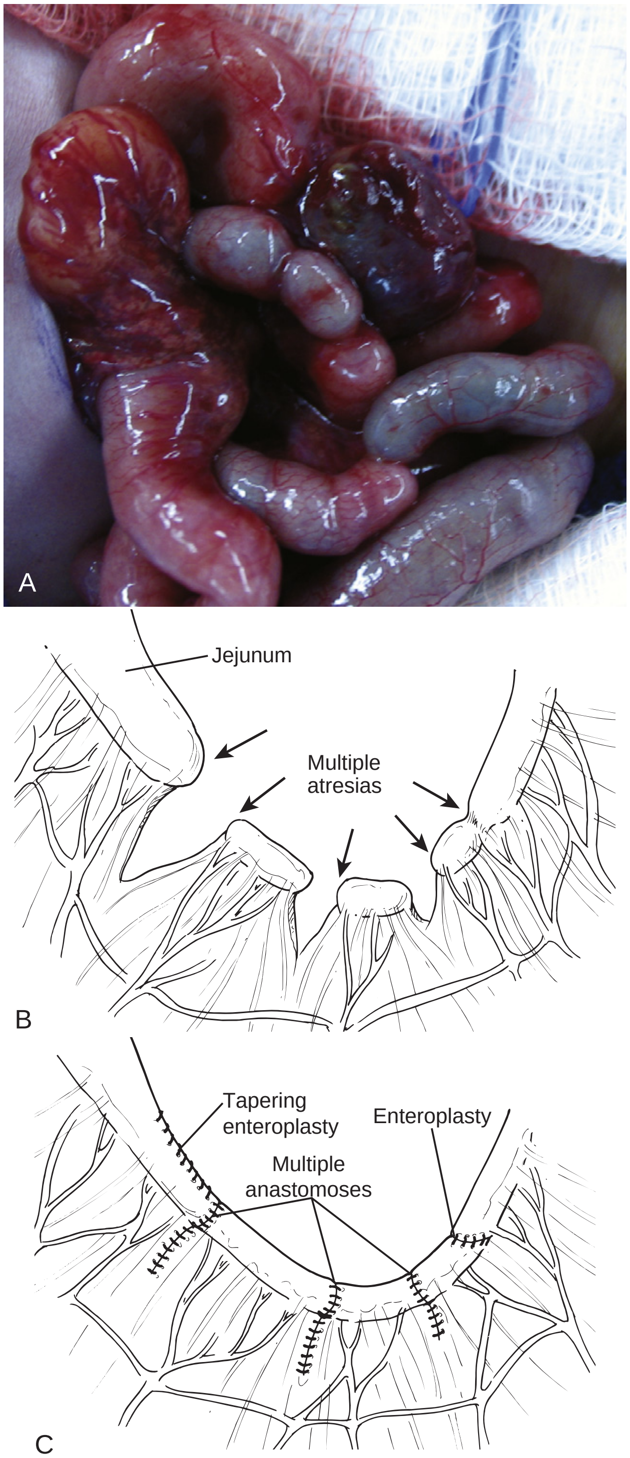


**FIGURE 82-10** Repair of type IV jejunoileal atresias. **A,** Operative photograph of a neonate with multiple small bowel atresias. **B,** Illustration documents multiple atresias. The distal atresias are not dilated. **C,** Proximal tapering jejunoplasty and multiple anastomoses for types II and IIIa atresias and a transverse enteroplasty for type I atresia were performed to preserve bowel length.

and fixed to the abdominal wall with a minimal number of interrupted 5-0 or 6-0 absorbable sutures. Depending on anatomy, as well as the surgeon's preference, the location of the enterostomy and the mucous fistula can also be positioned outside of the wound. Less frequently used but acceptable

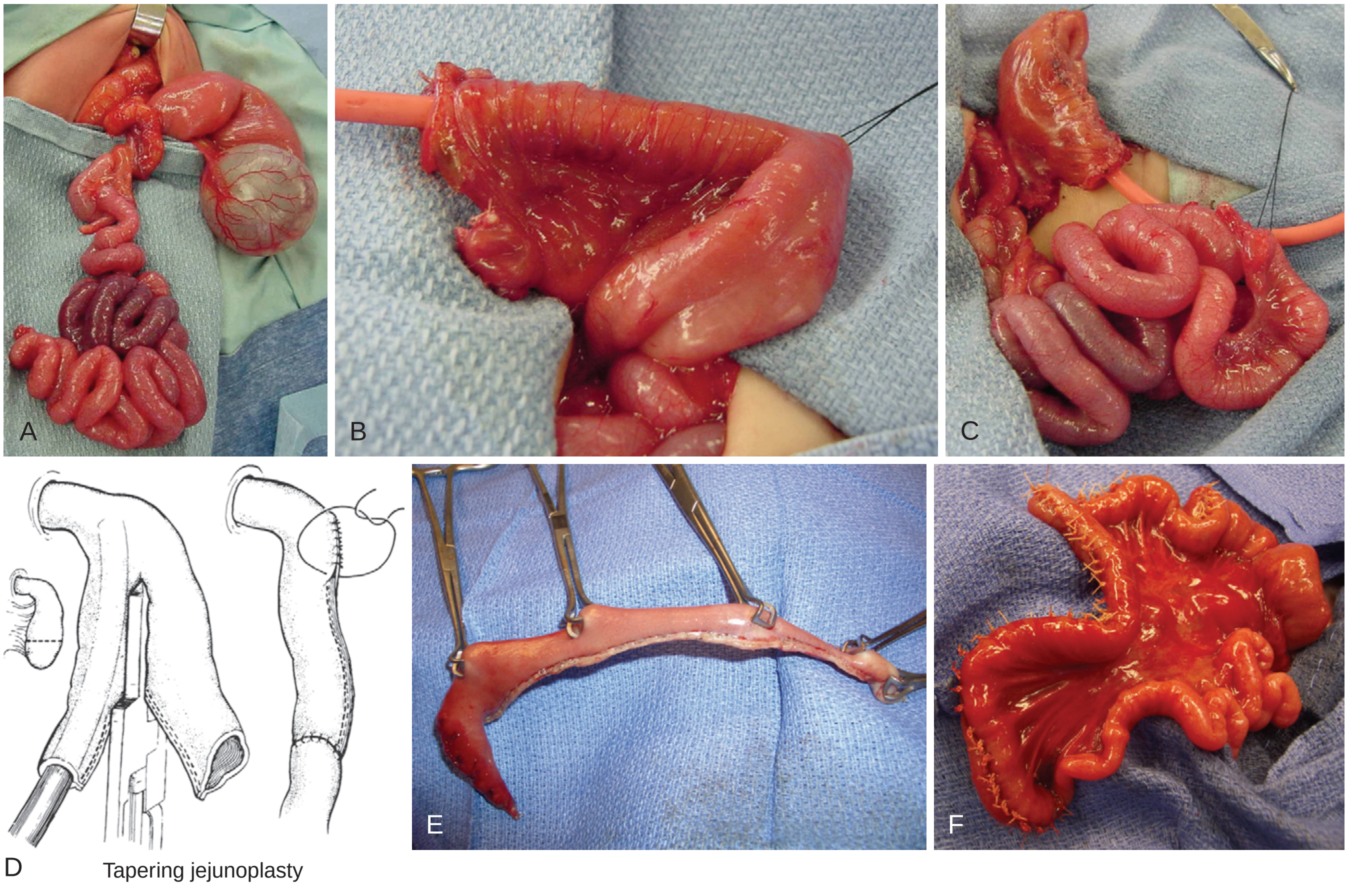


**FIGURE 82-11** Tapering enteroplasty. **A,** Dilated proximal jejunal atresia (type IIIb). Repair was performed with a tapering enteroplasty. **B,** Dilated jejunum is decompressed, and a 26-Fr catheter is positioned on the mesenteric side of the lumen to help size the enteroplasty. **C,** Operative photograph demonstrating a hand-sewn jejunoplasty. **D,** Illustration of a stapled enteroplasty with an antimesenteric resection. The staple line is oversewn with interrupted suture. **E,** Intraoperative photograph of a stapled enteroplasty. **F,** Tapering enteroplasty and anastomosis have been completed.

alternatives in these situations are the creation of a Bishop-Koop (distal stoma),[98] Santulli (proximal stoma),[35] or Rehbein tube[61] anastomotic enterostomies (Fig. 82-12). If an atresia is present in the setting of a gastroschisis, the unrepaired atretic segments of bowel are typically returned to the abdominal cavity, either as part of a primary closure or following silo placement with delayed abdominal closure. The volume of gastrointestinal succus is monitored closely with the use of a Replogle tube. Delayed anastomosis to restore intestinal continuity is performed 3 to 12 weeks after abdominal closure.

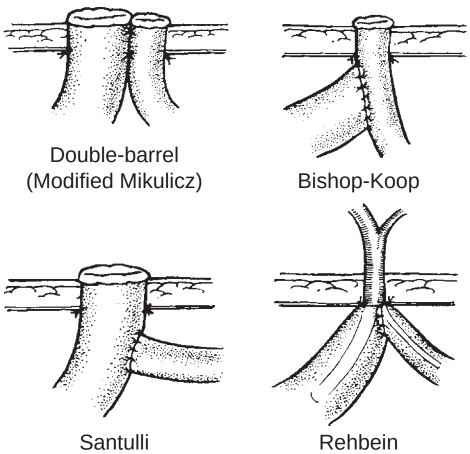


**FIGURE 82-12** Types of exteriorization procedures. These procedures can be used in instances of severe peritonitis, questionable bowel viability, and meconium ileus.

## Postoperative Care

At completion of the procedure, care is taken to ensure the baby is kept warm and is well monitored during transport back to the neonatal intensive care unit (NICU). Maintaining fluid and electrolyte balance is a key component of postoperative care. Intravenous fluids (10% dextrose in 0.25% normal saline along with 2 to 3 mEq/kg/day of potassium chloride) are administered, with a total fluid volume goal of approximately 100 mL/kg/day. If the gastric output is clear and greater than 30 mL/kg/day, it is replaced with 0.45% normal saline. If the output is bilious, it is replaced with lactated Ringer solution. Hydration status should be closely observed, primarily by monitoring urine output. An output of 1.5 to 2 mL/kg/hr, specific gravity of 1.005 to 1.015, and body weight stability usually indicate appropriate hydration. Because of excessive third-space losses, additional fluid boluses with 0.9% normal saline may be required. Postoperative laboratory examination includes serum electrolytes, glucose level, a complete blood

count, and acid-base balance. Serum electrolyte values are monitored over the first few postoperative days. Total parenteral nutrition is initiated after the first 24 hours, with a gradual increase in the glucose infusion rate.

When bowel function returns and the gastric drainage fluid is clear and of minimal volume, the Replogle tube is removed. This tube can be placed to gravity or elevated with a Farrell bag before removal, which tests for gastric or intestinal reflux. Once satisfactory return of bowel function is confirmed, enteral feeding is initiated. The approach to introducing feeds varies, depending on both the institution and the physician. One option is to use a small nasogastric feeding tube with the gradual introduction of either breast milk or formula. Once tube feeds are tolerated, the patient is transitioned to oral feeds. An alternative approach is starting with small amounts of oral clear liquids (Pedialyte) and transitioning to milk-based feeds. The quantity with which to initiate feeds ranges from 5 mL to 15 mL and depends on patient factors such as the size and the length of the gut. The overall feeding goal is to provide the nutritional requirements sufficient for growth; for the newborn, this is approximately 120 calories/kg/day. Breast milk is the preferred feeding choice; however, if this is not available, a low osmolar small-curd formula (Isomil) is initially given. Lactose intolerance is frequently a problem after major bowel resection, and milk-curd obstruction of the small intestinal anastomosis may occur if a large-curd formula is given at this time.[144]

In the case of an extended bowel resection or conditions in which bowel function is compromised, diarrhea or malabsorption may be significant. Formulas that contain long-chain fats should not be used. Rather, a medium-chain triglyceride or casein hydrolysate formula (Pregestimil) is given. Parenteral nutrition, with special attention to lipid and protein administration, should be carefully watched and liver-sparing strategies should be optimized. Further details about the treatment of short-bowel syndrome are discussed in Chapter 88.

## Morbidity and Mortality

Infections related to pneumonia, peritonitis, or sepsis are the most common causes of early death in infants with jejunoileal atresia.[22] Functional intestinal obstruction at the site of the anastomosis and anastomotic leak are the two most significant postoperative complications and are associated with a reported mortality rate of 15%.[20,22] Other factors affecting morbidity and mortality include the presence of associated anomalies, respiratory distress, prematurity, short-bowel syndrome, and postoperative bowel obstruction resulting from volvulus with bowel infarction[22] Before the 1990s, the survival rate of infants with jejunal atresia was lower than that of infants with ileal atresia (58% vs. 75%, respectively). Also, the mortality rate was higher in infants with multiple atresias (57%) and apple-peel atresias (71%) and when atresia was associated with meconium ileus (65%), meconium peritonitis (50%), and gastroschisis (66%).*

Before the routine use of parenteral nutrition, Nixon and Tawes[20] proposed a risk stratification schema to allow for a more critical evaluation of survival in infants with jejunoileal atresia. According to this schema, infants were placed into one of three risk groups: group A comprised infants weighing more than 5.5 lb and having no other significant abnormalities; group B comprised infants weighing from 4 to 5.5 lb or those having a moderately severe associated malformation; and group C comprised infants weighing less than 4 lb or having a severe associated abnormality. The authors reported a much higher survival rate in infants in groups A and B (81%) as compared with those in group C (32%). In conjunction with this risk assessment, infants were further subdivided by anatomic location of the atresia into those with high-jejunal, mid-small-bowel, and distal ileal atresias. Findings showed that patients with high-jejunal atresia in group A or B had a 60% survival, whereas all of the patients in group C died. Infants with mid-small-bowel atresia in group A or B had an 82% survival, whereas those in group C had only a 32% survival. Survival for atresias involving the distal ileum in infants in group A or B was 100%; for those in group C, survival dropped to 50%.

In 1969 de Lorimier and colleagues[20] investigated the effect of wide proximal resection and end-to-end anastomosis on survival. Their findings demonstrated that resection improved survival in patients with jejunal atresia, increasing it from 39% to 66%; however, resection had little effect on the survival of patients with ileal atresia. Louw[147] reported a 94% survival rate after wide proximal resection with an end-to-oblique single-layered anastomosis in 33 patients with jejunoileal atresia. In this series, two patients had anastomotic leaks and two deaths occurred in neonates categorized as group C patients. In 1976 Martin and Zerella[118] reported a 100% survival rate in a series of 23 patients with jejunoileal atresia.

A number of reports published from 1985 to 2001 describe overall survival rates in patients with jejunoileal atresia that range from 80% to 90% or greater.[43,77,87,148] Owing to advancements in NICUs in regard to ventilation management, infection control, and treatment of sepsis, prematurity and low birth weight have a less adverse impact than indicated in earlier reports. Factors currently considered to have an adverse impact include the presence of malrotation, associated anomalies, and the need for stomas, particularly those that are multiple or proximal.[145] Late death occurs in patients with jejunoileal atresia when complicated by gastroschisis and short-bowel syndrome; these patients may succumb to infectious complications or liver failure.

A review (1999) of 449 cases of intestinal atresia at the Beijing Children's Hospital indicated a reduction in mortality from 64.7% to 18.6%; this reduction was attributed to successful parenteral nutrition and adoption of longitudinal oblique anastomoses.[149] Excellent long-term outcomes (80% survival) have been achieved with this approach, even in patients with apple-peel atresia.[87,150,151] Parenteral nutrition avoids protein-calorie malnutrition, establishes positive nitrogen balance, and allows for a relatively safe waiting period in infants with short-bowel syndrome and in those who have undergone temporary exteriorization procedures. A recent (2009) study by Stollman and colleagues looking at infants with jejunoileal atresia in the Netherlands over more than 3 decades reported decreased mortality but increased morbidity.[11] The authors report that short-bowel syndrome presents a significant management challenge and often results in a longer hospital stay, more feeding problems, and higher morbidity and mortality rates.[11] In another recent (2008) study, Piper and colleagues[152] found that infants with

*References 22, 72, 75, 77, 111, 118, 145, 146.

intestinal atresia, a birth weight less than 2 kg, and associated anomalies are at an increased risk for prolonged hospital stay and mortality. Twenty-five percent of patients in this study required a second operation, including lysis of adhesions (33%), a tapering enteroplasty (33%), and resection of a stenotic segment of bowel with tapering (33%). Despite these complications, overall mortality was only 3.3%.

Several studies[26,32,153] have shown that infants with more distal ileal resections are more prone to malabsorption (fat, bile salts, vitamin $B_{12}$, calcium, magnesium), diarrhea (steatorrhea), and increased bacterial proliferation and overgrowth. Although many infants with short-bowel syndrome survive, they require ongoing monitoring for renal stones, gallstones, and malabsorption. Late anastomotic ulcers presenting as either melena or iron-deficiency anemia have also been reported.[154,155] In view of these collective findings, we strongly recommend long-term follow-up of all neonates treated for complicated jejunoileal atresia.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 83

# Meconium Ileus

Moritz M. Ziegler

## History

Meconium ileus was first described in 1905 when Landsteiner linked the observation of meconium obstructing the small bowel with pathologic changes in the pancreas, which he attributed to a putative enzyme deficiency. Subsequent authors recognized a similar association of a thickened and tenacious meconium with a mechanical pancreatic duct obstruction or stenosis.[1–4] The term *cystic fibrosis* of the pancreas was first coined in 1936 by Fanconi to describe the association of chronic pulmonary disease of infancy with pancreatic insufficiency.[5] However, it was Anderson who described, in 1938, the relationship of the histologic likeness of pancreatic abnormalities in both meconium ileus and cystic fibrosis (CF) and described meconium ileus as an early and more severe manifestation of the overall lung and pancreatic insufficiency.[6,7] Subsequent authors defined the inspissated nature of meconium, linking the finding to both pancreatic insufficiency, as well as to abnormal mucus secreted by the intestine of patients with CF.[8–13]

With progress in the science of genetics, CF is now recognized as the most common potentially lethal autosomal recessive disease in the Caucasian population. Meconium ileus itself carried an almost uniformly fatal prognosis into the late 1940s,[13–15] when a series of interventions were devised that by design either eliminated or bypassed the obstructing inspissated intraluminal meconium, minimizing the operative intestinal manipulation and even the need for a general anesthetic to minimize the physiologic insult to the infant. In 1969 a novel therapy applied a transrectal irrigation and solubilization of the desiccated and tenacious meconium with the use of the hyperosmolar diatrizoate (Gastrografin) enema, permitting treatment of uncomplicated meconium ileus without the need for any operative intervention, a success that has been sustained for more than two thirds of patients.[16] By the early 1970s these advances along with an improved management of the electrolyte, nutritional, and pulmonary abnormalities of CF had improved patient survival to almost 75%.[17,18]

In the past 2 decades we have seen continued progress. First, the genetic lesion of a mutation in the CF transmembrane regulator *(CFTR)* gene was defined as the causal lesion of CF,[19,20] and it is now recognized that patients with meconium ileus likely represent a distinct phenotype with earlier presentation and worse pulmonary function.[21,22] Second, the diagnostic criteria remain largely the same clinically, with definitive diagnosis achieved by a combination of biochemical and now genetic testing. Interestingly, when enema irrigation is not successful in managing meconium ileus and relieving its bowel obstruction, the preferred operative intervention is that described originally in 1948, namely, enterotomy followed by irrigation, typically using meconium-solubilizing agents. These strategies, coupled with aggressive attention to the pulmonary and nutritional status of the patient, have seen a continued improvement of patient survival now approaching 95% to 100%.[17,23,24]

## Pathophysiology

### GENETICS

Cystic fibrosis is an autosomal recessive disease that occurs among whites with a heterozygote frequency of 1 in 29 births. It is rare in blacks (1/17,000 live births), and it is almost unheard of in Asians (1/90,000 live births) and Africans. The 5% to 6% carrier rate of the abnormal gene in whites results in a CF incidence of 1 per 1150 to 2500 live births. An offspring of two heterozygous parents has a 1 in 4 chance of developing the disease.[25] Meconium ileus, potentially unique to CF, represents a disorder of neonates characterized by intestinal obstruction secondary to the intraluminal accumulation of inspissated and desiccated meconium. Meconium ileus is the earliest clinical manifestation of CF because such patients are typically diagnosed and treated in the immediate neonatal period.[26] Meconium ileus has been reported to be the presenting feature of 20.8% of the CF population in the United States. Importantly for in-utero diagnosis, a family history of CF has been found in 10% to 40% of new patients with meconium ileus. In the presence of an index case of meconium ileus complicating CF, reports have suggested that an incidence of subsequent meconium ileus in the presence of CF varies from 30% to 40%.

In 1989 the genetic mutation that codes for the cell membrane protein termed the *CF transmembrane regulator* was identified by Francis Collins as that locus associated with the diagnosis of CF.[27,28] This locus was identified on the long arm of chromosome 7, band q31.[29] The protein was identified as a cyclic adenosine monophosphate–induced chloride channel that regulates ion flow across the apical surface of

epithelial cells.[30] One of more than 400 mutations of the *CFTR* that have been identified produces abnormal electrolyte content along the external apical environment of epithelial membranes. Tubular structures lined by such affected epithelia will be characterized by desiccation and reduced clearance of their secretions, and the affected systems include epithelial cells of respiratory, gastrointestinal, biliary, pancreatic, and reproductive systems. The clinical correlate of this pathophysiology has included pancreatic insufficiency (90%), meconium ileus (10% to 20%), diabetes mellitus (20%), obstructive biliary disease (15% to 20%), and azoospermia (nearly 100%). The exact mechanism of the epithelial glandular abnormality and the elaboration of a hyperviscous mucin remain unsolved. Certainly, the tenacious meconium protein and water content and its increased viscosity have all been described.

The *ΔF508* mutation is the most common of many *CFTR* gene locations, occurring as a homozygous pair in almost 50% of CF patients, whereas another 25% to 30% of patients will have one copy of this mutation. Such homozygous individuals nearly always phenotypically express pancreatic exocrine insufficiency, and they also present with a higher incidence of meconium ileus. A similar higher frequency of meconium ileus is also seen in *ΔF508*-expressing patients who also express *G542X*. However, the disease etiology is less clear when it is recognized that not all such genotypic patients will have meconium ileus. The association of obstructive lung disease with meconium ileus suggests other *CFTR* modifier genes or even environmental factors that may play a role in this disorder. Furthermore, large patient consortia have failed to identify predictors of the complications of CF including an incidence for meconium ileus.

## PATHOGENESIS

The defect of CF is an exocrine-eccrine gland dysfunction, particularly of the mucus-secreting and sweat glands.[31] Pancreatic achylia was thought to be the mechanism responsible for meconium ileus because of early reports of meconium-induced bowel obstruction in patients with congenital stenosis of the pancreatic ducts. However, data that began accumulating in the 1940s suggested that lesions in the pancreas of patients with CF were variable and were most profound in children older than 1 year of age. In contrast, the preponderance of intestinal mucosal gland abnormalities in the subset of patients with CF and meconium ileus was more striking, suggesting that these glandular lesions were the more likely origin of the tenacious material that causes the intraluminal obstruction in patients with meconium ileus.[32] Additional pathologic data have been interpreted to suggest that intestinal glandular disease plays the dominant role and pancreatic disease a secondary role in the pathogenesis of meconium ileus.[33,34]

The glandular abnormality accounting for or producing these changes is less certain. Various explanations include the glandular secretion of hyperpermeable mucus mediated by calcium that influences the physicochemical properties of mucus to be viscid and permeable to the loss of water, further concentrating intraductal secretions. This glandular-obstructing mucus would lead to the pathologic lesions noted earlier. A second hypothesis is that an impairment of fluid movement to and from the extravascular space through secretory cells exists that may prevent the normal dilution of the cellular lumen.[26,35] The highly concentrated material then becomes toxic to those cells laden with the product.

Soon after the *CFTR* gene was located on chromosome 7 by restriction fragment length polymorphism analysis, it was recognized that *CFTR* was itself a membrane chloride channel and that it further regulated chloride conductance through other channels.[36] This may be the mechanism that forms the basis for the increased levels of sodium and chloride in the eccrine sweat gland secretions that characterize patients with CF. Here a defect in electrolyte resorption of sodium and water by ductular cells and the impermeability of these cells to chloride ions result in an excretory product high in both sodium and chloride. This theory may be supported by the known characteristics of the CFTR membrane protein, which as a chloride channel, functions to regulate salt and water transport onto epithelial surfaces. Thus a disturbed function alters exocrine secretion electrolyte content and may lead to desiccation and reduced clearance of such secretions.

Meconium itself has a variable composition, as seen from samples from varying intestinal locations of normal infants at varying gestational ages that are contrasted to meconium isolated from patients with CF with and without meconium ileus.[37] The meconium concentrations of sodium, potassium, and magnesium are almost twice as high in samples from normal children or well siblings than in samples from children with CF with or without meconium ileus. Similarly, the enzyme-catalyzing heavy metals are also at higher levels in meconium from control and well siblings than from children with CF with or without meconium ileus. Samples from patients with meconium ileus also differ from normal meconium by containing greater amounts of protein nitrogen and lesser amounts of carbohydrate. Analysis of the protein content of abnormal meconium results in a further identification of abnormal mucoproteins. These products are two-thirds protein and one-third carbohydrate, a composition similar to duodenal fluid from patients with CF. The origin of these proteins is uncertain, but they may arise from either glandular secretions or swallowed amniotic fluid in utero. Because most of this protein is albumin, it is speculated that the intraluminal proteins are of plasma origin. They react with mucopolysaccharides, and, in the absence of degrading enzymes, they impart a highly viscid rubbery character to the involved secretions. The viscosity of these mucoproteins could be further influenced by the surrounding electrolyte environment. Finally, this increased albumin content of meconium from patients with CF has led to the development of a meconium screening test for the diagnosis of the disease.

In summary, two simultaneous pathogenetic events in meconium ileus appear to begin in utero and result in an intraluminal accumulation of a highly viscid and tenacious meconium: the developments of pancreatic exocrine enzyme deficiency and the secretion of hyperviscous mucus by pathologically abnormal intestinal glands. The thickened meconium accumulates and begins in utero to obstruct the intestine lumen. This accumulation accounts for the mechanism of the complications of meconium ileus (i.e., twist of a heavy loop with perforation, peritonitis, and cyst or atresia) and the pattern of abdominal distention and obstruction seen in the neonate. The proximal ileum dilates, and its wall thickens as it becomes filled with the tenacious and tarry meconium. Concomitantly, the narrowed distal small bowel

and, at times, the colon contains beaded or "boxcar" concretions of gray-white, putty-like inspissated meconium. The more distal colon is small or unused, a microcolon.

## Clinical Features

### SPECTRUM OF THE DISORDER

Meconium ileus presents in the neonate as uncomplicated or simple or as complicated. In the older child or young adult the presentation is as a meconium ileus equivalent or distal ileal obstruction syndrome.

Uncomplicated meconium ileus typically presents immediately at birth with the recognition of abdominal distention, a unique feature of inspissated meconium filling and obstructing the distal small bowel. This problem may first have been heralded by an in utero genetic diagnosis of CF and an ultrasound suggestive of intestinal obstruction with echogenic bowel. In addition to the distention, intestinal obstruction is heralded by bilious vomiting and failure to stool.

In contrast, complicated meconium ileus will present either in utero or postnatally with evidence of bowel obstruction complicated by evidence of previous intestinal perforation and/or necrosis: Crescents or speckles of intra-abdominal calcification may be present, or on clinical assessment there may be evidence of peritonitis including an erythematous or edematous abdominal wall and/or demonstrable abdominal tenderness.[38]

### CLINICAL HISTORY

A family history of CF is present in 10% to 33% of patients with meconium ileus.[39] This history, coupled with in utero amniocentesis with restriction fragment length polymorphism analysis, permits the accurate diagnosis of the fetus afflicted with CF. Coupling this information with the results of serial in utero sonography permits the accurate predication of which infants are at risk for the development of the intestinal obstruction of meconium ileus (about 20% of the CF population) with or without a complicating meconium cyst. Maternal polyhydramnios may be a feature of in utero meconium ileus, a finding putatively resulting from the high-grade intestinal obstruction. Such excess maternal fluid accumulation occurs in the mothers of almost 20% of newborns with meconium ileus and at a frequency still higher for the patient with a complicated meconium ileus. Although in utero growth retardation is common, prematurity and other associated anomalies are rare.

### PHYSICAL EXAMINATION

Neonates with meconium ileus are often born with abdominal distention (Fig. 83-1). In fact, meconium ileus is the only variety of neonatal intestinal obstruction that produces abdominal distention at birth before the neonate swallows air. Visible peristaltic waves and palpable, doughy bowel loops are often present. Finger pressure over a firm loop of bowel may hold the indentation, the so-called putty sign. In simple or uncomplicated meconium ileus, no findings of peritoneal irritation are present. The findings of a rectal examination are unremarkable, but characteristically on withdrawal of the examining finger a spontaneous expulsion of meconium does not follow. In the presence of an in-utero perforation with meconium peritonitis and "cyst" formation, a palpable abdominal mass, discoloration of the abdominal wall, and signs of peritoneal irritation are often observed. Physical evidence of hypovolemia may rapidly develop in infants with peritonitis. On passage of a nasogastric tube, a quantity of bile-stained gastric fluid usually exceeds 20 mL.

FIGURE 83-1 Newborn with abdominal distention at birth. The family had a history of cystic fibrosis, and this newborn had a cytogenic diagnosis of cystic fibrosis in utero. On fetal ultrasound examination there was evidence of a hyperechoic bowel wall compatible with a diagnosis of meconium ileus.

### RADIOLOGIC STUDY

In utero, meconium ileus bowel may be distended but an echogenic bowel wall in the third trimester may be diagnostic as well.[40–42] After delivery, uncomplicated meconium ileus is characterized by a typical plain obstruction radiographic series of the abdomen (Fig. 83-2).[43,44] In addition to the supine and erect films appearing remarkably similar, the characteristic findings include (1) great disparity in the size of the intestinal loops because of the configuration of different segments of the bowel; (2) no or few air-fluid levels on the erect film because swallowed air cannot layer above the thickened inspissated meconium; and (3) a granular, "soap bubble," or "ground-glass" appearance seen frequently in the right half of the abdomen, a finding that requires swallowed air bubbles to intermix within the sticky meconium (Fig. 83-3).[45] Each of these features alone is not exclusively diagnostic of meconium ileus and may be seen with other causes of intestinal obstruction. Collectively, however, they strongly suggest meconium ileus. Plain radiography done for differential diagnosis will include any cause of a distal small bowel obstruction including ileal atresia, Hirschsprung disease, or the meconium plug syndrome. A confirming study that may support the plain radiographic diagnosis of meconium ileus is the contrast enema. A contrast enema (whether with barium, Gastrografin, or any water-soluble contrast agent) will outline a normally positioned colon of appropriate length but of small caliber (see Fig. 83-3).[46] It will be empty or will contain pellets of inspissated meconium. The colon will be the typical "unused" colon or "microcolon." If reflux of contrast agent into the terminal ileum occurs, it will outline pellets of inspissated meconium.[44,47] If the contrast agent refluxes more proximally

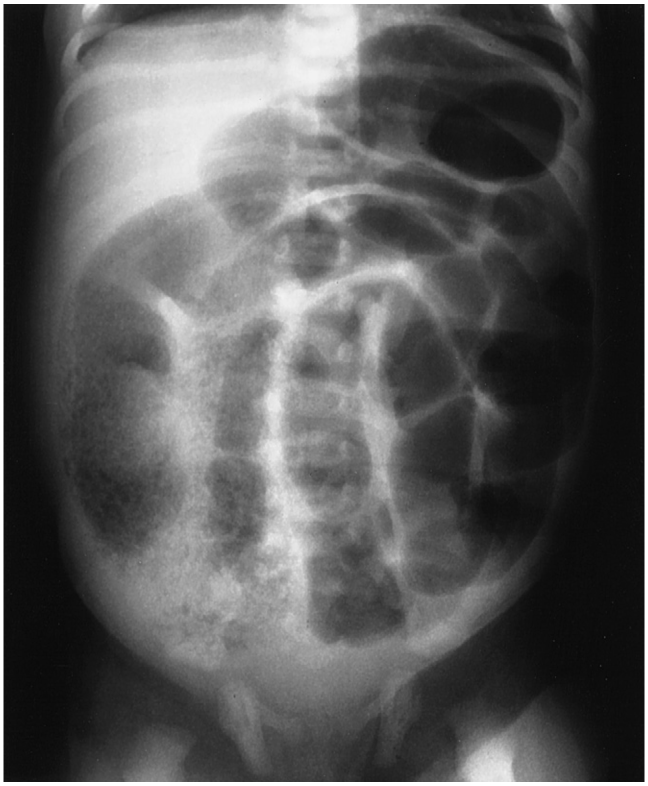

FIGURE 83-2 An abdominal plain upright radiograph is compatible with the diagnosis of meconium ileus. There are dilated small bowel loops of disparate size, few air-fluid levels, and a "ground-glass" or "soap-bubble" appearance in the right lower quadrant. (From Rescorla FJ, Grosfeld JL: Contemporary management of meconium ileus. World J Surg 1993;17:381.)

into the ileum, the transition into dilated loops of small bowel will be encountered. Failure to reflux contrast medium into the proximal dilated small bowel will neither prove the diagnosis of meconium ileus nor determine the exact level of the intestinal obstruction; and with this failure of the contrast medium to reflux into the dilated segment, operative intervention for diagnosis and treatment becomes necessary.

## Laboratory Testing

The definitive study to confirm the diagnosis of CF is the sweat test. With the use of the pilocarpine iontophoresis method, sweat is collected from the infant's forearm, leg, or back; the amount is quantified, and the concentration of sodium and chloride in the sample is measured.[48,49] The minimum amount of sweat to be collected is 100 mg, and a measured concentration of sweat chloride in excess of 60 mEq/L is diagnostic of CF. The adequacy of the size of the sweat sample is the factor that usually precludes application of this test to the newborn, despite reports to the contrary. A few individuals have been identified with elevated sweat chloride levels but with no other features of CF. These problems, plus a potentially elevated sweat sodium and chloride level in normal newborns, may make it necessary to defer application of the sweat chloride test until the neonate reaches several weeks of age.

Genetic testing for CF can be done by analyzing cellular DNA for CFTR, thus establishing the carrier status of parents of a putative child with CF presenting with features of meconium ileus. However, because of the minimum number of mutations tested by these commercial analyses, negative results become less meaningful. If a family has known CFTR mutations, then amniocentesis with fetal DNA restriction

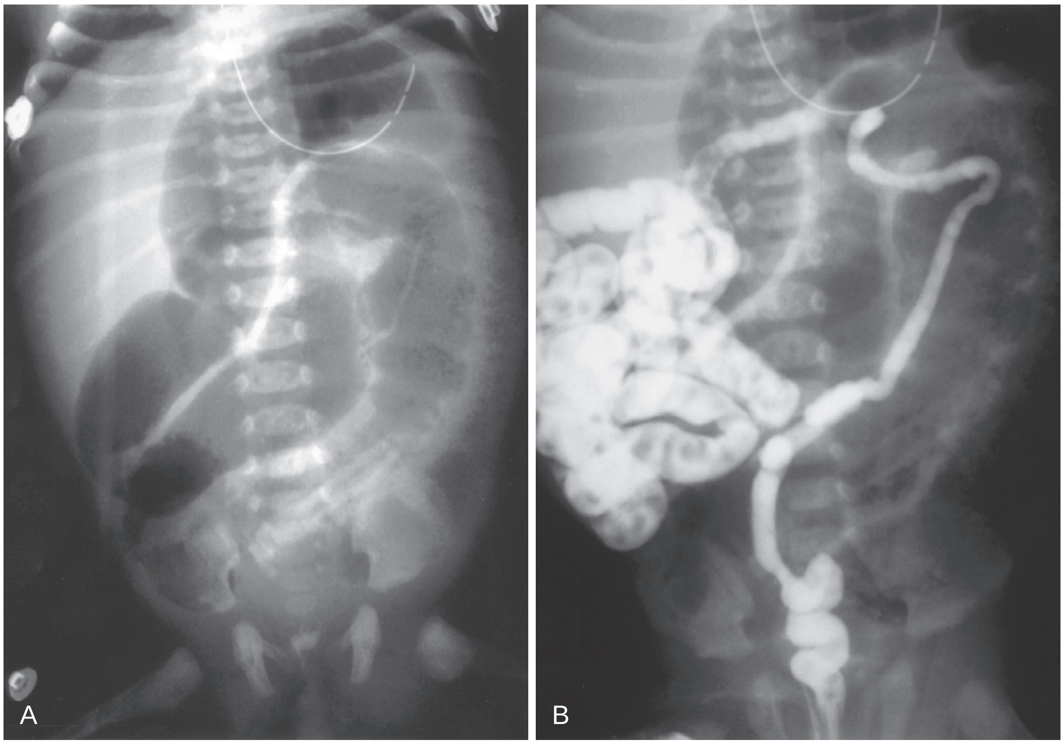


FIGURE 83-3 **A,** Abdominal plain radiograph is compatible with the diagnosis of meconium ileus. There are distended bowel loops of disparate size, few air-fluid levels, and a "soap bubble" right lower quadrant appearance. **B,** Same patient as in A is studied further with a contrast enema. A microcolon or unused colon is demonstrated, and contrast agent refluxes into dilated, more proximal small bowel where inspissated intraluminal pellets of meconium are seen. These findings strongly suggest the diagnosis of meconium ileus.

fragment length polymorphism analysis may predict a fetal CF diagnosis.

The pathophysiologic alteration of an increased albumin concentration in meconium may prove useful as a diagnostic screening tool for meconium ileus.[50,51] This test, which uses a tetrabromophenolethylester blue indicator, detects meconium albumin concentrations in excess of 20 mg/g of stool; however, a persisting incidence of false-positive results was seen from such factors as prematurity, melena, gastroschisis, and intrauterine infection. A false-negative rate has been reported as well. This simple and relatively inexpensive tool is straightforward and rapid, and the colorimetric indicator is easy to interpret.[23,52] Meconium from normal neonates has an albumin concentration of less than 5 mg/g of stool, whereas meconium from neonates with CF has values at times in excess of 80 mg/g.[53,54]

Stool trypsin and chymotrypsin analysis has historically been a popular screening test for meconium ileus.[53–55] A trypsin level less than 80 mg/g of stool, coupled with operative findings, supports the diagnosis of meconium ileus. Some centers have advocated for population CF screening using a measurement of immunoreactive trypsinogen in blood.

Operative tissue specimens that aid in the diagnosis of CF include intestinal (rectal) or appendiceal pathognomonic changes that include goblet cell hyperplasia and the accumulation of secretions within the crypts or within the lumen.[56] If operation is done for putative meconium ileus and an appendicostomy is used as a bowel intraluminal irrigation site, appendectomy may be warranted to obtain such a diagnostic pathologic specimen.

## DIFFERENTIAL DIAGNOSIS

The combination of family history, physical examination, and radiologic evaluation in the neonate are the three criteria of high sensitivity that permit an accurate clinical diagnosis of meconium ileus. The addition of linkage analysis on maternal amniocentesis samples or a sweat test confirms the diagnosis of CF. A definitive diagnosis depends on the confirmation of the cause of intestinal obstruction. Meconium ileus accounts for 10% to 25% of cases in large series of patients with neonatal intestinal obstruction. Therefore the major differential diagnosis lies with the variety of causes of neonatal intestinal obstruction including ileal atresia, Hirschsprung disease, neonatal small left colon, and the meconium plug syndrome.[57]

Ileal atresia is usually suggested by a distal bowel obstruction pattern on plain radiographs with the associated presence of air-fluid levels.[58,59] If a microcolon is demonstrated on contrast enema, the contrast agent will not reflux into the proximal dilated "atretic" bowel as it might in both meconium ileus and Hirschsprung disease (Fig. 83-4). Once ileal atresia is suspected, the final confirmation of the diagnosis requires operative exploration. Meconium ileus can be associated with ileal atresia, and at operation the findings characteristic of the sticky meconium of meconium ileus should raise this possibility (Fig. 83-5). Hirschsprung disease, especially total colonic aganglionosis, as well as extended small bowel aganglionosis, may also mimic meconium ileus.[60–62] In fact, nearly all cases of total intestinal aganglionosis were initially misdiagnosed as meconium ileus.[63] A definitive diagnosis of Hirschsprung disease may be suggested both radiographically and by anorectal manometrics, but ultimately it depends on the histochemical findings of increased acetylcholinesterase content or the histopathologic findings of aganglionosis seen on rectal biopsy. The radiographic features of colonic Hirschsprung disease likely will include a transition zone; in patients with total colonic Hirschsprung disease, a reflux of contrast medium into the terminal ileum will typically not demonstrate the filling defects of meconium ileus but, rather, will show air-fluid levels and a proximally dilated bowel.

FIGURE 83-4 A contrast enema is done in a newborn with a distal bowel obstruction evident on plain radiography. A microcolon is found leading to a small-caliber distal ileum, and contrast agent does not reflux into the dilated intestine. This is most compatible with the diagnosis of a distal intestinal atresia. (From Rescorla FJ, Grosfeld JL: Contemporary management of meconium ileus. World J Surg 1993;17:381.)

FIGURE 83-5 Operative findings of a case of meconium ileus complicated by an acquired ileal atresia. The small bowel is distended proximal to the atresia, and there are inspissated pellets of meconium in the distal ileum and colon.

Neonatal small left colon syndrome may also require the differentiation from meconium ileus.[64–66] This abnormality is confined to the left colon, appears as a funnel-shaped tapering on contrast enema, and is often associated with a diagnosis of maternal diabetes, hyperthyroidism, drug abuse, or

eclampsia (Fig. 83-6). Rectal biopsy is required to exclude Hirschsprung disease. Other features of meconium ileus are usually not present.

Meconium plug syndrome is usually confirmed by a contrast enema radiograph with the finding of "plugs" or "casts" of meconium in the sigmoid or descending colon (see Fig. 83-6).[67–70] Such plugs will often spontaneously pass after withdrawal of the enema catheter and expulsion of the enema. There is a significant association of meconium plug syndrome with other gastrointestinal anomalies, and up to 14% of neonates with CF will be seen to have meconium plug syndrome.[71] The pathogenesis of the meconium plug is poorly understood but may relate to a bowel hypomotility. Meconium plug syndrome has also been associated with prematurity, hypotonia, hypermagnesemia, respiratory distress, sepsis, hypothyroidism, diabetes, and Hirschsprung disease.[72,73] These associations suggest that patients with meconium plug syndrome should be studied with both a sweat test to exclude CF and a rectal biopsy to exclude Hirschsprung disease after symptoms of obstruction have been relieved.[74,75]

Meconium ileus may occur in the absence of CF in term or preterm infants with pancreatic or intestinal insufficiency from a variety of causes.[39,76,77] These intraluminal obstructions result from the accumulation of an inspissated sticky meconium in the terminal ileum or right colon, but the meconium is neither tarlike nor resistant to conventional enema irrigation that usually proves to be therapeutic. Whether intestinal secretion insufficiency or a pancreatic achylia is etiologic is variable, but rarely has pancreatic insufficiency been documented. Definitive exclusion of CF clinically requires a sweat chloride analysis, DNA analysis, or both.

## Nonoperative Management

Nonoperative management of meconium ileus depends on the dissolution of the inspissated intraluminal meconium in an otherwise patent and uncompromised ileocolon.[47,78,80] Although various solubilizing agents historically had been administered by mouth, intraoperatively, or by rectum, the mainstay of meconium ileus treatment remained an operative procedure.[80] In 1969 several additional reports suggested that solvents were effective and the value of nonoperative application of such solvents was suggested both clinically and experimentally.[81] Noblett reported the successful use of a hypertonic contrast enema in four neonates with uncomplicated meconium ileus. She described the need to fulfill the flowing criteria before applying such therapy: (1) an initial diagnostic contrast enema should exclude other causes of distal intestinal obstruction; (2) the complications of volvulus, atresia, perforation, or peritonitis must be excluded; (3) the enema must be performed with careful fluoroscopic control; (4) intravenous antibiotics should be administered; (5) the patient should be attended by a pediatric surgeon during the procedure; (6) the patient should have a full fluid resuscitation with fluids given aggressively (one to three times maintenance) during the procedure; and (7) the patient should be prepared for imminent operation should

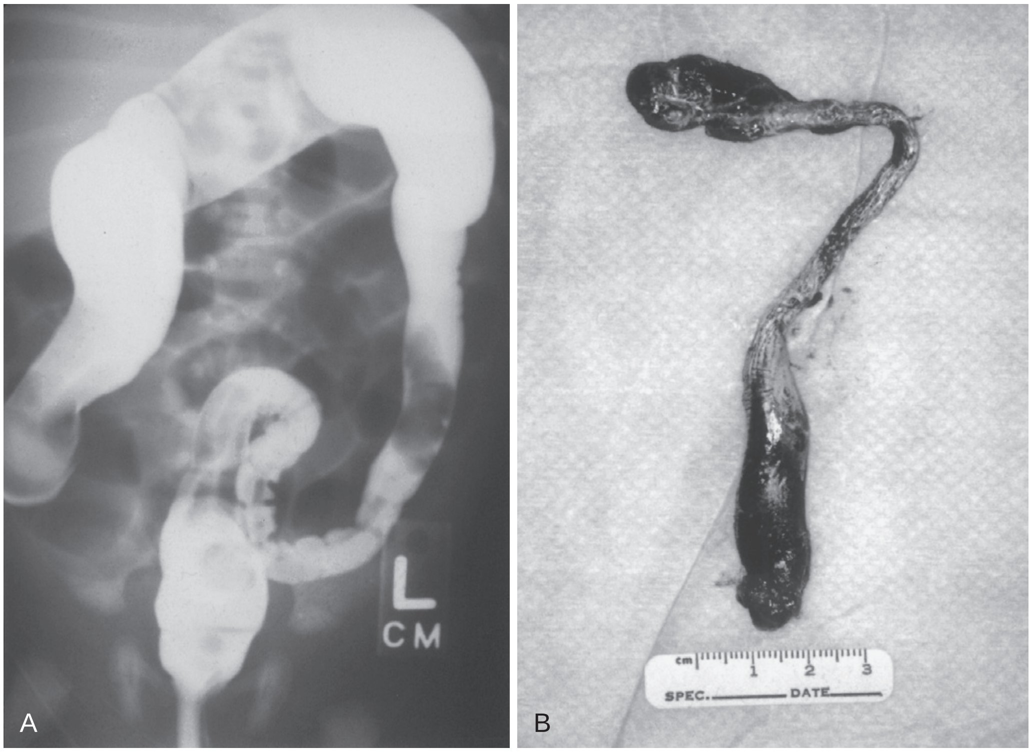


FIGURE 83-6 The differential diagnosis of meconium ileus includes several entities characterized by left colon pathology. **A,** A contrast enema in a newborn presenting with a plain radiographic pattern of a distal bowel obstruction depicts tapering of the colon below the splenic flexure and an intraluminal filling defect in the rectosigmoid colon. These findings would suggest Hirschsprung disease, neonatal small left colon syndrome, or meconium plug syndrome. **B,** After the removal of the enema catheter, the patient spontaneously passed a "plug" of meconium and the obstruction was relieved. A sweat test and a rectal biopsy may be indicated to exclude the diagnoses of cystic fibrosis and Hirschsprung disease, respectively.

complications develop.[82,83] Since that report, a Gastrografin enema has been the standard of nonoperative treatment. Meglumine diatrizoate is a hyperosmolar, water-soluble, radiopaque solution containing 0.1% polysorbate 80 (Tween 80), a solubilizing or wetting agent, and 37% organically bound iodine. The meglumine is a 76% aqueous solution of sodium-methyl-glucamine salt of n1n1-diacetyl-3,5-diamino-2,4,6-triiodobenzoic acid, and this hypertonic solution has an osmolality of 1900 mOsm/L, a property that draws fluid into the intestinal lumen and aids in the release of the inspissated meconium. After administration, both a transient osmotic diarrhea and a putative osmotic diuresis occur, factors that emphasize the importance of aggressive fluid resuscitation. In addition, the product is radiopaque, which enables a safe fluoroscopically monitored administration. Polysorbate 80 (Tween 80) is a nonionic surface-active emulsifier that may not only better define radiographically the bowel mucosal pattern but also facilitate the passage of the hypertonic Gastrografin between the mucosa and the adherent meconium at the site of obstruction. Polysorbate 80 as a 10% solution has been administered intraoperatively by way of an enterostomy to liquefy meconium. Other hypertonic water-soluble agents (e.g., 40% sodium diatrizoate [40% Hypaque]) not containing polysorbate 80 are also effective in relieving the obstruction, and they may prevent the adverse influence of Gastrografin on colonic mucosa.[79,84]

The technique of solubilizing enema treatment of meconium ileus continues to use the aforementioned guidelines of Noblett. After fluid resuscitation and nasogastric decompression have been performed and after physical examination assessment and plain abdominal radiographs have excluded the diagnosis of peritonitis or perforation, the diagnostic contrast enema with barium or water-soluble agent is administered. When the preliminary diagnostic study has been completed, an enema-tip nonballoon catheter is inserted into the anorectum and the buttocks are taped together around the catheter. With fluoroscopic guidance and an initial solution of 50% Gastrografin in water, the contrast agent is slowly injected by a catheter-tipped syringe. When contrast medium traverses the colon and reaches the dilated meconium-impacted ileum, the study is terminated and the infant is returned to a bed for monitoring, fluid administration (two times maintenance), and normalization of body temperature. Spontaneous passage of the inspissated meconium per rectum should follow. An abdominal radiograph should be repeated in 8 to 12 hours to determine whether the obstruction has been relieved. If instead the evacuation is incomplete and obstruction persists, the enema may be repeated with the same concentration of Gastrografin. If either no evacuation occurs after a successfully refluxing enema or if contrast medium cannot be refluxed into dilated bowel, then this technique should be abandoned and operative intervention planned. Similarly, signs of worsening obstruction, clinical distention, greater distention of loops on radiograph, or signs of peritonitis resulting from a possible perforation are also indications for operative intervention. Noblett suggests that after a successful enema, 5 mL of a 10% N-acetylcysteine solution should be administered every 6 hours through a nasogastric tube to liquefy upper gastrointestinal secretions.[85] Furthermore, when formula feedings are begun, supplemental pancreatic enzymes must be administered with each feeding.[86,87]

The success of nonoperative treatment is variable.[88,89] The initial report of Noblett suggested that up to two thirds of patients were successfully treated by this technique. Advantages of the nonoperative therapy include a reduction in pulmonary morbidity and a reduced length of hospital stay. Disadvantages of therapy include a delay in operative intervention for those unsuccessfully treated by the enema, the risk of immediate and delayed intestinal injury or perforation, and the induction of hypovolemia. Bowel injury leading to a potential perforation may be a product of repeated enemas, injudicious inflation of an enema catheter balloon, or a direct mucosal injury induced by the enema agent.[90–94] The mechanism of such an injury may be related to bowel distention or to the polysorbate 80 content. The latter injury may be prevented by using a solubilizing enema agent containing 1% to 2% polysorbate 80 with isotonic Gastrografin diluted with water to a final osmolality of 320 to 340 mOsm/L or by using an alternate isotonic contrast agent.

# Operative Management

Multiple indications for operative intervention in the management of meconium ileus exist.[95–97] One third to one half of patients undergoing operation represent cases of simple or uncomplicated meconium ileus that have failed to respond to nonoperative treatment with enema solubilizing agents. The remaining one half to two thirds of patients have complications of meconium ileus, which include intestinal atresia, volvulus, perforation, meconium cyst formation with peritonitis, intestinal gangrene, or combinations of these events. In the management of simple meconium ileus, the goal of operation is the relief of intraluminal ileocolonic obstruction by either the evacuation of the adherent intraluminal meconium or by resection of the portion of bowel filled with inspissated material.[98]

## SIMPLE MECONIUM ILEUS

A variety of operative procedures are available for the management of patients with meconium ileus (Figs. 83-7 and 83-8).[98] The initial patient survivors underwent enterotomies with irrigation coupled with a limited resection. This operative technique is the one most commonly in use today. Irrigating solutions may include warmed saline, a 50% diatrizoate solution, a 1% solution of pancreatic enzymes (Viokase; A.H. Robbins Co., Richmond, Va.), hydrogen peroxide, and, most commonly, either a 2% or a 4% solution of N-acetylcysteine (Mucomyst; Apothecon, Princeton, N.J.).[85,99] More concentrated solutions of N-acetylcysteine or Gastrografin or the use of hydrogen peroxide and its attendant risk of air embolism may produce greater risk than benefit. After solubilization by the irrigant, injected through an enterotomy catheter, the meconium is gently milked distally into the colon or evacuated through the enterotomy (see Fig. 83-7). The enterotomy and the abdomen may then be closed, an enterostomy may be created, or the site can be controlled by insertion of a T tube.[100–103] This last treatment has been designed to be located at the junction of proximal distended ileum with distal (more collapsed) ileum where intraluminal balls of inspissated meconium are found. Leaving this tube in place and attaching the enterotomy site against the anterior abdominal wall ensures a controlled fistula, as well as a route

of gastrointestinal access for the instillation of pancreatic enzyme solutions beginning on the first postoperative day. By the seventh to fourteenth postoperative day, the irrigant should pass freely into the colon, the obstruction should be relieved, and thereafter the catheter can be removed. This avoids the need for reoperation and enterostomy closure. An alternative technique is appendectomy with appendicostomy, with meconium evacuation or irrigation through this route.[104] A temporary indwelling tube cecostomy may alternatively be left in place. For such an irrigant technique to be successful, the bowel must be handled gently, not overdistended, and not excessively massaged or "milked" in an effort to evacuate the inspissated meconium.

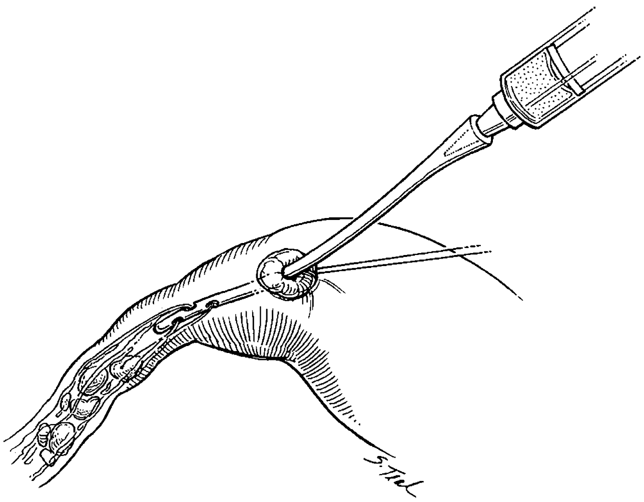


**FIGURE 83-7** The most commonly preferred contemporary operative management of meconium ileus is shown. An enterotomy is made in the dilated small bowel segment just proximal to the site of inspissated distal meconium, and an irrigating catheter is inserted. After instillation of solubilizing agent, the catheter may be removed and the enterotomy closed; instead, the catheter may be left in place or replaced with a T tube for continued postoperative solubilizing agent instillation. (From Rescorla FJ, Grosfeld JL: Contemporary management of meconium ileus. World J Surg 1993;17:381.)

An alternative operation to enterotomy-irrigation is placement of a temporary obstruction-relieving stoma with or without an associated partial resection. Gross initially advocated placement of the Mikulicz double-barreled enterostomy, which could be performed quickly and which did not require intraoperative meconium evacuation (see Fig. 83-8). The exteriorized bowel loop could be opened after the abdominal incision has been closed, thereby minimizing intraperitoneal contamination. After the obstruction is relieved and the infant has recovered, a spur-crushing Mikulicz clamp can be applied externally at the stoma to complete a side-to-side anastomosis. It may not be necessary to return to the operating room to close the stoma because after the clamp-induced anastomosis, the residual enterocutaneous fistula may spontaneously close. An alternative to such an "extraabdominal resection" and delayed stomal closure was the primary resection and anastomosis recommended a decade later by Swenson and Noblett. After meconium had been evacuated, a primary intraperitoneal anastomosis could be performed, or the infant could be allowed to recover more fully, after which the stoma could be closed in delayed fashion by an end-to-end anastomosis. An alternative operation is resection coupled with a distal chimney enterostomy, the so-called Bishop-Koop procedure (see Fig. 83-8).[105] This technique was developed with the

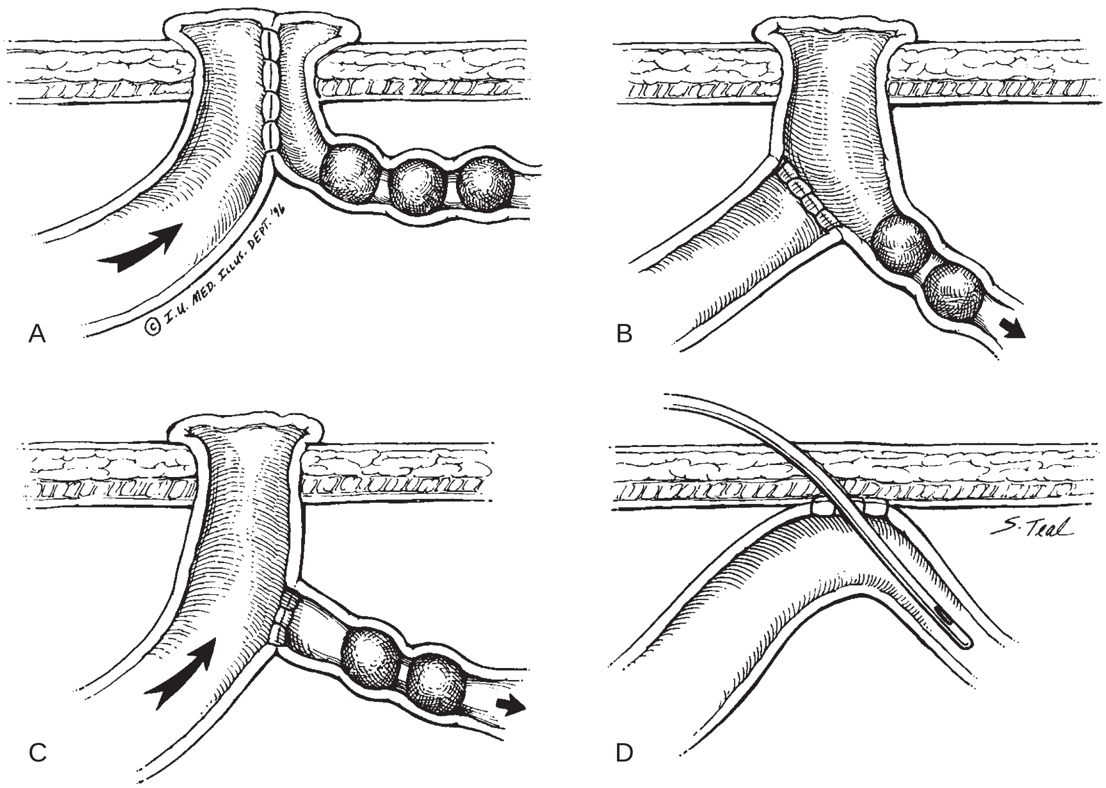


**FIGURE 83-8** The operative options for simple meconium ileus. **A,** The Mikulicz resection and enterostomy. **B,** The Bishop-Koop resection and enterostomy. **C,** The Santulli enterostomy. **D,** Tube enterostomy. (From Rescorla FJ, Grosfeld JL: Contemporary management of meconium ileus. World J Surg 1993;17:381.)

following criteria: (1) limit intraoperative bowel trauma in the neonatal period; (2) resect the disparately enlarged ileal loop filled with inspissated thickened meconium; (3) create an appropriately sized end of proximal to side of distal ileum anastomosis close to the abdominal wall exiting the distal ileum, to serve as a functionally decompressing "proximal stoma" while distal obstruction persisted; (4) provide access for insertion of a catheter into the distal bowel containing inspissated meconium pellets so that solubilizing pancreatic enzymes could be instilled postoperatively; and (5) permit an eventual enterostomy closure by bedside ligation of the "chimney stoma," putatively avoiding the risks of an additional anesthetic in a child with known CF. Intraoperatively, an 8-Fr rubber catheter is passed through the ostomy chimney into the distal ileum. Within 12 to 24 hours after the operation, catheter irrigations are begun with a pancreatic enzyme solution (1 teaspoon Viokase per 1 oz water) repeated every 4 to 6 hours until the distal intraluminal obstruction is relieved, at which time the catheter is removed. After an initial large volume of enterostomy output, the ostomy drainage will diminish as the more distal obstruction is relieved. The transcolonic passage of stool will follow. Thereafter, the output from the stoma may cease altogether. Eventually the chimney may be treated by one of two techniques. At the bedside the "stoma" may be ligated. If the result of this noninvasive technique is a persistent enterocutaneous fistula, then a formal intraperitoneal or extraperitoneal stomal closure can be performed with the patient under a general anesthetic. This latter procedure is necessary in approximately 75% of patients treated by this technique.[17]

Santulli described a proximal chimney enterostomy, an operation that in essence is the reverse of the resection coupled with a distal chimney enterostomy (see Fig. 83-8). The distal ileal end is anastomosed end-to-side to the proximal ileum at a level corresponding to an immediate subfascial plane, and the proximal ileum is exited as an end enterostomy. With this stoma arrangement, irrigation and decompression of the proximal ileum is enhanced. As with the Bishop-Koop procedure, an intraoperative catheter passed through the stoma is positioned into the distal ileum for the postoperative instillation of solubilizing agent. Because a high-output functional end enterostomy has been created, it is necessary to close such a stoma early to avoid the complications induced by excessive fluid and electrolyte losses.

### COMPLICATED MECONIUM ILEUS

The treatment of complicated meconium ileus almost always requires an operation,[106] an exception being the rare in utero perforation that has left a telltale remnant of extraluminal intraperitoneal calcified meconium, a spontaneously sealed perforation, and no interruption in intestinal continuity.[105] Another finding for the latter process is calcified meconium seen in a patent processus vaginalis during a hernia operation or by abdominal radiograph later in life. In contrast, operative indications include persisting intestinal obstruction, an enlarging abdominal mass, and signs of peritonitis, which may include abdominal wall edema and discoloration, tenderness on physical examination, and clinical and laboratory signs of ongoing sepsis (Fig. 83-9).

Meconium peritonitis may be seen as one of several varieties. A meconium pseudocyst is a result of meconium accumulating in the peritoneal cavity for weeks to months. A calcified

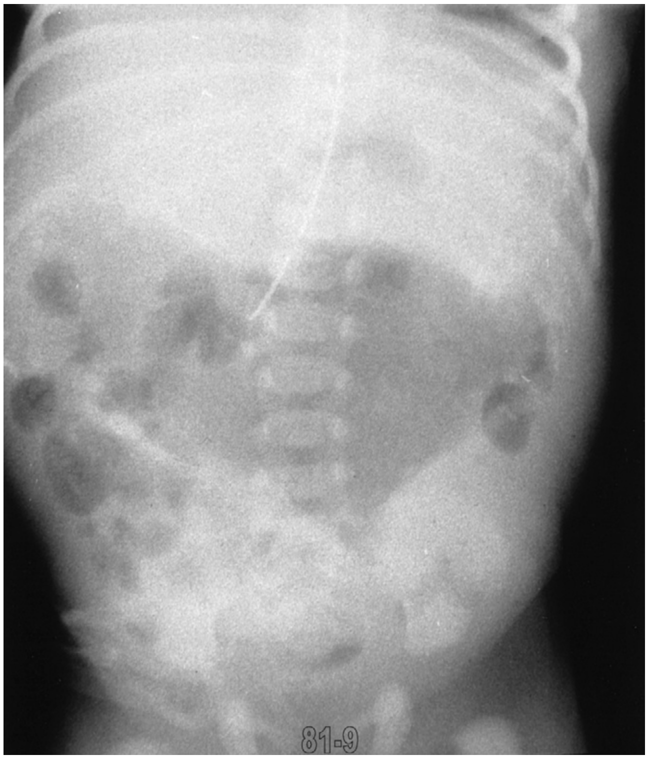


**FIGURE 83-9** A plain abdominal radiograph compatible with the diagnosis of complicated meconium ileus. The large, central, air-filled mass suggests intestinal perforation and giant meconium cyst formation. If the perforation has been of longer standing, intraperitoneal calcification may also be present. (From Rescorla FJ, Grosfeld JL: Contemporary management of meconium ileus. World J Surg 1993;17:381.)

"pseudocyst" fibrous wall forms around an accumulation of meconium, and spared bowel loops are peripheral to this cyst (see Fig. 83-9). Adhesive meconium peritonitis follows meconium contamination of the peritoneal cavity for days to weeks before delivery. Dense and vascular adhesions make operative relief of the adhesive intestinal obstruction difficult. Scattered calcifications may be present. When intestinal perforation occurs only a few days before delivery, an abdomen filled with meconium ascites results and calcification is absent. The fourth variant of meconium peritonitis is bacterially infected ascites, which occurs when colonized intestinal organisms penetrate from the perforated intestine into the peritoneal cavity.

At operation, it is mandatory to assess residual intestinal length, and it is critical to use conservative resection. An effective armamentarium of operative options is necessary to optimize treatment of meconium peritonitis, volvulus, atresia, or the ischemic intestine that may be encountered. Only the presence of a diffuse bacterial peritonitis precludes a primary anastomosis. The Bishop-Koop, Mikulicz, and Santulli procedures each have application in the management of patients with complicated meconium ileus.

## Postoperative Management

After the operative management of meconium ileus, care must be centered on support of the infant's general physiology, as well as on the evacuation of any residual proximal or distal gastrointestinal inspissated intraluminal meconium. Generally, the

latter can be treated by instillation of 2% or 4% acetylcysteine (Mucomyst) delivered through a nasogastric tube, which will solubilize the residual meconium. When gut patency is verified clinically or by plain film radiograph, enteral nutrition may begin with an elemental formula such as Pregestimil (Mead-Johnson, Evansville, Ind.). When enteral feedings begin, supplemental pancreatic enzymes must also be started (Viokase, Pancrease [McNeil Pharmaceuticals, Spring Hill, Pa.] and Cotazym-S [Organon Inc., West Orange, N.J.] are alternatives). If postoperative ileus is prolonged or if short-bowel syndrome is a product of the operative treatment, then total parenteral nutrition becomes an important early and potentially prolonged form of postoperative nutritive therapy. Early enteral or parenteral nutrition therapy must include maintenance of salt and mineral balance; appropriate vitamin supplementation including vitamin K; and aggressive management of any associated short-bowel syndrome deficiencies. The association of the inherent malabsorption of CF coupled with the potential of an extreme short-bowel syndrome resulting from complicated meconium ileus makes for an extremely difficult management combination.[107,108]

Short-term postoperative parenteral antibiotics are used for the care of either simple or complicated meconium ileus, but directed and more prolonged antibiotics may be continued to minimize potential pulmonary complications. Vigorous pulmonary physiotherapy is initiated early after operation and is continued indefinitely. Teaching parents to perform such pulmonary physiotherapy that includes postural drainage is a mandatory component of predischarge planning. In those patients with an enterostomy, teaching parents appropriate stomal care is also important. Only in those circumstances in which a Bishop-Koop ileostomy or a Mikulicz ileostomy was created would bedside ligation of the chimney or application of a Mikulicz clamp, respectively, be considered before hospital discharge.

Perhaps the most important feature of postoperative care is to secure the diagnosis of CF as the cause of the patient's meconium ileus. A series of reports exist in which neonatal intraluminal inspissated meconium is the cause of small bowel obstruction and the same management scheme as outlined earlier is applied. However, postoperatively these patients are not found to have abnormal sweat electrolytes. Such cases have been carefully distinguished from the colonic meconium plug syndrome because the plugging has been confined to the small bowel. This condition has been reported in premature infants, in siblings without CF, in patients with partial pancreatic aplasia, and in patients with pancreatic ductal stenosis.[109] These findings remain an important distinction if the alternative diagnosis is meconium ileus associated with CF.

# Complications

## GASTROINTESTINAL

Many gastrointestinal complications of meconium ileus exist and include an increased incidence of intussusception and rectal prolapse. However, in the child and adolescent with CF, the most common gastrointestinal problem is distal intestinal obstruction termed *meconium ileus equivalent* or *distal intestinal obstruction syndrome.*[110] A partial bowel obstruction by intraluminal material may be a product of steatorrhea or noncompliance with oral enzyme therapy. Signs and symptoms are heralded by crampy abdominal pain, distention, and a palpable right lower quadrant mass; and a high-grade obstruction is associated with obstipation, distention, and vomiting. It is important to consider a broad differential diagnosis that may include constipation, intussusception, and even appendicitis; and the plain abdominal radiograph supplemented with contrast body imaging should prove diagnostic. Once the diagnosis is established, the preferred treatment is solubilizing agents such as acetylcysteine and Gastrografin, given both orally and per rectum. Operative intervention is rarely required. Adjustment of oral enzyme therapy supplemented with better hydration and the use of stool softeners may be used to prevent recurrence. Both histamine $H_2$ blockers and proton pump inhibitors may prove efficacious by increasing intestinal pH, and prokinetic agents have also been used.

Appendiceal luminal obstruction that produces signs and symptoms compatible with both acute and "chronic appendicitis" may also occur.[111] The diagnosis of appendiceal pathology depends on both clinical assessment and the potential use of contrast medium-enhanced computed tomography. These complications and the most common gastrointestinal complication, malabsorption, are improved with appropriate enzyme replacement therapy. Malabsorption of carbohydrates, protein, and fat may all occur, a problem worsened both by the extent of peritoneal inflammation and the magnitude of the short-bowel syndrome. The latter may be functional or anatomic, an anatomy foreshortened because of atresia or a resection. The malabsorption is worsened by a disaccharidase deficiency and by inspissated biliary secretions that produce both jaundice and impaired fat absorption. This same pathophysiology may account for the occurrence of gallstones in about one fourth of patients with CF, as well as the incidence of symptomatic chronic calculous cholecystitis or biliary dyskinesia, which also characterizes this population. The nutrient malabsorption takes on greater significance if a concomitant increased energy need occurs in the presence of recurrent and chronic pulmonary infection. The application of total parenteral nutrition may prove beneficial to supplement enteral nutrients and to provide gut rest, as well as appropriate calories during periods of prolonged postoperative ileus, especially if anastomotic healing or closure of enterocutaneous fistulas is required. Furthermore, evidence suggests that the malnutrition of meconium ileus is significantly different or even worse than that seen in age-matched peers who have CF without meconium ileus.

Intussusception occurs in approximately 1% of older CF patients, likely secondary to inspissated intraluminal stool serving as the lead point. The site of pathology is typically ileocolic, but small bowel and large bowel intussusception may also occur. Typically, the diagnosis is difficult to establish and distinguish from other right lower quadrant CF pathology, and operation with reduction and/or resection becomes the usual therapeutic outcome.

Rectal prolapse may be the first clinical presentation of a child subsequently proven by sweat test to have CF. Up to one third to one fifth of children with CF develop prolapse typically between the ages of 1 and 3 years of age. The preferred treatment after the diagnosis of CF is established is oral enzyme therapy, and rarely will more aggressive transanal rectal submucosal sclerotherapy or operative rectopexy be indicated.

Colonic strictures[86,87,90,94] presumptively secondary to large-dose oral enzyme therapy have been reported in CF children, half of whom previously have had meconium ileus. Most commonly such disease is localized to the right colon, but segmental colitis and even pancolonic disease has been reported. The local signs of obstruction and pain must be distinguished from the meconium ileus–equivalent patient, and a contrast enema is typically diagnostic. Regulation of enzyme therapy may be tried, but most commonly resection is indicated for intractable strictures.

### PULMONARY

The early morbidity and mortality of meconium ileus predominantly has a pulmonary origin, the products of which include bacterial sepsis and bronchopneumonia. Some authors suggest that beyond 6 months after the treatment of meconium ileus, the prognosis and morbidity assume that of a patient with CF without meconium ileus. However, other studies suggest that children with meconium ileus have worse lung function and more obstructive lung disease between ages 8 and 12 years than those with CF but without meconium ileus. These changes occur with relatively reduced lung volumes. When *Pseudomonas,* coliforms, or other specific colonizing or pathogenic organisms are identified, the early and aggressive use of aminoglycosides and semisynthetic penicillins has been shown to improve survival and outcome, even if used in a prophylactic manner. Finally, the use of aggressive physical therapy and postural drainage may further minimize pulmonary complications.

### INGUINOSCROTAL DISEASE

Children with CF have been reported to have an increased incidence of inguinal hernias and hydroceles, as well as an increased incidence of cryptorchidism.[112,113] Two operative findings at the time of inguinal hernia repair may suggest the underlying diagnosis of CF, namely, the presence of calcified meconium in the hernia sac and the absence of a vas deferens.[114] Both findings in the absence of a previous diagnosis of CF suggest the need for a diagnostic sweat test. In addition, infertile males without a vas deferens may actually be asymptomatic heterozygotes carrying the CF gene.

## Results of Treatment

The outcome of the treatment of patients with meconium ileus, whether the condition is complicated or simple, has steadily improved during the past 3 decades, the most recently reported survival rates approaching 100% (Fig. 83-10).[115,17] In a series of patients treated both nonoperatively and

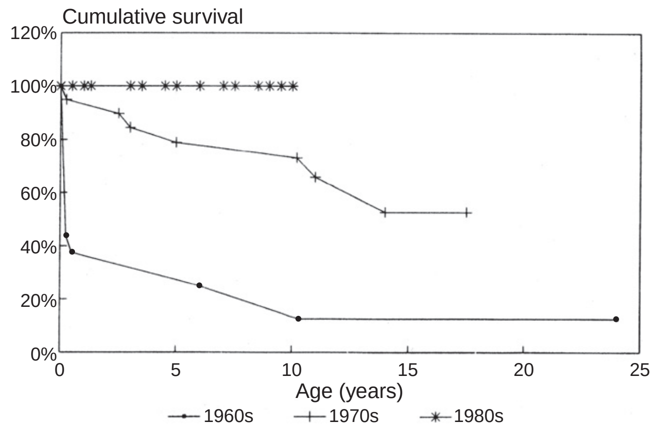


**FIGURE 83-10** Long-term survival rates of patients with meconium ileus depicted by decade. A statistically significant improvement in survival is seen when 1960s, 1970s, and 1980s survival data are compared ($P < 0.0001$). (From Del Pin CA, Czyrko C, Ziegler MM, et al: Management and survival of meconium ileus: A 30-year review. Ann Surg 1992;215:179-185.)

operatively, survival rates at 5 and 10 years for the two categories improved steadily from the 1960s (30% and 10%, respectively) through the 1970s (80% and 70%, respectively) and the 1980s (100% at 5-year follow-up).[27,116–118] In the past, nonoperative treatment had contributed to an improved survival rate. But in the past decade the survival rate for both operative and nonoperative treatment was 100%. The significant improvement in operative survival has come since the 1960s when the 6-month survival rate was only 33%.[119] The operative 6-month survival rate had improved to 60% before 1979 and to 100% between 1979 and 1989.[120] No significant overall differences in outcome were observed with regard to patient gender, whether complication of meconium ileus was present, or with regard to the type of operation performed (ileostomy, resection with primary anastomosis, resection and Mikulicz ileostomy, and Bishop-Koop enterostomy). Additionally, the long-term survival rates (measured at 6 years) of patients treated with the Bishop-Koop procedure (62% survival) did not differ from those of patients with alternate operations. Furthermore, all deaths in patients older than 6 months of age were cardiopulmonary or pneumonitic deaths related to the underlying CF and not to complications of operation. Interestingly, both simple and complicated cases of meconium ileus had 72% 10-year survival rates.[121,122]

Death occurs from multiple causes, which include intraperitoneal sepsis from unrecognized leakage, pulmonary sepsis and bronchopneumonia, or short-bowel syndrome with complicating liver failure.[123–125]

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 84

# Meckel Diverticulum

Charles L. Snyder*

## History

In 1598 Fabricus Hildanus first described an "unusual" diverticulum of the small intestine.[1,2] Lavater also reported a diverticulum in 1671.[3] Littre noted its presence in a hernia in 1700.[4] Ruysch published a copperplate illustration in 1701[5] and thoroughly described the anatomy.

Johann Friedrich Meckel (1781-1833) was an eminent anatomic pathologist.[6] His grandfather, also named Johann Friedrich Meckel (1724-1774), was a well-known professor of anatomy, botany, and obstetrics in Berlin. To avoid confusion, the grandson (of eponymous diverticular fame) is known as "the younger" and his grandfather is referred to as "the elder." Meckel the younger's father, Phillip, was also a professor of anatomy and surgery at Halle (Prussia).

Johann Friedrich Meckel the younger became professor of normal and pathologic anatomy at the University of Halle in 1808, where he remained for the rest of his career.[7] Although he was not the first to identify it, he published a series of articles in the early 1800s describing the anatomy, embryology, and clinical attributes of the diverticulum that bears his name.[8–13] In 1812 Meckel suggested that the incidence of complications developing in a diverticulum was about 25%,[9] a figure that is high by current estimates. Obliged to retire at age 50 because of paranoia, he died a recluse 2 years later.[14]

A specimen from 1846 is the first known example of intussusception from a Meckel diverticulum.[15] Heterotopic pancreatic mucosa was reported in the diverticulum by Zenker in 1861,[16] and gastric mucosa was found in 1904 by Salzer.[17] The association of the diverticulum with adjacent ulceration of the ileum was discovered by Deetz in 1907.[18] A carcinoid tumor originating in a Meckel diverticulum was identified in 1907.[19] Gramen described a presentation similar to appendicitis in patients with an inflamed/perforated Meckel diverticulum in 1915.[20]

Harper suggested the technetium-99m pertechnetate scan in 1962 as a method of diagnosing Meckel diverticulum because the material is concentrated in gastric mucosa.[21] However, Jewett and colleagues were the first to apply it clinically in 1970.[22] Attwood performed the first laparoscopically assisted resection of a Meckel diverticulum in 1992.[23] The historical timeline is illustrated in Figure 84-1.

## Embryology

During early embryonic development, the yolk sac nourishes the embryo via the vitelline circulation. *Vitellus* in Latin means "yolk." *Omphalos* is Greek for navel (the term *omphaloskepsis* means "meditation while gazing at the navel").

The intracoelomic yolk sac forms the gut, and the extraembryonic yolk sac begins to regress as it is replaced by the placenta as the primary source of nourishment for the developing fetus.[24,25] With growth, the fetal intestine becomes separated from the yolk sac, leaving only a ductal communication (vitelline/omphalomesenteric duct), which obliterates between the fifth and seventh weeks of fetal life (Fig. 84-2, *A* to *C*). A variety of anomalies can result from failure of involution of the omphalomesenteric duct: The classic Meckel diverticulum accounts for 90% of cases (Fig. 84-3).

Vessels on the yolk sac coalesce to form the paired omphalomesenteric arteries and veins. The enteric portion of the right artery persists as the superior mesenteric artery, and the left regresses. Distal vitelline artery remnants may persist as mesodiverticular bands, extending out to the tip of the diverticulum and occasionally attaching to the abdominal wall. A patent vitelline remnant can regress, even postnatally.[26,27]

## Epidemiology

Meckel diverticulum is the most common congenital anomaly of the gastrointestinal tract and is found in 1.2% to 3% of the population.[28–32] The male-to-female ratio is nearly equal in asymptomatic patients; among symptomatic patients it is twice as frequent in males. The "rule of 2" is often cited with regard to the diverticulum: 2 types of heterotopic mucosa, 2 feet from the ileocecal valve, 2 inches long, 2 cm in diameter, usually discovered before 2 years of age, 2 times as common in males, and it is found in 2% of the population.

*The author would like to express his appreciation to Dr. Raymond A. Amoury, without whom this chapter could not have been written.

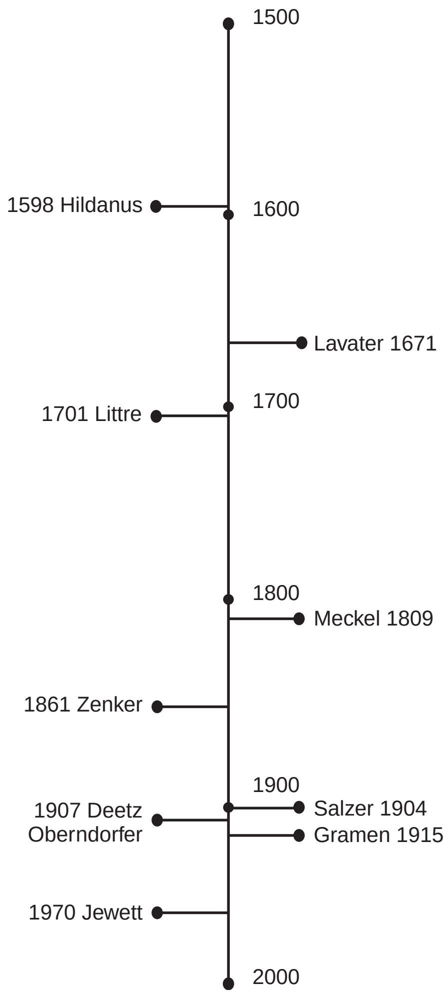


**FIGURE 84-1** The historical timeline of Meckel diverticulum, from original observation to current day. The significant points are discussed in the text.

## Pathology

Meckel diverticulum is a true diverticulum, containing all the normal bowel wall layers. It is almost always on the antimesenteric border. Three fourths of Meckel diverticula are unattached to the abdominal wall and free-floating within the peritoneal cavity.[24,33] Most diverticula are located within 100 cm of the ileocecal valve, but the location can be quite variable. The median distance from the ileocecal valve to the diverticulum was 40 cm in one series, but the range was wide.[30] At least 5 feet of distal small bowel should be thoroughly examined to rule out the presence of a diverticulum. Mean diverticular length is 2 to 3 cm.[24,34,35] Some studies have suggested that symptomatic diverticula tend to be longer and have a narrower base,[35,36] but other reports found no difference in length or diameter of asymptomatic versus symptomatic diverticula.[37]

The incidence of heterotopic mucosa in surgically removed Meckel diverticula is estimated at 15% to 50%, but these reports usually include both incidental cases and symptomatic patients. In autopsy series, the numbers are lower.[29,32,38,39] In collected series the incidence of heterotopic mucosa in asymptomatic patients is about 15%.[31,36,38,40–42] Symptomatic patients are

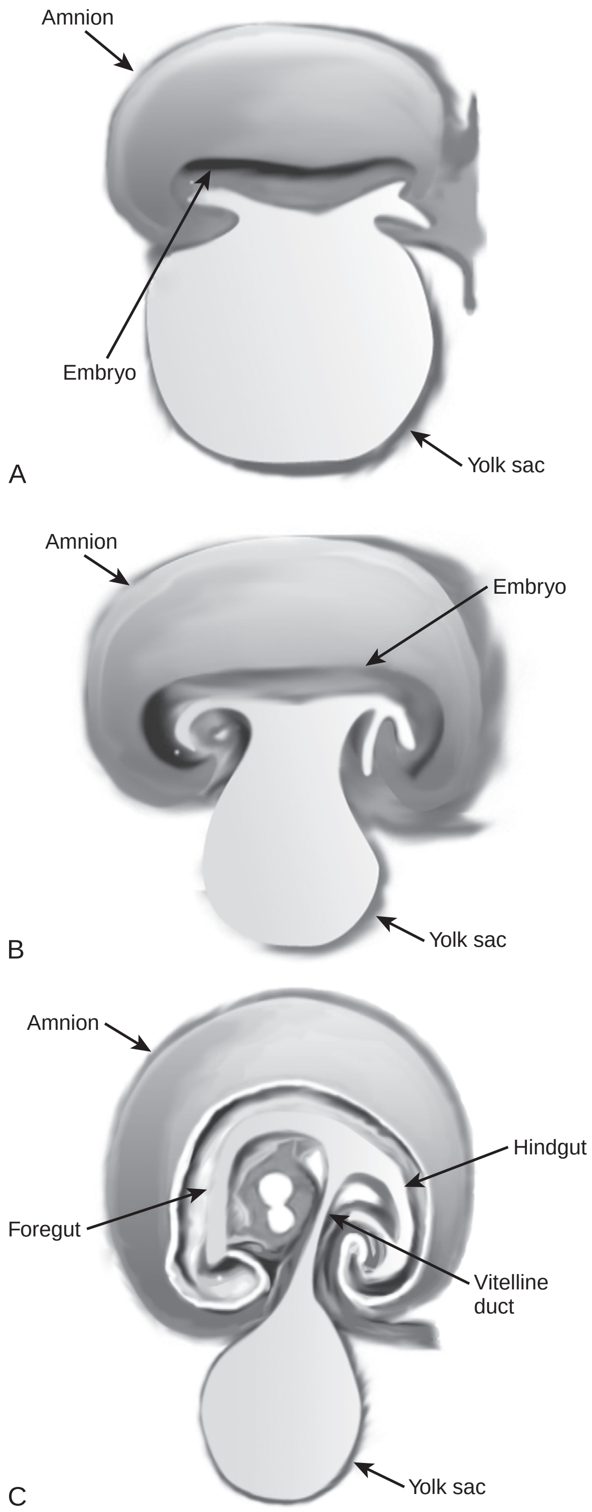


**FIGURE 84-2** Stages in the development of the fetal membranes. **A,** The relatively small amniotic cavity is located atop the embryonic disc, which separates it from the larger yolk sac below. The beginnings of the hind gut and foregut (formed from the yolk sac) are visible. This corresponds to approximately the third week of fetal life. Not pictured are vessels on the surface of the yolk sac. **B,** The amniotic cavity has expanded, and the yolk sac is elongating and diminishing in size (fourth week of fetal life). The allantois and fetal heart tube are visible. **C,** The embryonic gut is forming, and there remains a narrow communication (vitelline duct) with the yolk sac. Further expansion of the amniotic sac and development of the embryo has occurred. This roughly corresponds to the fifth week of development.

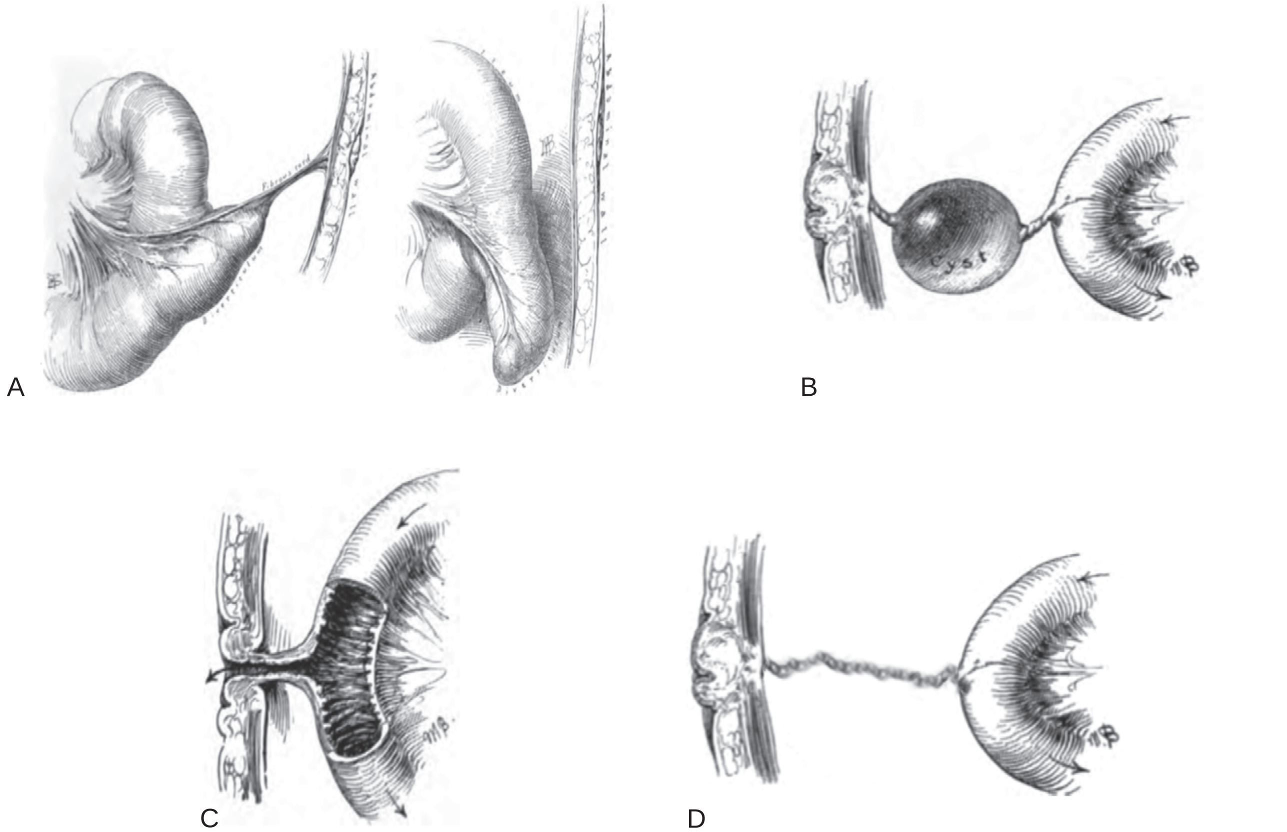


**FIGURE 84-3** Meckel diverticulum and vitelline abnormalities. **A,** Meckel diverticulum with (25%) and without (75%) abdominal wall attachment. **B,** Vitelline cyst with mucosal lining. These may be just under the peritoneal lining of the abdominal wall. **C,** Patent omphalomesenteric duct with mucosal lining (omphalo-ileal fistula). **D,** Fibrous vitelline attachment without a diverticulum. Other variants include vitelline cysts within the umbilical cord but external to the infant; umbilical polyps (although usually independent anomalies, these polyps may penetrate the abdominal wall and connect with deeper structures); or a blind-ending umbilical sinus. (From Cullen TS: Embryology, Anatomy, and Diseases of the Umbilicus. Philadelphia and London, WB Saunders, 1916.)

far more likely (40% to 50%) to have heterotopic mucosa.[31,34,43] Gastric is the most common type, followed by pancreatic. Other types of heterotopia (colonic, endometrial, pancreatic islets) are rare. A review of 21 resected specimens with known heterotopic tissue found that it was palpable in less than half (48%)[38] and was located at the base of the diverticulum in 13% (Fig. 84-4).

Bleeding and inflammatory complications of Meckel diverticula are usually attributable to the abnormal mucosa. The incidence of gastric mucosa in *bleeding* Meckel diverticula has been estimated to be as high as 80%.[44] Gastric acid production causes ulceration, usually at the base of the diverticulum at the junction of ectopic gastric mucosa and normal ileal mucosa. The ulcer may also be found within the ectopic gastric mucosa itself or on the mesenteric side of the ileum opposite the diverticulum.

**FIGURE 84-4** Meckel diverticulum with thickening near the tip from heterotopic gastric mucosa.

## Associations

Most cases of Meckel diverticula are sporadic. The presence of a diverticulum alone does not mandate a search for other anomalies because less than 5% of patients will have any associated abnormalities.

Simms and colleagues[45] reviewed 5919 autopsies over a 20-year period to identify congenital malformations with a higher than expected incidence of Meckel diverticulum. They found a 12% incidence in patients with esophageal atresia, 11% with imperforate anus patients, 6% in those with neurologic abnormalities, 4.6% in congenital cardiovascular abnormalities, and a 4.2% incidence with duodenal atresia.[45]

In their much smaller clinical series ($n$ = 81), there was a surprisingly high incidence of Meckel diverticulum in association with small omphaloceles (24.5%). Several other reports have noted a similar association of Meckel diverticulum and omphalocele minor, with an incidence ranging from 15% to 40%.[42,46,47]

An association with Crohn disease has been suggested: A 5.8% incidence of Meckel diverticulum was found in 294 patients undergoing right hemicolectomy for Crohn disease.[48] However, a review of 877 patients with Crohn disease found an incidence of only 1%.[49] None of the patients had active Crohn disease in the diverticulum. Most series found no evidence of heterotopic mucosa in any patients.

A Littre hernia is defined as one containing a Meckel diverticulum. The usual sites are inguinal (50%), umbilical (20%), and femoral (20%); the most common location in children is umbilical.[50] Most of these rare hernias occur in the elderly population.

# Incidental Diverticulectomy

In the voluminous literature on Meckel diverticulum, the controversy regarding incidental diverticulectomy is longstanding. A systematic review of the population of King's County, Wash., over a 15-year interval found a declining incidence of complications from Meckel diverticula with age (as have others).[51,52] Soltero and colleagues[51] identified 202 symptomatic Meckel diverticula. The total complication rate was estimated to be 4.2%, and they estimated that 800 diverticula would have to be removed to prevent one death.[51] These authors argued that asymptomatic Meckel diverticula should not be removed.

Cullen and colleagues[34] estimated that the lifetime risk of patients with a Meckel diverticula developing a complication was 6.4%. They found that the risk of complications did *not* decrease with age and suggested that the benefits of removing the incidental Meckel diverticula found at operation outweighed the risks. They also noted an increased risk of complications in men compared with women.

Many other series advocated basing the decision to incidentally remove an asymptomatic Meckel diverticulum on its clinical characteristics (length, width, thickened tip); the gender or age of the patient; or other factors.[38,53] Park and colleagues[38] reviewed 1476 patients undergoing diverticulectomy over a 52-year interval; 16% were symptomatic. They performed a logistic regression analysis to identify factors associated with a symptomatic diverticulum. Statistically significant associations included age younger than 50 years (odds ratio—OR 3.5), diverticular length greater than 2 cm (OR 2.2), and male gender (OR 1.8). The presence of histologically abnormal tissue in the diverticulum was strongly associated (OR 13.9) but may not be identifiable before resection. Others have suggested that the risk (albeit small) of neoplastic degeneration supports incidental diverticulectomy.[54]

A recent meta-analysis of 244 studies with more than 3000 patients, by Zani and colleagues,[31] concluded that resection of an incidental Meckel diverticula has a statistically significantly higher early complication risk than simply leaving it in situ (5.3% vs. 1.3%, $P < 0.0001$). Similar to Soltero's report, they estimated that 758 patients would have to undergo elective resection to prevent one death. They estimated that an individual with a Meckel diverticulum has a lifetime chance of complications requiring an operation of 2.9%. The future risk of death attributable to a Meckel diverticulum did not increase significantly with age.

It has been estimated that appendicitis is more than 50 times as common as a symptomatic Meckel diverticulum. Incidental appendectomy is currently rarely recommended—some have argued that this would be a statistically more justifiable proposition than incidental diverticulectomy.

# Clinical

Charles Mayo famously wrote that "Meckel's diverticulum is frequently suspected, often looked for, and seldom found."[55] Most Meckel diverticula are clinically silent. It has been called the "great imitator" because of its relative infrequency and protean manifestations.

Symptomatic patients are usually younger.[35,37,38,40,56] Up to half of symptomatic Meckel diverticula will present in the first 2 years of life, and most complications will develop before 10 years of age. The type of complication also varies with the age of the patient. Hemorrhage and obstruction predominate in the very young, and obstruction and inflammatory symptoms occur in adults.[36,42,43,53,57,58] Neoplasia becomes a more frequent complication in the elderly.

## RADIOLOGY

The technetium-99m pertechnetate radionuclide study ("Meckel scan") is commonly used today (Fig. 84-5). The accuracy of the study is improved by the administration of pentagastrin (which increases gastric mucosal uptake and is a potent stimulator of gastric acid secretion and increased gastric motility) and H2 blockers (which inhibit the excretion of the isotope into the bowel lumen and increase the cellular concentration). Giving both H2 blockers and pentagastrin together is not recommended because the former antagonizes the latter.[59] Glucagon slows bowel transit and allows the isotope to persist longer in the diverticulum.[60] A urinary catheter is used to diminish bladder accumulation, which may obscure the diverticulum.

Technetium 99m has a half-life of 6 hours with a maximum concentration occurring 15 to 30 minutes after intravenous injection.[22] The isotope is taken up by gastric mucosal cells.[61] Estimated radiation dosimetry in a 5-year-old child from a standard Meckel scan is 0.11 to 0.66 milli-Curies, with maximum exposure in the large intestine (0.78 rads).[59] The study is, of course, negative in the absence of heterotopic gastric mucosa.

The relatively high false-negative rate of the Meckel scan in bleeding diverticula has been a significant concern. Several recent summaries of the literature found that the Meckel scan had a sensitivity of only 60% to 84% in children, with a high false-negative predictive value, especially in anemic patients.[44,57,62,63] Repeating the scintiscan is sometimes recommended to decrease false-negatives, but some authors recommend proceeding straight to laparoscopy for both diagnosis and treatment.[44,57,62] False-negatives may be due to rapid dilution of the radiotracer from a high bleeding rate, poor blood supply to the diverticulum, or an inadequate amount of gastric mucosa. Meckel scans are even less accurate in the diagnosis of a bleeding diverticulum in adults, where the accuracy ranges from 15% to 50%.[64–67]

False-positives may be due to intestinal duplications with heterotopic gastric mucosa. Other causes include obstructed

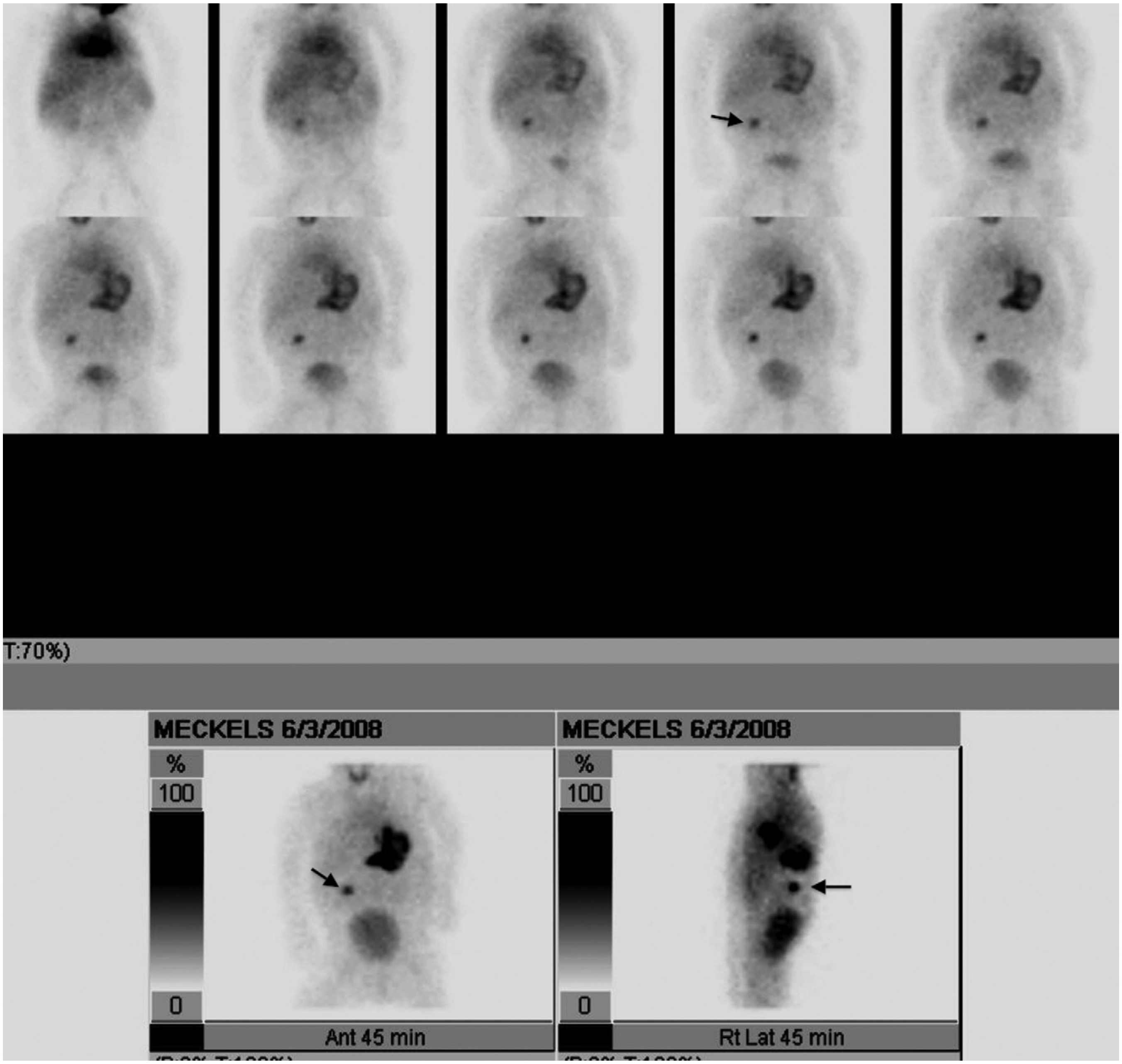


**FIGURE 84-5** Meckel scan. Technetium-99m pertechnetate selectivity concentrates in gastric mucosa whether in stomach or a Meckel diverticulum. It is excreted from the stomach into the duodenum and proximal small bowel. Isotope excreted in the urine collects in the bladder. Sites of isotope accumulation appear as dark areas on the scan. In this case, isotope outlines stomach, proximal intestine, Meckel diverticulum (*arrow*), and urinary bladder. (Photo courtesy Douglas Rivard, MD, Children's Mercy Hospital, Kansas City, Mo.)

loops of bowel, intussusception, inflammatory lesions, arteriovenous malformations, ulcers, and some bowel neoplasms.[39]

Angiography is usually negative unless the bleeding rate is greater than 0.5 mL/min. This study is rarely if ever indicated in the evaluation of a suspected Meckel diverticulum.

A recent review of children with a Meckel diverticulum found that the diagnosis was made by computed tomography (CT) scan findings (small bowel obstruction, intussusception, cystic mass) 2.3 times more commonly than via a Meckel scan.[68,69] This may reflect the type of complications (obstruction, inflammation) seen in the authors' patient population.

Wireless capsule endoscopy has been used to identify a Meckel diverticulum.[70,71] In one multicenter European study, the procedure was performed on 80 children (mean age approximately 6 years) with varying symptoms, and a Meckel diverticulum was identified in 2.

## BLEEDING

In patients who present with bleeding, the correct diagnosis is often made preoperatively; this is uncommonly the case with inflammatory or obstructive symptoms.[67] Meckel diverticulum accounts for nearly 50% of all lower gastrointestinal bleeding in children, usually occurring in infants and toddlers. The differential diagnosis includes intestinal polyps, inflammatory bowel disease, intestinal duplications, hemangiomas, and arteriovenous malformations.

The color of the stools is inconsistent with rectal bleeding and may be bright red (35%), maroon or dark red (40%), or less commonly, tarry (7%).[43] Younger children with bleeding often have anemia (Hgb < 8 g/dL) at presentation.[44] Many children will require transfusion, but life-threatening bleeding is uncommon. Episodic painless bleeding is the most common scenario. Unexplained isolated anemia is the sole presentation in a small fraction of children.

*Helicobacter pylori* is a gram-negative spiral bacterium responsible for most ulcers in the duodenum and stomach. However, it is rarely found in the heterotopic gastric mucosa of a Meckel diverticulum.[29,72–74] A recent analysis (via polymerase chain reaction) of 12 diverticula with heterotopic gastric mucosa demonstrated no *Helicobacter*.[74] Their literature survey of 375 patients noted a 7% incidence of *H. pylori* positivity. Bile, especially in an alkaline pH, causes inhibition of *H. pylori* growth and is the most commonly postulated mechanism for the absence of the bacterium in Meckel diverticula.[75]

## Obstruction

Meckel diverticula can cause a bowel obstruction via intussusception, volvulus, vitelline bands/remnants, incarcerated Littre hernia, and other mechanisms (Fig. 84-6). Intussusception is slightly more common in children, and volvulus in adults. Intussusception is a result of the diverticulum acting as a pathologic lead point. Pathologic lead points are infrequent in children with intussusception younger than the age of 2 years. In Harkin's classic review of 160 intussusceptions from Meckel diverticula, the mean age was 13 years; however, 60% were younger than 10 years of age. Overall, less than 3% of all intussusceptions are due to a diverticulum.[15]

Intussusception usually presents with vomiting, intermittent abdominal pain, bloody stools, a palpable lower abdominal mass, and eventual progression to dehydration and lethargy. Either ultrasound or pneumatic enema usually confirms the diagnosis of intussusception but rarely identifies the underlying cause. Complete reduction is usually unsuccessful when a pathologic lead point is present, and the diverticulum

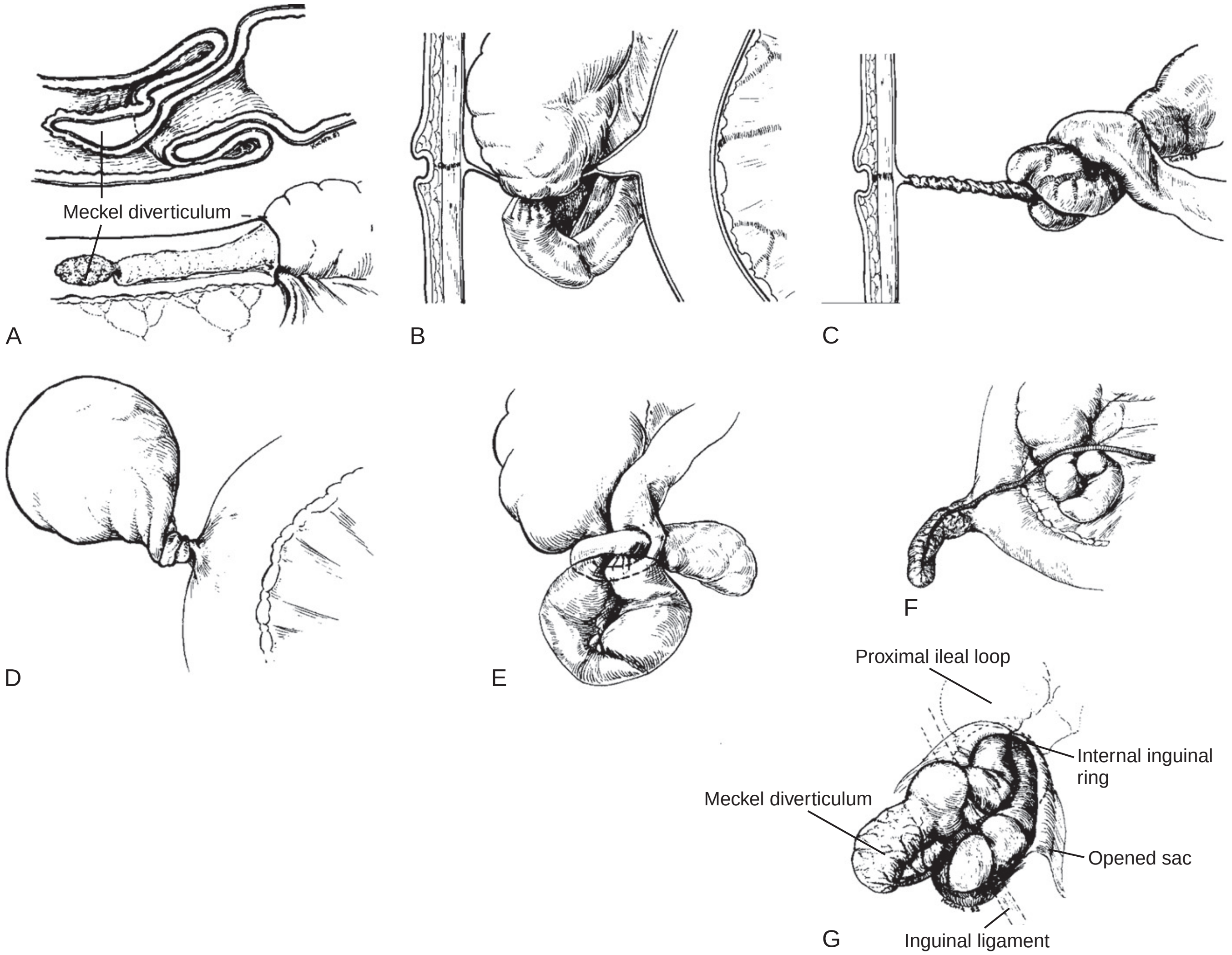


**FIGURE 84-6** Mechanisms of intestinal obstruction due to a Meckel diverticulum. Intussusception and volvulus are the most common. **A,** Intussusception with the diverticulum acting as a pathologic lead point. **B,** Loop of intestine "kinked" around a fibrous vitelline remnant. **C,** Volvulus around a fixed, tethered vitelline remnant attached to the abdominal wall. **D,** Volvulus of a diverticulum around its own base. **E,** "Self-knotting" Meckel diverticulum. **F,** Internal herniation of ileum under a mesodiverticular band/vessel. **G,** Littre hernia, illustrated here in an indirect inguinal location.

is often discovered unexpectedly during surgery or when the resected specimen is examined. Surgical management usually consists of resection of the obstructed bowel with end-to-end anastomosis.

Volvulus can result from an omphalodiverticular (from the tip of the diverticulum to the abdominal wall) fibrous or a vascular vitelline remnant, which provides a point of fixation for the bowel to twist around. A long diverticulum can even knot on itself, causing obstruction, or it may twist around its base. Giant Meckel diverticula or vitelline cysts may result in volvulus, usually in newborns (Fig. 84-7).[76,77]

Mesodiverticular vitelline remnants (from the mesentery to the tip of the diverticulum) can create an internal hernia under which small bowel becomes entrapped and strangulated. Adhesions due to an inflammatory process may also result in obstruction. A rare cause of obstruction secondary to Meckel diverticulum is an incarcerated Littre hernia.

Preoperative preparation consists of intravenous hydration, correction of electrolytic abnormalities, nasogastric decompression, and antibiotics. Resection of the diverticulum and involved bowel is the treatment of choice. Reanastomosis is usually possible.

## INFLAMMATION

Diverticular inflammation usually occurs in older children and is commonly misdiagnosed as appendicitis. A Meckel diverticulum was found to be the source of the symptoms in 0.76% of 8385 operations performed for presumed appendicitis.[28] A search for a Meckel diverticulum should be undertaken in children suspected of having appendicitis, but in whom the appendix is normal at operation.

Although inflammatory changes are usually due to the presence of gastric or pancreatic tissue in the diverticulum, other mechanisms include stasis of contents in the diverticulum (kinking, narrow neck), enterolith, foreign body, and parasitic or other infection. An obstructive pattern from adhesions or ileus may be the presenting feature, or perforation may occur. The correct preoperative diagnosis is uncommon in Meckel diverticulum with inflammatory complications. Occasionally a CT scan will show a midline mass with a normal appendix, suggesting the diagnosis (Fig. 84-8).

Inflammatory complications are treated by resection, either of the diverticulum alone or including the involved bowel. Primary reanastomosis is usually possible. On rare occasions, the child is so ill that exteriorization or a temporary stoma is necessary.

## NEOPLASIA

Overall, neoplasia is found in 0.5% to 4% of Meckel diverticula,[78–82] and malignant tumors predominate. Benign tumors include leiomyomas, lipomas, angiomas, and neurofibromas. A variety of malignancies have been reported (leiomyosarcoma, carcinoids, adenocarcinoma, villous adenoma, gastrointestinal stromal tumors, and others). Overall, carcinoid is the most common tumor arising in the diverticulum. More carcinoids occur in a Meckel diverticulum per centimeter than in any other area of the gastrointestinal tract (due to the small mucosal area).[83]

Neis and colleagues performed a comprehensive review of carcinoid tumors arising in a Meckel diverticulum.[84] There were 104 cases, with a mean age of 56.6 years and a male predominance; less than 5% of their patients were younger than 20 years of age. Approximately three fourths of the tumors were found at the tip of the diverticulum. Tumors larger than 5 mm were more likely to metastasize, but only 24% had metastasized at the time of diagnosis, with a significantly higher incidence of metastases in women. Slightly more than half were asymptomatic. The classic carcinoid syndrome was present in 8% at diagnosis.[84] Clinically, the biologic behavior of carcinoids in a Meckel diverticulum is closer to that of an ileal rather than an appendiceal carcinoid.[84,85] Excision of a segment of ileum and mesentery containing the diverticulum is recommended.

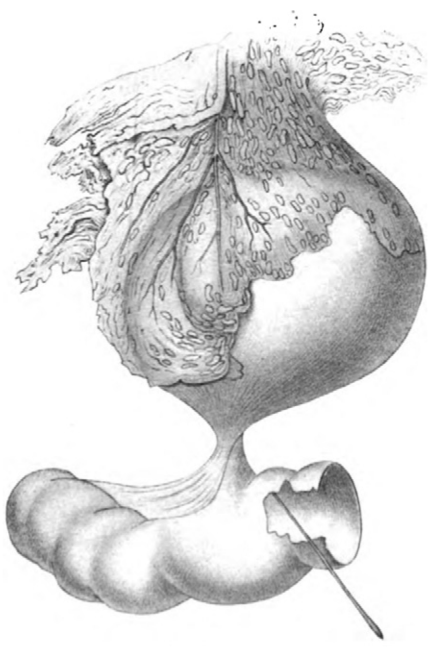

**FIGURE 84-7** Giant cystic Meckel diverticulum. These are rare; the largest reported was 56 cm in diameter. (From Cullen TS: Embryology, Anatomy, and Diseases of the Umbilicus. Philadelphia and London, WB Saunders, 1916.)

**FIGURE 84-8** Computed tomography scan in a 5-year-old boy with symptoms of appendicitis. The appendix (not shown) was normal, but a tubular edematous mass in the pelvis (*arrow*) suggested the diagnosis of Meckel diverticulum.

### OTHER

Enteroliths are a relatively uncommon occurrence in Meckel diverticula. However, in one large series, 10 of 84 patients (12%) had an enterolith.[86] The median age was 45 years, and all were symptomatic (most chronically). The mean stone diameter was 3 cm, and more than half had multiple stones. None had heterotopic mucosa. In another report of 1476 Meckel diverticula, 6% of those resected had an enterolith.[38]

Up to 8% of resected diverticula are due to a foreign body in adult series.[66] Fish and chicken bones, toothpicks, coins, and many other objects have been identified.[87,88] Even wireless video capsules have been lodged in a diverticulum.[89,90]

Parasitic infections in Meckel diverticula can occur, more commonly in underdeveloped countries. *Schistosomiasis mansoni, Ascaris* (roundworm), *Taenia saginata* (tapeworm), and others have been identified.[91,92]

A neonatal presentation of Meckel diverticula is quite unusual; most of the few reported cases have been of perforation or bowel obstruction in this age group.[93]

## Treatment

The treatment of a symptomatic Meckel diverticulum is resection. This can be done with open or laparoscopic techniques. There are several large series of laparoscopic or laparoscopically assisted Meckel diverticulectomies.[94] The procedure is often diagnostic and therapeutic, and some have argued forgoing the Meckel scan entirely because their algorithm for bleeding children with otherwise negative evaluations is to perform laparoscopy if a Meckel scan is positive and to do the same if the study is negative.[44,63,94] The diverticulum is often laparoscopically identified and grasped but removed extracorporeally, particularly if a segmental bowel resection is performed.

A Meckel diverticulum can be removed by either simple resection of the diverticulum and transverse closure across the base, or resection of a short segment of ileum containing the diverticulum with reanastomosis. In patients with bleeding or inflammatory symptoms, ulceration may be present on the mesenteric border or at the margin of the diverticulum, and resection of the ileal segment with the diverticulum is the safest option. The feeding (diverticular) artery should be clearly identified and ligated.

## Outcome

Most series report a short-term complication rate (wound infection, leak, bowel obstruction) after diverticulectomy of about 5% to 10%, lower (1% to 2%) for incidental resection.[31,38,51,65]

In the extensive meta-analysis of 244 articles in the literature since 1950, the historical mortality rate for resection of Meckel diverticula was 0.01% and the current mortality was 0.001%.[31]

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 85

# Intussusception

Paul M. Columbani and Stefan Scholz

## History

Intussusception was recognized as a disease in the late 1600s in Europe (Barbette, Peyer), but Hunter provided the first detailed description of intussusception in 1793.[1–3] Treatment of intussusception at that time included bleeding and quicksilver, to which Hunter added emetics followed by purgatives. Hand bellows to attempt pneumatic reduction per anus were possibly tried as early as Hippocrates' time.[4] In the early 1800s, the first documented descriptions of pneumatic reduction for intussusception appeared in the medical literature.[5] In 1864 the Scottish surgeon Greig[5,6] was the first to lay down strict criteria for the clinical diagnosis of intussusception. He claimed that he successfully reduced four of five actual pediatric intussusceptions with hand bellows: "Contrary to our expectations the air passed readily into the bowel and seemed to give the child great relief." Despite this report of success, there were many competing methods to treat intussusception (effervescent powder, cold water, hypertonic saline, long bougies per rectum, electricity, belladonna, opium). Most were not successful. As a result, the condition remained fatal in most infants and children.

Wilson (1831) reported the first successful operative reduction in an adult, and Hutchinson reported it in an infant 40 years later (1871).[7,8]

Any operative intervention in children at that time was quite hazardous. Treves (1885) reported a 73% mortality rate for his first 33 operative cases.[9,10] In 1876 Hirschsprung published the first of a series of reports on hydrostatic reduction with much decreased mortality (23%) than operation.[11] In the late 1800s various devices for hydrostatic or pneumatic reduction were developed. Forest (1886) calculated that 6 lb of pressure per square inch was acceptable for reduction,[12] and Mortimer (1891) discussed the danger of this new method.[13] Hydrostatic reduction gained wide acceptance as primary treatment around 1900, when both Clubbe and Peterson reported the successful resection of pediatric intussusception.[14,15] Despite Hirschsprung's much lower (23%) mortality rate (in 84 patients, 1905) for hydrostatic reduction, surgical treatment predominated.[5,16] As operative technique evolved, results improved.

In 1913 Ladd reported the use of diagnostic imaging with bismuth enemas and published the first photographs of roentgenologic pictures of an intussusception.[17] Ladd, however, saw this as a good diagnostic technique but did not recognize its therapeutic value. Fourteen years later (1927), Olsson and Pallin,[18] Poulquien,[19] and Retan[20] used hydrostatic reduction of intussusception with barium-guided fluoroscopy.

By this time, hydrostatic reduction was accepted as the preferred method in Australia, Scandinavia, and South America.[5] Hipsley in Australia (1926) published a series of 62 cases treated by hydrostatic saline enema with only 1 death.[21] Despite its inferior results, operation had become the primary method of choice in the United States. Attention only shifted to nonoperative reduction after Ravitch and McCune reported a surgical mortality of 32% in 1948.[22] Reduction via hydrostatic barium enema (BE) and fluoroscopy (contrast enema) was popularized by Ravitch and supported by both his laboratory research and clinical confirmation. In 1953 Gross, much like his predecessor Ladd,[17] acknowledged nonoperative treatment as possibly being effective but opposed it in favor of definite operative treatment.[23] By 1958, nonoperative reduction rates of up to 75% were achieved with a mortality rate close to zero.

Proponents of the hydrostatic method persisted in the United States, and eventually this technique became the primary, safest, and successful means of treating intussusception.

Radiologists began to report on clinical results. Fiorito and colleagues (1959) performed pneumatic reduction with air as the contrast medium.[24] Burke and Clarke (1977) used only ultrasonography (US) for screening, diagnosis, and monitoring the reduction of intussusception.[25] Guo and colleagues (1986) successfully tried delayed repeat enema reduction attempts.[26]

Today, operation is the accepted norm for failed radiologic-guided reduction of intussusception.

## Introduction

The word *intussusception* is derived from the Latin words *intus* (within) and *suscipere* (to receive).[27] Intussusception is the invagination of one part of the intestine into another (Fig. 85-1).

Three cylinders of intestinal wall are involved. The inner and middle cylinders are the invaginated bowel (intussusceptum), and the outer cylinder is the recipient of the invaginated bowel (intussuscipiens).[28]

Intussusception is one of the most frequent causes of acute bowel obstruction in infants and toddlers (Fig. 85-2). It is

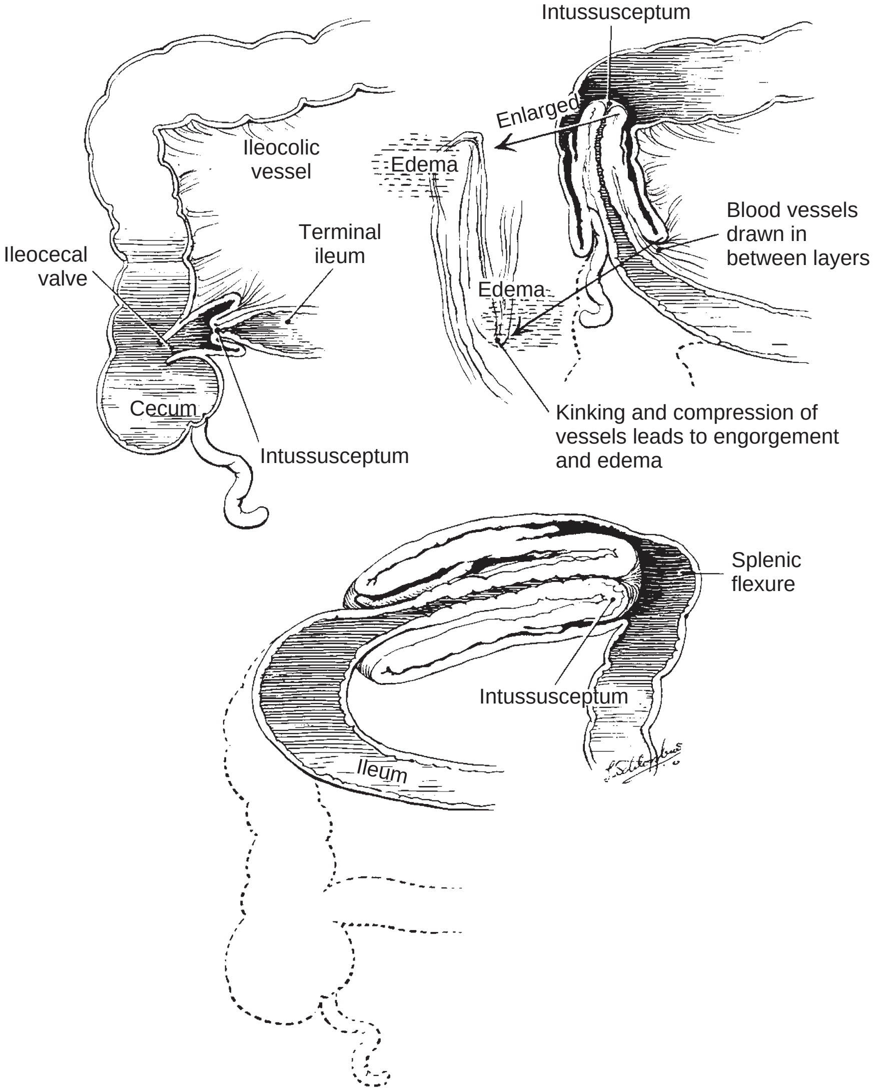


**FIGURE 85-1** Diagram of the most common (idiopathic, ileocolic) type of intussusception. As it develops in the terminal ileum with its prograde bowel peristalsis, the proximal invaginated bowel (intussusceptum) carries its mesentery into the recipient bowel (intussuscipiens) and the mesenteric vessels are angulated, squeezed, and compressed between the layers of the intussusceptum. This causes intense local edema of the intussusceptum, which produces venous compression, stasis, and congestion leading to an outpouring of mucus and blood from the engorged intussusceptum, often producing stool with the appearance of currant jelly. If this vicious cycle continues, ischemic changes will lead to bowel gangrene. The outermost layer of the intussusceptum becomes devitalized first, the innermost layer of the intussusceptum becomes gangrenous much later, and the outermost layer of bowel (intussuscipiens) loses its viability last. Most perforations, however, are located in the colon near the intussusceptum.

probably the second most common cause of acute abdominal pain in infants and preschool children after constipation.

In 1953 Gross stated: "There are few illnesses in which the clinical history and physical findings are more suggestive of the correct diagnosis."[23]

At present, diagnosis and treatment is a combined effort among the pediatrician, the pediatric radiologist, and the pediatric surgeon.

## Incidence and Demographics

Intussusception occurs throughout the world with an incidence of approximately 1 to 4 in 2000 infants and children.

Most series report more males than females with intussusception, usually at a 2:1 or 3:2 ratio (Fig. 85-3), which may be more evident (78% males) after 9 months of age than before (55%).[29,30] Intussusception is reported to occur in greater numbers in Caucasian infants and children.

Although intussusception can be seen in all pediatric ages from prenatal to the late teens (and in adults and animals as well), 75% of cases occur within the first 2 years of life and 90% in children within 3 years of age. More than 40% are seen between 3 and 9 months of age.[31]

In utero, intussusception may lead to intestinal atresia, most commonly ileal atresia.[32–35] Perinatal intussusception in newborns (0.3% of all intussusceptions) is more likely caused by a pathologic lead point like in older patients.[36–38] Sometimes, the disconnected end of the intussusceptum can be found in the distal part of the bowel.[39]

Intussusception has been reported in families and relatives (identical twins, sibling cases, as well as in fathers and sons), but their histories seem to indicate a common viral cause rather than a genetic cause.[15,40] No evidence points to an increased likelihood of intussusception in a sibling once one child of the family has been affected.

The frequency of intussusception displays a seasonal variation that usually correlates with viral infections (respiratory, gastrointestinal, or both), with most cases seen in May, June, and July.[15,29,41] The incidence of a preceding viral illness has been reported as high as 20%.[30,31,42]

Children with intussusception have been described as being generally healthy, sturdy, well developed, and well nourished, supporting Hirschsprung's classic statement: "I never saw a malnourished child with an intussusception."[16,43] Series from South Africa and Chicago[44,45] could not confirm this observation. Children with intussusception exhibited lower weight percentiles irrespective of socioeconomic status.

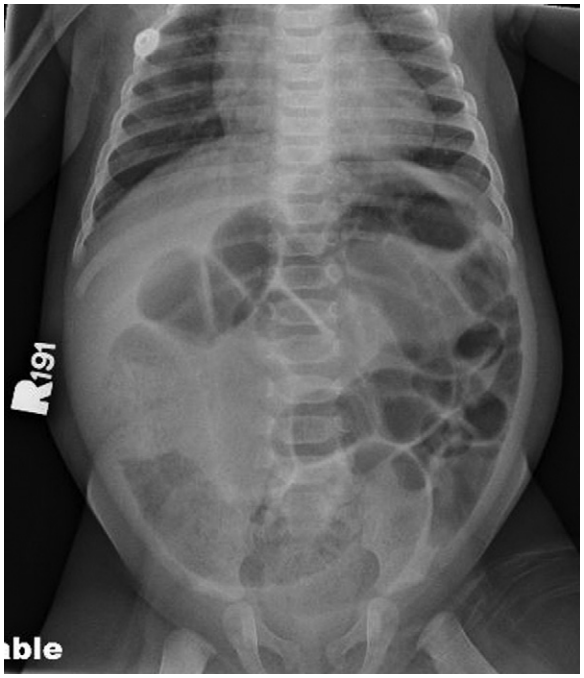


FIGURE 85-2 Radiologic picture of idiopathic intussusception in an infant.

## Pathophysiology

### PATHOLOGIC ANATOMY

Each intussusception has the following pathologic anatomy: as the intussusception develops with its prograde bowel peristalsis, the proximal invaginated bowel (intussusceptum) carries its mesentery into the distal recipient bowel (intussuscipiens). The mesenteric vessels are angulated, squeezed, and compressed between the layers of the intussusceptum. This causes intense local edema of the intussusceptum, which in turn produces venous compression, congestion, and stasis leading to an outpouring of mucus and blood from the engorged intussusceptum, the classic red currant jelly stool (Fig. 85-4). If this process continues unabated, bowel congestion and pressure increase and ultimately produce ischemic changes leading to bowel necrosis in the intussusceptum. In his classic experiments about intussusception, Ravitch[17] already noted in 1959 that the outermost layer of bowel containing the intussusceptum becomes devitalized first, the innermost layer of the intussusceptum becomes gangrenous much later, and the outer layer of the intussuscipiens rarely, if ever, loses its viability.

In most cases, ischemic necrosis needs more than 72 hours to develop.[46]

Karnak and colleagues[47] noticed a weakened longitudinal whitish line in resected intussusception bowel segments. Microscopically the authors found mucosal necrosis, disruption of the muscularis mucosa, and loss of some of its muscular tissue. This location on the antimesenteric border and under the taenia libera can be explained by local vascular compromise as a result of the distribution of the terminal arteries of the colon. After manual reduction, this area should be checked carefully for a longitudinal weakened pressure line. Recognition of such a potentially dangerous weak line on the bowel wall may be an indication for resection.

If the ischemic process goes undiagnosed, bowel obstruction, perforation, or sepsis leads to death within 5 days. In rare cases, the intussusceptum can become gangrenous, and slough and the bowel may fuse. No free perforation occurs, and the separated necrotic intussusceptum may pass out of the rectum.

### TYPES

Intussusception can be categorized into four main types: general, specific, anatomic, and other. (1) The two general types are permanent (fixed, 80%) and transient (spontaneous

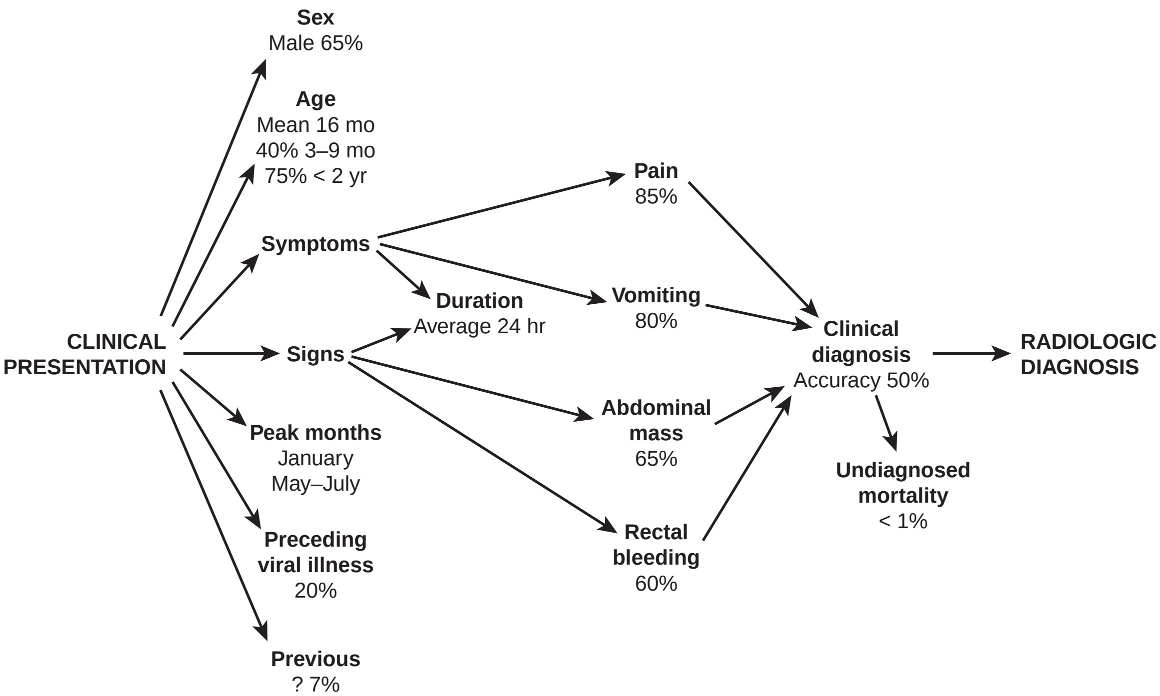


FIGURE 85-3 Algorithm detailing the clinical features and diagnosis of intussusception.

reduction, 20%); (2) the specific types can be described as idiopathic (no pathologic lead point [PLP], 95%), PLP (4%), and postoperative (1%); (3) when classified by anatomic types, their actual occurrence is ileocolic (85%); ileoileocolic (10%); appendicocolic, cecocolic, or colocolic (2.5%); jejunojejunal, ileoileal (2.5%); and those occurring around indwelling tubes; and (4) the fourth type is "other" (Fig. 85-5). Under this category are recurrent (5%) and neonatal (0.3%) intussusception.

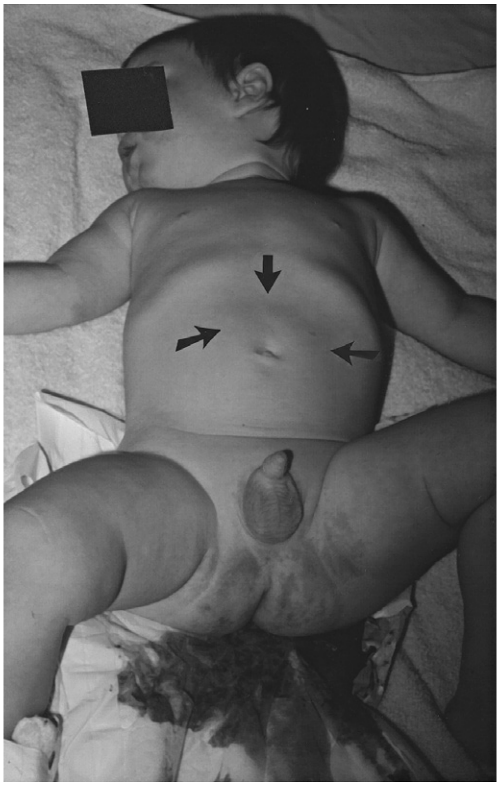

FIGURE 85-4 Pale, lethargic infant with intussusception and the classic currant jelly stool. The *arrows* point to the epigastric mass.

## General

***Permanent (Fixed)*** The vast majority (80%) of intussusceptions are fixed and permanent. They are mostly symptomatic (85%), and all require treatment.

***Transient (Spontaneous Reduction)*** Spontaneous reduction of an intussusception has been reported to occur in almost 20% of intussusceptions.[48,49] During laparotomy, it is a common observation that there are occasional small bowel intussusceptions of a few (<2) centimeters at different sites that spontaneously reduce. Most spontaneously reducing intussusceptions are incidentally seen on abdominal computed tomography (CT) or US performed for other reasons.[48–50] Transient intussusception may also be seen with gastroenteritis, probably because of hyperactivity of the inflamed bowel. Eighty-six percent of these transient intussusceptions involve only the small bowel and are noted in the central and left abdominal regions.[51] Most of these patients are asymptomatic.

Only 6% of symptomatic children with intussusception have gastrointestinal pathology serving as lead point.[48,52,53] The majority of patients with asymptomatic small bowel intussusception can be assumed to reduce and require only clinical observation. No additional imaging is necessary as long as the intussusception remains asymptomatic.

## Specific

***Idiopathic (No Pathologic Lead Point)*** All intussusceptions have some kind of a lead point. In contraindications to cases with pathologic lead points, thickened bowel wall lymphoid tissue (Peyer patches) functions as a lead point in

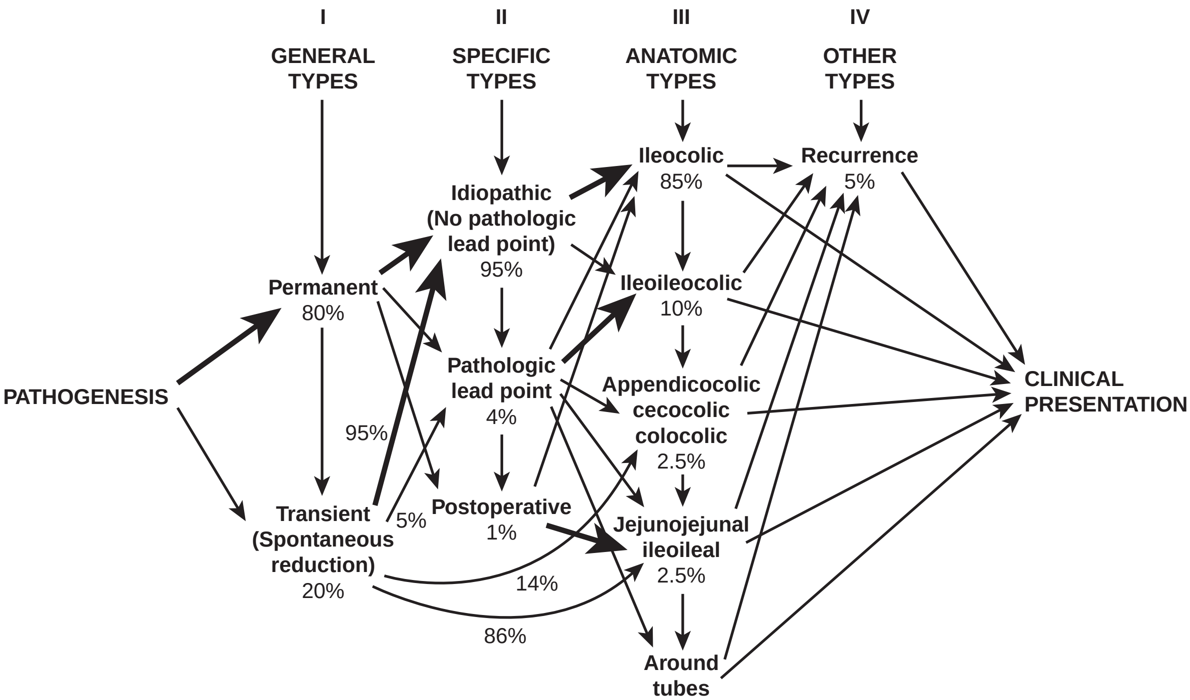


FIGURE 85-5 Algorithm of the pathogenesis of intussusception.

so-called idiopathic intussusception, which forms the majority of all cases (95%).

Infants and children have considerable masses of lymphoid tissue.[54] Peyer patches are usually located in the antimesenteric area of the bowel wall. In the distal ileum, Peyer patches involve the entire circumference of the bowel. With respiratory or gastrointestinal viral infection, the distal ileal wall lymphoid tissues and the nearby mesenteric lymph nodes may enlarge and form a lead point. However, in a mouse model, the Peyer patches did not appear to act as the anatomic lead point for intussusception.[55]

Both adenovirus[56,57] and rotavirus[58,59] infections have been associated with childhood intussusception. No doubt exists about the connection of adenovirus and intussusception.[60] Rotavirus as cause for intussusception has been extensively debated in the literature. Recent large reviews from several countries could not establish an association between rotavirus infection and intussusception.[58,60–63]

In July 1999 the U.S. Food and Drug Administration suspended the tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV, RotaShield) for a strong association between vaccination with RotaShield and intussusception among otherwise healthy infants.[64]

In 2006 the World Health Organization (WHO) recommended two live oral rotavirus vaccines, RotaTeq (RV5) and Rotarix (RV1), for inclusion into the national immunization programs of countries worldwide.[65] The two new rotavirus vaccines underwent large clinical trials of more than 60,000 infants each to assess safety with regard to intussusception. In 2009 the WHO's Global Advisory Committee on Vaccine Safety recommended its use in children younger than 15 weeks, citing no increased risk for intussusception. Especially in countries with high childhood mortality due to diarrheal illnesses, the benefits of rotavirus vaccination exceed the possibly increased risk of intussusception.

Dietary factors have also been shown to influence the incidence of intussusception. Malnourished children are considered to have a lower risk of intussusception because of less prominent intestinal lymphoid tissue, which may be less suitable to act as a lead point. Johnson and colleagues[66] found that the risk of intussusception among U.S. infants varied on the basis of their feeding patterns. Using breast milk as the reference group, infants who consumed soy milk–based formula had a much lower risk, and infants who consumed cow's milk formula had an increased risk for intussusception.

***Pathologic Lead Point*** The incidence of intussusception caused by a PLP in an infant or child ranges from 1.5% to 12%.[48,67] It increases with age from about 5% in the first year to 44% within the first 5 years of life and 60% in 5- to 14-year-olds. PLPs can be found in 4% of infants and children who have one recurrent intussusception and in up to 19% with multiple recurrences.

The most common focal cause of a PLP is an inverted Meckel diverticulum[68–70] followed by intestinal polyps[71] and duplications (Fig. 85-6).[72] Other less common focal PLPs that have been reported are periappendicitis; appendiceal stump; inversion appendectomy[73]; appendiceal mucocele; local suture line; massive local lymphoid hyperplasia; ectopic pancreas; abdominal trauma; benign tumors (adenoma, leiomyoma, carcinoid, neurofibroma, hemangioma); and malignant tumors (lymphoma, sarcoma, leukemia).[48,74]

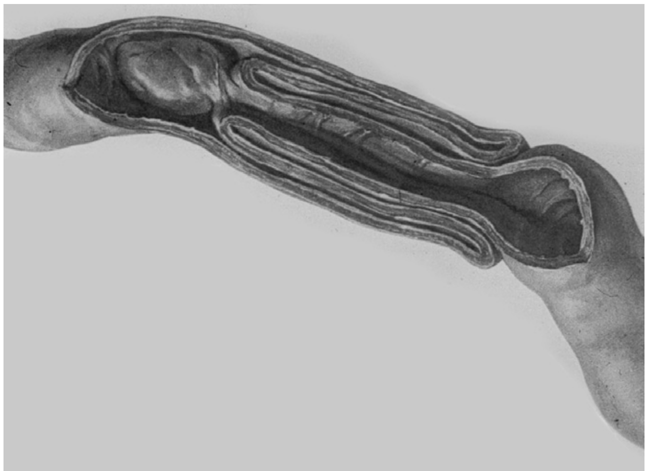

**FIGURE 85-6** Small bowel intussusception caused by a polyp as pathologic lead point.

Other intestinal processes that cause multifocal bowel wall thickening or affect bowel motility include Henoch-Schönlein purpura,[75] cystic fibrosis,[76] celiac disease, disordered coagulation, hemophilia, neutropenic colitis, Hirschsprung enterocolitis, Peutz-Jeghers syndrome, and familial polyposis.[77]

Intussusception caused by a PLP remains a diagnostic challenge[78,79] and has to be differentiated from the more common idiopathic ileocolic intussusception. Most commonly, signs and symptoms are similar but, manifestations can vary and are often nonspecific because of the wide spectrum of lesions or intestinal abnormalities.[48,80]

In 35% of all PLP cases the intussusception is caused by thickened bowel wall, abnormal motility, impaction of secretions, or the presence of multiple polyps. Other important risk factors are ileoileocolic intussusception, an older child, the association of a long duration of symptoms with weight loss, and recurrent intussusception.

Most PLPs manifest as ileoileocolic intussusceptions (40% of all ileoileocolic), with a smaller percentage being jejunojejunal, ileoileal, ileocolic, appendicocolic, cecocolic, and colocolic intussusceptions.

The risk of missing a malignant small bowel tumor is relatively low according to the literature.[81,82] Lymphomas quite commonly present as intussusceptions (17.5%) but are picked up on either US or contrast enema.

No clinical pattern of recurrence is predictive of a PLP, and imaging plays the major role in detection of a PLP. The vast majority of infants and children with recurrent intussusception will not have a PLP. PLP is present in about 5% of patients with one recurrence, as opposed to up to 19% of children with multiple recurrent episodes.[48,83]

Most intussusceptions caused by PLP can be reduced by enema techniques.[84–86] US and reduction enema are the cornerstones of diagnosis of lead points.[87] US is heavily operator dependent, and results vary in different institutions. Diagnosis of 74% of all focal PLPs, 40% of diffuse PLPs, and diagnosis of the exact type of PLP in 32% has been reported. US is most successful for diagnosing a duplication cyst or lymphoma as PLP but less for a Meckel diverticulum.[48]

Other imaging modalities such as CT are of limited value to diagnose PLP.[88,89] Upper contrast studies of the small and

large bowel and colonoscopy may be of value if a polyp is suspected despite negative US results.[90,91]

In suspicious cases, an initially negative US study should never exclude a second repeat US.

***Postoperative*** Postoperative intussusception manifests as a small bowel obstruction (SBO). It is the third most common intussusception (1%) and found most often in the small bowel after prolonged laparotomy with significant bowel handling.[92–96] Typically, there is no lead point present. The risk for SBO after pediatric laparotomy is about 5% (with 80% occurring within the first 2 years after laparotomy). Three to ten percent of those are caused by postoperative intussusceptions.[92,97] They often occur after retroperitoneal dissection (Wilms tumor, neuroblastoma) or an extensive bowel procedure (abdominoperineal pull-through, the Ladd procedure, manual reduction of intussusception).[48,98,99] Recently, several cases of postoperative intussusception were reported after pancreatic surgery.[100]

Postoperative intussusception has been reported after operation outside the abdomen.[67] Abnormal peristalsis from abnormal serum electrolytes, anesthesia, drugs, and neurogenic factors has been implicated.

The key to the diagnosis of a "true" postoperative intussusception is to remember that it can occur, especially after a major laparotomy, and presents as early postoperative obstruction.

Abdominal US is diagnostic, and enema reduction is indicated in case of rare ileocolic intussusception. In all other cases, an operation is required. Further postoperative recurrence is exceedingly rare.[95]

### Anatomic

The most common type of intussusception is ileocolic (85%) (Fig. 85-7). The second most common type (10%) is ileoileocolic and often characterized by complete bowel obstruction. The ileoileal portion invaginates into the cecum and colon and is more difficult to reduce. About 40% are found to have a PLP as its underlying cause.[48]

Appendicocolic, cecocolic, and colocolic intussusceptions are much less common (2.5%) and are usually associated with PLPs.

FIGURE 85-7 Ileocolic intussusception. The hand is milking the most distal intussusceptum retrograde. Note the forceps on the appendix and the pneumatosis of the cecal wall.

Jejunojejunal and ileoileal intussusceptions occur infrequently (2.5%) and usually have a PLP, except when they occur as a postoperative intussusception.

***Around Tubes*** Intussusception is a common complication of the use of indwelling gastrojejunostomy tubes with a reported incidence of 16%.[101–103] Catheters with a distal pigtail appear to have a higher risk and typically cause antegrade jejunal intussusceptions, either along or at the end of the gastrojejunostomy tube. These patients usually present with high SBO and bilious vomiting but without abdominal pain or cramps. Incidental detection in an asymptomatic child is common, and the only treatment may be clinical monitoring.

The diagnosis is often incidentally made on US or CT scan. Removal or conversion to a gastrostomy or nasogastric tube will cure the problem. Many of these intussusceptions are also transient and undergo spontaneous reduction, which suggests that their actual prevalence is probably underestimated. Rarely, there is need for a surgical procedure.[104]

Retrograde jejunoduodenogastric intussusceptions[105–107] occur when gastrostomy tubes migrate through the pylorus by gastric peristalsis.

They develop painlessly in a child with a functioning feeding tube (with the feedings going in distally) and cause high SBO accompanied by bile vomiting without any evidence of the feeding. An operation may be required.

An unusual intussusception is antegrade or retrograde jejunogastric intussusception through a gastroenterostomy causing gastric outlet obstruction. This intussusception almost always requires operative reduction and revision.

### Other

***Recurrent*** Reported recurrence rates range from 8% to 15% following barium enema reduction, 5.2% to 20% following sonography-guided hydrostatic enema reduction, 5.4% to 15.4% following fluoroscopy-guided air enema reduction, and 6.25% to 7% after sonography-guided air enema.[108] Recurrence rates, age and sex distribution, pattern of recurrences (including number of and interval between recurrences), reducibility, documentation of pathologic lead points, operative findings, and long-term follow-up were similar.[109] Recurrence rates are lower after manual operative reduction (3% to 4%) and operative resection and anastomosis of an intussusception (0%).[110]

Most recurrences occur within the first few days after the initial reduction, some within hours. About 70% of children have only one recurrence, but up to eight recurrences have been reported in children without lead points.

Lin and colleagues[111] used intramuscular dexamethasone as premedication before air enema to decrease lymphoid hyperplasia and the rate of early recurrence. The steroid group had only one recurrence in 6 months in 122 children, whereas the control group had 8 in 117 children.

Recurrent intussusceptions have a high reducibility rate (100% for initial recurrence and 95% for multiple recurrences). Perforations are rare.[108] The time between onset of symptoms and arrival in the hospital is shorter because of the awareness of the parents. The earlier the diagnosis, the greater is the chance for successful reduction. Recurrent intussusceptions may be looser and easier to reduce but also have a greater chance of repeat recurrence.

Earlier reports recommended operative reduction in children with one or two recurrences.[112] Reasons were operative exclusion of a PLP (particularly malignancy such as lymphoma) and the reduced recurrence rate after operative intervention.

The presence of a pathologic lead point should always be considered (4% in children with one recurrence and 14% with multiple recurrences), but most children with recurrence will not have one.[48]

Because of the high reduction rate of recurrences, the low perforation rate (<1%), and the favorable long-term follow-up, it is generally recommended that image-guided reduction be undertaken for any and all recurrent intussusceptions.

Operation should only be used for irreducible recurrences after unsuccessful delayed repeat enema attempts, perforation from the enema, clinical evidence to suggest a PLP, or documentation of a PLP by US or enema.

***Neonatal*** Intussusception in neonates is infrequent (0.3% of all cases) and more likely is caused by a pathologic lead point.[36,37] Signs and symptoms resemble those seen in necrotizing enterocolitis such as abdominal distension (17/17), bilious gastric aspirates (13/17), bloody stools (10/17), and rarely a palpable abdominal mass (5/17).[113] Difficulties in establishing the correct diagnosis led to a delay of 7 to 10 days between the onset of symptoms and abdominal surgery, increasing the risk of developing a compromised bowel.[37,114,115] Sometimes, the disconnected end of the intussusceptum can be found in the distal part of the bowel.[39]

Diagnostic features are signs of SBO on the abdominal radiographs. An early diagnosis may be achieved with a high index of suspicion and the use of ultrasound scan. Contrast enema has limited diagnostic and therapeutic capability.

These cases carry a mortality of around 20% in neonates, largely because of sepsis and the delay in diagnosis. If diagnosed in time, it can be treated successfully with resection and primary anastomosis.

## Clinical Findings and Physical Examination

Intussusception should be suspected with any of the two classic symptoms (abdominal pain or vomiting) or two classic signs (abdominal mass or rectal bleeding) (see Fig. 85-3).[30] Most cases are diagnosed within 24 hours of the onset of symptoms. In case of recurrent intussusception the diagnosis is often easier and made in less than 8 hours.[116]

A high level of suspicion is necessary in any infant or toddler with a history of crampy abdominal pain. One, two, or three of the other classic signs or symptoms are often present to help make the diagnosis. All four classic signs and symptoms can only be found late in the disease process and in less than 30% of cases.[117] In about 20% of patients, diarrhea precedes other symptoms and may lead to incorrect diagnosis and triage.

The sudden onset of severe, colicky, intermittent abdominal pain, which makes infants pull up their legs, is the most common classic symptom of pediatric intussusception in about 85% of patients. This pain episode typically lasts only a few minutes. Afterwards, the infant is often quiet, pale, and sweaty and then returns to normal activity for a while. The absence of pain, however, does not rule out intussusception but may delay the diagnosis. It is important to know that about 15% of infants and children present without any obvious pain.[117] These children are often pale and listless and appear quite ill. Infants present more often with vomiting than older children do (up to 45%). Bilious vomiting tends to be found in delayed cases of intussusception with SBO.[15,39,46]

The two classic signs, abdominal mass and rectal bleeding, can be found with about the same frequency (see Fig. 85-4). The often curved, sausage-shaped abdominal mass can be palpated in the right upper quadrant of the abdomen about 65% of the time and usually extends to the left along the transverse colon.[30] The mass may be slightly tender and may be appreciated only when the patient is lying quietly between attacks of pain. Sometimes the mass can be visually appreciated during clinical inspection. The right lower quadrant may be flat or empty, a finding known as the Dance sign.[23] Occasionally, the intussusception passes quite far distally and can be palpated on rectal examination (5%). Prolapse of the intussusceptum out the rectum may be a grave sign and can be mistaken for a rectal prolapse.[15] The longer the symptoms of intussusception persist, the higher the likelihood of occult or gross rectal bleeding. Rectal bleeding is usually the last sign to occur. The blood has a mucus-like texture and, classically, a currant jelly appearance. It is most alarming to parents and physicians. If there has been a delay in seeking medical care before this event, it usually gets the patient to the hospital quickly.

If the delay in diagnosis allows bowel ischemia to occur, fever, tachycardia, and hypotension can be signs of bacteremia and bowel perforation. Rapid diagnosis and emergent operation are essential to prevent a fatal outcome.

## Diagnosis

### LABORATORY STUDIES

No specific laboratory studies aid in the diagnosis of intussusception. As the intussuscepted bowel becomes ischemic, associated leucocytosis, acidosis, and electrolyte abnormalities worsen.

## Radiologic Diagnostic Evaluation

The correct diagnosis of intussusception can only be made clinically about 50% of the time. The diagnostic evaluation relies on radiologic imaging to either confirm or make the correct diagnosis.[118]

### PLAIN RADIOGRAPH OF THE ABDOMEN

The role of abdominal radiographs in pediatric patients with suspected intussusception remains controversial.[78] It was routinely used for the diagnosis or exclusion of intussusception by 73% of the radiologists in a 1999 survey of members of the European Society of Pediatric Radiology.[119]

Few published studies have evaluated the accuracy of this modality in this clinical setting. In two series, intussusception could only be correctly identified on plain radiographs in up to 50% of cases.[120,121]

The abdominal radiograph can confidently exclude intussusception if the bowel is filled with gas throughout or the colon is completely outlined with stool. These findings could also be defined by US or fluoroscopy at the start of the contrast enema. Supine, upright, or cross-table lateral radiographs are often not helpful because their interpretation can be variable and false negatives occur much more frequently than false positives.[122,123]

Characteristic signs of intussusception on a plain radiograph are meniscus sign and target sign.[78] Nonspecific radiographic findings such as a right-sided soft tissue mass combined with an absence of cecal gas are easier to detect (Fig. 85-8). In half of children younger than 5 years, the sigmoid colon filled with gas and stool occupies the right lower quadrant and may be misinterpreted as the cecum.[124] In one report, exclusion of intussusception in three view radiographs of the abdomen was only successful in 25% of patients.[125] These views are obtained to detect air-fluid levels and free air. Air-fluid levels are nonspecific for intussusception, and free air has not been reported in untreated intussusception and perforation before enema reduction.[78] In rare cases the intussusception itself can be clearly visualized on abdominal radiograph (Fig. 85-9).

In most infants and children with suspected intussusception, the abdominal radiograph may be safely omitted. In unclear or delayed cases with concerning physical examination and higher incidence of nonviable bowel, the plain abdominal radiograph may be obtained.[126]

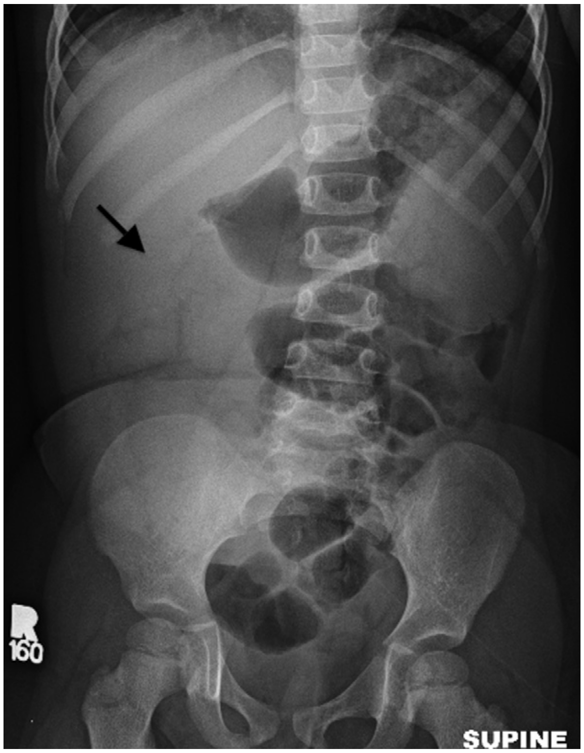


**FIGURE 85-8** Plain radiograph of the abdomen with nonspecific findings suggestive of a right-sided soft tissue mass (*arrow*) combined with an absence of cecal gas.


**FIGURE 85-9** Radiographic finding of ileocolic intussusception seen in Figure 85-7. Note the severe pneumatosis. This patient was later diagnosed with cytomegalovirus colitis likely acting as a lead point.

## ULTRASONOGRAPHY

In the hands of an experienced examiner, ultrasound can have 100% accuracy for the diagnosis of intussusception.[79,127,128] The major advantage of ultrasound for detection of intussusception is that it is portable, noninvasive, and without radiation. With the use of modern high-resolution transducers, the diagnosis of intussusception is straightforward. The characteristic finding is a 3- to 5-cm diameter mass, the typical target or doughnut sign, which is usually found just deep to the anterior abdominal wall on the right side (Figs. 85-10 and 85-11).[80] The viability of the bowel can be evaluated by Duplex ultrasound (Fig. 85-12).


**FIGURE 85-10** Ultrasonography showing intussusception on cross section in the right lower quadrant just deep to the anterior abdominal wall (target or doughnut sign).

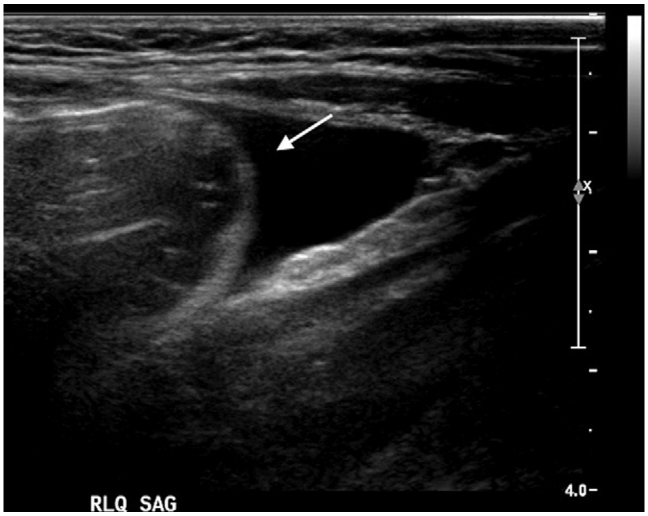


FIGURE 85-11 Ultrasonography showing tip of intussusception (*arrow*) in longitudinal plane just deep to the anterior abdominal wall.

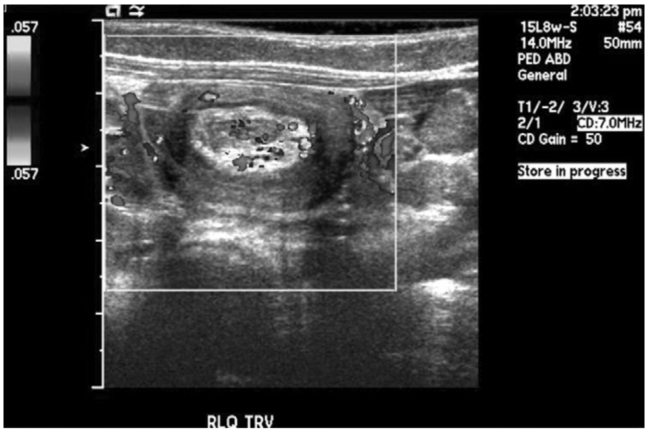


FIGURE 85-12 Duplex ultrasonography showing the target sign of an intussusception and confirming viability of the intussusceptum.

In addition, ultrasound can detect a possible pathologic lead point with higher frequency (66%) than contrast (40%) or air enema (11%).[129]

The role of abdominal ultrasound is not limited to diagnosis or exclusion of intussusception. Other abdominal disease processes such as urinary tract pathology, ovarian torsion, appendicitis, or small bowel volvulus can be detected.[130]

Others oppose the use of ultrasound.[131] The author argues that, if positive, it leads to a second study, the therapeutic enema, and increased health care costs since the US could have been avoided. If negative, the study was likely lengthy and an intussusception may have been missed. If clinical symptoms are very suspicious, a diagnostic contrast enema should be performed.

Ultrasound cannot predict well if the intussusception is already necrotic or amendable to nonoperative reduction and should therefore not preclude reduction by enema. Warning signs of necrosis or possibly unsuccessful enema reduction include, most importantly, the absence of blood flow in the intussusception on Doppler interrogation, a thick peripheral hypoechoic rim, free intraperitoneal fluid, fluid trapped within the intussusceptum, enlarged lymph nodes dragged with the mesentery into the intussusception, or a pathologic lead point.[132]

### COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Most institutions do not routinely use CT and magnetic resonance imaging (MRI) to evaluate intussusception. Intussusception may be found incidentally on imaging performed for another suspected diagnosis.[133] The characteristic finding is a target or doughnut sign. Possible pathologic causes for the intussusception such as lymphoma or masses may be revealed.[88]

Ko and colleagues[89] developed a protocol to detect ileoileal intussusception using immediate CT scanning if the initial abdominal US was suspicious (target sign with a diameter $\leq$ 3 cm and/or atypical location in the left abdomen or at the umbilicus). They were able to avoid unnecessary reduction enemas and facilitate faster operative intervention.

Short transient small bowel intussusceptions can often be seen on CT or MRI and are usually not clinically significant. Repeat imaging usually shows resolution of intussusception.[52,134]

### CONTRAST ENEMA

Before ultrasound became widely available in the mid 1980s, barium contrast study of the colon (BE) was considered the gold standard to diagnose or exclude intussusception. In some institutions it is still the preferred diagnostic modality. It is well known to all radiologists, quick, and considered the most cost-effective method with an accuracy of 100%.[127,135] If positive, the diagnostic procedure may become therapeutic. In addition, an experienced ultrasonographer may not be available during off hours.

In the European survey of pediatric radiologists from 1999, the contrast enema was used as the initial tool for diagnosis by 34% of the respondents.[119]

The clear disadvantages of contrast enema are that it is an invasive procedure and requires radiation. More than 50% of diagnostic contrast enemas in children with suspected intussusception turn out to be negative.[79] In this case, ultrasound is a better modality to diagnose other acute abdominal problems that mimic intussusception.[127,130]

## Treatment

Treatment of an infant or child with an intussusception must start in the emergency department, and the surgeon should be involved from the initial presentation.[136,137] When the clinical history confirms the suspicion of intussusception, the surgeon must evaluate the patient for peritonitis or shock on physical examination to rule out the rare need for emergent operation. It is paramount to promptly fluid resuscitate the patient. If the patient suffers from recurrent vomiting, a nasogastric tube is placed.

A broad-spectrum antibiotic should be given as for any other situation in which the vascular supply of the bowel may be jeopardized, and bowel surgery is a possibility. The patient's blood is cross-matched in case a transfusion is necessary.

While all of this is being done, preparations should be made for radiologic confirmation of the diagnosis, followed by the necessary treatment. The operating room should be notified so that if the nonoperative management is unsuccessful, the patient can go from the radiology suite directly to the operating room.

The treatment options are simple: medical (under occasional and specific situations), radiologic reduction or operative reduction, resection, closure of an enema perforation, or excision of a PLP by laparotomy or laparoscopy.

Currently, virtually all hemodynamically stable infants and children with the absence of peritoneal signs of perforation receive an attempt at nonoperative reduction with water-soluble contrast or pneumatic reduction with air, regardless of the length of the history.[137,138]

## NONOPERATIVE MANAGEMENT

### Medical

In a stable patient, intussusception caused by diffuse thickened bowel wall acting as a pathologic lead point can sometimes be treated with steroids before, along with, and/or after radiologic reduction attempts. Three cases of successfully treated lymphoid hyperplasia[139,140] and three of seven cases of Henoch-Schönlein purpura (HSP) have been reported.[141] The mechanism by which steroid treatment affects lymphoid hyperplasia remains unclear. If steroid treatment is initiated with the intussusception still unreduced, the patient must be observed closely. As Sönmez and colleagues[141] stated: "Conservative therapy is feasible for HSP patients with small bowel intussusception as long as the time of onset is known, an ultrasonographic and x-ray diagnosis is confirmed, emergency operating facilities are available, and an experienced pediatric surgical team follows up the patients."

Most patients with HSP have gastrointestinal symptoms, which are initially treated medically.[142,143] Laparotomy performed for life-threatening complications has to be performed in up to 22% of cases.[144] Intussusception is the most common surgical complication of HSP in childhood, occurring in 0.7% to 13.6% of patients. It is uncommon in children younger than the age of 3. The sites of intussusception are most frequently ileoileal (51%), then ileocolic (39%), and rarely jejunojejunal (7%). There have been only four reported cases of colocolic intussusception.[145] The predominance of small bowel involvement is due to the pathologic lead point being intramural hemorrhage and edema in that area of intestine. Only the ileocolic intussusceptions are amenable to enema reduction attempts.[146] If the ileoileal type does not reduce spontaneously over 24 hours, surgical intervention is probably required.

## RADIOLOGIC REDUCTION

It is important to carefully differentiate those patients who are suitable candidates for attempted image-guided enema reduction from those who will require immediate operative management. Contraindications to attempted enema reduction include clinical evidence of dehydration, shock, peritonitis, or radiographic evidence of perforation with free air. Dehydration should be corrected early, and only then can an enema be performed safely. Immediate operative management is indicated in those patients with peritonitis or free air.

Several factors such as younger age (<6 months), rectal bleeding, radiographic signs of intestinal obstruction, or longer duration of signs and symptoms (>72 hours) have been found in some series to decrease the success rate of reduction.[108] However, successful reduction can be achieved in the presence of any of these factors, and therefore none of them preclude an attempted enema reduction if the patient is well hydrated and clinically stable (Fig. 85-13).

The approach varies from one treatment center to another and in different parts of the world. In the developed world, intussusception is diagnosed early in the vast majority of pediatric patients and medical care provided in timely fashion. Two recent series from Australia and the United States quote the rate of attempted initial enema reductions with 97%[59] and 78%.[147]

Two recent studies reviewed their data for predictors of success of reduction enema and its importance to avoid complications.[148–150] Their conclusion was that hydrostatic or pneumatic enema should be attempted in all children without peritonitis. Predicting the outcome is not crucial because of the high success rate and low complication rate.

In contrast, operative management remains the usual primary treatment in much of the developing world, as has been described in recent reports from Nigeria[151] and Kenya.[152]

In these areas of the world, access to radiographic equipment may be limited. Infants and children have a significantly longer

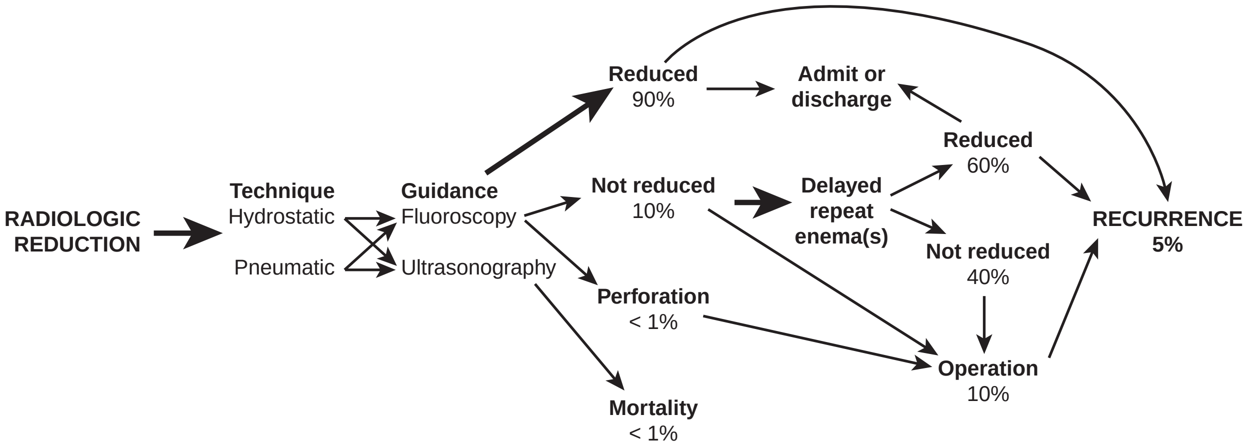


FIGURE 85-13 Algorithm for radiologic reduction of intussusception.

duration of symptoms and signs, an increased incidence of nonviable bowel, and a mortality rate up to 20%.[108,153]

Meier and colleagues[126] suggested that the use of nonoperative enema reduction would not significantly improve the high mortality rate. However, Abantanga and colleagues from Kenya[154] recently reported their use of on-table air reduction under general anesthesia in the operating room in all patients with intussusception without peritonitis (50% of patients). Their success rate was 60% without mortality. The authors' conclusion was that on-table air enema reduction is possible, practical, and reliable in patients without peritonitis and must be tried first before laparotomy, especially in countries with limited resources.

Currently used techniques for nonoperative reduction of intussusception include pneumatic or hydrostatic pressure enemas under fluoroscopy or US.[155] One must be cautious when attempting to make comparisons among the various series, even when they use an apparently similar technique. Reduction rates vary considerably depending on the patient population, the exclusion criteria for enema reduction, and the lack of standardized techniques used by radiologists.

Surveys of pediatric radiology departments in North America[156] and Europe[119] showed that management of intussusception varied greatly with a trend to pneumatic reduction techniques with greater use of ultrasound. Some pediatric radiologists combined fluoroscopy and sonography to a hybrid approach (18%).[119]

The clear advantage of US is that it avoids radiation exposure and provides more information than fluoroscopic techniques do. It has high accuracy and reliability for monitoring the reduction process, visualizes all components of the intussusception, including the postreduction edematous ileocecal valve, and can more easily recognize pathologic lead points. The main disadvantage of US is the need for a radiologist who is comfortable using US for reduction guidance. There is less experience with pneumatic reduction under US guidance, especially recognizing a perforation when using either hydrostatic or pneumatic reduction techniques.[137]

There has been no large, controlled, prospective study comparing the various techniques. Several relatively small series have compared the results of hydrostatic and pneumatic reduction under fluoroscopic control. Most have shown higher reduction rates with the pneumatic techniques.[157–159] Several series have achieved equally high reduction rates using hydrostatic or pneumatic reduction under sonographic guidance.[160–162]

On the basis of these success rates published in the recent literature, one should aim to achieve reduction rates of at least 80% and even as high as 95%.[108,137,162]

In conclusion, successful reductions can be achieved whether one chooses to use the hydrostatic or pneumatic reduction technique under fluoroscopic or sonographic guidance. The choice of technique used will depend largely on the experience, personal preference, and expertise of the radiologist involved, as well as on the local conditions in a particular institution and the type of patient population seen.

### Pneumatic Air Enema

The air enema technique is well described in the literature.[59] The enema tip should be placed within the child's rectum and taped securely in place. The child is placed in a prone position to allow the radiologist or assistant to squeeze the buttocks closed and prevent air from leaking. Air is rapidly insufflated into the colon under fluoroscopic observation. Once the intussusception is encountered, reduction is followed fluoroscopically until it is completely reduced (Fig. 85-14). Air should flow freely from the cecum into the distal small bowel loops to signify complete reduction (Fig. 85-15). One critical safety issue is to keep air pressure below a maximum limit of 120 mm Hg to avoid the risk of perforation.[163,164]

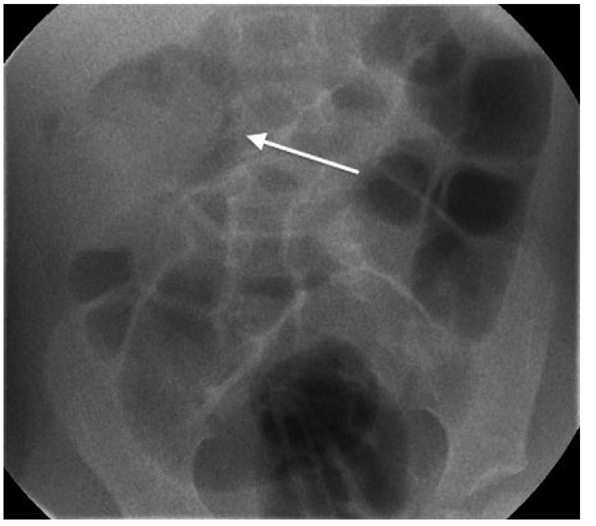

**FIGURE 85-14** Air enema showing the head of the intussusceptum (*arrow*).

The pneumatic reduction technique under fluoroscopy has gained wide acceptance because of several advantages over hydrostatic reduction: it is easy to perform and can be done quickly, is less messy, delivers less radiation exposure, is more comfortable, and results in smaller perforations and less peritoneal contamination.[163] Disadvantages of this technique are the passage of air into the terminal ileum without complete reduction of the ileocolic intussusception[165,166] and a possible tension pneumoperitoneum should a rare perforation occur.

**FIGURE 85-15** Successful reduction of the intussusception by air enema confirmed by sudden reflux of air into the ileum.

### Hydrostatic Barium Enema

Although the air enema may be preferred in experienced hands, the liquid enema is simple, safe, and effective, and most radiologists have experience with its use.[108,162,167] Ultrasound for monitoring of hydrostatic reduction is relatively easy to use and the imaging modality of choice in many centers.[162,168,169]

The disadvantages are that it is messy to use and perforation may occur with larger colonic tears, increased peritoneal contamination, and rapid fluid shifts with hypertonic water-soluble agents.[170,171] Barium is no longer the liquid contrast medium of choice due to the risk of barium peritonitis, infection, and adhesions when perforation occurs during the enema.

The "rule of threes" (three attempts, each of 3 minutes' duration and with enema bags 3 feet above the table) used by many radiologists to guide the liquid enema technique is supported by limited evidence.

Hydrostatic reduction may occur rapidly or stubbornly slowly. There is usually a pause when the barium column meets the intussusception (Fig. 85-16). Typically, the rounded barium column suddenly becomes concave and forms a meniscus around the head of the intussusception. When the intussusception is displaced, the meniscus flattens out.

Because the intussusceptum fits more loosely in the larger-caliber intussuscipiens, barium seeps between the two and produces the characteristic radiologic appearance of a coiled spring. Filling of the cecum is often slow, and it may become quite distended for a while before the sudden rush of barium into the distal ileum indicative of reduction.

If the ileum does not fill freely for several feet (not inches), one should not assume that the reduction is complete (Fig. 85-17).

This process may have to be repeated if the liquid contrast agent leaks out of the rectum or if the tube becomes dislodged or plugged. Once the reduction is successful, the infant or child is relieved of the pain and usually falls asleep.

### Methods to Improve Reduction Rates

Some authors have advocated practices that they believe may improve the rate of enema reduction.

FIGURE 85-16 Hydrostatic contrast enema showing intussusception in the left transverse colon. Note the concave meniscus the contrast forms around the head of the intussusceptum.

***Medications*** Some irreducible intussusceptions are already found reduced after initiation of general anesthesia in the operating room. Either they reduced spontaneously or, more likely, reduction was induced by the sedation and muscle relaxation from general anesthesia.

Smooth muscle relaxants such as glucagon have been tried to improve results of intussusception reduction, with indefinite and variable results.[172–174]

Some hospitals always use sedation for radiologic reduction of intussusception and claim improved results.[175] One third of European pediatric radiologists use sedation for reduction in a 1999 survey.[119] The use of sedation may reduce the intra-abdominal pressure children create by the Valsalva maneuver and therefore reduce success rates.[138]

FIGURE 85-17 Hydrostatic contrast enema showing incomplete reduction of intussusception with only a trickle of contrast into the terminal ileum (*left*). Note the complete reduction with flooding of the terminal ileum with contrast on the right.

Overall, little evidence supports the use of glucagon or sedation in reducing intussusception, and neither is routinely used in most institutions.[137,176]

***Transabdominal Manipulation*** Grasso and colleagues[177] found that transabdominal manipulation improved their reduction rate with air enema from 58% to 76%. The true benefit may be difficult to evaluate because higher rates of reduction than those reported in Grasso's series have been achieved without manipulation. On the other hand, this technique may be more widely used than reported in the literature.[108]

***Delayed Repeat Enema*** In the past it was considered standard practice that immediate operative intervention was required for all patients, in which the intussusception was irreducible by enema techniques. In the operating room about 10% of intussusceptions were found to be already reduced, and another 40% were easily reduced manually.[30] The conclusion was that surgical intervention could possibly have been avoided in half the cases if radiologists used a different or more aggressive approach to their enema technique.

With this rationale, an operation would then be required only for cases that are difficult to reduce manually or have necrotic intussusceptions, enema perforations, or pathologic lead points.

The earliest reports describing the use of delayed repeat enema before proceeding to the operating room were published in the 1980s.[26,178] The time intervals and number of repeat reduction attempts were variable in different studies and ranged between minutes and days and up to three attempts.[179–181] Success rates between 50% and 84% have been reported.[59] Some authors perform delayed attempts only under general anesthesia.[108]

Although delayed repeat enema without anesthesia has only recently received more attention in the literature, it had been used successfully in Toronto institutions for years.[108,182–184]

It has yet to be defined what the optimal time delay between attempted enemas should be and how many attempts should be made. This should probably be tailored to the individual patient and the experience of the radiologist on a case-by-case basis.

Given the initial high success rate of current radiologic enema techniques (close to 90% in some institutions), the need to rely on repeat, delayed enema attempts is only applicable to a minority of children. Therefore the deferral of surgical intervention can be carefully considered in any infant who remains clinically stable, with no evidence of peritonitis and only if the initial enema manages to move the intussusception, achieving at least a partial reduction.[182] Partial reduction and the time interval between attempts may allow the venous congestion and the edema of the bowel wall to decrease, thus facilitating the reduction of the residual, less congested intussusception in a repeated, delayed attempt. Contraindications to a delayed, repeat reduction attempt include failure to move the intussusception at all when it is first encountered at the initial enema or if the patient becomes unstable.

Close cooperation between experienced pediatric radiologists and surgeons and careful clinical monitoring of the patient are essential requirements for this approach. The risks may outweigh the benefits unless staff and equipment are available to observe these patients meticulously between reduction attempts. Widespread acceptance of this approach may require documentation of its success in larger series of children.

### Postreduction Care

After successful enema reduction, the infant or child should be observed closely for at least a few hours, depending on the general condition of the patient.

If the intussusception was recognized early and the enema reduction was relatively easy, the child can be discharged home from the emergency department. Prerequisites are that the parents are reliable and the patient is asymptomatic and tolerates fluids for a short period after the reduction.[185,186] Whitehouse and colleagues[187] reviewing 309 patients with intussusception at Children's Hospital of Wisconsin found that it was safe to discharge 48 (26%) out of 186 patients managed nonoperatively with enema reduction directly from the ED. Recurrence rates did not differ between children observed as inpatients and those discharged home, and there were no missed pathologic lead points.

Most patients, even those with a successful enema reduction, are admitted to a pediatric general surgical unit for observation and further treatment.

If the enema reduction is successful, the child can be started on clear fluids and progressed to a regular diet as tolerated. Intravenous fluids can be decreased and discontinued accordingly. If the patient initially had SBO with vomiting and required insertion of a nasogastric tube, it may take a number of hours for the obstructed small bowel to decompress. It may be preferable to leave the nasogastric tube in place overnight or maintain the child non per os with an intravenous infusion.

The preoperative gram-negative and anaerobic bacterial coverage does not need to be continued unless the patient was febrile before or after reduction and the reduction was difficult.

The presence of fever usually indicates bacteremia, endotoxemia, cytokine (tumor necrosis factor, interleukin) and lysozyme release, and even the production of reactive lymphocytes, in which case antibiotics may be continued for 48 hours.[188–190] In addition, bacterial translocation (the old theory of transmural migration of bacteria) may in part account for the common high fever that accompanies reduction.[191] Animal studies have shown that even when viable intussusceptions are reduced operatively under sterile conditions and tissue for culture is taken from the apparently intact serosal surface, pathogenic bacteria are frequently recovered.[17]

On the other hand, Somekh and colleagues[188] performed serial blood cultures before attempted air enema reduction, immediately after, and 1 hour later to assess the risk for bacteremia. Their results showed that although fever may develop after air enema reduction attempts, the risk for clinically significant bacteremia and sepsis was extremely low.

At discharge, the parents should be aware of the relatively high recurrence rate after an enema reduction.[108,109] Recurrence rates as high as 20% have been described in the literature with an average of about 10%.

A repeat abdominal US study should be performed if any doubt remains about the success of the enema reduction or the abdominal pain recurs.[192] If the intussusception recurs, the enema process can be repeated. After any successful

enema reduction, the ileocecal valve often remains edematous and thickened for a day or more.[108] This appearance can easily be differentiated from a recurrence because it lacks the typical concentric rings. The invaginated mesentery is smaller than the typical target sign of a true intussusception and will disappear with time.[193] The ileocecal thickening can also be appreciated as a filling defect or narrowing if a contrast enema is performed. Recognition of these signs is important when attempting to confirm complete reduction and also to differentiate postreduction edema from pathologic lead point or recurrent intussusception.

Postreduction US[192] becomes essential in the following difficult situations: to confirm the reduction by air enema when the intussusception disappears but there is minimal or no passage of air into the distal end of the small bowel, to delineate an unreduced ileocolic or ileoileal component of an ileoileocolic intussusception even if there is a large amount of air in the large and small bowel,[194] and to rule out a pathologic lead point. If US shows only enlarged mesenteric lymph nodes, marked bowel wall thickening, and hyperemia (on Doppler evaluation), there may be an ongoing inflammatory process (bacterial enteritis with *Yersinia* or *Clostridium*) that originally caused the intussusception.[195,196]

Sonography is an important tool to reevaluate a previous partial reduction and to exclude spontaneous reduction before attempting delayed repeat enema reduction.

## OPERATIVE MANAGEMENT

Operation becomes necessary when radiographic reduction is contraindicated, has failed or is incomplete, peritonitis or pneumoperitoneum is detected, or a pathologic lead point is found (Fig. 85-18). The decision to start laparoscopically or perform immediate laparotomy is decided by the surgeon on a case-to-case basis.

After initiation of fluid resuscitation and application of preoperative broad-spectrum antibiotics, the patient is taken to the operating room and placed in a supine position. Under general anesthesia, the stomach is decompressed with a nasogastric tube. Now, the abdominal mass can generally be palpated, and its position may influence the incision of the surgeon.

### Laparoscopy

Initially, laparoscopy was only used to confirm either a successful radiologic reduction[197] or the correct diagnosis of intussusception before reduction per laparotomy.[198]

Recent studies have reported successful laparoscopic reduction of intussusception in more than 60% of patients.[199–201] A French retrospective study from 2008 including 69 patients from seven centers reported a conversion rate of 31.9% (16% for unsuccessful laparoscopic reduction). The risk for conversion to open surgery was higher with longer duration of symptoms (3.1 vs. 1.6 days in laparoscopic group) and the presence of a pathologic lead point (50% vs. 17%).[202] It was concluded that the optimal candidate for laparoscopic reduction is the child seen early after onset of symptoms (<36 hours) without signs of peritonitis.

A recent retrospective study published in 2009 reviewed 22 patients (average age, 2.9 years) over 10 years whose intussusception could not be radiographically reduced.[203] Twenty patients (91%) could be safely managed laparoscopically or with a small extension of the umbilical incision. Ten patients (46%) had a bowel resection, and nine patients had a pathologic lead point (four with Meckel diverticula, five with lymphoid hyperplasia). The average length of stay was only 2.67 days (median, 2 days). The authors concluded that laparoscopy is a reasonable approach to pediatric intussusception, even when bowel resection becomes necessary.

Most described laparoscopic techniques use three ports (one on the umbilicus and two on the left side of the abdomen). Using atraumatic graspers, gentle pressure is applied distal to the intussusceptum. In difference to the open method, traction must often be applied proximal to the intussuscipiens to succeed with reduction. After reduction, the bowel must be carefully inspected for injury, necrosis, or perforation.

Particular attention, however, must be paid to search for a pathologic lead point because most tactile cues are lost. Postoperative intussusception, adhesions, and obstruction may be reduced with less bowel handling and retraction.

### Laparotomy

The standard incision in infants is a fairly small right-sided transverse incision above or below the umbilicus.

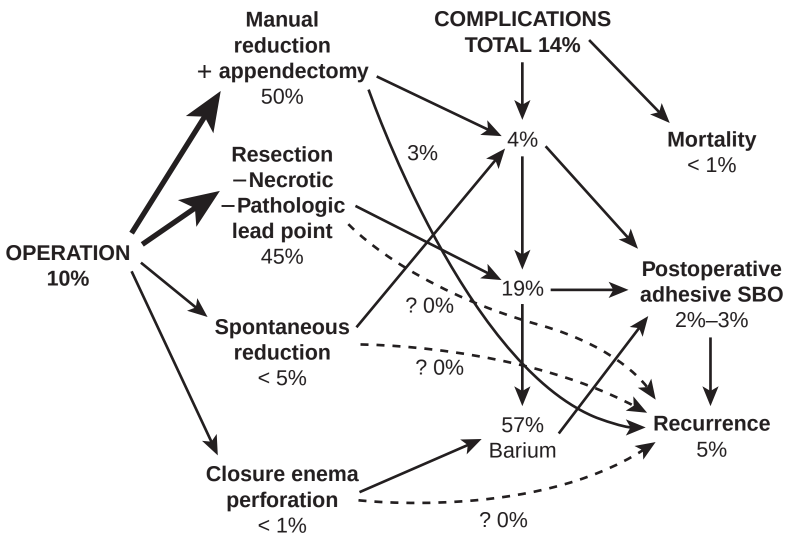


**FIGURE 85-18** Algorithm for surgical intervention for intussusception.

The more distal the intussusception, the more difficult it is to reduce. The cecum in an infant is usually poorly fixed, allowing delivery of most intussusceptions through the incision. If the incision is located lower on the right side resembling an appendectomy incision, the appendix should be removed. Some surgeons remove the appendix after reduction of the intussusception to create local adhesions to decrease the likelihood of recurrence. If serosanguineous peritoneal fluid is encountered on entering the abdomen, bowel necrosis must be suspected.

The key to successful manual reduction is slow constant pinching and squeezing of the most distal part of the intussusceptum, just like squeezing a tube of toothpaste (Fig. 85-19). The intussusceptum is milked in retrograde fashion out of its surrounding intestinal trap. To aid with the reduction, the intussusceptum is gently and slowly pulled out of the intussuscipiens. It is essential to perform both, the retrograde milking and the gentle pulling, slowly and steadily to increase the intraluminal pressure just like the enema does (Fig. 85-20). It should be performed without interruption until the reduction is completed.

The index finger can be used to gently create a wider space between intussuscipiens and intussusceptum (modified Hutchinson maneuver).[204]

The experience of the surgeon plays a significant role in manual reduction. Small serosal tears during reduction are acceptable and can be repaired if necessary. They are warning signs for impending perforation caused by undue pressure. As long as there is progress with the reduction, the operator may press on. If progress stalls during manual reduction and serosal injuries occur, the decision should be made to resect the irreducible intussusception.

In case of ileoileocolic intussusception, the ileocolic component is reduced first and then the remaining ileoileal.

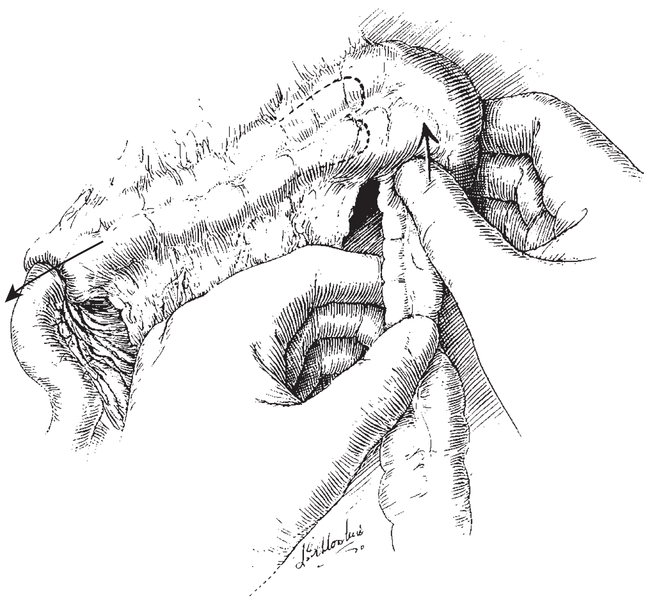

**FIGURE 85-19** The key to successful manual reduction of an intussusception is slow constant squeezing (like a tube of toothpaste) or retrograde milking of the most distal intussusceptum. This can be aided by the assistant gently and slowly pulling the intussusceptum out of the intussuscipiens.

**FIGURE 85-20** Ileocolic intussusception incompletely reduced. Note the partially reduced, congested, but viable terminal ileum.

After successful reduction, the previously intussuscepted bowel may look quite congested, bruised, and possibly not vital (Fig. 85-21). The leading edge of the intussusceptum may look particularly ischemic. In almost all cases the bowel will become pink and vital after application of warm saline towels for less than 10 minutes.

The concept that it is impossible to reduce necrotic bowel anywhere in a pediatric patient may not be always true. In an early study from 1971, Ein and Stephens reported they were able to reduce 50% of all nonviable intussusceptions before resection.[30] After successful manual reduction, a limited bowel resection for ischemia instead of an en mass right hemicolectomy may be performed. Too forceful manipulation of the bowel, however, may cause perforation and contamination. If there is any doubt about the viability of the bowel after reduction, it should be resected. It is rarely feasible to resect or invert a small area of suspected necrosis.

In most patients, a primary end-to-end anastomosis can be fashioned after the ischemic bowel is resected. If the infant is in critical condition or unstable, the ischemic bowel can be quickly resected and both bowel ends exteriorized as temporary stomas.

Perforations during enema reduction usually occur early during the procedure before the intussusception is reduced.[108]

**FIGURE 85-21** Ileoileocolic intussusception after manual reduction. Note the congested and bruised terminal ileum with several serosal tears.

Most will have necrotic bowel. About 50%, however, may be manually reduced in the operating room and require less resection of bowel length.[30] If this is not possible, the intussusception should be resected en mass.

When a perforation is caused, hydrostatic fluid enemas usually result in large colon tears. Hypertonic water-soluble contrast rapidly sequesters fluid into the peritoneal cavity and thereby increases fecal contamination. For radiographic reduction of intussusception, barium is no longer recommended. Colonic perforation with barium causes significant intra-abdominal morbidity and may leave the permanent radiologic picture of a snowstorm (Fig. 85-22).[170,171]

In contrast, perforation after air enema usually leads to a small hole in the colon and much less peritoneal contamination. The free air can easily be recognized during fluoroscopy. Immediately after perforation on the fluoroscopy table, a tension pneumoperitoneum leading to rapid decompensation of the child may occur. Urgent needle decompression may become necessary to stabilize the patient (best done in the midline above the umbilicus with an 18-gauge needle).[205] The enema must be immediately discontinued and the rectum decompressed with the enema tube.

After successful reduction of the intussusception, a pathologic lead point must be manually excluded and, if found, resected. A Meckel diverticulum or ileal polyp is commonly found after ileoileocolonic intussusception.[147,206]

# Complications

## RADIOLOGIC

Bowel perforation is the major complication during enema reduction.[108] Perforation with various techniques is extremely uncommon and quoted less than 1% in most series.[46,207–209]

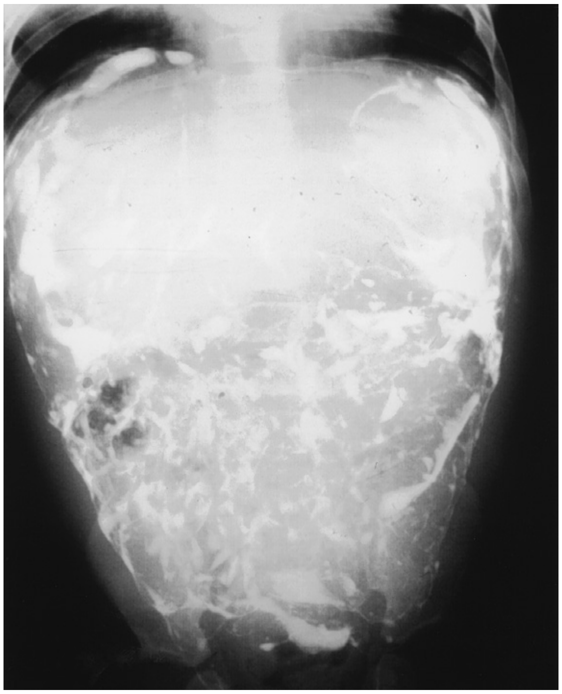

FIGURE 85-22 Postoperative radiograph after perforation caused by hydrostatic barium enema. This snowstorm picture lasts for life.

Perforation rates are comparable with saline or air enema and are rather related to the amount of pressure delivered.

Most perforations occur in the outer intussuscipiens and in the absence of necrosis.[46] Technical factors may play a role such as using too high pressures or too rapid pressure changes. Performing the enema more slowly and keeping the pressure as low as possible may diminish the risk for perforation.

Risk factors for perforation are infants younger than 6 months and a longer duration of symptoms (>36 hours).[210,211] Perforations have been described with low pressures such as 60 mm Hg, suggesting that the perforation was possibly present before enema reduction but covered by the intussuscepted bowel. Partial reduction then uncovered the existing perforation. This may explain why free air is rarely found on plain radiographs in intussusception.[46,209,210]

## SURGICAL

Complications after laparotomy and laparoscopy for intussusception include common postoperative problems such as wound infection, fascial dehiscence, and SBO. Reported complications rates are lower (4%) when no enterotomy or bowel resection had to be performed (26%).[30] The risk of postoperative adhesive SBO after operation for nonperforated intussusception compares with the rate for any pediatric laparotomy. Most cases (80%) occur within the first 2 years.[212] Bowel obstructions caused by stricture after uneventful manual operative reduction of intussusception have been reported.[213] Postoperative complication rates for perforation after barium enema can reach above 50%.

## RECURRENCE

Recurrent intussusception can occur in up to 20% of the cases (average in published series 5%). Most intussusceptions recur within 6 months of the original episode with one third within the first 24 hours.[109,112,214] They are less likely after surgical reduction or resection, and usually there is no lead point.

Parents are more aware of symptoms of recurrent intussusception, which are usually subtle, and present earlier to the hospital. Enema reduction for recurrence is as successful as for the initial episode.

Multiple recurrences can occur in the same child and should prompt a search for a pathologic lead point such as an occult malignancy. The recommended imaging modality is US.[108] Operative exploration is indicated when the ultrasound suggests a pathologic lead point, the reduction enema was unsuccessful, or clinical symptoms persist postreduction.[109]

# Results and Outcome

## CLINICAL

Pediatric intussusception often presents with a wide range of nonspecific symptoms, which can make it challenging to diagnose clinically. The four classic symptoms of pain, emesis, and bloody stools with or without a mass are together present in less than 25% of children. A high index of suspicion is necessary in many cases. It is not surprising that the accuracy of clinical diagnosis is about 50%. Radiographic studies, however, such as abdominal ultrasound and contrast enema

approach 100% accuracy.[137,215] The clinical outcome after treatment of pediatric intussusception continues to be good.

Major improvements over the past 20 years have been made in the success of nonoperative treatment with an average reduction rate of 74% in stable patients.[108] Success rates well above 90% with hydrostatic or pneumatic reduction have been reported, depending on the part of the world.[39] Others report successful initial reduction in 46% and only 36% when symptoms lasted more than 24 hours.[108] Delayed repeat enemas are used to reduce up to 82% of the initial treatment failures.[59,155]

A small number of pediatric patients with intussusception will have to go to the operating room. Reasons for this include an unstable or stable patient with suspected ischemic bowel and peritonitis, unsuccessful enema reduction, suspected pathologic lead point, or, rarely, perforation after pressure enema (<1%). A small number of intussusceptions self-reduced under general anesthesia.[155]

Recurrence occurs in up to 20% of cases.[108,109] Most recur after pressure enema reduction, a small minority after operative manual reduction with or without appendectomy and virtually none after bowel resection.

Most children with recurrence have only one episode (68%), mostly within the first few days after their initial event. About 32% have multiple recurrences that occur as isolated episodes over days, weeks, or years.[108]

The reduction rate for recurrent intussusceptions is higher (95%), possibly because the diagnosis is made earlier by the parents.[109] After recovery, infants and children with intussusception have a normal long-term outcome.

### MORTALITY

Mortalities associated with pediatric intussusception have seen a steady decline. The current overall mortality rate in the pediatric population in developed countries is low (<1%).[216] It is less than 1% for radiologic reduction and less than 1% for surgical intervention.[39]

In 1953 Gross noted that the mortality rate in Boston fell from 59% in 1922 to 2.7% in 1947.[23] His observation remains true to this day: “The interval between onset of symptoms and institution of treatment is of paramount importance and the mortality rates will more nearly approach zero the more frequently treatment is instituted within 24 hours of onset.”

However, deaths continue to be reported occasionally. Stringer and colleagues[77,217] reviewed mortalities after childhood intussusception in England and Wales from the 1980s (overall < 1%) and identified preventable factors in more than 60% of cases. Contributing factors included delay in diagnosis, inadequate intravenous fluid resuscitation and antibiotic therapy, delay in recognizing recurrent or residual intussusception after nonsurgical reduction, and surgical complications.

One of the most recent reviews from the U.S. monitoring trends in intussusception-associated hospitalizations and deaths among U.S. infants until 1997 stated that intussusception-associated infant mortality rates declined from 6.4 per 1 million live births in 1979 to 1981 to 2.3 during 1985 to 1997.[216] Infants whose mothers were younger than 20 years, nonwhite, unmarried, and with an education level below grade 12 were at risk for intussusception-associated death. The authors concluded: “Although intussusception-associated infant deaths in the United States have declined substantially over the past 2 decades, some deaths seem to be related to reduced access to, or delays in seeking, health care and are potentially preventable.”

In a report from 2007, Kaiser and colleagues[147] looked at all 244 children with intussusception admitted to Riley Hospital for Children in Indianapolis from 1990 to 2004. The authors attributed the two deaths (mortality 0.8%) to the delay in diagnosis. Both children presented to the hospital in critical condition and died within 24 hours.

Byard and Simpson[218] reported two intussusception-related deaths at Women’s and Children’s Hospital in Adelaide, Australia, under more than 200 patients between 1975 and 1995. Both infants (5 and 6 months of age) did not appear particularly sick with only nonspecific symptoms until rapid deterioration occurred.[218] A study from Royal Children’s Hospital in Melbourne, Australia, reviewing the 232 patients admitted with intussusception from 1995 to 2001 had no mortality.[59]

In the developing world, intussusception is a common surgical problem with mortality rates as high as 20%.[126] Most infants present later than 3 days after the start of symptoms to medical facilities and even later to a surgeon. Radiologic reduction is often unavailable or not feasible. Recently, tertiary care hospitals in Africa have reduced their mortality rates through increased awareness and education of first-line health care providers and parents. Bode[219] from the University Hospital in Lagos, Nigeria, reported a mortality of 12.1% in 174 consecutive children between 1995 and 2001. At the University of Nigeria Teaching Hospital in Enugu, the routine treatment for intussusception was surgical between 1995 and 2006.[151] Of 71 patients treated, 6 died of sepsis (mortality 8.5%). Kuremu quotes a mortality of 14% after surgical treatment at Moi University in Eldoret, Kenya.[152] Ameh from Zaria, Nigeria, reported 8% mortality rate after operative manual reduction. However, in patients in whom manual reduction was unsuccessful, all six of nine children who underwent right hemicolectomy died from postoperative complications.[220,221] Four of five children (80%) who presented with transanal protrusion of intussusception died. The median onset of symptoms in this group was 21 days (between 6 and 28 days).[222]

Reduction enema has been used successfully in the developing world. Abundanga and colleagues[153] from the tertiary care teaching hospital in Kumasi, Ghana, treated half of their 44 patients with US-confirmed intussusception with air enema reduction in the operation room under general anesthesia. They were successful in 60% of cases and had no mortality.

## Future

Intussusception will continue to occur in children with predominantly gastrointestinal viruses and pathologic lead points. US, not only for diagnosis but also during pneumatic or hydrostatic enema reductions, will play a larger role in the future, predominantly due to evidence of adverse impacts of medical radiation on small children.[223–225] US screening in children with abdominal pain will be routinely performed by pediatric emergency department physicians or pediatric surgeons, therefore reducing the time delay to

diagnosis and treatment.[226–228] Enema reduction rates will increase past 90% as radiologists become more familiar with improved reduction techniques such as pneumatic or delayed enemas, and institutions will aspire to the new standard of care. In the operating room, minimally invasive techniques will be more broadly used by well-trained pediatric surgeons.

## Summary

Intussusception is a common cause of abdominal pain and gastrointestinal obstruction in infants and children. Ninety percent of cases occur between the ages of 3 months and 3 years. A careful history is the mainstay of diagnosis. The classic symptoms of abdominal pain or vomiting and the two classic signs of abdominal mass or rectal bleeding are present in 85% of patients. A high index of suspicion must be maintained for atypical cases, such as the 15% whose intussusception is painless. Abdominal US is the primary adjunct to clinical diagnosis. Idiopathic intussusception is ileocolic in 95% of cases and optimally managed by hydrostatic or pneumatic enema reduction. If these nonoperative methods fail, manual reduction and/or resection in the operating room is performed. If radiographic imaging such as US or contrast enema detects a pathologic lead point, the patient should be taken to the operating room for resection. Delay in diagnosis is the primary avoidable factor that contributes to morbidity and mortality. The mortality rate has steadily declined during the past century to less than 1% in developed nations.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 86

# Disorders of Intestinal Rotation and Fixation

Melvin S. Dassinger and Samuel D. Smith

## History

Information on the failure of rotation and fixation of the intestinal tract has accumulated slowly. Before 1900, only individual cases found at surgery or autopsy were described; these reports could not be placed in context until the embryology was understood.

The first meaningful description of the embryology was written in 1898 by Mall,[1] professor of anatomy at Johns Hopkins University, who had studied in Germany with His, the celebrated embryologist. On the basis of his own studies of reconstructed embryos, as well as those of His, Mall described the process of rotation and then fixation of the bowel. Fraser and Robbins[2] expanded Mall's observations with their own studies of a large group of embryos.

In 1923 Dott[3] published his classic paper on the embryology and surgical aspects of anomalies of intestinal rotation. This was the first clear correlation between clinical and embryologic observations. Dott correlated the findings in 2 of his own cases and 40 collected from the literature with various failures of development. Most subsequent articles described clinical cases in relation to Dott's analysis of the stage of embryologic failure. In 1928 Waugh[4] described two cases of volvulus due to nonrotation. In 1931 Haymond and Dragstedt[5] described the clinical findings and embryology of one type of internal hernia. In the 1930s Gardner and Hart[6] reported 2 cases of their own and classified 104 additional reported cases, Wakefield and Mayo[7] described 13 cases, and McIntosh and Donovan[8] described 20 cases. In 1932 Ladd[9] described 10 cases of malrotation with volvulus and recommended treatment by counterclockwise detorsion. In 1936 Ladd[10] wrote the classic article on the treatment of this condition and described 21 cases. He emphasized the importance of dividing the bands over the duodenum and then placing the cecum in the left upper quadrant. This article shows that Ladd focused his attention on the rarely found bands that go to the right of the duodenum. He did not identify the more frequently encountered bands that enclose the duodenum and cecum. Ladd's procedure of releasing the duodenum and placing the cecum in the left upper quadrant remains the cornerstone of surgical treatment for nonrotation with midgut volvulus. Fixation by sutures has been reported but is no longer advocated because it is not effective.[11,12] In 1953 Gross[13] reported 156 cases in the first comprehensive review of the subject. The Boston Children's Hospital's experience has been updated.[5,14] In 1954 Snyder and Chaffin[15] published a clear and insightful description of anomalies of rotation. In this report, the embryology of malrotation was compared to the twisting of a loop of rope around a central band that represented the superior mesenteric vessels. To date, this remains a useful image.

## Normal Rotation and Fixation

Rotation may be described according to how it affects the two ends of the intestinal tract (i.e., the proximal duodenojejunal loop and the distal cecocolic loop) and the simultaneous rotation of these two components. Most authorities refer to the process as involving the midgut, but it is best to include the entire intestinal tract.[13,16]

### DUODENOJEJUNAL LOOP

The normal adult position of the stomach, duodenum, and first part of the jejunum is well known. Starting at the upper end of the adult intestinal tube and observing its fixed relation to the superior mesenteric artery, it is clear that the stomach is above or anterior to the artery, the second portion of the duodenum is to the right of the artery, the third portion of the duodenum lies beneath the artery, and the fourth portion (the distal duodenum and first part of the jejunum) is to the left of the artery. The duodenojejunal loop starts in the embryo in the same position as that of the stomach in the adult (Fig. 86-1). If the other components of the loop eventually take the position as previously described, the duodenojejunal loop has rotated around the superior mesenteric artery from above (see Fig. 86-1), to the right 90 degrees (Fig. 86-2), and to the bottom another 90 degrees, for a total thus far of 180 degrees (Fig. 86-3), then to its final place to the left of the artery for an additional swing of another 90 degrees, or a total arc of 270 degrees (Fig. 86-4). The direction of the swing is determined by the normal final position of the stomach and all four portions of the duodenum.

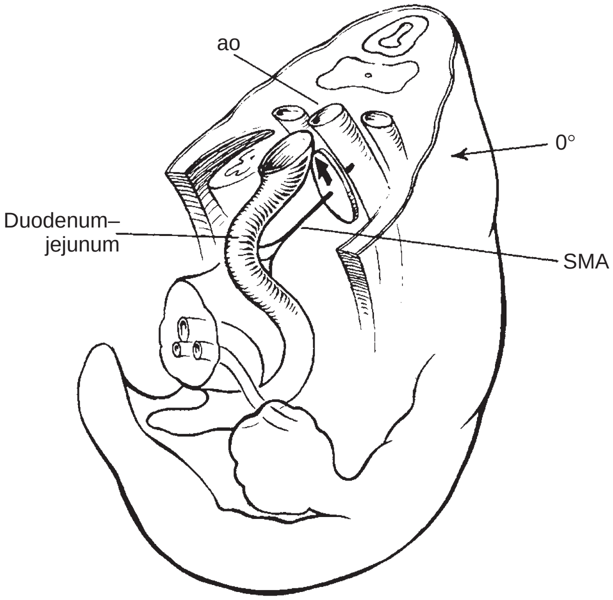


FIGURE 86-1 Schematic ventrolateral view of a 5-mm embryo. The intestinal tract forms a slight curve forward. The superior mesenteric artery (SMA) passes at right angles from the aorta (ao) to the curve of the intestine. A disk has been drawn around the SMA at its base; the arrow points superiorly to the starting position, or 0 degrees rotation, of the duodenojejunal loop. Rotation proceeds around the artery as an axis.

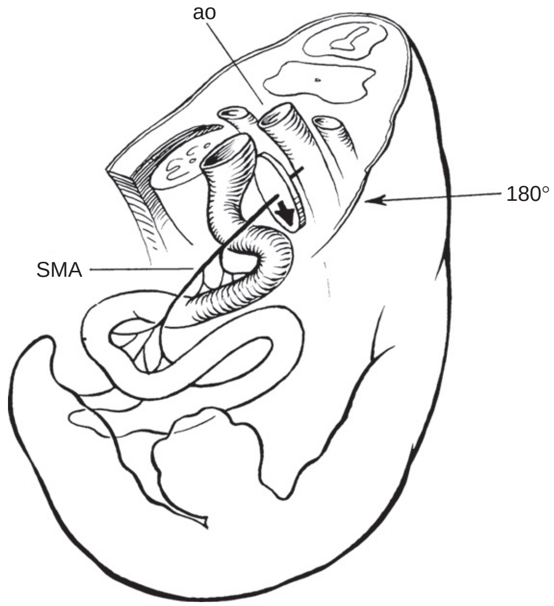


FIGURE 86-3 Schematic ventrolateral view of a 25-mm embryo, indicating further rotation of the duodenojejunal loop to a position below the superior mesenteric artery (SMA), through an arc of 180 degrees. Extension of the remainder of the intestines into the cord is not shown. *ao,* aorta.

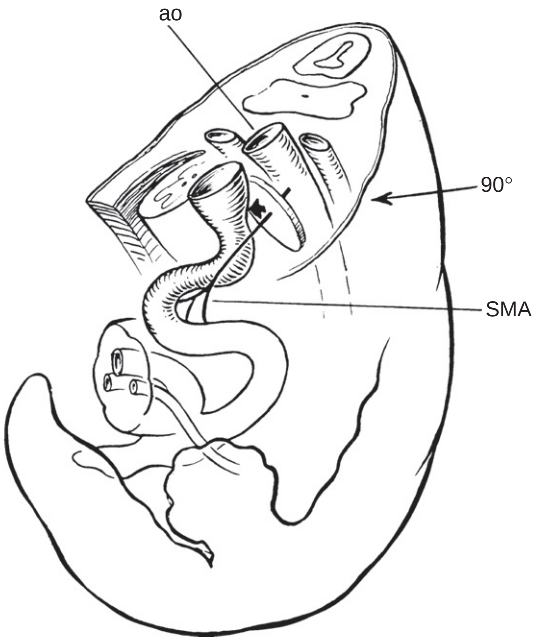


FIGURE 86-2 Schematic ventrolateral view of a 10-mm embryo. The duodenojejunal loop has passed from a position above the superior mesenteric artery (SMA) to the right of the artery and thus has rotated through an arc of 90 degrees from its starting position, as indicated by the arrow in the disk. *ao,* aorta.

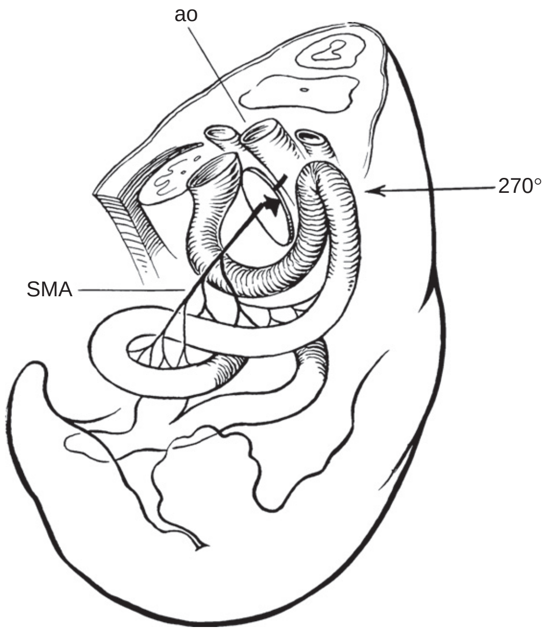


FIGURE 86-4 Schematic ventrolateral view of a 40-mm embryo, indicating final rotation of the duodenojejunal loop to a position immediately to the left of the superior mesenteric artery (SMA). This loop has passed from a position superior, to the right beneath, and to the left, or through an arc of 270 degrees in a counterclockwise direction. This final rotation of the duodenojejunal loop takes place as the intestines return from the cord. *ao,* aorta.

## ORIENTATION FOR SIDE AND DIRECTION OF ROTATION

In the preceding description, the right side is the patient's right, not the right side of the observer facing the patient. However, when the usual direction of rotation is described according to the hands of a clock, the direction noted is from the viewpoint of the observer. If an imaginary clock is placed face up on the posterior wall of the embryo or baby, the pivot point of the hands (i.e., the axis of their rotation) is the superior mesenteric artery. The duodenojejunal loop moves counterclockwise.

## CECOCOLIC LOOP

In the adult, the terminal ileum, cecum, and right colon reside on the right side of the abdomen to the right of the superior mesenteric artery. In the embryo, they lie beneath the artery. This cecocolic loop, like the duodenojejunal loop, passes counterclockwise from its starting point beneath the artery (Fig. 86-5), to the left of the artery 90 degrees (Fig. 86-6), above to 180 degrees (Fig. 86-7), and to the right of the artery, through a total arc of 270 degrees (Fig. 86-8). In this manner, the cecocolic loop normally achieves its adult position.

## SIMULTANEOUS ROTATION OF BOTH ENDS AND OF THE ENTIRE INTESTINAL TRACT

Rotation is best visualized by attaching a loop of rope above and below a metal spoke (wire) on a piece of wood (Fig. 86-9). The loop is grasped in the left hand and turned through three quarters of a turn to the left. The proximal portion of the upper limb of the rope should be watched. This portion turns from its initial position above the wire, to the right of it, beneath it, and to the left of it. At the same time, the lower limb of the rope lies beneath the wire at the start of the turn, then goes to the left, above, and finally to the right of the wire. If the upper limb of the rope represents the duodenojejunal loop, the wire represents the superior mesenteric artery, and the lower limb represents the cecocolic loop, the position of these structures in the process of rotation should be clear. The entire process can be studied in minute detail with a dissecting microscope and a large series of embryos ranging in age from 4 to 12 weeks. In the fourth week of fetal life, or when the embryo has reached the 5-mm stage, the intestinal tract is almost a straight tube, with a slight anterior bulge in the central portion. The superior mesenteric artery comes forward from the posterior wall to the center of the bulge (see Figs. 86-1 to 86-5). Changes occur rapidly as the intestine forms within an extension of the abdominal wall into the umbilical cord. The stomach remains in its original position anterior and above the superior mesenteric artery. The duodenum then begins to curve downward and to the right of the artery. The jejunum and small intestine extend into

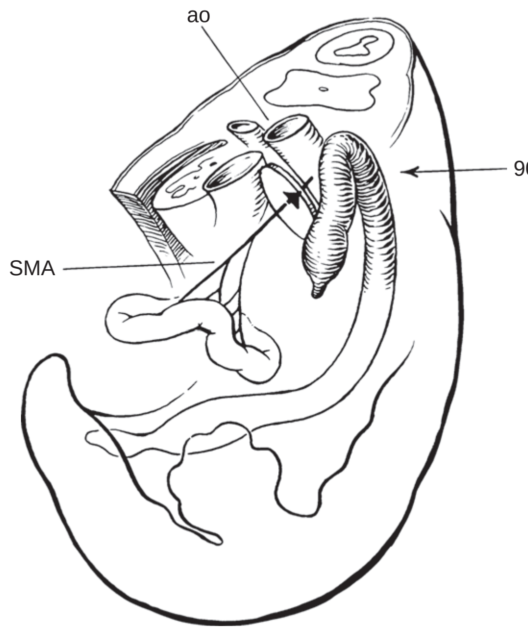


**FIGURE 86-6** Schematic ventrolateral view of a 40-mm embryo, showing the position of the cecocolic loop at the left of the superior mesenteric artery (SMA). The loop has rotated through an arc of 90 degrees from its starting position inferior to the artery (see the disk at the base of the SMA). This phase of rotation is maintained while the intestines are in the cord and at the moment they drop back into the abdomen. *ao,* aorta.

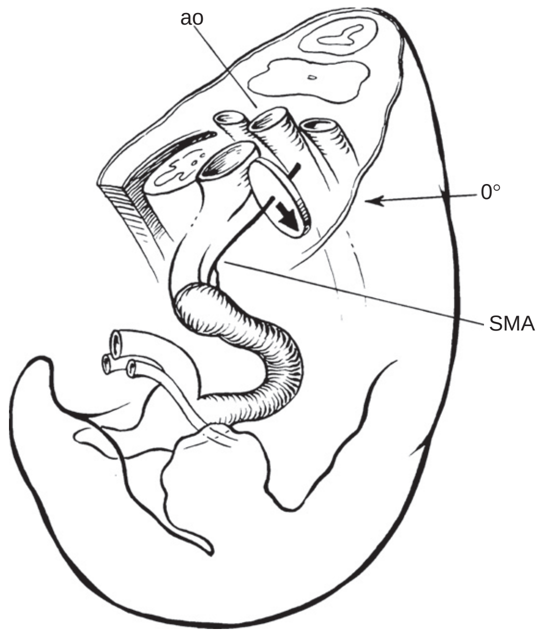


**FIGURE 86-5** Schematic ventrolateral view of a 5-mm embryo, indicating the forward bend of the intestinal tract. The cecocolic loop is emphasized as it lies inferior to the superior mesenteric artery (SMA), or in a position of 0 degrees rotation, indicated on the disk around the base of the SMA. The 0-degree rotation position for this loop is inferior to the SMA, whereas that for the duodenojejunal loop is superior. *ao,* aorta.

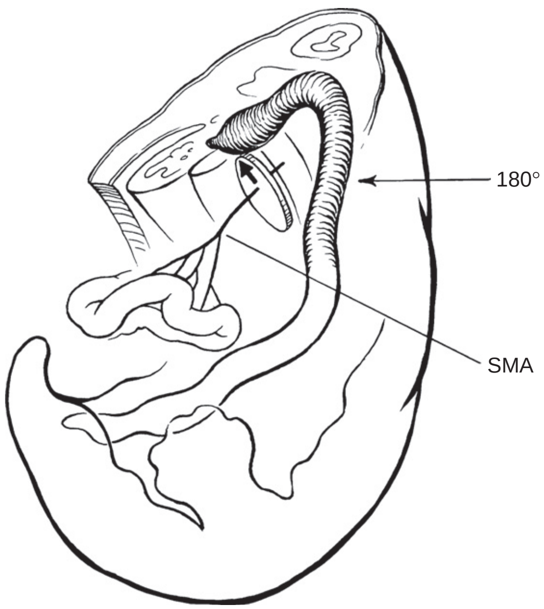


**FIGURE 86-7** Schematic ventrolateral view of a 40-mm embryo, indicating rotation of the cecocolic loop to a position superior to the superior mesenteric artery (SMA), or rotation through an arc of 180 degrees from the starting position inferior to the SMA. This phase takes place immediately after return of the intestines from the cord into the abdomen.

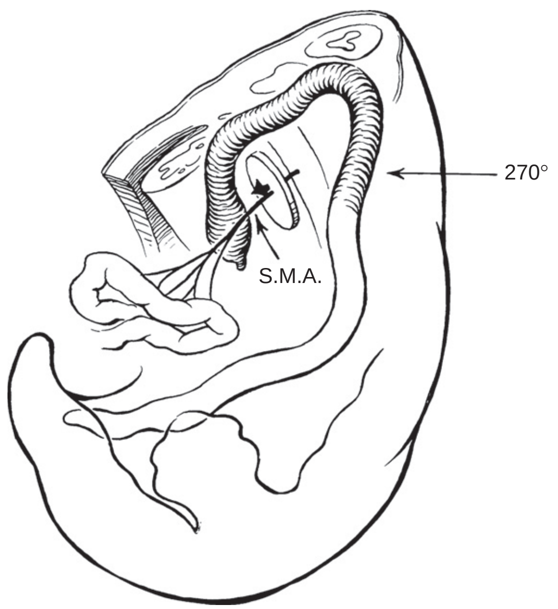


FIGURE 86-8 Schematic ventrolateral view of a 40-mm embryo, showing the final position of the cecocolic loop to the right of the superior mesenteric artery (SMA). This loop has passed from a position beneath, to the left, superior, and finally to the right of the SMA, or through an arc of 270 degrees in a counterclockwise direction.

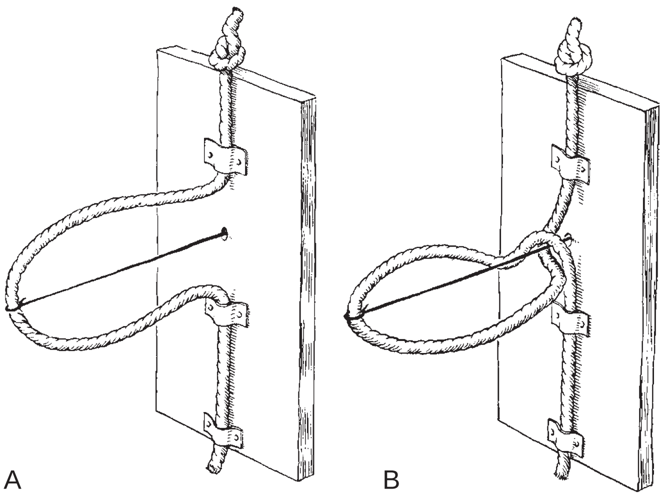


FIGURE 86-9 Mechanical demonstration of intestinal rotation. A rope is attached to a board at both ends, with a wire extending at right angles from the board to the base of the loop. **A,** The top limb of the rope corresponds to the duodenojejunal loop, the wire corresponds to the superior mesenteric artery, and the bottom limb corresponds to the cecocolic segment. **B,** The rope loop has been grasped by the hand and rotated through an arc of 270 degrees, or three quarters of a complete turn around the wire as the axis, in a counterclockwise direction. Thus the top limb has become the bottom one, and the bottom limb the top. By following the movements of the two limbs around the wire close to the board, one can visualize the process of rotation of the intestine in the embryo.

the umbilical cord, along with the cecum, right colon, and part of the transverse colon. Both loops have thus passed from a position in front of the artery to the side of the artery (see Figs. 86-2 and 86-6).

It was previously thought that both loops remained in this position until the intestines returned from the cord into the abdomen.[2,3] However, it was demonstrated by Mall[1] and verified by Snyder and Chaffin[15] that the duodenojejunum continues to rotate during the extracoelomic phase of intestinal development, and at about the eighth week, the third portion of the duodenum comes to lie beneath the artery (see Fig. 86-3). This increases the rotation of this segment to 180 degrees. Finally, at about 10 weeks (or when the embryo is about 40 mm long), the intestines return to the abdomen. This must be a rapid process because few specimens of this stage of development have been described. The small bowel is the first segment of the intestines to return to the abdominal cavity, and it pushes the fourth portion of the duodenum and jejunum to the left of the superior mesenteric artery. This completes the rotation of this segment of the bowel (see Fig. 86-4). The cecum and right colon return to the abdomen last, on the left side (see Fig. 86-6). This loop then passes anterior or above the artery (see Fig. 86-7) and finally to its adult position on the right side of the artery (see Fig. 86-8).

To use another analogy, placing a hand on top of an imaginary automobile steering wheel and making a three-quarter turn to the left executes the process of rotating the duodenojejunal loop around the steering post (superior mesenteric artery). With a hand on the bottom of the steering wheel, a three-quarter turn to the left executes the rotation of the cecocolic loop.

This is the process of normal rotation; the sequence of events has been postulated from bits of evidence contributed by many observers. It does not lend itself to a breakdown into stages I, II, and III, as previously described, because it is a continuing process and is better understood by comparing it to the swing of a twisted rope or the turn of a steering wheel.[2] That description may be an oversimplification, but it is easy to remember in the operating room.

Kluth and Lambrecht[17] proposed a slightly different explanation for intestinal malrotation on the basis of rat embryo studies. They emphasized that rapid growth and lengthening of the duodenum force the tip of the duodenojejunal loop to grow under the mesenteric root. The distal midgut also rapidly lengthens and forces the cecum from a caudal to a cranial position; this may appear to be rotation, but the rest of the colorectum is not involved in the process. These authors view fixation and position of the intestine to be a process of differential growth rather than rotation because they did not find gross changes in the straight midgut in their embryo studies. They postulate that maldevelopment of the embryonic duodenal loop is the major problem involved in the pathogenesis of midgut malformations. Reduced growth of the duodenal loop or abnormal insertion of the mesenteric root, functioning as a barrier to growth of the duodenal loop, may explain the abnormal location of the duodenum and the ligament of Treitz. They believe that cecal and colonic movement plays a more passive or minor role in causing abnormalities of intestinal position and fixation.

## CLASSIFICATION OF ABNORMALITIES OF INTESTINAL ROTATION

Normal fixation of the duodenum and colon is illustrated in Figure 86-10. The normal mesenteric attachment extends from the ligament of Treitz, located at the level of the gastric outlet, to the cecum. Both the ascending and descending colon are fixed retroperitoneally. The abnormalities of intestinal

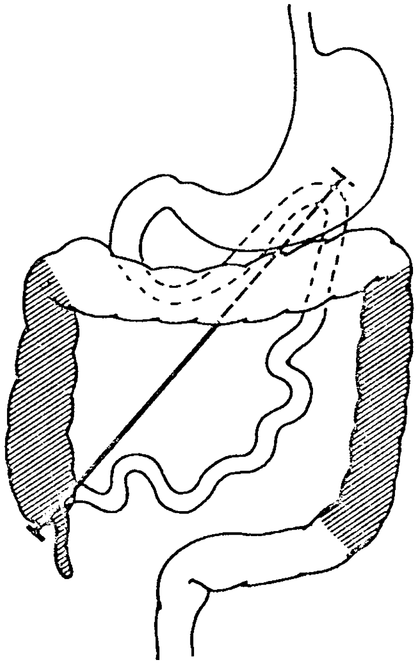

**FIGURE 86-10** Normal fixation of the mesentery of the midgut. The normal broad base extends from the ligament of Treitz to the ileocecal junction and prevents twisting of the intestine. Both the ascending and descending colon are fixed retroperitoneally. (From Filston HC, Kirks DR. Malrotation—the ubiquitous anomaly. J Pediatr Surg 1981;16:614.)

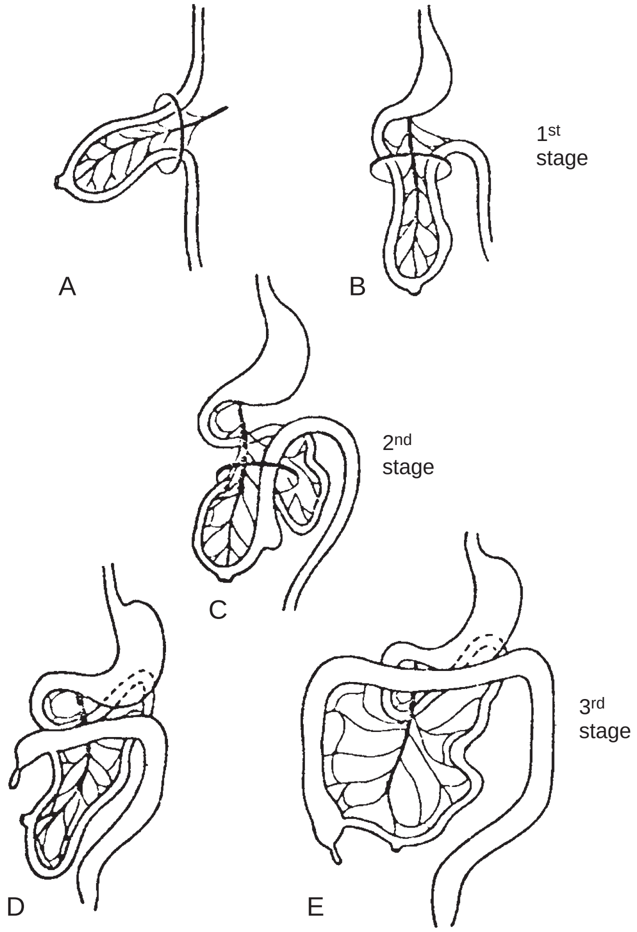


**FIGURE 86-11** Normal intestinal rotation. **A,** Six weeks' gestational age: nonrotation. **B,** Eight weeks' gestational age: incomplete rotation. **C,** Nine weeks' gestational age: incomplete rotation. **D,** Eleven weeks' gestational age. **E,** Twelve weeks' gestational age. (From Filston HC, Kirks DR. Malrotation—the ubiquitous anomaly. J Pediatr Surg 1981;16:614.)

rotation represent a spectrum with many variations. The surgical problems resulting from these abnormalities of rotation are best classified by understanding the errors in growth, rotation, and position of the duodenum and ligament of Treitz. Any defined stages are arbitrary, but referring to Figure 86-11, which shows the stages of normal rotation, may be helpful in determining the maldevelopment that may have occurred in an individual case.[18] The term *malrotation* refers to all abnormalities of intestinal position and attachment[19] and includes the more recent concept of atypical malrotation or malrotation variant. Atypical malrotation results when the ligament of Treitz is to the left of midline, defined by the vertebral body, or below the gastric outlet on upper gastrointestinal (GI) contrast studies. The term nonrotation is used for the first stage (see Fig. 86-10), and the terms incomplete rotation and mixed rotation are used for abnormalities of the second stage.

Reverse rotation is a rare anomaly in which the duodenum and colon rotate clockwise in relation to the superior mesenteric artery and vein. The transverse colon eventually lies behind the vessels, which may result in acute or chronic colonic obstruction.

Rotation and fixation abnormalities are also known to coexist with heterotaxia, but rarely with situs inversus.[20] Heterotaxia, previously known as situs ambiguus, is defined as an abnormal arrangement of body organs or complete situs inversus. Major cardiac anomalies are commonly associated with heterotaxia. GI anomalies include midline liver, malposition of the stomach, anomalies of intestinal rotation and fixation, intraperitoneal pancreas, and either asplenia or polysplenia.[20]

Malrotation is an integral part of congenital diaphragmatic hernia and all abdominal wall defects. In gastroschisis, the midgut is nonrotated and may be suspended and stretched outside the fetal abdominal cavity; this leads to ischemic injury without volvulus. Infants with omphalocele or diaphragmatic hernia have varying degrees of normal rotation and fixation, depending on the extent of intestinal displacement.

Associated anomalies are found in 30% to 60% of patients with malrotation.[7,21–23] Duodenal atresia has been found in conjunction with malrotation and perinatal volvulus. Intrinsic duodenal obstruction from a partially obstructing web must not be overlooked in cases of malrotation. Filston and Kirks[21] found midgut malrotation as an associated malformation in half of jejunal and one third of duodenal atresia cases. Malrotation is rarely associated with Hirschsprung disease and anorectal malformations.[1] Mesenteric cysts have been observed in association with malrotation, but whether this is a primary anomaly or results from lymphatic obstruction due to chronic volvulus is not clear.[24]

## CLINICAL MANIFESTATIONS

Various clinical presentations, ranging from chronic abdominal pain to acute midgut volvulus with ischemic bowel injury, may result from failure of normal intestinal rotation and fixation. In general, it is possible to correlate the various clinical syndromes with the observed anatomic findings, but there are many variables and exceptions.

### Acute Midgut Volvulus

The narrow pedicle formed by the base of the mesentery in malrotation predisposes the midgut to clockwise twisting from the duodenum to the transverse colon (Fig. 86-12). Excessive length of the mesentery or a point of adhesion at the convexity of the loop may act as an axis for a twist.[3] The actual inciting mechanism is unknown, but various possibilities have been suggested including unusual movement of the torso, abnormal intestinal peristalsis, or segmental bowel distention.[25]

Most patients with midgut volvulus present in the first month of life.[26] In a group of 74 patients, 23 were seen in the first 7 days of life; 16 from 7 to 30 days of life, and 24 from 1 to 12 months; only 11 were older than 1 year.[27] Fourteen of 22 patients described by Torres and Ziegler[28] presented during the first month of life.

The primary presenting sign of malrotation is the sudden onset of bilious vomiting in a previously healthy, growing infant.[29] With the onset of proximal intestinal obstruction, the distal colon empties; soon after the onset of vomiting, the lower abdomen may appear scaphoid. As vascular compromise progresses, intraluminal bleeding may occur and blood is often passed per rectum. Crampy abdominal pain is common. Innocent "colic" or hypertrophic pyloric stenosis may be ruled out on the basis of bilious vomiting.

Infants with complete obstruction rapidly develop intestinal ischemia with a firm, distended abdomen; hypovolemia; and shock. Abdominal tenderness varies with the degree of vascular compromise, but signs of peritonitis are invariably present.

A high index of suspicion for midgut volvulus is based on the history, physical examination findings, and presence of metabolic acidosis. The decision whether to confirm the diagnosis by either Doppler ultrasonography or upper GI contrast radiography or to proceed directly to laparotomy or laparoscopy must be based on the condition of the patient and the risk of vascular compromise if there is any delay.

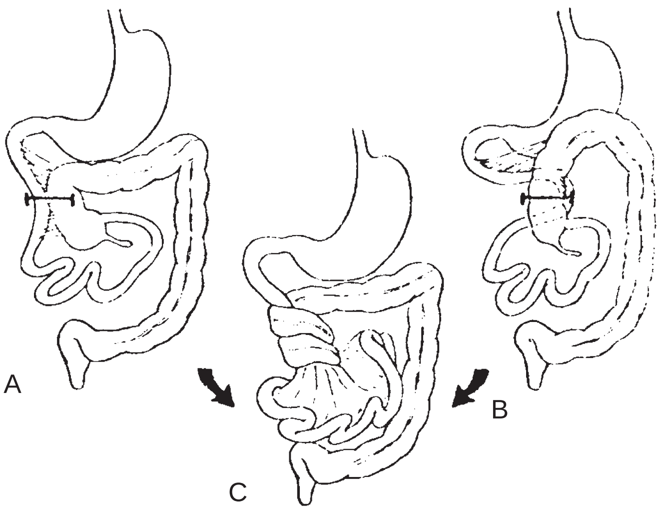


**FIGURE 86-12** Pathophysiology of midgut volvulus with malrotation. **A,** The narrow mesenteric attachment in nonrotation **(B)** or incomplete rotation **(C)** predisposes the patient to midgut volvulus. (From Filston HC, Kirks DR. Malrotation—the ubiquitous anomaly. J Pediatr Surg 1981;16:614.)

## CHRONIC MIDGUT VOLVULUS

Intermittent or partial midgut volvulus results in lymphatic and venous obstruction, with enlargement of the mesenteric lymph nodes. This situation is more commonly encountered in children older than 2 years.[29–33] On the basis of our review of malrotation in children older than 2 years, the most frequent presenting complaints are chronic vomiting (68%), intermittent colicky abdominal pain (55%), diarrhea (9%), hematemesis (5%), and constipation (5%).[34] The average duration of symptoms before an operation was performed was 28 months. Absorption and nutrient transport can be impaired by venous and lymphatic stasis, leading eventually to protein-calorie malnutrition in severe cases of long-standing incomplete rotation with partial obstruction.[31,33] An increased predisposition to infection has also been observed.[31]

Failure to suspect this diagnosis has resulted in dietary manipulation and even psychiatric evaluation in some patients. Bilious vomiting in conjunction with abdominal pain should be considered a surgical problem until proved otherwise.[35] Nonbilious vomiting may also occur as a neurogenic response to gastroduodenal distention.

## TYPICAL MALROTATION IN ASYMPTOMATIC OR MINIMALLY SYMPTOMATIC PATIENTS

The incidental finding of malrotation on radiography or at the time of an operation raises the question of the eventual risk of complications in an asymptomatic patient. In a study of 50 adults with malrotation, Wang and Welch[36] found that 26 actually had symptoms referable to the abnormality. The general consensus is that a corrective surgical procedure is indicated at any age.[21,26,37]

The issue of asymptomatic patients with malrotation was brought into focus by Chang and colleagues,[20] who reported on 34 patients with heterotaxia and complex heart disease. Four of 28 developed acute or chronic signs of midgut volvulus requiring an emergency Ladd procedure. A subsequent group of six patients with heterotaxia had upper GI radiography that detected anomalies of intestinal fixation and rotation in all of them. Each patient underwent an uncomplicated elective Ladd procedure once the cardiac condition stabilized.

The first indication of malrotation may be noted during surgical exploration for an acute abdomen. Locating an acutely inflamed appendix in a patient with malrotation may be anticipated by radiographic absence of a cecal shadow in the right lower quadrant. In Collins's[38] study of 71,000 human appendix specimens, 2849 were in an abnormal position because of incomplete rotation of the large bowel. Further evaluation of such patients by upper GI radiography is indicated after their recovery from emergency operation.

## ACUTE DUODENAL OBSTRUCTION SECONDARY TO CONGENITAL BANDS

Acute duodenal obstruction results from peritoneal bands (Ladd bands) extending across the third portion of the duodenum, causing extrinsic compression of the lumen or kinking of the bowel at the site of fixation. Duodenal obstruction is more common in neonates and infants but can occur later in life as well. Volvulus is not a principal finding in these patients.

An infant or newborn usually presents with forceful, bilious vomiting. Abdominal distention may or may not be present, depending on the degree of gastric emptying achieved by vomiting. Gastric peristaltic waves may occasionally be observed.[39] The obstruction may be complete or incomplete, so meconium or stool may have been passed. Jaundice may be seen.[40] In a newborn, symptomatic malrotation with bands is often associated with intrinsic duodenal obstruction. A "double bubble" due to duodenal obstruction is usually seen on plain abdominal radiographs, but an upper GI contrast study of the duodenum is diagnostic.

### CHRONIC DUODENAL OBSTRUCTION SECONDARY TO CONGENITAL BANDS

Chronic, recurrent, or subacute obstruction of the duodenum results when the prearterial limb does not complete its normal rotation and is fixed by adhesions and peritoneal bands that may twist, angulate, or kink the duodenum.[41] Some degree of volvulus may pull on the bands and contribute to the kinking. The obstruction is usually in the third portion of the duodenum.

Bilious vomiting is the main finding at presentation. Failure to gain weight and intermittent colicky abdominal pain are commonly observed. The age at diagnosis ranges from infancy to preschool age. Transient dilatation of the duodenum without reflux can, by reflex, stimulate gastric regurgitation. Contrast studies, although diagnostic, must be performed carefully because the degree of enlargement may be subtle.

### REVERSE ROTATION WITH COLONIC OBSTRUCTION

In this rare abnormality (Fig. 86-13), the duodenum and jejunum lie anterior to the superior mesenteric vessels and obstruct the posteriorly lying transverse colon. The transverse colon must pass through a tunnel beneath the mesentery, and this produces a chronic incomplete or complete obstruction of the colon. This condition is usually seen in adults and is rarely reported in children.[36]

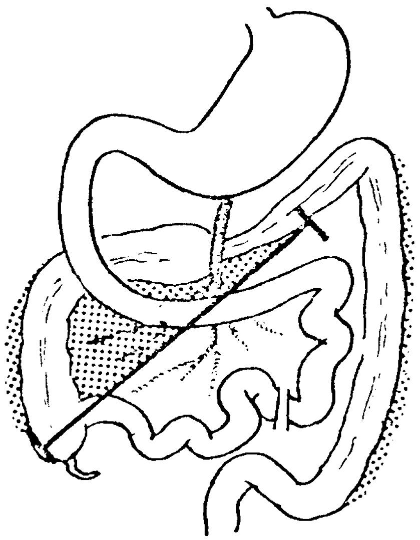

**FIGURE 86-13** Reverse rotation of the duodenum and colon. When the colon rotates beneath the superior mesenteric artery, the midtransverse colon may become partially obstructed. This is caused by pressure of the vessels and by bands from the mesentery to the small bowel.

### INTERNAL HERNIA

Lack of fixation of the mesentery of the right or left colon, or of the duodenum, may result in the formation of potential spaces for hernias. Internal hernias are associated with recurrent entrapment of bowel with partial obstruction, which may eventually progress to complete obstruction and strangulation. The most commonly seen internal hernias are the right and left mesocolic hernias described by Willwerth and colleagues.[42] The term *mesocolic* is preferred to the alternative term *paraduodenal*. A right mesocolic hernia is produced when the prearterial limb fails to rotate around the superior mesenteric artery and the bowel loops are entrapped by the mesentery of the cecum and colon (Fig. 86-14, *A*). A left mesocolic hernia is produced when the unsupported area of the descending mesocolon between the inferior mesenteric vein and the posterior parietal colonic attachment is ballooned out by the small intestine as it migrates to the left superior portion of the abdominal cavity. Usually, the cecum has completely rotated and lies in a normal position in the right lower quadrant. The ileum exits from the sac, but at a variable distance from the ileocecal valve (Fig. 86-14, *B* and *C*).

Signs and symptoms of an internal hernia are related to recurrent, intermittent bouts of intestinal obstruction characterized by recurrent colic. The latter may lead to constant abdominal pain, vomiting, and, sometimes, constipation. The symptoms are often mild and are occasionally thought to be psychologic. Radiographs obtained during an attack of colic may suggest obstruction of the small intestine.

### VOLVULUS OF THE CECUM

Cecal volvulus, seen most often in patients older than 60 years, is caused by lack of fixation of the cecum, terminal ileum, and proximal ascending colon. The main symptoms are acute, severe abdominal pain and nausea associated with right-sided abdominal distention. Complete obstruction frequently develops. The characteristic abdominal radiograph shows a large air-filled loop of colon occupying the left upper quadrant (the convex surface faces the left lower quadrant), associated with small bowel obstruction.[43]

## Radiologic Diagnosis of Abnormalities of Rotation and Fixation

Contrast radiography is essential for the clinical evaluation and diagnosis of disorders of intestinal rotation and fixation. The normal relations of the stomach, duodenum, ligament of Treitz, and ileocecal area are shown schematically in Figure 86-11 and radiographically in Figure 86-15. The extent of normal mesenteric attachment is largely predictive of the radiographic findings.[18,44–46]

Plain abdominal radiography is often nondiagnostic because differentiation between gas-filled small intestine and large intestine may be difficult in neonates and small infants.[47] However,

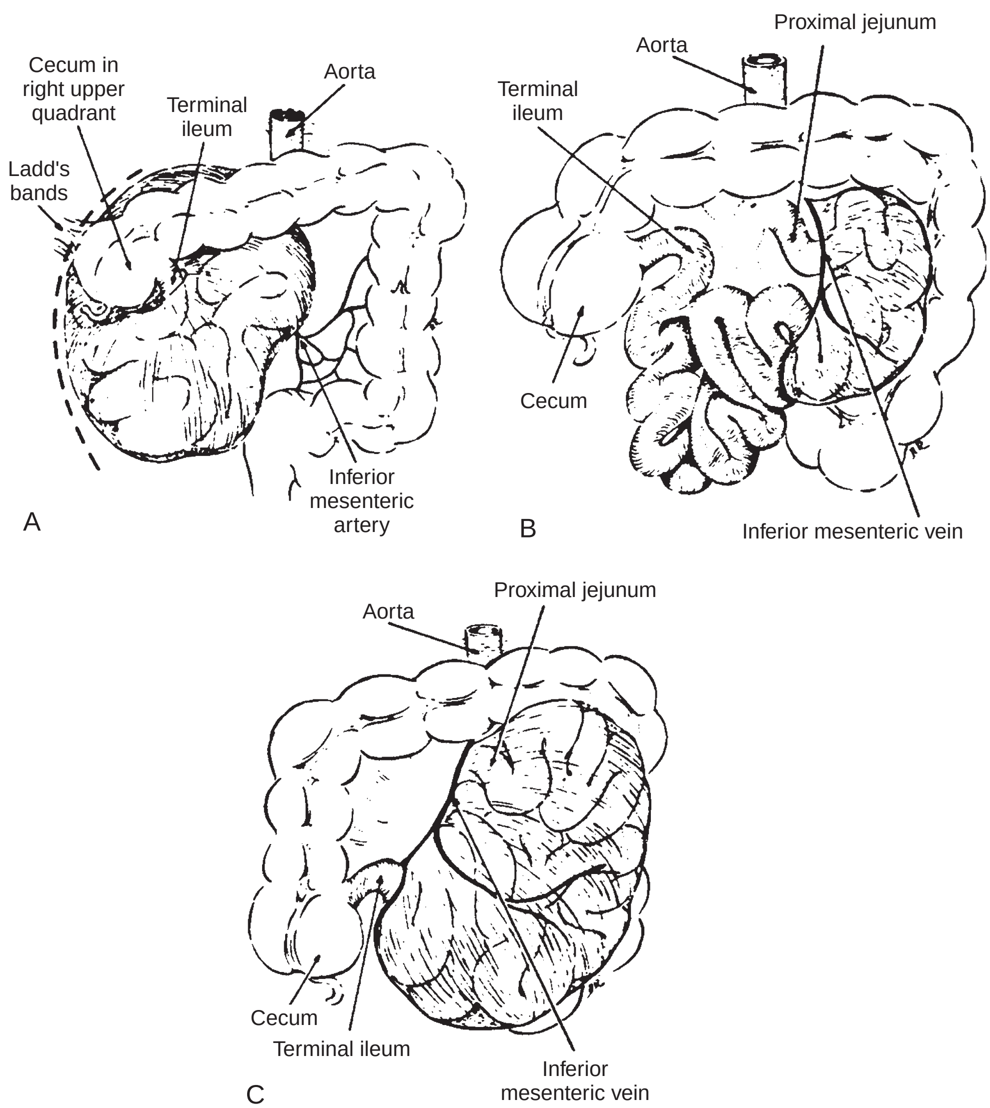


**FIGURE 86-14** Mesocolic hernias. **A,** Right mesocolic hernia. The prearterial segment of the midgut has failed to rotate. The postarterial segment does not rotate and traps most of the small bowel behind the right mesocolon. The hatched line indicates the surgical incision used to reduce the hernia. **B,** Left mesocolic hernia. Initial rotation of the small intestine is normal. During migration to the left superior portion of the abdomen, the bowel invaginates an avascular portion of the left mesocolon posterior to the inferior mesenteric vein. **C,** Left mesocolic hernia. The small intestine, except for portions of the distal ileum, is trapped beneath the left mesocolon. Note that the inferior mesenteric vein delineates the right margin of the sac and is an integral part of the neck of the sac. (From Willwerth BM, Zollinger RM, Izant RJ. Congenital mesocolic [paraduodenal] hernia: Embryologic basis of repair. Am J Surg 1974;128:358. **B** and **C,** Based on Callander CL, Rusk GY, Nemir A. Mechanism, symptoms and treatment of hernia into the descending mesocolon (left duodenal hernia). Surg Gynecol Obstet 1935;60:1052-1071.)

some useful signs are occasionally seen including the "double bubble" of acute duodenal obstruction (Fig. 86-16, *A*) or the absence of a normal colonic gas pattern in an older patient with a displaced cecum. Volvulus of the midgut is often characterized by a "gasless" abdomen, but distal intestinal obstruction may also be found.[47] In these instances the intestine may be thickened and edematous (Fig. 86-16, *B*).

Ultrasonography has become a useful study for the detection of many intra-abdominal conditions. It is a good screening device for infants suspected of having midgut volvulus because it can define vascular flow through the superior mesenteric vessels. Pracros and colleagues[48] reported an ultrasonographic "whirlpool" flow pattern of the superior mesenteric vein and mesentery around the superior mesenteric artery in 15 of 18 patients with midgut volvulus; this pattern was best seen using color Doppler imaging (Fig. 86-17). Additional ultrasonographic findings are a fluid-filled, distended duodenum and dilated, thick-walled bowel loops located mainly to the right of the spine. Computed tomography may also demonstrate a "whirlpool" flow pattern with intravenous and oral contrast (Fig. 86-18). More recently, Yousefzadeh has proposed that ultrasound be used to diagnose malrotation without volvulus on the basis of the position of the duodenum and the superior mesenteric artery. As mentioned in the embryology section, the third portion of the duodenum assumes a retroperitoneal position anterior to the aorta and posterior to the superior mesenteric artery in individuals with normal intestinal rotation. Verification of this position by ultrasound potentially obviates the need for further imaging. Application of this technique prospectively in multiple institutions is likely needed before widespread acceptance.[49]

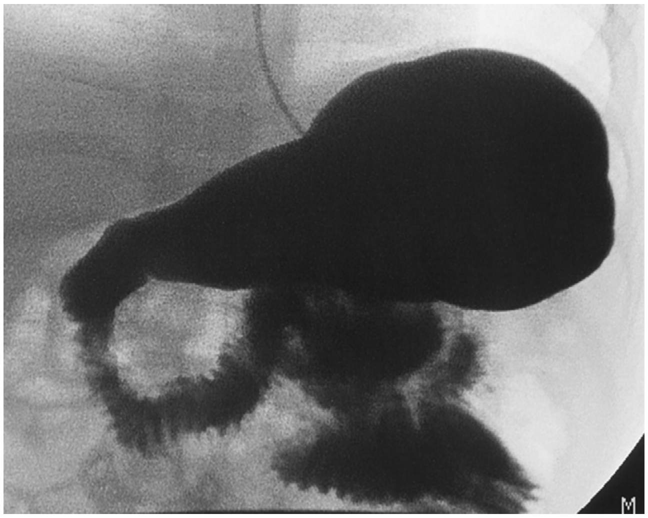

FIGURE 86-15 Normal duodenal rotation and duodenojejunal fixation. The duodenum descends to the right of midline, courses transversely to the left, and ascends to the left of midline to the level of the duodenal bulb before becoming intraperitoneal beyond the duodenojejunal junction. (Courtesy Marc S. Keller, MD, Yale University School of Medicine.)

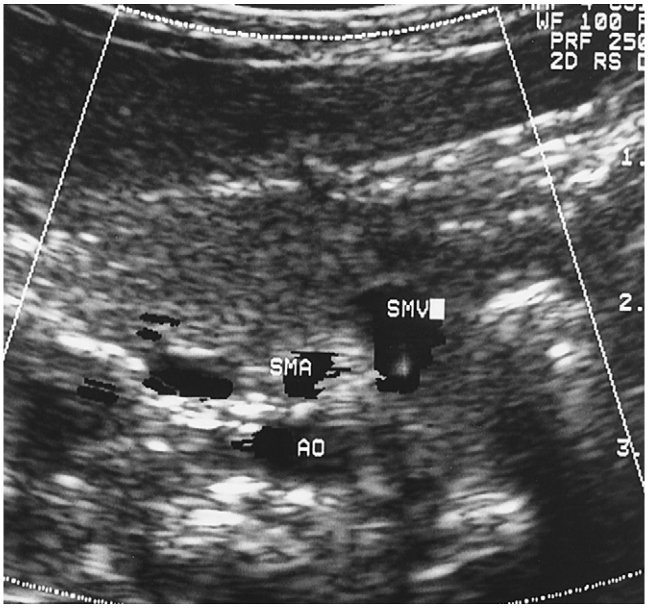


FIGURE 86-17 Color Doppler image of malrotation of a transverse upper abdomen. The abnormal position of the superior mesenteric vein (SMV) to the left of the superior mesenteric artery (SMA) can be seen just anterior to the abdominal aorta (AO). (Courtesy Marc S. Keller, MD, Yale University School of Medicine.)

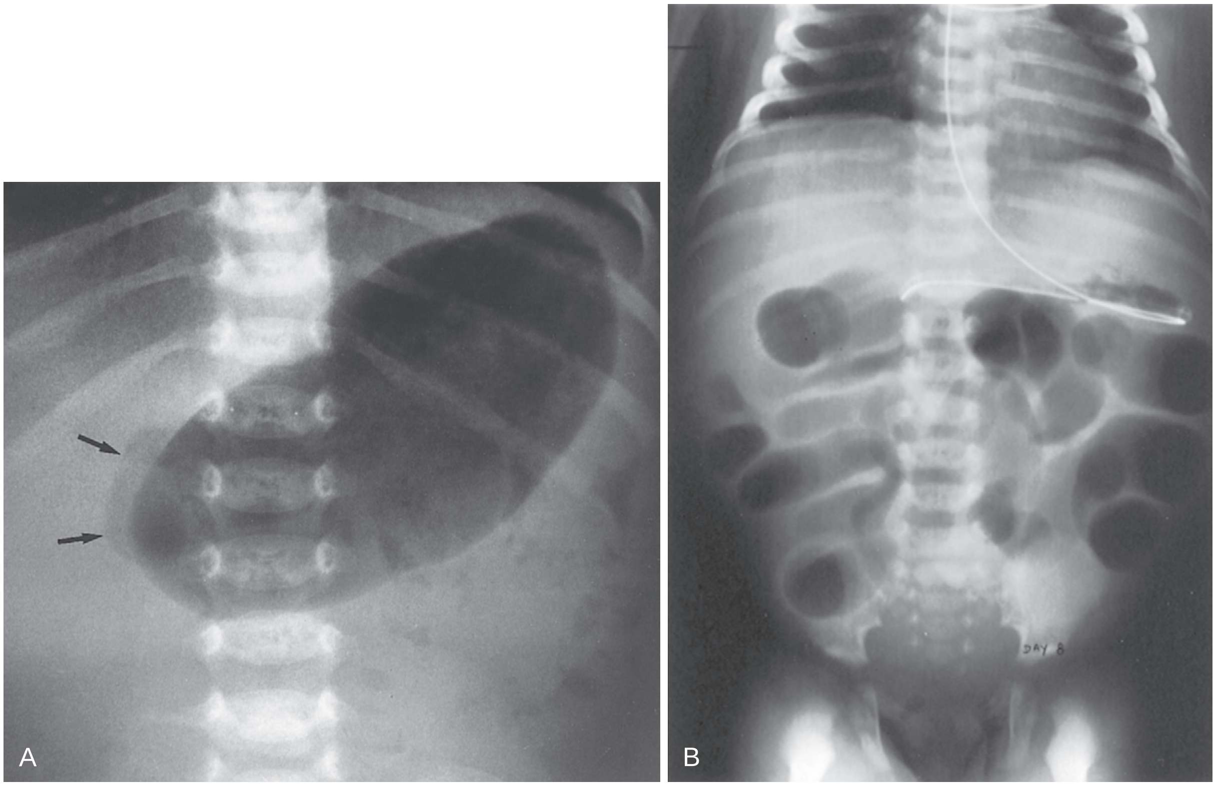


FIGURE 86-16 **A,** Plain radiograph of an infant with midgut volvulus. Obstruction of the descending duodenum may result in the pattern of gaseous distention of the stomach and duodenum (*arrows*) seen here, with a paucity of gas noted distally. **B,** Eight-day-old infant with midgut volvulus. This pattern of distal intestinal obstruction with thickened walls is much less common than that of proximal duodenal obstruction, but it is associated with more severe vascular compromise and clinical illness. (**A,** Courtesy Marc S. Keller, MD, Yale University School of Medicine.)

**FIGURE 86-18** Computed tomography scan of malrotation with volvulus (note the spiral configuration of the mesenteric vessels [*arrow*]).

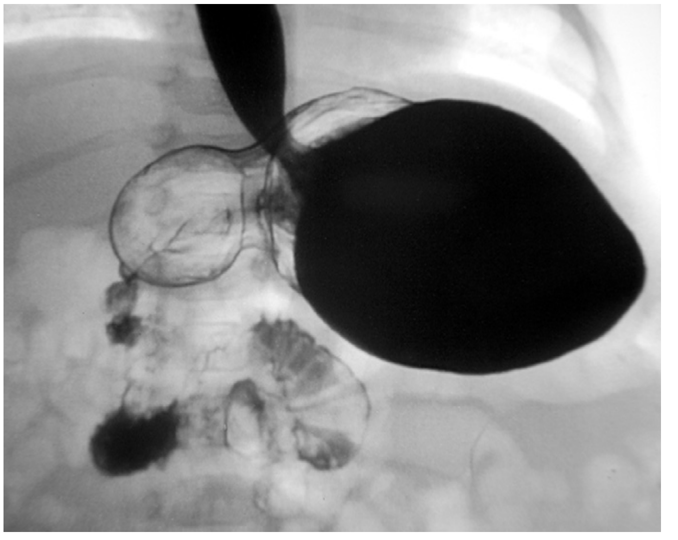

**FIGURE 86-20** Contrast study of atypical malrotation or malrotation variant. The ligament of Treitz fails to reach its normal position left of midline and at the level of gastric outlet.

An upper GI contrast study with careful delineation of the duodenojejunal course is now the preferred study for evaluating a patient with a possible abnormality of intestinal rotation. The position of the ligament of Treitz is assessed relative to the midline or center of the vertebral body and the level of gastric outlet. A normal finding is defined as the ligament of Treitz to the left of the vertebral body and at the level of the gastric outlet (Fig. 86-19). Malrotation is described by many pediatric radiologists as "typical" if the ligament is to the right of midline or absent, and "atypical" if the ligament of Treitz is midline or to the left and below the gastric outlet (Fig. 86-20). Cecal position is classified as either right lower quadrant (normal) or somewhere other than right lower quadrant (abnormal). The surgical dilemma of managing patients with atypical malrotation is discussed later.

The radiographic distinction between midgut volvulus and obstruction from peritoneal bands may be subtle. Ablow and colleagues[50] described a Z-shaped duodenojejunal loop in older children with intermittent abdominal pain and vomiting. Upper GI contrast radiography reveals a sharply angulated, to-and-fro course of the distal duodenum and jejunum, which may cross to the left of the midline, rather than the usual smooth duodenojejunal loop at the ligament of Treitz (Fig. 86-21, *B*).

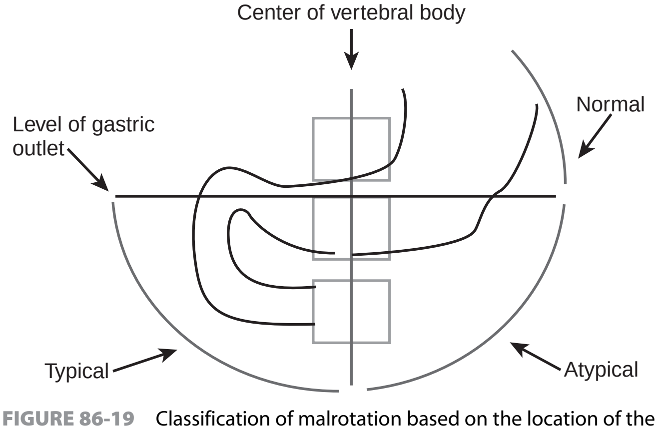


**FIGURE 86-19** Classification of malrotation based on the location of the ligament of Treitz in comparison with the midline of the vertebral body and the level of gastric outlet.

The Z sign is diagnostic of incomplete rotation and broad peritoneal bands extending across and fixing the involved small intestine without an accompanying volvulus. These Z-band findings can be distinguished from the corkscrew appearance of midgut volvulus.

Radiographic examination of an infant with heterotaxia is particularly challenging because of the ambiguous location of the stomach, liver, and spleen. In our experience,[20] most patients have a fixation abnormality of the duodenum and jejunum that is recognized by contrast radiography regardless of whether the stomach is right or left sided (Fig. 86-22).

Thickening of the mucous membrane of the small intestine, often seen in malabsorption syndromes, is an additional sign of chronic obstruction and volvulus.[19] With a right mesocolic hernia, the relation of the ascending and transverse colon may be abnormal, and contrast studies may show entrapment of the small intestine.

# Treatment

## PREOPERATIVE MANAGEMENT

Infants with suspected midgut volvulus and vomiting may be dehydrated and show signs of hypovolemia and hypochloremia. They require rapid intravenous resuscitation with a physiologic salt solution. Prolonged resuscitation efforts are not warranted, however, because expeditious laparotomy is essential to preserve intestinal viability. Additional measures including placement of a nasogastric tube, satisfactory intravenous access, and administration of parenteral antibiotics should be accomplished as quickly as possible.

## OPERATIVE TECHNIQUE

The Ladd procedure corrects the fundamental abnormalities associated with malrotation with or without midgut volvulus. This procedure consists of the following important steps, which must be carried out in the proper sequence: (1) evisceration of the bowel and inspection of the mesenteric

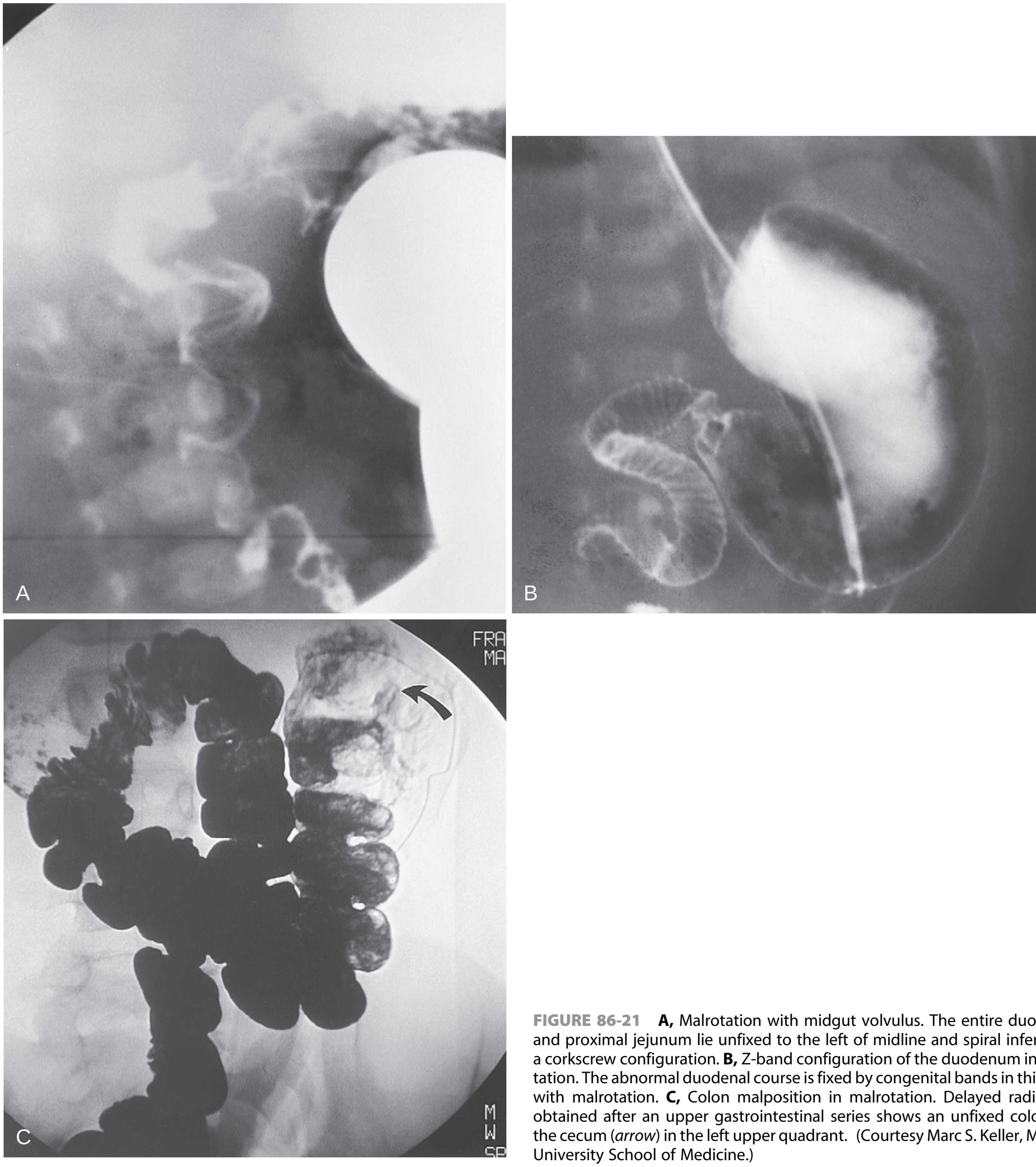


**FIGURE 86-21** **A,** Malrotation with midgut volvulus. The entire duodenum and proximal jejunum lie unfixed to the left of midline and spiral inferiorly in a corkscrew configuration. **B,** Z-band configuration of the duodenum in malrotation. The abnormal duodenal course is fixed by congenital bands in this infant with malrotation. **C,** Colon malposition in malrotation. Delayed radiograph obtained after an upper gastrointestinal series shows an unfixed colon with the cecum (*arrow*) in the left upper quadrant. (Courtesy Marc S. Keller, MD, Yale University School of Medicine.)

root; (2) counterclockwise derotation of the midgut volvulus; (3) lysis of Ladd peritoneal bands, with straightening of the duodenum along the right abdominal gutter; (4) appendectomy; and (5) placement of the cecum in the left lower quadrant.

### Recognition of Abnormalities of Rotation and Fixation

The peritoneal cavity should be entered through a supraumbilical right transverse incision extending from the midline laterally. The incision must be long enough to permit adequate inspection of the entire midgut. The entire bowel should be removed from the abdomen so that its orientation and fixation can be examined completely.

The two most constant anatomic points in the abdomen are the pylorus and the splenic flexure; their positions are not altered in patients with malrotation. A seemingly normal position of the cecum in the right middle or lower abdomen and a partial leftward course of the duodenum neither prove normal rotation nor rule out malrotation.

Several signs suggest a rotational anomaly: (1) abnormal peritoneal bands extending from the ileum or right colon

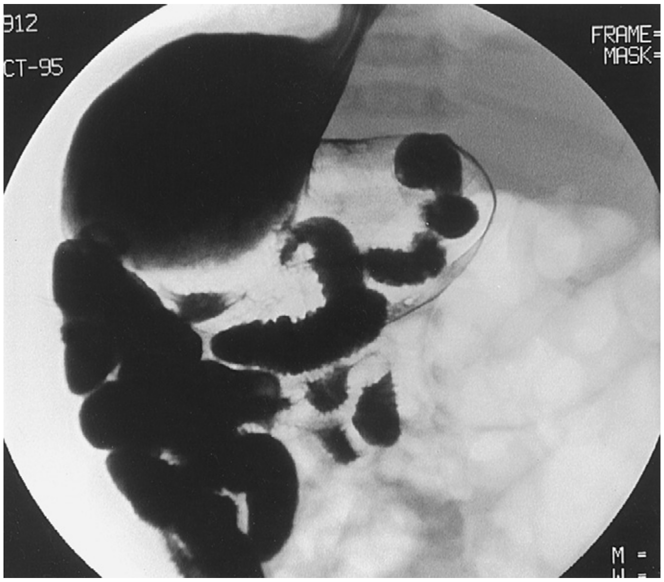


**FIGURE 86-22** Malrotation with heterotaxy. Note the horizontal liver margin and the right upper quadrant stomach in this neonate with congenital heart disease. The duodenum descends left of midline and courses transversely to the right but does not ascend to a point of duodenojejunal junction fixation. (Courtesy Marc S. Keller, MD, Yale University School of Medicine.)

to the parietal peritoneum over or to the duodenum; (2) fixation of the duodenum or upper jejunum to the cecum or right colon; (3) visualization of the entire duodenum, particularly the third and fourth portions at the base of the transverse colon mesentery; and (4) abnormal position and mobility of the cecum or of the duodenum along the right gutter.

It is helpful to locate the ileocecal region and orient the ileal mesentery so that it lies flat on the surgeon's palm. If normal, the cecum lies to the right of the ileum. In many cases, the location of the mesentery is uncertain, but a narrow mesenteric attachment is usually apparent. Sometimes, only after the cecum and right colon separate at the duodenocolic isthmus, a malrotation is clearly evident.

### Reduction of Volvulus

With midgut volvulus, the colon is not evident as the abdomen is opened because it lies posteriorly. In addition, the small bowel may appear congested and blue, with dilated mesenteric veins (Fig. 86-23, *A*).

The entire mass of small and large intestine should be delivered from the peritoneal cavity, avoiding traction on the mesentery. With this maneuver, the twist at the base of the mesentery may be visualized (Fig. 86-23, *B*). The bowel should then be cradled between the surgeon's hands and the volvulus derotated in a counterclockwise fashion (Fig. 86-23, *C*). The author prefers to reduce the bowel in steps of 180-degree turns until the transverse colon and cecum are brought into view anterior to the mesenteric pedicle (Fig. 86-23, *D*). Improvement in the color of the intestine usually accompanies the reduction unless the bowel is already severely compromised or necrotic. Generally, two to three full rotations of the bowel are required to completely reduce the volvulus.

### Relief of Duodenal Obstruction and Division of Ladd Bands

After reduction of the volvulus, any duodenal bands causing obstruction should be identified; division is then begun at either the pyloric or the duodenojejunal end (see Fig. 86-23, *D*). The bands usually attach the duodenum to the cecum or the right colon near the superior mesenteric vessels, the so-called *duodenocolic isthmus*. Dissection is carried out close to the serosa of the duodenum (with careful attention to the superior mesenteric vessels) and to the hepatoduodenal ligament superiorly and medially. Obstructing bands may also involve the ileum or progress down onto the jejunum. Houston and Wittenborg[45] pointed out that these bands may also extend superiorly to the gallbladder and the liver. Sharp dissection is used in most cases. Fairly vascular attachments can be anticipated in older children with chronic duodenal obstruction.

In all cases, it is imperative to prove that no associated intrinsic obstruction exists. This can be tested by passing a nasogastric tube of adequate size or, alternatively, a catheter through a gastrotomy, through the duodenum, into the jejunum (Fig. 86-23, *E*). Demonstrating that air passes through the duodenum is not sufficient to rule out a duodenal diaphragm or "windsock" web, a condition that may be totally unsuspected in a neonate.

Once Ladd bands have been dissected, the duodenum should have a relatively straight downward course along the right abdominal gutter (see Fig. 86-23, *E*). Failure to lyse all the bands may cause recurring duodenal obstruction or midgut volvulus. Any temptation to "stabilize" the mesentery by fixation of the duodenum or colon should be resisted, because this procedure may actually increase the risk for recurrent obstruction from adhesions or internal hernia.[14,22,27,51]

The Ladd procedure is completed by performing an appendectomy. Some authors[28] have advised an inversion-ligation appendectomy to avoid the unlikely possibility of fecal contamination in an otherwise clean case. The cecum is then placed into the left lower quadrant to maximally widen the mesentery.

## LAPAROSCOPIC VERSUS OPEN REDUCTION

Minimally invasive techniques have been used to both diagnose and correct malrotation.[52–54] However, because laparoscopy is believed to cause fewer postoperative adhesions, theoretically, an increased risk of future volvulus may exist. The largest series to date is a single-institution, retrospective comparison of open and laparoscopic techniques used to correct malrotation.[55] The 29 patients who underwent a laparoscopic Ladd procedure had a shorter hospital stay and an earlier return to full enteral feeds. This cohort had no episodes of postoperative volvulus at a mean follow-up period of approximately 2 years. However, the authors readily acknowledge that the nature of the study and the relatively short follow-up period does not allow for definitive recommendations to be made. Therefore although laparoscopy may have benefits, until prospective trials are published comparing the open and minimally invasive approaches, no clear statement can be made regarding optimal operative management. At the authors' institution, they find laparoscopy helpful in diagnosing malrotation when imaging studies are equivocal; the Ladd procedure is typically performed via laparotomy.

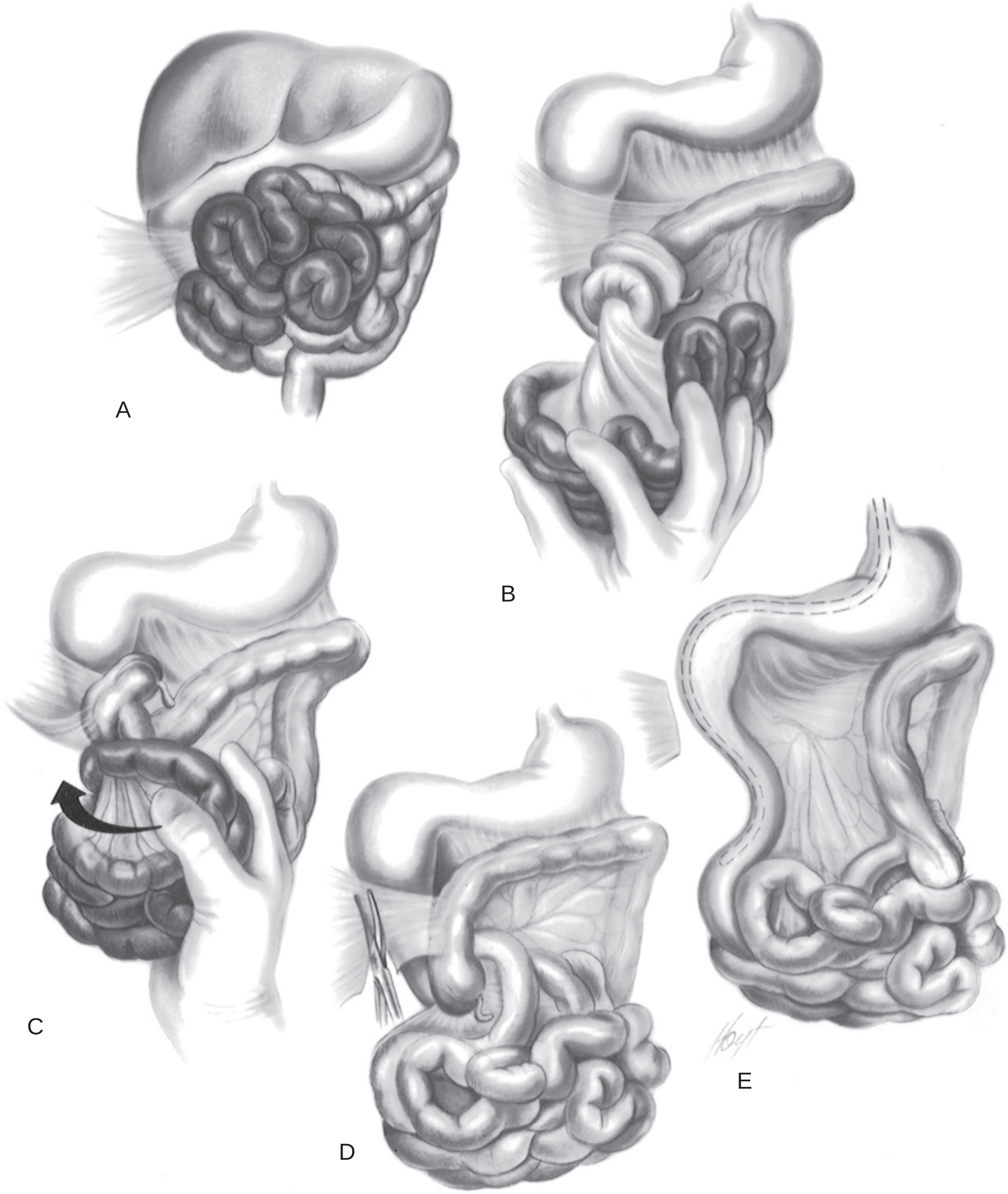


FIGURE 86-23 Malrotation of the intestine. **A,** Appearance of viscera as the abdominal cavity is opened. The small intestine is seen at once and seems to hide the colon. Vascular compromise of the intestine may be obvious. **B,** The entire intestinal mass is delivered out of the wound and drawn downward, showing the base of the mesentery. Coils of intestine or ascending colon are wrapped around the root of an incompletely anchored mesentery. The volvulus has taken place in a clockwise direction. The descending duodenum is dilated because of extrinsic pressure from Ladd bands or peritoneal folds that cross it. **C,** The volvulus is reduced by taking the entire intestinal mass in the hand and rotating it counterclockwise (in most cases). **D,** With reduction of the volvulus, the cecum lies in the right paravertebral gutter. The peritoneal folds from the cecum obstruct the duodenum. The folds are incised close to the lateral serosal border of the duodenum. The underlying superior mesenteric pedicle is identified and carefully preserved. **E,** Appearance of the intestines and ascending colon at the end of surgery. The duodenum descends along the right gutter. The small intestine lies on the right side of the abdomen, and the cecum and ascending colon are in the midline or on the left side of the abdomen. The superior mesenteric artery and its branches are left exposed, as shown. A nasogastric tube has been passed into the jejunum to rule out intrinsic obstruction. (Modified from Ladd WE, Gross RE: Abdominal Surgery of Infancy and Childhood. Philadelphia, WB Saunders, 1941.)

### INTESTINAL RESECTION AND SECOND-LOOK PROCEDURES

When the intestine appears viable, simple enterolysis and a Ladd procedure suffice. A localized gangrenous segment may be resected and a primary anastomosis performed if there is ample remaining bowel that is viable. The incidence of ischemic injury requiring resection varies with the duration of symptoms. Thirty percent of Torres and Ziegler's patients had intestinal necrosis,[28] but only 3 of 40 patients (7.5%) required resection in Seashore and Touloukian's series.[26]

Second-look laparotomy is usually performed when there are multiple areas of bowel of questionable viability, when the entire midgut appears nonviable, or when clinical signs and symptoms suggest progressive loss of intestine. At 12 to 24 hours, recovery of questionable bowel or demarcation of the areas of frankly necrotic bowel requiring resection is usually obvious.

Although the management of patients with frankly necrotic or marginally viable intestine must be individualized, three principles should be considered: (1) preserving the minimum length of intestine required for survival has the highest priority; the surgeon should err on the side of preserving intestine, particularly the terminal ileum and ileocecal valve, for a second-look procedure; (2) anastomoses between ends of intestine of questionable viability should be avoided; and (3) resection of the entire midgut will necessitate lifelong parenteral nutrition or small intestinal transplantation.

### ATYPICAL MALROTATION OR MALROTATION VARIANT

The diagnosis of malrotation variant is increasingly made by radiologists on upper GI contrast studies.[56] Patients with this finding are frequently referred to pediatric surgeons for evaluation and possible surgical treatment. These patients present a dilemma for surgeons because the risks of operation versus nonoperative treatment are not clear in this subgroup of patients, many of whom were diagnosed during a workup for presumed gastroesophageal reflux. The authors and their colleagues reviewed their experience with the surgical treatment of malrotation variant over a 5-year period,[39] during which 201 patients underwent operation for malrotation (excluding infants with diaphragmatic hernia and abdominal wall defects). Typical malrotation was present in 75 patients, and malrotation variant in 101. Volvulus and internal hernia were more common in typical malrotation (16% vs. 2% and 21% vs. 7%, respectively). Persistent symptoms and complications such as postoperative obstruction were more common in the malrotation variant group (21% vs. 12% and 12% vs. 0%, respectively). The only patients who presented with ischemic volvulus were those with typical malrotation. These data reaffirm the importance of operative correction of typical malrotation. However, because patients with malrotation variant were less likely to have volvulus or internal hernias, and because of the higher rate of postoperative complications in those patients, the authors questioned the need for operative correction in asymptomatic atypical malrotation patients or those with only gastroesophageal reflux symptoms.

### COLONIC OBSTRUCTION SECONDARY TO REVERSED ROTATION

In the past, division of the colon with anastomosis anterior to the duodenum was recommended for treating colonic obstruction secondary to reversed rotation. It is now recognized that this form of obstruction can be relieved by freeing the duodenum and the underlying mesenteric vessels anteriorly and laterally off the transverse colon.[36]

### MESOCOLIC HERNIA

Right mesocolic hernia is best treated by incising the lateral peritoneal reflection of the right colon and rotating the colon to the left, thereby freeing the small intestine.[42] Treatment of left mesocolic hernia is more technically challenging. The small intestine can sometimes be reduced through the neck of the sac. The key to repair and reduction is mobilization of the inferior mesenteric vein; this vein, which runs along the anterior margin of the neck of the sac, should be spared (see Fig. 86-14, *B* and *C*). The bowel can be reduced if an incision is made to the right of the vein. The peritoneum adjacent to the vein is sutured to the posterior peritoneum to close the neck of the sac.

### CECAL VOLVULUS

Reduction of cecal volvulus is followed by fixation or cecostomy when the bowel is viable. Resection is advised if the bowel is compromised.

## Postoperative Management and Complications

Return of intestinal function depends on the duration of obstruction and the extent of bowel compromise. In an uncomplicated extrinsic obstruction caused by duodenal bands, peristalsis returns in 1 to 5 days, at which point feedings may be initiated.[22] In patients without evidence of volvulus or obstruction, the authors no longer routinely decompress the stomach with a nasogastric tube. Older patients with chronic malrotation or those with evidence of chronic obstruction frequently have a prolonged ileus that requires nasogastric drainage and parenteral support.

Patients who have marginally viable bowel with mucosal injury and short-bowel syndrome pose special problems. Total parenteral nutrition is essential to sustain infants with massive loss of intestine until adaptation and compensatory growth of the residual bowel can occur.[57] Small amounts of enteral nutrition are recommended to encourage adaptation and provide nutrition for the intestinal mucosa. The need for gastrostomy tube insertion to assist in nutrition must be assessed individually; a gastrostomy tube does facilitate "drip" feeds.

Coombs and colleagues[25] described a group of children with malrotation who were older than 1 year and had recurrent and often long-standing symptoms suggestive of intestinal dysmotility. Such children did not seem to benefit from a Ladd procedure. These findings of pseudo-obstruction may be incidental or may be related to a neurogenic bowel injury from long-standing partial obstruction.

Complications encountered (aside from those related to malnutrition, diarrhea, and dehydration in short-bowel syndrome) are similar to those associated with any type of abdominal operation. Postoperative intussusception was noted in 3.1% of all patients who underwent a Ladd procedure, compared with 0.05% of other laparotomies.[58] The typical presentation was distention and bilious emesis between 5 and 8 days after the procedure. The incidence of postoperative adhesive bowel obstruction was 4%.

The incidence of recurrent volvulus is low. In the Boston series of 441 patients, only 2 had recurrent obstruction; in the Los Angeles series, no patients had recurrence.[27] Only 2 of our 159 patients who underwent a Ladd procedure had recurrent midgut volvulus.[39]

Death is associated primarily with peritonitis from extensive intestinal necrosis in midgut volvulus, late nutritional complications, or catheter sepsis, particularly in infants younger than 1 year. The mortality rate is at least 65% when more than 75% of the bowel is necrotic.[39]

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 87

# Other Causes of Intestinal Obstruction

Wolfgang Stehr and Cynthia A. Gingalewski

Intestinal obstruction can occur at any age from newborn infants to adults. The etiology of the obstruction varies greatly, depending on the age and past surgical history of the patient. Common congenital causes including atresia, stenosis, malrotation, Hirschsprung disease, imperforate anus, and meconium diseases of the newborn are discussed in detail in other chapters of this text. In this chapter, other common and uncommon causes of intestinal obstruction are reviewed.

## Embryology

With a few exceptions, the etiology of bowel obstruction in infants younger than 1 year is embryologic in origin. These entities are discussed in detail in other chapters. Where relevant, the embryologic basis of obstruction is discussed in this chapter.

## Spectrum of Disorders

Small bowel obstruction in infants and children is more common than large bowel obstruction. By far the most common of these is adhesive small bowel obstruction, which accounts for up to 60% of small bowel obstructions. Adhesions are followed by tumors (20%), hernias (10%), inflammatory bowel disease (5%), volvulus (3%), and various intramural and extramural causes of intestinal obstruction.[1]

## Postoperative Adhesions

Differentiating a prolonged postoperative ileus from an early postoperative bowel obstruction can be difficult. Radiographic demonstration of dilated bowel loops may not distinguish between the two entities. Adhesive small bowel obstruction most commonly develops after pelvic surgery including appendectomy, gynecologic procedures, and colorectal surgery. The obstruction is thought to be secondary to adhesive band formation in the pelvis, where the bowel is more mobile and likely to twist and obstruct around the adhesions.

The incidence of postoperative small bowel obstruction in children ranges from 2% to 30% and is greater in neonates. Festen[2] documented a 2.2% incidence of adhesive small bowel obstruction in 1476 abdominal operations. Eighty percent of obstructions occurred within 3 months of the initial operation, and 70% were secondary to a single adhesive band. The incidence was 57% greater in neonates than in infants and children and was more common after procedures for gastroschisis and atresias. Eighteen percent of children born with an abdominal wall defect developed a small bowel obstruction in a recent 30-year review.[3]

In children the most common inciting operation was appendectomy, and there was no difference in occurrence after perforated, nonperforated, or negative appendectomies. A 2007 review out of Kansas City comparing laparoscopic with open appendectomies showed an advantage of laparoscopic over open appendectomy, when comparing postoperative bowel obstruction from adhesions.[4]

A review of 1581 patients from the Scottish National Health Service Medical Record Linkage database showed that patients undergoing surgery on the ileum had the highest risk of readmission because of adhesions in the subsequent 5 years after surgery (9.2%). Formation/closure of ileostomy had the greatest risk (25%). In addition, 6.5% of children were readmitted after general laparotomy, 4.7% after duodenal surgery, and 2.1% after colonic surgery.[5]

### DIAGNOSIS

The key to the diagnosis of adhesive bowel obstruction is abdominal distention and emesis in a patient with previous abdominal surgery. In the early stages of intestinal obstruction, it may be difficult to discern obstruction from infectious gastroenteritis. Initially, the emesis may be nonbilious, but with time it progresses to bilious or "feculent" emesis. The child complains of crampy abdominal pain and has anorexia. With

a partial obstruction there continues to be passage of flatus or small stools. In children with complete obstruction, both cease. As the obstruction progresses, the child becomes increasingly lethargic. The presence of a fever or pain should make one suspect bowel compromise.

Physical findings may not be initially obvious, but abdominal distention with either high-pitched or hypoactive bowel sounds evolves over time. Eventual progression of the obstruction leads to continuous, localized pain that is not relieved by nasogastric decompression. This ominous sign is the only reliable predictor of ischemic intestine. In a series of 131 obstructions reported by Janik and colleagues,[6] persistent pain after nasogastric decompression was a 100% predictor of intestinal gangrene.

Radiographs can help to differentiate obstruction from infectious causes. All children should have at least two view radiographs of the abdomen (Fig. 87-1). Obstruction is manifested by dilated bowel loops with air-fluid levels. The presence of air in the colon and rectum may signify an early or partial bowel obstruction. Free intraperitoneal air is indicative of bowel perforation and requires urgent operative treatment. The diagnosis of intestinal obstruction can be confirmed with computed tomography (CT) or a contrast-enhanced upper gastrointestinal series with small bowel follow-through (UGISBFT) (Fig. 87-2). The advantage of a CT scan is that it can rule out other diagnoses and identify an abnormal vascular course or a transition zone of the obstruction.[7]

## TREATMENT

There continues to be debate whether immediate operation is warranted in all cases of small bowel obstruction as opposed to nonoperative management with nasogastric decompression. All children with suspected obstruction should receive aggressive intravenous fluid and electrolyte replacement and placement of a nasogastric tube to decompress the stomach. A complete blood count should be obtained because the presence of leukocytosis with a left shift in the differential count should raise suspicion of compromised intestine. The decision to proceed to the operating room should be based on the child's physical condition. If there is complete obstruction with fever, pain, and no passage of flatus or stool, the child needs immediate exploration.

Observation is warranted, however, if there is a partial bowel obstruction in the absence of fever, leukocytosis, and localized abdominal pain. Observation should include frequent abdominal examinations, serial abdominal radiographs, and frequent measurement of serum electrolytes. Nonoperative treatment was successful in 74% of patients in a retrospective review of 230 adhesive obstructions.[8] However, patients treated this way had a 36% incidence of recurrent episodes of obstruction as compared with a 5% to 19% incidence in those treated by lysis of adhesions.

Laparoscopic lysis of adhesions can be performed in instances of obstruction despite the presence of dilated intestinal loops. The more proximal the obstruction, the easier it is to accomplish adhesiolysis with laparoscopic techniques. The reported rate of bowel injury during open laparotomy for adhesive obstruction is 11%,[6] and there was a 32% conversion rate from laparoscopic to open technique because of an inability to find the transition point, inability to achieve pneumoperitoneum, dense adhesions, and gangrenous intestine.[9] Morbidity was higher in the open group and included pneumonia, prolonged ileus, and wound infection. A conversion rate of greater than 50% was found in another retrospective study in adults.[10] A higher incidence of complications was observed in the laparoscopically treated group including bowel injury and anastomotic leak. No such studies have been performed in children.

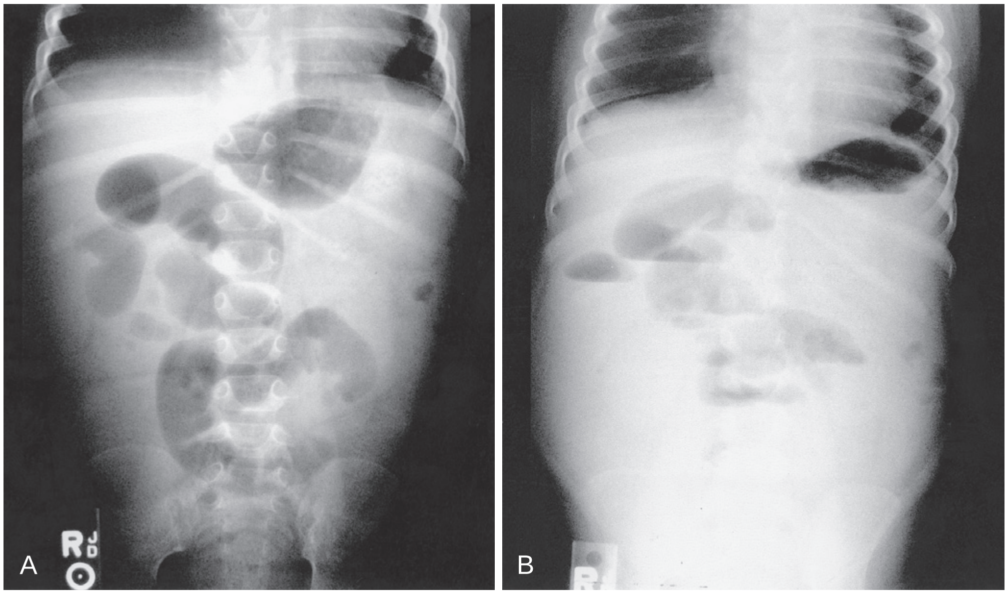


FIGURE 87-1 Complete intestinal obstruction. **A**, Supine plain abdominal radiograph demonstrating dilated small bowel loops and absence of air in the colon in a child who had previously undergone a Ladd procedure for malrotation. **B**, Upright abdominal radiograph from the same patient illustrating air-fluid levels in the dilated small bowel loops and absence of gas in the large intestine.

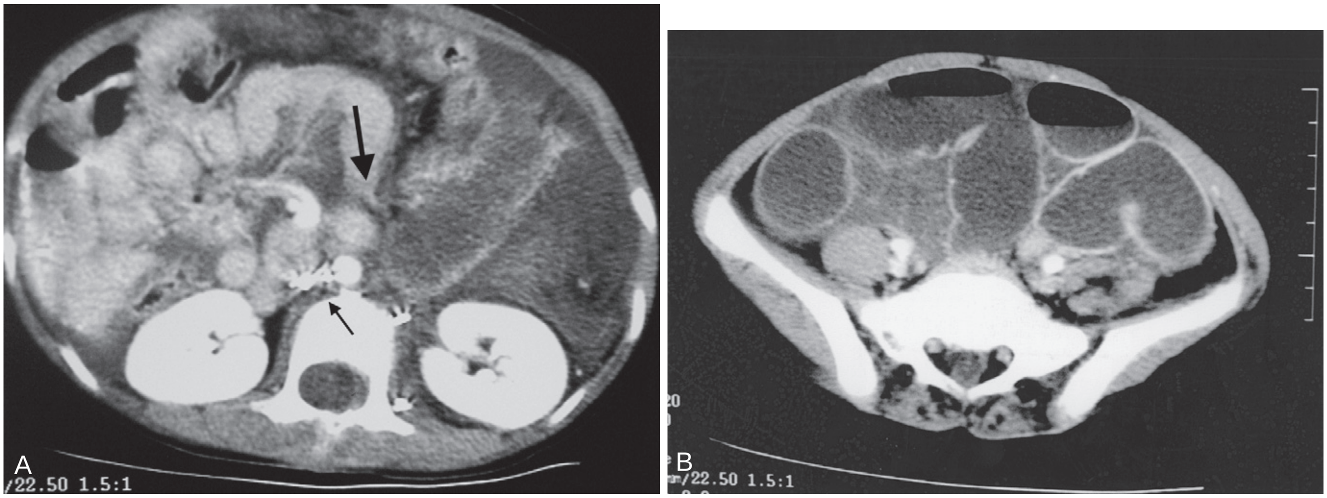


**FIGURE 87-2** Incomplete small bowel obstruction. **A**, Contrast computed tomography (CT) scan of child with a partial small bowel obstruction after resection of a ganglioneuroma. The *small arrowhead* points to surgical clips from the previous resection. The *large arrowhead* demonstrates the transition zone of the obstruction. Note the dilution effect of the contrast in the dilated bowel. Partial obstruction is noted with passage of contrast past the transition point. **B**, Contrast CT scan from the same patient demonstrating proximal dilated fluid-filled bowel loops in the pelvis with air-fluid levels present.

### PREVENTION

A multitude of reports have described the prevention of intra-abdominal adhesions; however, a "magic bullet" to prevent adhesion formation has yet to be found. General principles of gentle bowel handling, careful hemostasis, irrigation of the abdominal cavity, and prevention of prolonged bowel exposure to air have not eliminated the occurrence of adhesions. Commercially available adhesion barriers such as Seprafilm, a hyaluronic acid and carboxymethylcellulose membrane, have been widely used and publicized. Several clinical trials using Seprafilm have demonstrated a decreased incidence of postoperative adhesions in adults[11–13] and a decreased incidence and severity of postsurgical adhesions with Seprafilm in pediatric patients.[14]

However, one should avoid wrapping Seprafilm around an anastomosis because it may lead to an increased risk for anastomotic leaks. The only other substance that has shown a consistent reduction in adhesions in clinical trials has been Interceed.[15]

## Postoperative Ileus

In the majority of patients, postoperative ileus resolves within 5 to 7 days. Passage of flatus signifies the return of colonic function and usually indicates that the ileus has resolved. The duration of postoperative ileus is prolonged by use of narcotics in a dose-dependent manner. Anesthetic agents, excessive trauma to the bowel, intra-abdominal bleeding, and preoperative gastric obstruction also prolong the return of normal bowel function.

Opiates have an inhibitory effect on gastric motility, increase tone in the antrum and the first portion of the duodenum, and have a biphasic effect on the small intestine.[16] Morphine is initially stimulatory to phase II of the migrating motor complex (MMC), but this stimulation is followed by atony and slowing of gastrointestinal transit time.[17] Treatment with morphine antagonists such as naloxone have not proved beneficial in shortening the duration of postoperative ileus.[17,18]

Anesthetic agents exert their greatest antimotility effect on the large intestine because of the lack of intercellular gap junctions.[18] The anesthetic agents halothane and enflurane also cause decreased gastric emptying. Thoracic epidural anesthesia with local anesthetics increases splanchnic blood flow, impedes afferent and efferent inhibitory reflexes, and when administered in the thoracic region, has demonstrated a significant reduction in the duration of postoperative ileus.[19,20] Interestingly, lumbar epidural administration failed to have a similar effect on postoperative ileus.[21,22]

Laparoscopic surgery, early enteral feeding, and various pharmacologic agents have been used in an attempt to shorten postoperative ileus; early feeding has not shortened the duration of postoperative ileus.[23] On the other hand, both animal and human studies have demonstrated a reduction in ileus duration when the surgical procedure was performed laparoscopically.[24,25] Of the numerous pharmacologic agents tested, the only benefit in humans was achieved with cisapride (now unavailable except for compassionate use). The somatostatin analogue octreotide, known to inhibit several gastrointestinal hormones, shortened the duration of postoperative ileus in dogs.[26–28] Nonsteroidal antiinflammatory drugs (NSAIDs) help lessen the duration of ileus by reducing the dose of narcotic analgesia required. Metoclopramide hydrochloride (Reglan), a prokinetic agent that is a cholinergic agonist and a dopamine antagonist, stimulates phase II of the MMC. Repeated studies, however, have failed to demonstrate any benefit from postoperative administration. Erythromycin, a motilin receptor agonist, also failed to shorten the duration of postoperative ileus in prospective, randomized trials.[29] Recent attempts to postoperatively stimulate the cephalic-vagal axis through sham-feedings (chewing of gum) have been associated with improved outcomes but require further investigation.[30]

## Postoperative Intussusception

Children are more prone to the development of postoperative intussusception, especially after operative procedures for retroperitoneal tumors, Hirschsprung disease, and other neurocristopathies. The sudden occurrence of bilious emesis after a normal postoperative return of bowel function should make one suspect small bowel intussusception. The diagnosis can be made by a contrast-enhanced upper gastrointestinal series or an abdominal ultrasound. Because the majority of postoperative intussusceptions occur in the small bowel, they require surgical exploration for correction.

## Inflammatory Adhesions

Episodes of intra-abdominal inflammation including, but not limited to, ovarian torsion, ventriculoperitoneal shunt infection, Crohn disease, acquired immunodeficiency syndrome, and pelvic inflammatory disease can lead to adhesion formation and subsequent intestinal obstruction in the absence of previous surgical procedures.

## Hernias

Although hernias account for only 10% of small bowel obstructions, they are more likely to be associated with strangulation of the bowel. Such hernias include inguinal, ventral, and internal hernias. Internal hernias, caused by internal bands or defects in the mesentery after bowel resection, are likely to cause a "closed-loop" bowel obstruction. This condition can rapidly progress to bowel ischemia and is characterized by pain often out of proportion to an unimpressive abdominal examination.

Congenital hernias include paraduodenal hernias, inguinal hernias, internal hernias secondary to omphalomesenteric duct remnants, congenital bands of nonembryonic origin, and nonfixation of the falciform ligament. Postsurgical causes of hernia include incomplete closure of the mesentery and parastomal hernias.

### PARADUODENAL HERNIAS

Paraduodenal (mesocolic) hernias are rare congenital lesions that result from abnormal rotation of the gut. The name "paraduodenal" is a misnomer but implies herniation of the small intestine posterior to the mesocolon. A right mesocolic hernia occurs when the prearterial limb of the midgut fails to properly rotate around the superior mesenteric artery. The majority of the small bowel then remains to the right of this artery (Fig. 87-3, *A*). The etiology of a left mesocolic hernia is less clear. The rotation of the intestine is normal, and the intestine is introduced into an avascular area between the ligament of Treitz and the transverse colon, below the inferior mesenteric vein (Fig. 87-3, *B*). Fusion of the mesocolon and the mesentery of the duodenum is incomplete, thus resulting in a defect.[31] It may lead to incarceration of the jejunum and varying lengths of ileum in the left upper quadrant. Despite their congenital origin, mesocolic hernias are most frequently diagnosed in adults. Left mesocolic hernias are three times more common than those on the right. They are the most frequent cause of internal hernias and account for 50% of cases.

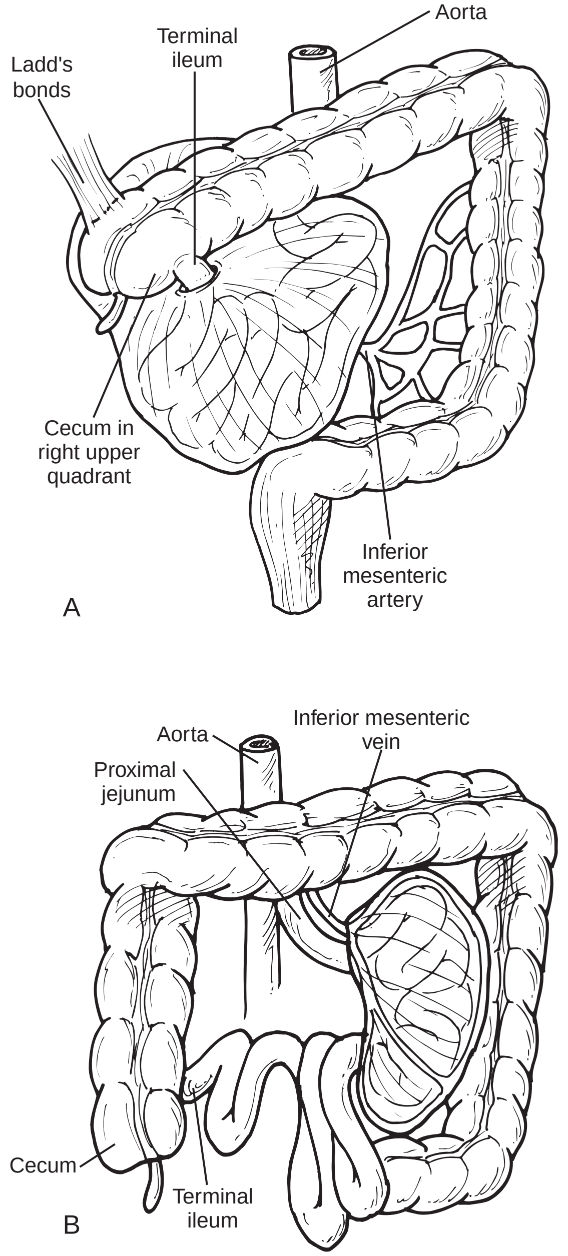


**FIGURE 87-3** Paraduodenal (mesocolic) hernias. **A**, Right paraduodenal hernia. Note the abnormal bowel rotation with the cecum in the right upper quadrant and the presence of Ladd bands. The majority of the small bowel is trapped behind the right mesocolon. **B**, Left paraduodenal hernia. The bowel rotation is normal in a left paraduodenal hernia. The small bowel becomes trapped behind the left mesocolon, posterior to the inferior mesenteric vein. (Modified from Willwerth BM, Zollinger RM Jr, Izant RJ Jr, et al: Congenital mesocolic (paraduodenal) hernia. Embryologic basis of repair. Am J Surg 1974;128:358-361.)

A high index of suspicion is necessary to make the diagnosis of a paraduodenal hernia. These internal hernias cause vague symptoms including recurrent bouts of abdominal pain, vomiting, abdominal distention, and melena.[32] Imaging techniques including an upper gastrointestinal series or CT scan are the only means of accurate preoperative diagnosis.

Surgical treatment of both right and left paraduodenal hernia consists of opening the sac, reduction of the small intestine, and repair of the defect. Sac removal should not be attempted. Laparoscopic repair of a paraduodenal hernia has also been reported.[33]

## OMPHALOMESENTERIC DUCT REMNANTS

The omphalomesenteric (vitelline) duct is a normal component of fetal development. It connects the fetal intestine to the yolk sac. When these structures persist in a newborn, they are called omphalomesenteric duct remnants. They vary in appearance from a fistula to the umbilicus, a fibrous band between the ileum and umbilicus, and a Meckel diverticulum. Though one of the most common congenital anomalies (2% prevalence in the population), they are least likely (2%) to cause symptoms. In a review of 46 cases, 28% of symptomatic omphalomesenteric remnants were associated with intestinal obstruction (intussusception, internal hernia, volvulus).[34] Treatment is surgical, and there have been reported cases of laparoscopic excision.[35]

## CONGENITAL BANDS OF NONEMBRYONIC OR INFLAMMATORY ORIGIN

The presence of intestinal obstruction as a result of congenital bands has been described sparingly in the literature. The etiology of these bands is unknown, but they are not secondary to known embryologic remnants such as omphalomesenteric duct or vitelline vessel remnants. A review of eight patients with anomalous bands demonstrated them to occur between the ascending colon and the terminal ileum (50%), the ligament of Treitz and the terminal ileum (25%), the right lobe of the liver and the terminal ileum (12.5%), and the right lobe of the liver and the ascending colon (12.5%).[36]

Patients may have chronic abdominal pain or an acute bowel obstruction. A high index of suspicion is required to make the diagnosis. Division of the band is therapeutic.

## NONFIXATION OF THE FALCIFORM LIGAMENT

The falciform ligament normally consists of two closely applied layers of peritoneum and attaches the liver to the anterior abdominal wall. It has three borders: the diaphragm, the anterior abdominal wall to the level of the umbilicus, and the free inferior edge of the liver, in which runs the obliterated umbilical vein. Failure of the peritoneum to fuse around the umbilical vein would lead to this unusual "nonfixation" of the falciform ligament and allow the small bowel to herniate around it like a congenital band (Fig. 87-4). The defect appears to be of congenital origin inasmuch as internal hernias around the falciform ligament have been reported in newborn infants.[37–39]

Such hernias commonly contain small intestine, but they can contain omentum or large intestine.[40]

The diagnosis is usually made in the operating room during exploration for an acute small bowel obstruction in the absence of external hernias or previous surgery. A preoperative CT scan showing intestine above the liver that is centered on the falciform ligament can be suggestive (Fig. 87-5). The presence of ascites is an ominous sign indicative of compromised bowel. Release of the obstruction by dividing the falciform ligament is therapeutic.

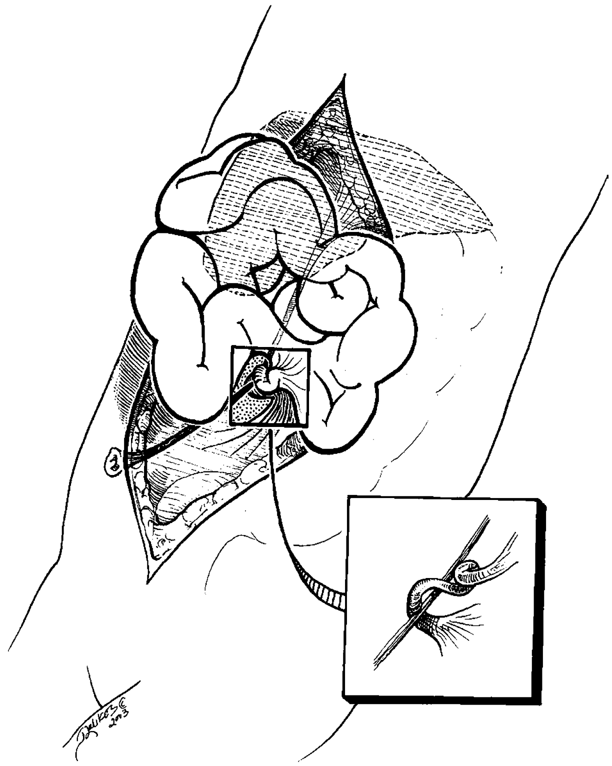

**FIGURE 87-4** Internal hernia secondary to nonperitonealization of the falciform ligament. The falciform ligament acts like a congenital band when it is not fixed to the anterior abdominal wall by the double layer of peritoneum. This allows the small bowel to herniate around the falciform ligament, thereby causing an internal hernia.

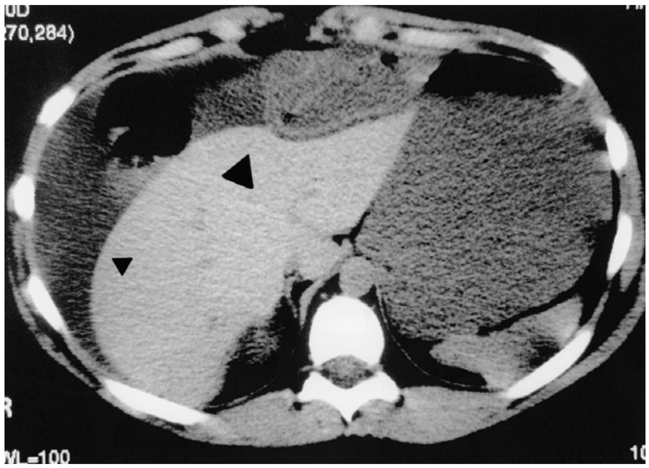

**FIGURE 87-5** Preoperative contrast-enhanced computed tomography scan of a patient with an internal hernia around the falciform ligament. The patient had feculent emesis and no past surgical history. The *large arrowhead* demonstrates small bowel loops around the falciform ligament, above the liver edge. The right colon is also noted to be above the liver in the right upper quadrant. The *small arrowhead* demonstrates the presence of ascites. The patient was found to have gangrenous small bowel loops present. The falciform ligament was divided, the gangrenous bowel resected, and primary anastomosis performed.

### MESENTERIC DEFECTS

During any surgical procedure involving bowel resection, great care must be taken to close all defects created in the mesentery. Closure can be performed with absorbable or nonabsorbable suture and in running or interrupted fashion. The advantage of interrupted suture is that unraveling of a single stitch is unlikely to make a large enough defect in the mesentery for an internal hernia to occur.

The risk for mesenteric hernias is particularly high in laparoscopic procedures with bowel anastomoses, specifically in gastric bypass procedures, because the closure of the mesenteric defect can be quite difficult in the laparoscopic setting, and a high index of suspicion and low threshold for reoperation should be applied in these patients.[41]

### PARASTOMAL HERNIAS

Parastomal hernias are a common problem after a colostomy. The incidence of parastomal hernia ranges from 2% to 35%. Most hernias appear within 2 years after creation of an ostomy and are more common in patients who are obese or malnourished. The use of steroids and postoperative wound infection also increase the risk. To minimize the risk for development of a parastomal hernia, the colon should be brought through the rectus muscle, the subcutaneous fat should be left in place, and the fascial defect created should not be excessive. Suture fixation of the bowel serosa to the stomal defect may reduce the risk for hernia in infants.

For repair, the colostomy should be taken down, if possible. In cases in which the colostomy is permanent, a small, asymptomatic parastomal hernia can be observed. Surgical repair should be offered when the hernia is large, interferes with appliance fitting, causes pain, or becomes incarcerated. Options include relocation, fascial closure, and mesh repair. The results of surgical repair in adults are dismal, with a recurrence rate of 33% to 50% after relocation, 50% to 100% after fascial repair, and 50% after mesh repair. A second recurrence of a parastomal hernia after initial attempts at repair is associated with even more dismal surgical outcomes approaching a 90% to 100% recurrence rate.

## Large Bowel Obstruction

### VOLVULUS

Though not an uncommon etiology of large bowel obstruction in adults, colonic volvulus is a rare entity in children. Several case reports, however, have described cecal, sigmoid, and transverse colon volvulus in children.[42–45] Associated medical problems include mental retardation, Hirschsprung disease, intestinal dysmotility, and chronic constipation. These children have an acute onset of abdominal pain and obstruction. Abdominal radiographs demonstrate dilated loops proximal to the obstruction, and barium enema is diagnostic by demonstrating the characteristic "bird's beak" appearance in the involved bowel segment.

Treatment options are sigmoidoscopy or colonoscopy, laparoscopy, or primary laparotomy with distorsion as the goal. Cecal volvulus should be managed by primary resection and anastomosis or cecopexy.[46] Volvulus of the transverse colon is the only bowel reported to twist in a counterclockwise direction. Resection plus end-to-end anastomosis is the treatment of choice for volvulus occurring in the transverse colon, splenic flexure, and sigmoid colon. In all cases, nonoperative reduction alone is not recommended because of the high risk of recurrence.

### CANCER

Only 1% of all colonic malignancies occur in patients younger than 30 years. Very few cases have been reported in children younger than 10 years. The mucinous adenocarcinoma, signet-ring variety, accounts for 48% of all tumors. In children, colon cancer is associated with rapid progression of disease and a poor prognosis. The overall 5-year survival rate is 2.5%.[4]

Treatment consists of surgical resection for cure or palliation. Unlike adult patients, chemotherapeutic regimens and radiotherapy provide little palliative or curative value.[47]

### COLONIC STRICTURE

Acquired colonic strictures can cause partial bowel obstruction, which may be high grade. Strictures may be the sequelae of necrotizing enterocolitis, inflammatory bowel disease, trauma, or cystic fibrosis (cystic fibrosis colonopathy). Treatment is similar for all and includes segmental resection and anastomosis.

## Miscellaneous Causes of Small and Large Intestinal Obstruction

### INTRAMURAL AND EXTRAMURAL LESIONS

Numerous causes of intramural and extramural lesions throughout the gastrointestinal tract can lead to intestinal obstruction. The obstruction can be a consequence of the lesion itself, secondary to intussusception with the lesion as a lead point, or due to volvulus around the lesion.

Various cancerous lesions occur both intramurally and extramurally including lymphoma (in particular Burkitt) and leiomyosarcoma. Any child older than 3 years with intussusception should have these diagnoses entertained as the culprit lead point. A detailed small bowel follow-through with specific attention paid to the right lower quadrant by a pediatric radiologist is helpful in identifying intraluminal lead points in this population.

Noncancerous causes include juvenile polyps of the colon, inflammatory polyps, submucosal hemorrhage, hemangiomas, and foreign body ingestion. Juvenile polyps are the most frequent type of polyp encountered in pediatric patients and are seen in 1% to 2% of children.[48] Their peak incidence is between 2 and 5 years. They are manifested as painless rectal bleeding. Initial complaints may also include a prolapsing rectal mass, mucopurulent stools, abdominal pain, and colocolonic intussusception. These polyps are hamartomas, and the etiology is unknown. Colonoscopy can be diagnostic and therapeutic with endoscopic removal at the time of diagnosis.

Inflammatory polyps, composed of chronic inflammatory cells such as eosinophils, are frequently found in the stomach

and small bowel, rarely in the colon, and are nonneoplastic. They can cause intussusception and obstruction at the level of the small bowel. They are frequently manifested as abdominal pain, and surgical excision is the treatment of choice. Because of their location in the small bowel, the diagnosis can be difficult to make. Endoscopy with a wireless capsule endoscope, as well as intraoperative endoscopy, may be helpful in locating the polyp.[49]

Submucosal hemorrhage can occur throughout the gastrointestinal tract. Causes include Henoch-Schönlein purpura, platelet disorders, anticoagulant therapy, and a complication of chemotherapy. They can also serve as a lead point for small bowel intussusception.

## FOREIGN BODIES

Ingestion of various foreign bodies including peanuts, phytobezoars, trichobezoars, and pica in the mentally disabled can cause partial or complete bowel obstruction in children. Common locations of intestinal obstruction caused by foreign bodies include the gastric outlet and terminal ileum. The ingestion of multiple magnets harbors its own set of risks for bowel obstruction, volvulus, and intestinal fistulas and usually requires operative exploration.[50]

## INFLAMMATORY PSEUDOTUMOR

Inflammatory pseudotumor (IPT) is synonymous with inflammatory myofibroblastic tumor (IMT) and plasma cell granuloma. IPTs represent a group of tumors that have been found throughout the gastrointestinal tract, thorax, head, and neck. The etiology of these lesions remains obscure. Histologically, these tumors consist of plasma cells, histiocytes, and lymphocytes in a matrix of myofibroblasts. Although they can be locally invasive, as a whole these tumors are benign.

Alimentary tract IMTs can cause obstructive symptoms, weight loss, and abdominal pain. Laboratory evaluation reveals anemia and elevation in the erythrocyte sedimentation rate. Typical abdominal locations include the appendix and stomach, but lesions have been reported to arise from the small intestine, colon, and Meckel diverticulum.

Treatment is complete surgical excision. The recurrence rate of this tumor ranges from 18% to 40%.[51] The risk of recurrence is greater with incomplete resection, and malignant degeneration has been associated with multiple recurrences of these tumors. There has been variable success with preoperative and postoperative treatment with NSAIDs in these patients.

## ASCARIASIS

A common tropical infection is infestation with the nematode *Ascaris lumbricoides*. The estimated worldwide prevalence of *Ascaris* infection is over 1 billion cases, and death primarily results from intestinal obstruction. Human transmission is hand to mouth. The infection is generally asymptomatic; however, heavy infestation (>60 worms) can cause partial or complete obstruction of the gastrointestinal tract or biliary tree.[52] The diagnosis is made by ultrasonographic demonstration of worms in the biliary tree, pancreas, or intestine. Treatment consists of antihelmintic chemotherapy with mebendazole, albendazole, levamisole, or pyrantel. If medical treatment fails, endoscopic retrograde cholangiopancreatography can be used to extract worms from the biliary tree, and surgical enterotomy can accomplish worm removal from the intestinal tract.

## POSTTRAUMATIC INTESTINAL STRICTURE

Acute perforations of the gastrointestinal tract are the most common intestinal injury after automobile accidents.[53] They are secondary to seat-belt trauma and are usually detected shortly after injury has occurred. A late sequela of a seat-belt injury is an intestinal stricture manifested as intestinal obstruction.

Abdominal pain and bilious vomiting 10 days to 3 weeks after blunt traumatic injury should lead one to suspect posttraumatic intestinal stricture.

## LYMPHATIC MALFORMATION

Cystic lymphatic malformations are rare causes of abdominal masses in infants and children. They are also known as *mesenteric* or *omental cysts* and can be manifested as an asymptomatic abdominal mass, with or without abdominal pain, intestinal obstruction, and volvulus. These are true cysts in that they are lined with endothelium, and it is postulated that they are secondary to ectopic proliferation of lymphatic structures that lack communication with the normal lymphatic system.[54] Mesenteric cysts may be found throughout the gastrointestinal tract and are most common in the ileum. They are best diagnosed by ultrasonography and appear as a well-circumscribed cystic structure with thin walls and septae. The diagnosis can be complemented by CT scan, which shows the extent of disease and rules out pancreatic, renal, and ovarian cysts. Treatment is complete surgical excision, which may require simultaneous bowel resection. The cyst can be marsupialized if complete enucleation is not possible. There has been a recent report of laparoscopic cyst excision in a young adult.[55]

## DUPLICATION CYSTS

Duplications of the gastrointestinal tract are uncommon congenital anomalies. They lie within the wall of a segment of intestine or within the mesentery. Duplications are diagnosed pathologically by the presence of smooth muscle in the wall of the cyst. They can exist anywhere in the gastrointestinal tract and are usually symptomatic early in life. Symptoms include an abdominal mass, pain, intestinal obstruction as a result of volvulus or intussusception, and free air secondary to perforation. The diagnosis can be made preoperatively with ultrasound and CT. Surgical excision is the treatment of choice.

## PSEUDOOBSTRUCTION

Intestinal pseudoobstruction is a syndrome in which there are signs or symptoms of intestinal obstruction without a mechanical lesion obstructing the intestinal lumen. Though typically associated with an older patient, pseudoobstruction can occur as a primary phenomenon in neonates, as well as be due to secondary causes in an adolescent patient (Table 87-1). The disorder is not confined to the small intestine. It is generally agreed that motility of the intestine is abnormal, the etiology of which is either myopathic or neuropathic.

Patients have recurrent attacks of variable length and frequency consisting of nausea, vomiting, abdominal distention, and diarrhea or constipation. They frequently have steatorrhea

| TABLE 87-1 Secondary Causes of Intestinal Pseudoobstruction |
| --- |
| Endocrine disorders |
| Diabetes mellitus |
| Pheochromocytoma |
| Hypoparathyroidism |
| Hypothyroidism |
| Neurologic disorders |
| Hirschsprung disease |
| Chagas disease |
| Familial autonomic dysfunction |
| Neurofibromatosis |
| Diseases involving intestinal smooth muscle |
| Muscular dystrophy |
| Nontropical sprue |
| Systemic lupus erythematosus |
| Pharmacologic causes |
| Narcotics |
| Tricyclic antidepressants |
| Phenothiazines |
| Clonidine |
| Amanita (mushroom) poisoning |

secondary to slow transit time and bacterial overgrowth in the small intestine. Radiographic studies demonstrate the slow gastrointestinal transit time with dilation of both small and large bowel loops.

Satisfactory treatment of this group of patients is difficult to achieve. After mechanical lesions are ruled out with a barium contrast study, the mainstay of therapy is medical. Erythromycin (50 to 100 mg) stimulates motilin receptors and enhances gastric emptying. At low doses it stimulates intestinal contractions, yet more is not better. At high doses it inhibits intestinal motility. Octreotide (50 μg, parenterally) has been used to stimulate rhythmic contractions of the small intestine. New treatment regimens aimed at serotonin receptors in the intestinal tract are now available (alosetron, 1 mg orally) or are currently in clinical trials. Surgical therapy is limited to patients who have a short segment of dysmotile intestine. Operation should be avoided in patients with diffuse dysmotility because recurrent symptoms and radiographic abnormalities are practically impossible to distinguish from adhesive small bowel obstruction in a previously operated patient.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 88

# Short Bowel Syndrome

Tom Jaksic, Ivan M. Gutierrez, and Kuang Horng Kang

The management of pediatric short bowel syndrome (SBS) remains a major clinical challenge. However, nutritional, medical, and surgical advances, in conjunction with the evolution of specialized multidisciplinary intestinal failure centers, have been associated with a significant improvement in patient outcome. Over the past 4 decades the mortality from pediatric SBS has decreased from almost 50% to approximately 10%.[1–3] The advent of promising new therapies suggests that further reductions in SBS morbidity and mortality are possible.

## Definitions

Pediatric intestinal failure may be defined as intrinsic bowel disease resulting in an inability to sustain growth, hydration, or electrolyte homeostasis. Classically SBS is a subset of intestinal failure consequent to actual small intestinal loss or resection. Mucosal enteropathies (i.e., microvillus inclusion disease, tufting enteropathy) and motility disorders (i.e., chronic intestinal pseudoobstruction [CIPO]) are other causes of intestinal failure that do not involve bowel loss. At times these etiologies coexist in a single patient. For example, a neonate with surgical necrotizing enterocolitis may have intestinal failure secondary to small intestinal loss, compounded by malabsorption and disordered motility due to damaged bowel that has remained in situ. In practice the terms *intestinal failure* and *SBS* are often used interchangeably.

Animal models of SBS are defined by a small intestinal resection of 80% or greater.[4] No such convention exists in patients, although the length of the remaining small intestine is highly correlated with parenteral nutrition (PN) dependence (Fig. 88-1). In the absence of any surgical bowel lengthening and tapering procedure, 35 cm of neonatal small bowel are associated with a 50% probability of weaning from PN.[5] However, a relatively wide variability is evident in Figure 88-1 and patients with much longer bowel lengths sometimes do not wean from PN. Poor motility and/or residual malabsorption in the injured remaining bowel may contribute to this finding. Conversely, neonates with as little as 10 cm of residual small intestine can sometimes be weaned from PN (Fig. 88-1).

The more premature the neonate, the more likely the intestine will subsequently grow in length, thus resulting in a greater capacity for adaptation. Some additional inaccuracies in small bowel length interpretation are introduced by different measurement techniques. The convention is to record the antimesenteric length with no tension applied to the intestine. Residual small intestinal length remains the major positive clinical predictor of ultimate enteral feeding tolerance.[5,6]

Although studies are somewhat conflicting, the presence of an ileocecal valve has historically been deemed a secondary favorable prognostic factor in SBS.[1,5] Conceptually it is important to realize that the presence of an ileocecal valve is a marker for remaining ileum, and this may in fact be the underlying important determinant for weaning from PN. The loss of colonic length has a relatively modest effect on nutrient transport because the colon's prime function is fluid and electrolyte absorption. The colon is also the site for some short chain fatty acid transfer. Reestablishing bowel continuity surgically sometimes significantly reduces intravenous (IV) hydration requirements, and the prompt closure of stomas is associated with improved SBS patient outcome.[5]

An alternate method of assessing intestinal mucosal mass is the serum citrulline concentration. This may be particularly useful if an accurate small intestine length measurement is unavailable. Citrulline is a nonstructural amino acid that is primarily synthesized in the intestinal mucosa, and serum citrulline levels are highly positively correlated with intestinal length and the ability to wean from PN.[7] Retrospective data indicate that SBS patients with a serum citrulline level persistently less than 12 μmol/L are usually unable to wean from PN.[7]

A purely functional definition of neonatal SBS may also be used. The simplest and most frequently applied is PN dependence for greater than 3 months.[5,6] More complex definitions based on amalgams of functional and anatomic considerations have also been suggested.[8]

## Etiology

The causes of pediatric SBS vary according to the specific clinical setting surveyed. The Center for Advanced Intestinal Rehabilitation (CAIR) at Children's Hospital Boston manages

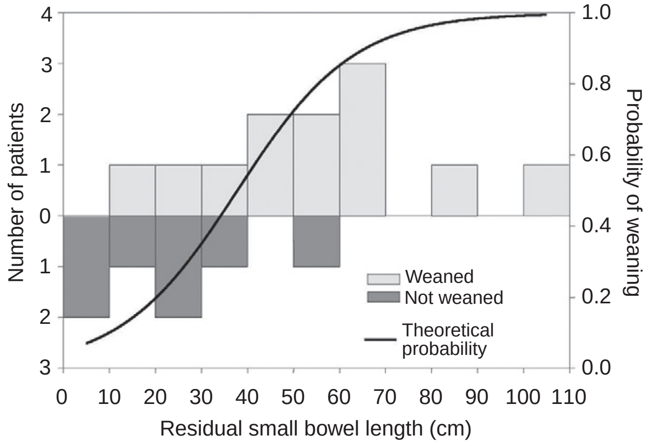


**FIGURE 88-1** This demonstrates the correlation between small intestinal length and parenteral nutrition dependence in neonates with short bowel syndrome. The *lightly shaded bars* represent those individuals weaned to full enteral nutrition while the *darkly shaded bars* reflect patients failing to attain enteral autonomy. The sigmoid-shaped *dark line* plots the theoretic probability of weaning from parenteral nutrition on the basis of the remaining small bowel length. It may be seen that 35 cm of residual small intestine is associated with an approximately 50% probability of weaning from parenteral nutrition. (Reproduced with permission from Andorsky DJ, Lund DP, Lillehei CW, et al: Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr 2001;139:27-33.)

more than 200 children with SBS, approximately 60 of whom are on home parenteral nutrition (HPN) at any one time. The primary etiologies of SBS in this cohort are necrotizing enterocolitis (35%), intestinal atresia (25%), gastroschisis (18%), and malrotation with volvulus (14%), with the remainder comprising a compendium of rarer diagnoses such as Hirschsprung disease extending into the small bowel (2%). When comparing the causes of intestinal failure among different centers it is important to note that the incidence of necrotizing enterocolitis (NEC) is highly dependent on birth weight (BW). Neonates between 500 and 750 gm have a 12% incidence of NEC and there is a symmetric 3% decrease in NEC occurrence for each 250 gm increment in BW over 750 gm.[9] It follows that centers with large numbers of extremely low-birth-weight infants (especially at the lower ranges) will have a greater preponderance of patients with SBS secondary to NEC. As noted for SBS in general, the prime predictor of eventual enteral tolerance in NEC is residual small bowel length.[6]

## Incidence, Morbidity, and Mortality

A large group of hospitalized neonates, encompassing 16 tertiary care centers in the United States, was found to have an incidence of SBS between 0.7% and 1.1% depending upon birth weight.[10] These estimates, however, did not include term infants. A study from the Province of Ontario, Canada, calculated the incidence of SBS to be 24.5 per 100,000 live births. The occurrence of SBS was much higher in infants born at less than 37 weeks estimated gestational age as compared to term newborns (353.7/100,000 live births vs. 3.5/100,000 live births, respectively). In this investigation the mortality was three times higher for SBS patients than a control group matched by underlying diagnoses.[11]

In 2002 it was estimated that 39,000 patients in the United States received HPN. Unfortunately, accurate data regarding underlying diagnoses and long-term outcomes remain unavailable. The American Society of Parenteral and Enteral Nutrition (ASPEN) in 2011 established the SUSTAIN cohort study registry for patients on HPN (www.nutritioncare.org). This should allow for more reliable future benchmarking of SBS morbidity and mortality.

Patients with SBS die from their underlying disease, as well as delayed complications such as intestinal failure–associated liver disease (IFALD), and sepsis. It is also of concern that approximately 1 out of 10 SBS patients successfully transitioned to full enteral nutrition has hepatic cirrhosis.[12] Despite this, recent reports indicate that long-term survival rates of 89% to 93% can be achieved in pediatric SBS patients.[1,3]

## Clinical Presentation

Patients with severe SBS tend to be intolerant of full enteral feeding, with resultant vomiting, diarrhea, or both. The clinical presentation of a young patient with SBS is reflected by the radiograph in Figure 88-2. It shows a typical bowel gas pattern, a central venous line for PN, and a gastrostomy tube (G-tube) for decompression and/or supplemental feeding. Even in the absence of mechanical obstruction, the residual small intestine may appear dilated. Although following small intestinal loss the bowel will lengthen with age, there is no compensatory acceleration in this process beyond the patient's genetic potential. This tendency of the bowel to dilate rather than lengthen is likely related to the fact that its blood supply is at a right angle to its longitudinal axis. The dilation of the bowel does tend to increase absorptive surface area, yet deleterious consequences such as dysmotility and bacterial overgrowth may follow.

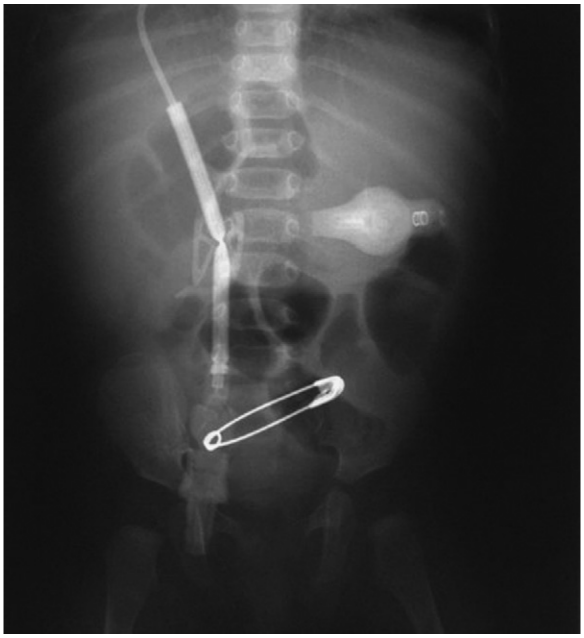

**FIGURE 88-2** This abdominal radiograph is stereotypical of a young child with short bowel syndrome. There are a few moderately dilated intestinal loops with no clear evidence of mechanical obstruction. A G-button and central line may be noted.

It is important to note that bowel adaptation is a prolonged process and may occur for years. Further, on a per-kilogram body weight basis, pediatric caloric and protein requirements drop dramatically over time.[13] Data from intestinal failure centers suggest that more than 80% of patients with SBS will eventually transition to full enteral nutrition. This conversion is not only more cost effective and desirable from a quality-of-life perspective but is also associated with a formidable improvement in morbidity and mortality.[5,14,15]

## Clinical Assessment

The first phase of successful SBS management is an accurate clinical assessment. As noted earlier in the definition of SBS, small intestinal length (or its proxy serum citrulline) is a key prognostic factor for determining the likelihood of attaining full enteral tolerance. Understanding the exact residual intestinal anatomy is also beneficial in identifying potential nutrient deficiencies. Patients without an ileum have reduced absorptive capacity for long chain fatty acids and are at risk for deficiencies of the fat-soluble vitamins A, D, E, K, the trace mineral zinc, and the water-soluble vitamin $B_{12}$.

An upper gastrointestinal series, with small bowel follow-through, should be done during the course of therapy if mechanical obstruction is suspected. This study will additionally evaluate the degree of intestinal dilation and estimate transit time. A contrast enema may be of utility in helping to rule out strictures and identifying atonic bowel segments. If Hirschsprung disease is suspected, a rectal biopsy or anal manometry is necessary. In the presence of chronic intestinal motility disorders, colonic and antro-duodenal manometry is useful in planning therapy. The specific underlying etiology of SBS is also pertinent. Because necrotizing enterocolitis patients frequently have remaining bowel that is functioning suboptimally, length considerations alone may underestimate potential problems. Neonates with gastroschisis may have disordered motility that precludes enteral feeding even if adequate bowel length is present.

Precise weight, length, weight for length, body mass index, and head circumference measurements should be followed longitudinally and compared with standardized growth charts. Overfeeding is usually evidenced by an increase in weight out of proportion to length and underfeeding by a plateau in weight gain. Body composition assessment reflected by anthropometry (i.e., triceps skin fold thickness and midarm circumference) is also important because alterations in fluid status or organ mass may affect weight without a change in lean body mass. Adequately calibrated PN maintains linear growth in pediatric SBS patients, and once they are weaned from artificial enteral and parenteral supplementation normal anthropometrics are usually attained.[16]

Micronutrient and vitamin deficiencies are frequent in patients with SBS and tend to be unmasked when PN is halted. A recent review of children with SBS noted a respective 70% and 77% incidence of vitamin and trace mineral deficiency.[17] An inadequacy may be present even if normal somatic growth is evident.[18] Trace elements that should be assayed are zinc, iron, copper, magnesium, manganese, and selenium. Aluminum is a contaminant that may be elevated in PN-dependent patients.

Metabolic bone disease has been widely noted in SBS patients.[19] It is related to an inability to provide adequate parenteral calcium and phosphate, calcium malabsorption, reduced physical activity, and inappropriate provision of vitamin D. Vitamin D status is best assessed by serum levels of 25-hydroxy vitamin $D_3$ because this form more accurately reflects hepatic stores. Dual-energy x-ray absorptiometry (DEXA) is used to follow bone density in older SBS children. In neonates a sudden spike in serum alkaline phosphatase may be the harbinger of pathologic fractures. These can be confirmed by plain radiographs.

The complete measurement of stomal, stool, and urine output is mandatory and aids appropriate fluid and electrolyte management. SBS patients are susceptible to diarrheal losses in the presence of viral (i.e., rotavirus) or bacterial (i.e., *Clostridium difficile*) infections. The presence of a nonanion gap acidosis with low bicarbonate is usually due to excessive small intestinal losses. Diarrhea and high stoma output will also cause loss of zinc. Zinc deficiency is evident clinically by acrodermatitis enteropathica, consisting of a rash of the face, hands, feet, and genitalia. Although zinc status is notoriously hard to determine because of stores present in bone, adequacy is estimated by serum levels. Gastrointestinal sodium losses are also frequently seen in SBS, and a urinary sodium concentration of less than 10 mEq/L is a better indicator of diminished total body sodium stores than serum sodium.[20] Low sodium reserves result in growth failure.[21]

At times the presence of variant quantities of red blood per rectum may be noted in children with SBS. The common causes are bacterial overgrowth, allergic enteritis, and anastomotic ulcers. Endoscopy with biopsy and quantitative culture is informative in such patients.[22] Less frequently global ischemia is the etiology of intestinal blood loss, and plain abdominal films may show pneumatosis.

The timely diagnosis of the SBS-engendered complications, IFALD, bacterial overgrowth, and catheter-associated blood stream infection (CABSI) is also extremely important and is discussed later in “Medical Management.”

## Nutritional Management

The nutritional management of intestinal failure patients is predicated on an appropriate provision of proteins, carbohydrates, lipids, electrolytes, vitamins, and trace minerals. Adequacy is judged by attaining optimal growth and development while minimizing the problems linked with intestinal failure.

It has been shown that both breast milk and amino acid (elemental) formulas are associated with a more rapid transition to full enteral nutrition in SBS neonates.[5] Interestingly, allergic (cell mediated) enteritis is not uncommon in young SBS patients because the mucosal barrier to proteins is compromised.[22] If allergic enteritis is suspected, amino acid formulas are used preferentially because they eliminate the possibility of peptide-mediated allergic responses. With time allergies tend to improve, and in infants the consumption of solid food can actually decrease diarrheal output. As soon as it is safe, oral intake is encouraged because oral aversion develops in SBS children and is difficult to overcome. Successfully orally fed patients tend to exhibit “hyperphagia,” a food requirement that seems excessive and is secondary to the obligate malabsorption of nutrients caused by SBS.

The benefits of enteral nutrition in SBS include decreased complications, higher survival, improved adaptation, and lower cost.[5,14,15,23] In the presence of inadequate oral intake, supplementation by direct enteral access is required. The placement of a gastrostomy allows for continuous or bolus enteral nutrition. The advantage of continuous feeds is that a relatively lower volume of nutrients is provided per unit time and intestinal transport mechanisms are less likely to be overwhelmed. Hence fluid and nutrient absorption tends to be improved.[24] Supplemental continuous feeds are usually given at night, whereas oral feeds are encouraged during the day.

No consensus exists regarding the optimal rate at which enteral feeds may be safely advanced, but initial increases of 10 mL/kg/day are reasonable. A common reason for limiting enteral nutrition is a stool or stoma output of greater than 2 mL/kg/hr. Although fluid/electrolyte problems and perianal skin irritation may ensue, clinical judgment is warranted and liberalization of this criterion may be feasible in stable patients. The provision of soluble fiber such as pectin may transiently worsen stool output before improving it, and its benefits are primarily associated with its effect on the colon.[25]

If upper gastrointestinal motility is problematic, a G-tube can be changed to a gastrojejunal tube (GJ) tube. The gastric portion of the GJ tube is used for decompression while feeds are undertaken distally. Disadvantages of GJ tubes are that radiologic replacement is necessary if they dislodge and that in severe SBS a portion of the potential absorptive surface is bypassed. GJ tubes are particularly useful if one of the reasons for the lack of enteral feeding advancement is refractory vomiting.

The enteral administration of prebiotics (substances that promote the "good" bacteria in the intestine) and probiotics (the "good" bacteria themselves) is highly controversial in SBS. No clear benefit has yet been established. In SBS patients who still have central lines, catheter-associated bloodstream infections have been reported with both bacterial and yeast probiotics.[25,26] It is unclear if the mechanism for these infections is translocation across the intestinal mucosal barrier or aerosolization of the organisms and resultant contamination of the line hub.

If appropriate growth cannot be obtained enterally, then PN is started. PN is a life-saving therapy for pediatric SBS that was first reported in 1968 and has become the standard of care.[27] PN formulations consist of amino acids, glucose, electrolytes, lipids, trace minerals, and vitamins. There is little compelling evidence that patients with SBS in the convalescent phase require parenteral amino acid and caloric allotments different from comparable healthy individuals. Both overfeeding (causing fatty liver, hyperglycemia, and increased $CO_2$ production) and underfeeding (resulting in poor growth) should be avoided.

Cycling of PN involves the provision of total fluid and nutrient allotments in less than 24 hours. From a practical standpoint it allows the patient and family to be free from PN for a portion of the day. It also tends to avoid persistent hyperinsulinism and theoretically decreases the likelihood of hepatic steatosis. Cycling is precluded if the serum glucose level decreases to below 60 mg/dL. The provision of enteral nutrition during the time of cycling off PN counteracts the tendency toward hypoglycemia. In an effort to maintain glucose stores, neonates are not left off PN for more than 6 hours.[28] In older children a minimum 12-hour period completely off PN is the therapeutic target.

The transition from parenteral to enteral nutrition is initiated in individuals who are growing and are tolerating a substantial allotment of enteral calories. The patient's parenteral intake is weaned (usually by reducing the amount of PN and then finally skipping a day of PN) while growth parameters are followed closely. If growth remains adequate, further nonconsecutive days of PN are eliminated until complete weaning has transpired. Hydration fluid may still be necessary to maintain fluid homeostasis.

Because bowel rehabilitation is a protracted process, the home provision of parenteral and enteral nutrition is often a necessary and desirable component of therapy. This is a feasible option throughout the United States, but meticulous physician monitoring is necessary. Peer support for HPN patients and their families is available through the Oley Foundation (www.oley.org).

# Medical Management

The medical management of pediatric patients with SBS focuses on the amelioration of complications induced by intestinal failure and the promotion of bowel adaptation.

## INTESTINAL FAILURE–ASSOCIATED LIVER DISEASE

The exact cause of IFALD remains to be determined. Known risk factors include low birth weight, prematurity, duration of PN, and number of septic episodes.[5,29,30] IFALD is reflected biochemically by elevations of serum transaminases and direct bilirubin, followed later by increases in the PT and INR. Once splenic enlargement occurs, thrombocytopenia may evolve. Hypoalbuminemia is usually an even later finding. Clinically one may note persistent jaundice, scleral icterus, and an enlarged liver and spleen. A large spleen may also portend thrombocytopenia. Routine liver function assessment is mandated in PN-dependent patients with SBS, and any signs consistent with portal hypertension require further Doppler ultrasound evaluation of the liver, spleen, hepatic arteries, portal vein, and hepatic veins. Liver biopsies of patients with IFALD show cholestasis, bile duct proliferation, periportal inflammation, and variable amounts of fibrosis.[12]

The improvement of IFALD is associated with a normalization of the direct bilirubin followed by a delayed resolution in elevated serum alanine aminotransferase concentrations.[31] Despite the normalization of bilirubin levels, significant residual liver damage and even cirrhosis may be present on subsequent liver biopsy.[12] In general liver damage of a degree less than cirrhosis is reversible. A recently reported nonradioactive IV $^{13}$C-methionine breath test differentiates cirrhotic from noncirrhotic infants with IFALD.[32] The prevalence of PN-associated cholestasis in neonates has been reported to be 25% to 33%, but recent therapy has reduced this substantially.[3,5,33]

The most efficacious treatment for IFALD is the institution of full enteral nutrition. This is associated with a normalization of direct bilirubin and elimination of the need for permanent venous access (the prime cause of sepsis in SBS). In a cohort of infants with IFALD and severe cholestasis it was noted that one quarter manifested a rapid decrease in serum direct bilirubin with the institution of enteral feeds and that

all patients normalized their direct bilirubins 3 to 4 months after the attainment of full enteral nutrition.[14] This argues strongly for the early and persistent advancement of enteral feeds in SBS.

In certain SBS patients the conversion to enteral feeds is impossible; however, modification of IV lipid dose and type is successful in avoiding and treating IFALD. For more than 10 years it has been known that the administration of standard soy-based (omega-6) IV fat emulsions (Intralipid) at greater than 1 gm/kg/day is associated with the evolution of IFALD.[34,35] Conversely, the infusion of lipid emulsions at doses of less than or equal to 1 gm/kg/day has been demonstrated to help prevent and treat IFALD in pediatric SBS patients.[35,36] Although concern for lipid deficiency states exist with fat restriction, biochemical evidence of essential fatty acid deficiency in neonates treated with omega-6 lipids at 1 gm/kg/day is rare. Even lower parenteral lipid allotments of less than 0.5 gm/kg/day have been suggested for the treatment of cholestasis, but lipid deficits do occur at these doses.[36]

The classic clinical sign of essential fatty acid deficiency is a dry, scaly rash, and its biochemical hallmark is an elevated triene-to-tetraene ratio. In human nutrition the requirement for essential fatty acids (α-linolenic acid, linoleic acid) is estimated to be only 2% of total calories provided; however, the lipids that are truly essential in neonates remain to be fully defined and may include the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[37] If lipid restriction is used in SBS patients, additional parenteral glucose calories are necessary to meet caloric requirements and complete lipid profile monitoring on a monthly basis is recommended.

A new finding in neonates with SBS is that the provision of parenteral fish oil (omega-3 fatty acids) at 1 gm/kg/day is associated with the reversal of hyperbilirubinemia (in 89% of patients) and that it has no evident adverse effects.[3,38] In these studies, resolution of cholestasis was achieved in a mean time of 81 days. This is roughly equivalent to the interval for normalization of direct bilirubin seen in children with IFALD after full transition to enteral feeding.[14] It is also of interest that the protracted provision of fish oil emulsions (containing primarily EPA and DHA) at 1 gm/kg/day was not associated with biochemical evidence of essential fatty acid deficiency in neonates.[39] The commercial product Omegaven, an IV fish oil formula, is not U.S. Food and Drug Administration (FDA) approved; however, it may be obtained on a compassionate-use basis with an investigational new device (IND) application as rescue therapy for patients with established IFALD. A randomized controlled trial of Omegaven at 1 gm/kg/day versus an equivalent quantity of soy-based lipid (Intralipid) has been initiated as a prophylactic treatment for pediatric IFALD. A randomized controlled trial of an FDA-approved oral fish oil preparation as therapy for SBS children with an elevated alanine aminotransferase (ALT) has also commenced. The mechanisms by which omega-3 lipids exert their putative protective effects on the liver remain to be elucidated, but it is known that the omega-3 fatty acids are antiinflammatory, whereas the omega-6 fatty acids tend to be proinflammatory.[40]

Other novel lipid emulsions are also being tested. SMOF, which contains lipids as 30% soybean, 30% medium chain triglycerides (MCT), 25% olive oil, and 15% fish oil, has been shown to be well tolerated in surgical patients.[41] Efficacy data in infants with IFALD are currently being obtained in a randomized controlled trial comparing SMOF to soybean-based Intralipid (both at 2 gm/kg/day).

In the presence of the described case series data, we use a prophylactic lipid strategy. This approach is additionally supported by the finding that the majority of patients with SBS, even those successfully enterally salvaged, appear to have fibrosis or cirrhosis on liver biopsy.[12] Hence all SBS patients (including neonates) who are not on a randomized controlled protocol and are projected to be PN dependent for longer than 3 weeks are placed on Intralipid at 1 gm/kg/day. If a patient evolves a direct bilirubin elevation higher than 2 mg/dL for 2 consecutive weeks while on lipid restriction (1 gm/kg/day), we switch lipids to Omegaven at 1 gm/kg/day. With this policy patients have attained adequate growth, not demonstrated biochemical fatty acid deficiency, and usually normalized their direct bilirubin levels. It is acknowledged that in the absence of randomized controlled trial data, the ideal lipid solution and dosing strategy remains to be determined.

Once some enteral intake is possible in patients with IFALD, the use of ursodeoxycholic acid to promote bile flow is considered. This medication may be taken orally or administered through a G-tube. Side effects are rare, but efficacy has not been well established in SBS patients with IFALD. Ursodeoxycholic acid has been studied prospectively in cholestasis of pregnancy, and reductions in transaminase elevations and hyperbilirubinemia have been noted.[42]

A concern in PN-dependent patients with IFALD is the potential for accumulation of copper and manganese in the liver.[43] Whether these trace elements cause an actual pathologic overload state in IFALD patients is undefined, but the usual practice is to halve the dose of the trace mineral mix in the PN and follow serum levels to ensure that no deficiency states evolve.

## CATHETER-ASSOCIATED BLOODSTREAM INFECTIONS

SBS patients often require a central venous catheter for the administration of PN or chronic hydration. This type of line may be placed at bedside, in the operating room, or in the interventional radiology suite. Key technical elements of insertion include the maintenance of aseptic technique, avoiding the ligation of vessels and obtaining radiologic confirmation of line position. Experienced interventional radiologists can even use collateral vessels as a means to enter the central circulation.

One of the major complications of central venous lines is catheter-associated bloodstream infections (CABSIs). Various protocols have been implemented to standardize line care, and salutary results have been reported.[44] However, SBS children on HPN remain a high-risk group, perhaps because of stool contamination of the central line or bacterial translocation. Their baseline infection rates are approximately 10/1000 catheter days, and the most frequent causative organisms are enteric gram-negative bacteria.[45]

Any suspicion for CABSI needs to be thoroughly assessed. A child with a catheter and symptoms of fever, lethargy, irritability, or ileus (abdominal distension) may have CABSI. The most important investigation to confirm CABSI is a blood

culture through the central line. If the patient's clinical presentation is congruent with CABSI, broad-spectrum IV antibiotics (such as a combination of vancomycin and piperacillin/tazobactam) are started immediately through the central line, as soon as blood cultures have been obtained. In the event that 48-hour blood cultures are negative, antibiotics may be halted. Otherwise, a 14-day course is completed. Once the organism's sensitivities are available, the antimicrobial therapy can be narrowed. Hemodynamic instability and fungal infections mandate central line removal. Three consecutive days of positive bacterial blood cultures despite appropriate IV antibiotics also usually culminate in catheter loss.

Ethanol has been demonstrated to have the ability to penetrate the biofilm that forms on central lines, and no bacteria or fungi have been reported to be resistant to this agent.[45,46] A recent retrospective study of infants with SBS who were on HPN and received 70% ethanol locks three times per week showed a greater than fourfold reduction in CABSI (from 9.9 to 2.2 infections/1000 catheter days) and a significant decrease in the need for line replacement.[45] It should be noted that the administration of metronidazole in patients with ethanol lock therapy may cause a disulfiram type reaction. A randomized controlled trial of ethanol locks for pediatric SBS has been registered.

## BACTERIAL OVERGROWTH

Bacterial overgrowth can occur in up to 60% of patients with SBS.[47] Areas of disordered motility and bowel dilation offer an ideal environment for abnormal bacterial propagation. The adverse effects of bacterial overgrowth consist of abdominal pain, worsening motility, mucosal ulceration with bleeding, deconjugation of bile acids, and the generation of toxic byproducts such as D-lactic acid. It is also thought (though not proven in humans) that bacterial overgrowth potentiates translocation and hence septicemia.

The treatment for suspected bacterial overgrowth is largely empiric. A typically used approach is the enteral administration of antibiotics for 7 days followed by an interval of no antibiotic administration for a week or greater. Antibiotics that are commonly used include those effective against anaerobes (i.e., metronidazole) or gram-negative organisms (i.e., ciprofloxacin). Endoscopy with quantitative duodenal cultures to guide therapy appears to be useful in selected cases,[22] and bowel lengthening and tapering operations should be considered in those SBS patients where the complications of bacterial overgrowth cannot be managed medically.[48]

D-lactic acidosis is a problem associated with SBS and bacterial overgrowth. In the course of normal anaerobic mammalian metabolism,[49] L-lactate is generated and easily converted to L-pyruvate, rendering it available for intermediary metabolism. However, bacteria produce D-lactic acid. This moiety is not metabolized by mammalian enzymatic systems and hence toxic levels can accumulate. Signs of D-lactic acidosis in neonates include an anion gap acidosis and seizures, whereas older children may additionally demonstrate confusion, slurred speech, and delayed cognition. The diagnosis is confirmed by laboratory assay of serum D-lactate. The treatment for this condition is rehydration and eradication of the underlying bacterial overgrowth using enterally administered antibiotics.

Another problem found with bacterial overgrowth is that serum vitamin $B_{12}$ levels may be inaccurate. Because bacteria can produce a biologically inactive analogue, accurate assessment for vitamin $B_{12}$ deficiency in SBS requires the measurement of serum methylmalonic acid and homocysteine.[50] If vitamin $B_{12}$ (which acts a cofactor) is not present in sufficient quantities, the metabolism of methylmalonic acid and homocysteine is impaired, hence elevating the serum concentrations of these substrates. Should a deficiency state be revealed, vitamin $B_{12}$ can be supplemented intravenously, by intramuscular injection, or in older children intranasally.

## DECREASED INTESTINAL MOTILITY

Bowel motility disorders are relatively frequent in SBS neonates and children. Erythromycin administered orally or directly into the stomach increases gastric emptying and improves antroduodenal coordination. Studies in normal individuals indicate that this augmentation of motility is, at least in part, due to the induction of phase III of the migrating motor complex.[51] Azithromycin, a longer-acting analogue of erythromycin, may also be used to improve gastric motility. Tachyphylaxis to both erythromycin and azithromycin is common.

In pediatric SBS the use of other agents that may promote motility is problematic. Octreotide may accentuate bowel ischemia, whereas metoclopramide can induce tardive dyskinesia. The latter complication has resulted in the FDA issuing a "black box" warning regarding the protracted use of metoclopramide. Domperidone is available for the treatment of gastroparesis in the United States only by an IND application through the FDA because of concerns regarding cardiac arrhythmias. In 2000 cisapride was also withdrawn from the U.S. market due to its association with the induction of torsades de pointes in susceptible individuals. Cisapride may be obtained from the manufacturer for patients who meet specific selection criteria (including a normal electrocardiogram), follow a defined monitoring protocol, and use a regulated dosage regimen. The reason that cisapride is still used, despite its potential for serious adverse side effects, is that it promotes motility in the stomach and throughout the small intestine.[52]

## INCREASED STOMA OUTPUT OR DIARRHEA

Diarrhea or high stoma output is common in pediatric SBS. Ileostomy effluent has high contents of zinc (17 mg/L), so careful monitoring and repletion are necessary.[53] Stoma refeeding may help obviate deficiency states and is generally an effective method of promoting fluid and nutrient absorption. If no mechanical, ischemic, or infectious problems are evident, loperamide may be used to decrease stool or stoma output. Unfortunately, loperamide elixir is sometimes solubilized in alcohol and this will cause paradoxical diarrhea in SBS. Alternatives include a specific request to the pharmacy that loperamide elixir be compounded without alcohol or the use of loperamide pills (that may be crushed and administered as a water suspension).

## HYPERGASTRINEMIA

It has been estimated that 50% of pediatric patients with SBS have gastric hypersecretion that manifests as high output and low pH.[54] As gastrin degradation occurs in the intestine, it is surmised that SBS with attendant intestinal loss may lead to elevated levels. The mechanism causing hypersecretion may

actually be more complex because many gastrointestinal regulatory hormones that act on the stomach are synthesized in the small intestine. The period of high gastric output tends to be early in the clinical course following massive intestinal excision and can be effectively blocked by proton pump inhibitors or H2-receptor antagonists. However, because idiopathic upper intestinal dysmotility and vomiting are frequently associated with intestinal failure, more extended courses of acid blockade may be necessary.

### PROMOTING BOWEL ADAPTATION

Bowel adaptation following substantial intestinal loss is characterized by enhanced villus height, greater crypt depth, thicker muscle, and an increase in protein and deoxyribonucleic acid content.[55,56] Although studies in humans are difficult, clinical data would suggest that adaptation begins within days of intestinal resection and progresses for years. This process may be quantified by an increase in the absorption of nonmetabolized sugars (D-Xylose and 3-0 methylglucose), higher serum levels of triglycerides and fat-soluble vitamins, improved weight retention, and the augmented synthesis of the nonstructural amino acid citrulline within the intestinal mucosa.[4,7,57] The two major means by which intestinal adaptation can be promulgated are the administration of intraluminal nutrients and the use of various trophic hormones. The best-studied hormonal therapy in SBS is a 33–amino acid peptide derived from the proglucagon gene called glucagon-like peptide 2 (GLP-2).

GLP-2 appears to enhance adaptation in most SBS animal models and is released by L-cells that are primarily resident in the ileum and right colon. The subcutaneous injection of teduglutide, a protease resistant form of GLP-2, was found in a randomized controlled trial to significantly increase villus height, plasma citrulline concentration, and lean body mass in adult patients with SBS.[58] A recently reported, but as yet unpublished phase III trial of teduglutide, appeared to attain its primary statistical end point of a 20% reduction in PN volume in 63% of treated adult SBS patients versus 30% of controls. As yet no clinical trial using teduglutide in pediatric SBS patients has been started. A detracting aspect of GLP-2 therapy is that its effects seem to be predicated on continued administration of the agent. Theoretic concerns also exist regarding the induction of gastrointestinal malignancy.

Growth hormone has been tested in adult SBS patients. However, an initially encouraging open-label study suggesting improved intestinal adaptation along with a decreased requirement for PN was not confirmed by a randomized prospective controlled trial.[59,60] Other trophic hormones with potential efficacy, but not as yet studied in humans with SBS, are insulin-like growth factor-1 and epidermal growth factor.[61]

## Surgical Treatment

The surgical treatment options for patients with SBS include bowel conservation at the time of first presentation, autologous intestinal reconstructive surgery, and intestinal transplantation.

### BOWEL CONSERVATION

The initial surgical operation in SBS is aimed at preserving as much intestine as possible. In cases where the viability of the bowel is in question, the use of a "second-look" operation within approximately 24 hours may be used. With this approach, marginally viable intestine is left in situ, the patient is resuscitated, and the bowel is then reassessed at a second operation. Only the frankly necrotic intestine is then excised. The use of a temporary transparent plastic silo to cover the bowel is also helpful to avoid the risk of inducing abdominal compartment syndrome. With the silo approach, delayed abdominal closure can be accomplished once bowel edema has subsided.

The prompt establishment of bowel continuity through stomal closure is associated with more rapid weaning from PN.[5] Usually the surgeon waits approximately 6 weeks between operations in an effort to minimize the vascularity of any adhesions that may have formed. In practice the closure of stomas is often governed by the anticipated stress that the operation would place on the ventilatory capacity of the child. For example, a neonate with underlying lung disease is likely to have an operation deferred if operative fluid loss and resultant replacement is anticipated to cause a marked exacerbation of pulmonary problems. Careful discussions among the surgeon, intensivist, and anesthesiologist are mandatory when considering the timing of surgery in ill SBS patients.

Massive pediatric small bowel loss, as is sometimes encountered in malrotation with volvulus and necrotizing enterocolitis ("NEC totalis"), has prompted some surgeons to recommend expectant management. This approach, as an automatic fallback, is to be discouraged. Advances in the treatment of SBS have made long-term survival of such patients likely, and a productive life on HPN is possible.[62] In most cases of severe SBS the family and surgeon should consider the options for bowel rehabilitation, HPN, and intestinal transplantation. Communication with a specialized SBS center may be highly beneficial in helping define expectations and planning appropriate care.

### AUTOLOGOUS INTESTINAL RECONSTRUCTION SURGERY

Autologous intestinal reconstruction surgery (AIRS) comprises a set of operations that use the patient's bowel to improve intestinal absorption and function. The initial procedures proposed included the creation of reversed (antiperistaltic) segments, recirculating loops, intestinal valves, and colon interpositions.[63–65] Pediatric surgeons also applied tapering and plication operations to promote motility in neonates with dilated bowel due to intestinal atresia.[66,67]

The first small intestinal "lengthening" procedure was described in 1980.[68,69] Called the *longitudinal intestinal lengthening and tailoring operation* (LILT), it is an ingenious but technically demanding operation that takes advantage of the fact that small intestine is supplied by two separate leaves of mesentery. By carefully splitting the mesentery and then severing and anastomosing the dilated (adapted) intestine in an isoperistaltic manner, the bowel is lengthened and tapered (Fig. 88-3). A helpful minor technical modification of the original operation can reduce the number of anastomoses

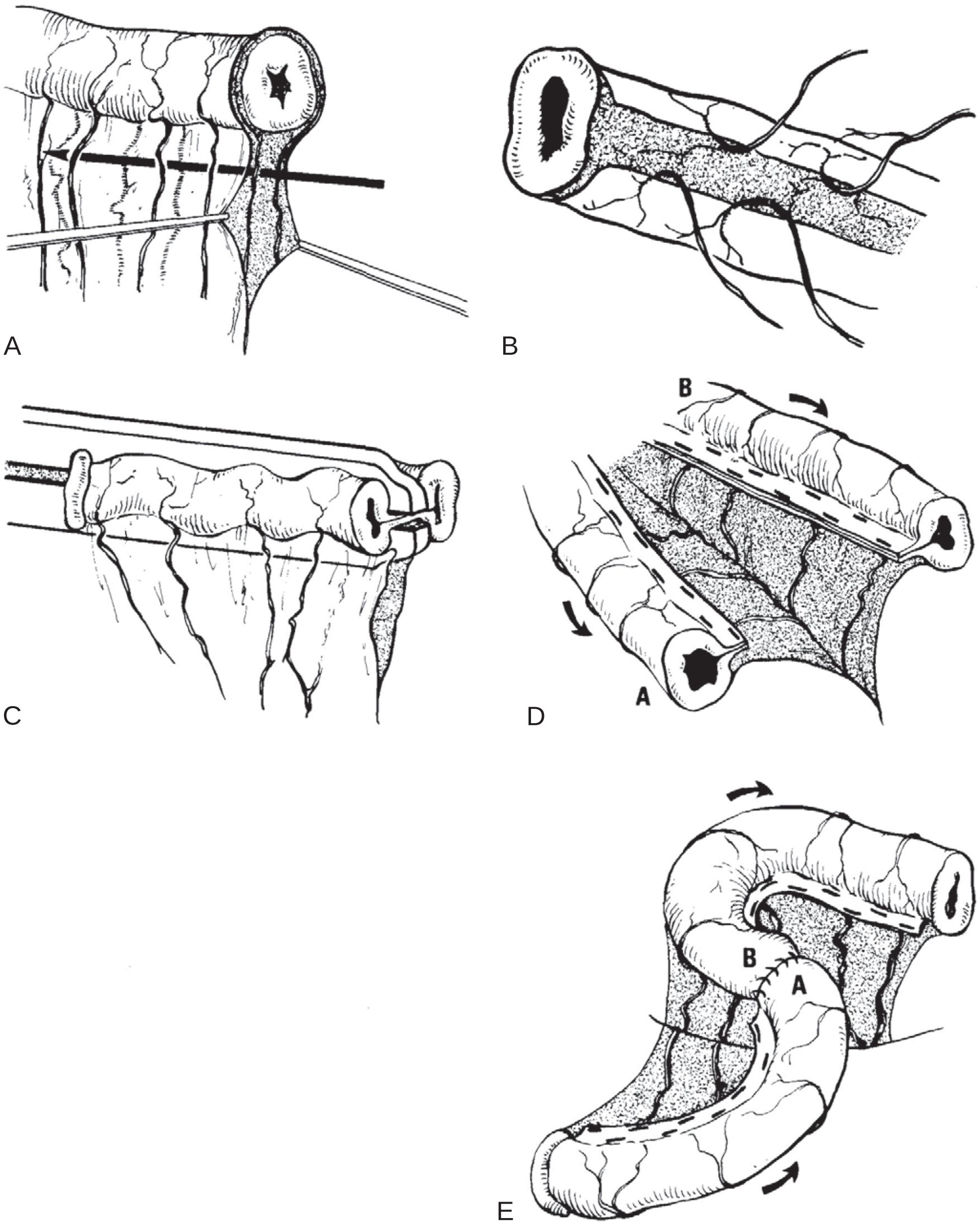


**FIGURE 88-3** Longitudinal intestinal lengthening and tailoring operation. **A,** Creation of the mesenteric tunnel. **B,** View of the divided mesentery. **C,** Division of the dilated bowel into two hemiloops. **D,** The two new hemiloops. **E,** Reanastomosis in an isoperistaltic manner. (Reproduced with permission from Bianchi A: Intestinal loop lengthening—a technique for increasing small intestinal length. J Pediatr Surg 1980;15:145-151.)

needed.[70] In pediatric patients the LILT is associated with an improvement of fat balance, carbohydrate absorption, and intestinal transit time.[71] Described complications of the LILT procedure include leak along the suture/staple lines or anastomoses, devascularization of the bowel after division of the mesenteric leaves, sepsis, recurrent bowel dilation, and dysmotility.[72]

Another creative, two-stage bowel elongation technique, termed the *Iowa I operation,* has been described.[73] It relies on the formation of collaterals between the antimesenteric portion of the small intestine and the abdominal wall during a first operation and then the transverse division, as well as isoperistaltic anastomosis of the bowel at a second operation (Fig. 88-4). This procedure was subsequently modified so that the small intestinal loop to be lengthened was approximated to the liver (Iowa II) or another intestinal loop (Iowa III).[74,75] A case report applying these principles was published, and the techniques used are diagrammed in Figure 88-4.[76]

In 2003 a conceptually simple bowel lengthening and tapering operation called the *serial transverse enteroplasty operation* (STEP) was introduced.[77,78] The three indications for this procedure are refractory SBS (in which enteral feeding advancement cannot be attained), neonatal atresia with limited distal bowel (usually $< 35$ cm in a neonate), and severe bacterial overgrowth. A contraindication to surgery is end-stage IFALD with portal hypertension; in this case transplantation rather than STEP is recommended. The STEP procedure is based on the alternate transverse application of surgical

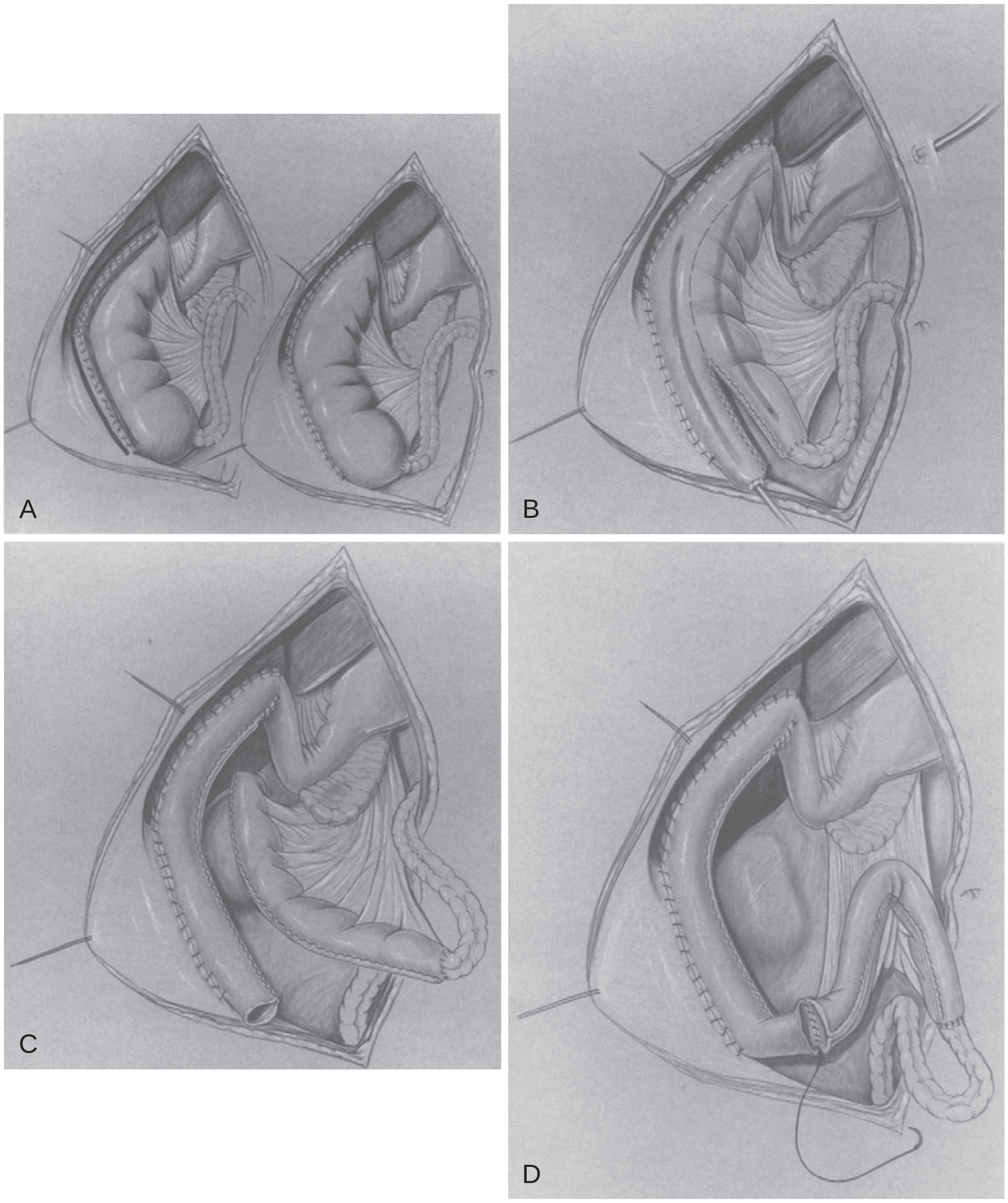


**FIGURE 88-4** Iowa procedure. **A,** Approximation of the dilated intestine to the liver and abdominal wall with a row of sutures. The creation of seromyotomies is then followed by a second row of sutures to create a hepatomyoenteropexy. **B,** Division of the bowel into two hemiloops. **C,** The newly divided hemiloops. **D,** Reanastomosis in an isoperistaltic manner. (Reproduced with permission from Kimura K, Soper RT: A new bowel elongation technique for the short-bowel syndrome using the isolated bowel segment Iowa models. J Pediatr Surg 1993;28:792-794.)

stapling devices to dilated bowel using a transmesenteric approach. A zigzag lengthening and tapering of the intestine ensues (Fig. 88-5). The post-STEP diameter of neonatal bowel is usually 1.5 to 2 cm, and in older children the final bowel width is often calibrated to the nondilated duodenal diameter. The ultimate lengthening obtained is contingent on the dilation of the original adapted bowel and can be greater than 100%. A complete video and technical review of this operation is available at http://www.orlive.com/childrenshospitalboston/videos/serial-transverse-enteroplasty-bowel-lengthening-and-tapering.

The salient advantages of this operation are that it is technically straightforward, can form a uniform bowel channel regardless of variable underlying bowel dilation, and can be repeated if the bowel subsequently redilates. Animal studies have shown that the STEP is associated with improved nutrient absorption, enhanced growth, and an overall increase in bowel surface area as reflected by elevated serum citrulline levels.[4] The latter effect is felt to be secondary to bowel adaptation that is induced by the STEP operation. Interestingly, a rodent model of the STEP has shown elevations of postprandial GLP-2 levels and increased GLP-2 receptor expression, both of which may mediate this adaptive response.[79] STEP operations performed in pigs also demonstrate that the surgery does not inhibit the migrating motor complex and hence may actually improve motility by reducing dilated bowel caliber.[80]

PN-dependent children who have been treated with the STEP operations have shown statistically significant increases in weight for age Z score, weight for height, upper arm

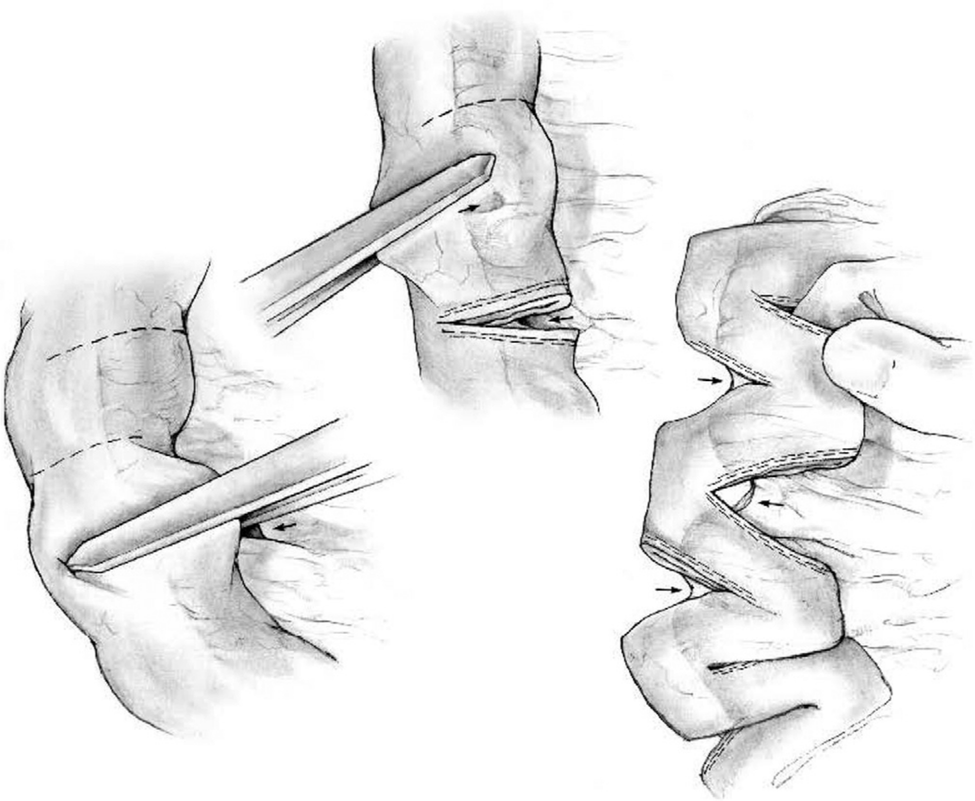

**FIGURE 88-5** The serial transverse enteroplasty. The dilated bowel is flattened, and the stapler is applied perpendicularly to the long axis of the bowel, from alternating sides. A small defect in the mesentery is created at each point of stapler application. The end result is a zigzag pattern to the lengthened bowel. (Reproduced with permission from Kim HB, Fauza D, Garza J: Serial transverse enteroplasty (STEP): A novel bowel lengthening procedure. J Pediatr Surg 2003;38:425-429.)

anthropomorphic tests, D-xylose absorption, and enteral tolerance.[81–83] As predicted from the initial animal paper, neonates with intestinal atresia have had successful bowel-preserving STEP operations on the dilated proximal bowel segment with a primary anastomosis to the distal remnant bowel.[77,84,85] Finally, the STEP has been used effectively to treat medically resistant bacterial overgrowth and D-lactic acidosis in an adolescent with SBS and segmental bowel dilation.[48]

Due to the observation that intestine dilates as it adapts, it is theoretically feasible to repeat bowel-lengthening operations. The original STEP operation case report described a child who was first treated by a LILT and then when enteral feeding advancement was not possible, a STEP was performed.[78] The LILT itself cannot be repeated because of the longitudinal mesenteric splitting that is required; however, no such technical restrictions exist for the STEP. Using a large animal model, it has been shown that an initial STEP operation can, after a period of adaptation, be safely followed by a second STEP.[86] This work has been confirmed by the clinical application of sequential STEP operations in SBS children.[87,88]

The International STEP Data Registry (www.childrenshospital.org/cfapps/step) is a voluntary web-based outcomes repository and has been helpful in tracking the results of the STEP operation. The first report of the Registry involved 19 centers with a median follow-up of 12.6 months.[89] The indications for STEP were SBS (76%), bacterial overgrowth (16%), and neonatal atresia (8%). The mean small intestine length was substantially increased in all groups, and for the SBS cohort, enteral tolerance was significantly increased from 31% to 67% of total calories. Notable complications included nonoperative bowel obstruction (5%) and fluid collection or abscess (8%). Late outcomes demonstrated progression to transplantation in 8% of patients and an overall mortality of 8%. The most recent compilation of data from the Registry was presented at the 2010 annual meeting of the Surgical Section of the American Academy of Pediatrics and consisted of 111 patients, 14 of whom had multiple STEP operations. Among the PN-dependent children, 66% showed improved enteral tolerance following the operation and 47% were weaned from PN completely. The median time to reach full enteral autonomy was 21 months.

Other promising approaches to AIRS are bowel stretch and the tissue engineering of small intestine. The application of tension across the gastrointestinal tract to induce growth has been used clinically in the treatment of esophageal atresia, and animal models using various small intestine lengthening devices have been described. These include the use of internal screws, extension struts, and Nitinol springs.[90–93] The ideal stretching modality would either induce growth rapidly or allow the lengthening bowel to remain in continuity during treatment. Using tissue-engineering principles, neonatal rat intestine has been implanted on a scaffold and anastomosed to the remaining bowel.[94] In this model weight gain, improved vitamin $B_{12}$ levels, and an increase in brush border enzymes have been noted. Further, the implantation of VEGF microspheres into the construct appeared to increase epithelial proliferation and microcapillary density.[95]

### INTESTINAL TRANSPLANTATION

The first successful combined liver intestine transplant in a patient with SBS was reported in 1990.[96] With the improvement of surgical techniques, as well as a better understanding of immunosuppression regimens, liver/intestinal and multivisceral transplantation has become feasible in neonates and children with SBS. The prime indication is progressing IFALD in the presence of intestinal failure. The decision when to transplant is a dynamic one. If IFALD can be ameliorated, transplant may be avoided. Patients with IFALD are best treated by early referral to an intestinal rehabilitation center (with transplant access). Recent data indicate that the majority of these patients will not require transplantation.[2]

The 10-year patient and graft survival for small bowel transplants that include the liver are 42% and 39%, respectively.[97] The major problems attendant with intestinal transplants remain infection, chronic rejection, poor growth while on immunosuppression (especially steroids), and posttransplant lymphoproliferative disease (PTLD). Nonetheless, liver/intestine and multivisceral transplant is a viable salvage option in selected children.

For HPN-dependent adolescents and young adults with stable liver function, a consideration of isolated intestinal transplant is sometimes warranted. Although many such patients are content with HPN, some are not. A careful appraisal of the risks inherent with isolated intestinal transplant needs to be balanced with the potential for an improved quality of life, namely being free of HPN and eating orally. Intermediate results such as receiving an intestinal graft but still requiring a central line for PN and/or hydration also need to be discussed. The decision to transplant in this cohort remains highly individualized and is hampered by a paucity of data regarding long-term quality-of-life outcomes.

## Multidisciplinary Short Bowel Program

Children with SBS require specialized, nutritional, medical, and surgical management. This has led to the evolution of intestinal failure centers across North America that, in turn, have been associated with reduced rates of morbidity and mortality.[2,98–100] The key elements of a successful SBS program include a multidisciplinary outpatient clinic, an expert inpatient ward, and a unified group of dieticians, nurses, pharmacists, social workers, gastroenterologists, and surgeons who work together. An integrated intestinal transplant service is ideal, and a close liaison with such a group is necessary. Other valuable input is derived from aligned gastrointestinal pathologists, diagnostic radiologists, interventional radiologists, endocrinologists, and speech pathologists. Commonly, SBS centers function under the joint leadership of a surgical and medical director. Although significant resources are required, multiple pediatric hospitals have recently established comprehensive regional SBS programs in an effort to enhance the quality and efficiency of care.

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 90

# Alimentary Tract Duplications

Dennis P. Lund

Duplications of the alimentary tract include a wide variety of mass lesions throughout the course of the gastrointestinal tract that are either tubular or cystic. The first report was by Calder in 1733,[1] and these lesions have been referred to by a number of descriptive names depending on their location and associated structures. What are now commonly referred to as *alimentary tract,* or *enteric, duplications* have been variously referred to as *giant diverticula, enterogenous cysts, ileum or jejunal duplex, giant thoracic cysts, duplications, reduplications,* and *unusual Meckel diverticula.* No single classification system adequately explains the embryology, location, and clinical manifestations of all of these lesions.

In 1937 William E. Ladd tried to simplify the nomenclature by suggesting the use of the term "duplications of the alimentary tract,"[2] and we owe the widespread use of the term to his influence. Ladd applied the term to congenital lesions having three characteristics: (1) the presence of a well-developed coat of smooth muscle, (2) an epithelial lining representing some type of intestinal tract mucosa, and (3) intimate anatomic association with some portion of the gastrointestinal tract. Ladd and Gross reported 18 such cases in their 1941 text *Abdominal Surgery of Infancy and Childhood,*[3] and Gross reported 68 cases in his 1953 text *Surgery of Infancy and Childhood.*[4] Swenson also devoted a chapter to the topic in his 1958 text *Pediatric Surgery.*[5]

Alimentary tract duplications have a reported incidence of 1 in 4500 by autopsy series[6] and can occur anywhere from the oropharynx to the anus. There seems to be a slight predominance in males.[7] A meta-analysis by Heiss of 12 large series of enteric duplications encompassing 580 patients is shown in Table 90-1. Heiss's study demonstrated that about 20% of these lesions occurred in the chest and the remainder were located in the abdomen, with a small percentage being thoracoabdominal.[8] Although the embryologic site of origin is not certain, it is common to refer to duplications as foregut, midgut, or hindgut derived, depending on their location. Enteric duplications frequently contain mucosa similar to that of their adjacent gastrointestinal location, but this is not always the case. For example, some duplications contain gastric mucosa and may cause peptic ulceration or bleeding as the presenting symptom regardless of location, and the presence of rectal mucosa has even been reported in cervical duplications. In 10% to 20% of patients, enteric duplications are multiple and the presence of one such lesion should warrant a search for others.[7]

Finally, children with enteric duplications seem to have a high incidence of other associated anomalies. Spinal malformations have been noted in a number of cases, particularly with thoracic or thoracoabdominal lesions, and intestinal malrotation or atresias have been associated with abdominal duplications. Urinary tract anomalies have been reported with midgut and hindgut malformations; and in one series, all patients with multiple duplications also had a skeletal or urinary tract anomaly.[7]

## Embryology

Ladd's motivation for use of the term *alimentary tract duplications* derived from his belief that they shared a similar embryologic mechanism. As the science of embryology has advanced, multiple theories have arisen to explain the occurrence of enteric duplications, but no single theory accounts for all the known variants. Four major theories have been implicated and are able to account for most of the variants seen.

### PARTIAL OR ABORTIVE TWINNING

The first possibility is that duplications may arise as a function of partial or abortive twinning. Doubling anomalies of the head, mouth, upper alimentary tract, hindgut, and lower genitourinary tract have been reported, and this mechanism seems most likely to account for them. Several cases that describe complete doubling of the colon, bladder, urethra, and external genitalia have been reported.[9] Some of these children had severe skeletal anomalies as well. The timing of these twinning anomalies may explain the extent of the twinning; for example, a split in the primitive streak earlier in gestation followed by subsequent caudal growth may result in complete twinning of the caudal end of the fetus, whereas a split at a later date may result in only colonic duplication.

**TABLE 90-1**
**Location of 580 Enteric Duplications**

| *Location* | *No.* | *%* |
|---|---|---|
| Cervical | 6 | 1 |
| Mediastinal | 95 | 18 |
| Thoracoabdominal | 13 | 2 |
| Gastric | 35 | 7 |
| Duodenal | 30 | 6 |
| Jejunal and ileal | 282 | 53 |
| Colonic | 68 | 13 |
| Rectal | 19 | 4 |
| Other | 3 | 0.5 |
| Total | 580 | 100 |

Meta-analysis from Heiss K: Intestinal duplications. In Oldham KT, Colombani PM, Foglia RP (eds): Surgery of Infants and Children: Scientific Principles and Practice. Philadelphia, Lippincott-Raven, 1997.

### SPLIT NOTOCHORD THEORY AND ANOMALOUS ADHESION

In 1960 Bentley and Smith postulated the theory of split notochord syndrome to describe the many anomalies involving the spine, gastrointestinal tract, and skin in the thoracic region.[10] According to this theory, in the third week of gestation (stage 8), the notochord appears growing cephalad, starting in close association with the endoderm, and normally separates from the endodermal cells. During this separation, a gap sometimes appears in the notochord through which a diverticulum from the foregut (endoderm) can herniate by incomplete detachment. These endodermal cells from the developing foregut then attach to ectoderm to form a cyst, or, if they remain attached to the notochord, may act as a barrier to later anterior fusion of the vertebral mesoderm, resulting in anterior spina bifida of the type seen with neuroenteric cysts. This mechanism may account for the dorsal location of most alimentary tract duplications in the chest and would explain those instances of spinal column anomalies associated with them. Whether it accounts for all foregut duplications is not known. A similar mechanism of anomalous adhesions may also explain the rare long duplications arising in the abdomen but seemingly tethered to the spinal column high in the chest. Such adhesions would have to occur early, possibly even before the appearance of the notochord, to account for the long distances such duplications sometimes traverse.[11]

### DIVERTICULA AND CANALIZATION DEFECTS

The fetal gastrointestinal tract goes through what some embryologists referred to as a “solid stage” after which progressive growth of the luminal side of the intestine generally from the cranial to caudal direction leads to the formation of a lumen. For years, it has been known that many diverticula exist in mammalian embryos.[12] These diverticula are most frequently located in the ileum, the site of most enteric duplications. Thus it seems reasonable to postulate that this mechanism may contribute to the formation of enteric duplications. However, this theory fails to explain instances of heterotopic mucosa, particularly that of stomach, or that the majority of duplications are in the bowel mesentery, whereas most diverticula are located on the antimesenteric side of the bowel. Bremer postulated that some enteric duplications result from errors in canalization of the intestine.[13] Moutsouris, who examined many embryos, thought this might also play a role in the formation of atretic segments.[14] What is clear is that the lumen is normally completely restored by the 18-mm stage. Bremer suggested that duplications arise as a result of incomplete or defective vacuolization of the intestine. This theory explains the presence of duplications without associated anomalies but suffers from many of the same shortcomings of the diverticula theory.

### ENVIRONMENTAL FACTORS

Lastly, it is known that there are significant environmental stresses on the fetus at different times. Mellish and Koop postulated that trauma and hypoxia could induce duplications and attempts at twinning.[15] This theory is supported by data that suggest other anomalies, particularly intestinal atresias, may be induced by intrauterine vascular accidents.[16] These embryologic theories are indeed theories, and it is unclear which, if any, play a role in the development of enteric duplications. It is clear, however, that during embryologic development, there is much tissue growth, differentiation, migration, preprogrammed cell death, and tissue adherence. Disorders of any of these mechanisms of development may be involved in the formation of enteric duplications. Most likely, just as there are many forms of malformations known as *enteric duplications,* there are also many factors leading to their development.

## Clinical Manifestations

Enteric duplications are generally cystic or tubular masses. They present in a variety of ways depending on their size, location, adjacencies, and whether they contain heterotopic gastric mucosa. The majority of duplications are diagnosed in the first 2 years of life. Frequently, the presenting symptoms of an enteric duplication can be confused with other gastrointestinal pathology such as acute appendicitis. Many duplications will have few or no symptoms and are found incidentally in the pursuit of symptoms such as cough, abdominal pain, or gastroesophageal reflux. The diagnosis of enteric duplication may be made by prenatal ultrasonography. Cystic masses appear as black holes on ultrasonography and are therefore easily seen if they are of sufficient size.[17]

If the mass is in the chest, it may present as wheezing, pneumonia, or dysphagia that may prompt a chest radiograph. Other potential symptoms include failure to thrive, respiratory distress, and vomiting. Chest pain is a rare symptom unless the mass acutely enlarges from hemorrhage or infection.

Abdominal pain, vomiting, and an abdominal mass are the most common symptoms and signs attributable to enteric duplications located in the abdomen.[18] Because a duplication is a cystic mass, acute distention with secretions or infection of the mass may cause severe abdominal pain. If the duplication contains heterotopic gastric mucosa, ulceration and bleeding or even perforation may result. An acutely enlarging cystic mass may cause obstruction of the adjacent bowel and result in nausea, vomiting, and cramping. A large duplication may even cause localized volvulus of the adjacent intestine. A mobile mass may be palpable in up to 50% of patients.[19] Gastric

and duodenal duplications may cause vomiting, abdominal distention, melena, and perforation. Gastric duplications in particular may be quite large. Duplications in the stomach have also been reported to present similar to hypertrophic pyloric stenosis with gastric outlet obstruction.[20] Duodenal duplications, which most often present with abdominal pain,[21] may be a cause of recurrent pancreatitis and may result in significant morbidity.[22]

Duplications of the midgut or hindgut are more likely to cause abdominal pain, distention, melena, or perforation. Those arising in the ileum may be confused with acute appendicitis and may be difficult to diagnose preoperatively. Small bowel duplications may also present as intussusception by acting as a lead point.

Colon and hindgut duplications may simply present as a second opening on the perineum. In females, this opening may be in the back wall of the vagina, suggesting the possibility of a rectovaginal fistula.[23] Hindgut duplications may also cause symptoms by mass effect, obstructing the urinary tract or causing severe constipation, particularly if they are intrapelvic. Presacral duplications can mimic sacrococcygeal tumors such as teratoma or dermoid cyst.

## Diagnosis

Antenatal diagnosis of duplications of the alimentary tract is becoming much more common because of the availability of prenatal ultrasonography. Experience with antenatal diagnosis began to appear in the literature as early as 1984,[24] but reports were rare. As more experience was acquired over the ensuing decades, the majority of cases were identified in the chest or the upper abdomen, where they were more easily visualized by ultrasound. Chest lesions may occasionally cause hydrops fetalis as a result of mediastinal shift and are managed with in utero thoracoamniotic shunting.[25] By 2000, 14 abdominal cases of duplication were diagnosed antenatally.[26]

The experience in prenatal ultrasound detection has increased rapidly: By 2003, the group in Montreal reported their 22-year experience with enteric duplications and described 18 patients who had a prenatal diagnosis.[27] Interestingly, in their cohort of neonates with the diagnosis of enteric duplication, the incidence of volvulus was 23.8%, arguing for either early surgical intervention or close postnatal follow-up when the prenatal diagnosis of enteric duplication is made.

The history and physical examination are extremely important in establishing any diagnosis, and this is no different in the case of an enteric duplication. The history may include the symptoms just mentioned, and on physical examination an abdominal mass may be palpable. The mass is typically boggy and mobile and may or may not be tender depending on the child's symptoms. Chest masses may be accompanied by locally diminished breath sounds if the mass is large. Laboratory evaluation is of little help except that the child may be anemic if the lesion has caused bleeding because of heterotopic gastric mucosa. The patient with a duplication cyst in the head of the pancreas may have elevated serum amylase and lipase levels along with the other manifestations of pancreatitis.

Postnatal diagnosis can also be aided by ultrasound examination because these lesions are usually quite visible. The cysts are typically anechoic on ultrasonography unless there had been ulceration and bleeding. The wall is typically 2 to 3 mm thick because it is composed of smooth muscle and mucosa, as opposed to other types of cysts such as mesenteric, omental, or ovarian cysts, which are typically larger and have a simpler wall. The mucosal lining of an enteric duplication cyst produces a characteristic echogenic signal on the inside of the cyst (Fig. 90-1).[27a] Other forms of ultrasound such as in endoscopic ultrasonography[28] have been used to accurately diagnose enteric duplications, particularly in the foregut.

Other radiologic studies such as plain radiographs, gastrointestinal contrast studies, and computed tomography (CT) or magnetic resonance imaging (MRI) may assist in the diagnosis and localization of the mass (Fig. 90-2). Gastrointestinal contrast often will not image the lesion per se because cystic duplications do not communicate with the intestine. However, gastrointestinal imaging may show an impression from the mass on the intestine and can be helpful in the diagnosis

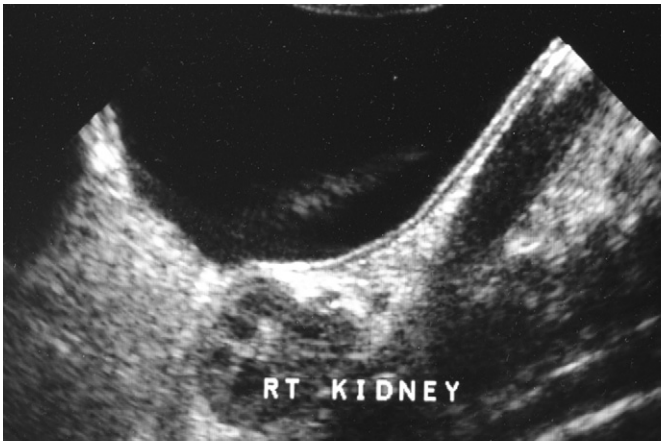


**FIGURE 90-1** Ultrasound study of an ileal duplication shows the characteristic echogenic signal of the mucosal lining.

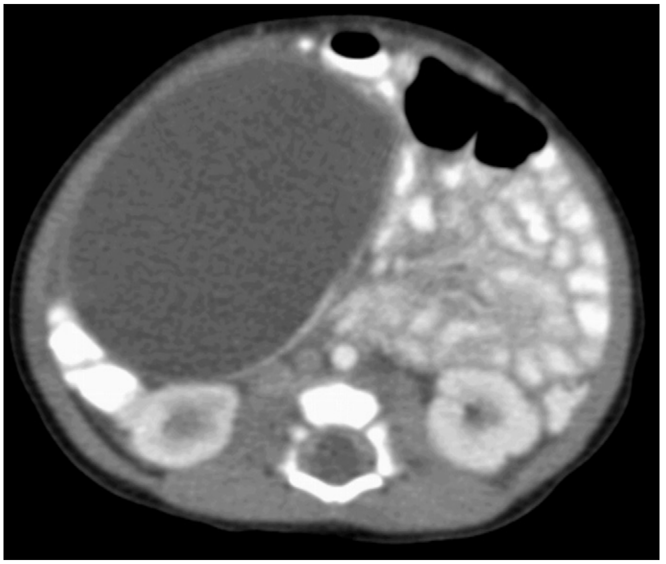

**FIGURE 90-2** Computed tomography scan demonstrates a large cystic mass in the region of the head of the pancreas that turned out to be a duodenal duplication. (Courtesy Dr. Aimen Shaaban.)

FIGURE 90-3 A barium enema study shows anterior compression of the rectum from a rare anterior rectal duplication.

(Fig. 90-3). On CT, enteric duplications typically appear as cystic masses with an enhancing rim and can therefore be confused with an abscess (Fig. 90-4). However, in the absence of a clinical picture of sepsis (e.g., fever and elevated white blood cell count), such an image on CT should suggest an enteric duplication rather than an abscess. Preoperative investigation of other structures including the urinary tract may be necessary to delineate the extent and the impact of the duplication on surrounding structures and may influence the safe treatment of the lesion.

Midgut and hindgut duplications may be more difficult to diagnose, and their diagnosis is often made at operation.

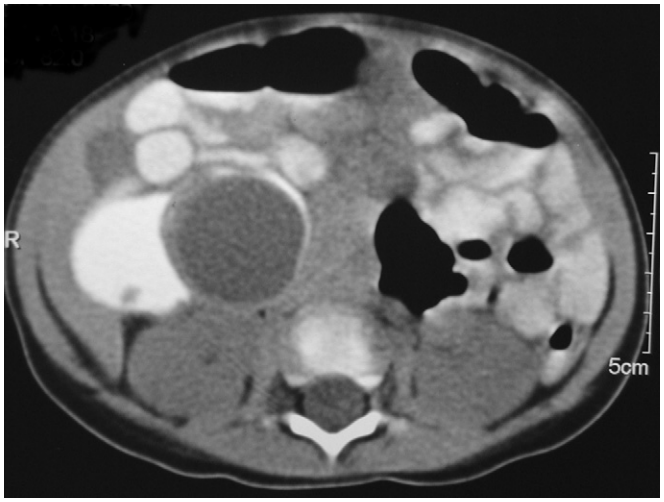


FIGURE 90-4 Computed tomography scan from an infant showing a cystic duplication of the ileum with an enhancing rim.

These lesions may present as volvulus or intussusception and are discovered only at exploration. In a child with anemia and abdominal pain, it may be helpful to evaluate the child with a technetium-99m pertechnetate scan just as one would use to diagnose Meckel diverticulum because ectopic gastric mucosa will concentrate the agent.[29] In fact, enteric duplications are often confused with Meckel diverticulum because many of them are located in the ileum. Therefore the wary surgeon should always include both conditions in the differential diagnosis when evaluating a patient for either.

## Cervical Esophageal Duplications

Duplication cysts of the cervical esophagus are exceedingly rare. A recent case report and literature review cites 18 cases requiring surgical intervention.[30] Almost all such cases present early in life with respiratory distress that can be life threatening. Symptoms often appear before a mass is apparent. Intubation, rapid diagnosis, and intervention are often necessary. The mass may be appreciated on physical examination, but CT is the best diagnostic modality. The differential diagnosis includes other cystic masses of the neck such as lymphatic malformations and cysts of the airway or bronchial apparatus, or thyroglossal cysts. Treatment consists of excision if possible. If complete excision is not possible, the mucosa should be removed from the duplication to allow for obliteration of the cyst cavity.

## Thoracic and Thoracoabdominal Duplications

Approximately 20% of alimentary tract duplications arise in the thorax or are thoracoabdominal. In the differential diagnosis of mediastinal masses in infants and young children, enteric duplications are second only to neurogenic tumors.[31] The majority of lesions are located in the lower half of the posterior mediastinum and may protrude into either hemithorax, or even both. Many of these fall into the class of lesions also referred to as *neuroenteric cysts* because they are associated with connections from the enteric duplication to the spinal canal with associated vertebral anomalies. There is also a class of rare cystic lesions existing in the central nervous system such as in the cerebellum or the optic nerve, without connection to the gastrointestinal tract but containing heterotopic gastrointestinal mucosa that cause symptoms by local pressure on the nervous structure.[32,33] Although neuroenteric cysts are most common in the thoracic region, they may occur in other locations where they make up a much smaller percentage of the enteric duplications seen below the diaphragm.[34] Lesions in the thorax should be suspected when vertebral anomalies are noted. Almost all patients with neuroenteric cysts have vertebral anomalies, but not all enteric duplications in the thorax are neuroenteric. In one series, 5 of 21 patients with thoracic duplications had vertebral anomalies.[35]

When thoracic lesions have been identified on prenatal ultrasonography, attempts at in utero therapy have been made in the setting of fetal distress such as hydrops.[25] The most common symptom of a thoracic enteric cyst is respiratory

distress, although often they are asymptomatic and may be noted on routine radiographs taken for other reasons.[7,35] Occasionally, enteric duplications may be noted in association with other anomalies such as esophageal atresia or diaphragmatic hernia. The combination of a thoracic enteric duplication with other anomalies including spinal anomalies should prompt a search for multiple duplications because these may occur in up to a third of cases. Once a cystic mass is suspected in the chest, the best technique for evaluation of the lesion is CT, which should include the abdomen because one fourth of thoracic enteric duplications are associated with a second duplication in the abdomen.[35,36] A barium swallow study may be helpful to delineate the relationship of the duplication to the esophagus and to help with operative planning (Fig. 90-5). An echocardiogram may also be helpful if a pericardial cyst is suspected; although the vast majority of enteric cysts will occur in the posterior mediastinum, pericardial cysts are more likely to be located in the anterior or middle mediastinum. Finally, if the cyst is neuroenteric, MRI of the spine will be helpful to detail the intimate nature of the cyst with the spinal column and spinal canal. MRI has largely replaced the use of myelography for this purpose.

Treatment of thoracic and thoracoabdominal alimentary tract duplications consists primarily of excision, and this should be performed whenever possible. Removal may be accomplished thoracoscopically, although this is not always possible. Decompression of the cyst may assist in removal, but often the dissection is aided by leaving the cyst intact as long as possible if the cyst is small. Cysts in the wall of the esophagus can be removed by opening the esophageal muscle and performing an extramucosal excision of the cyst, leaving the esophageal mucosa intact. After cyst removal, particularly if the removal was performed through the thoracoscope, the surgeon must be sure that the esophageal lumen was not entered by instilling fluid or air in the lumen. An unrecognized esophageal leak will lead to mediastinitis and severe morbidity.

If there is an intraspinal component to a neuroenteric cyst, collaboration should be sought with a neurosurgeon and the intraspinous portion of the cyst should probably be removed first. This will lead to less morbidity from the potential for meningitis and will reduce postoperative swelling when the cyst is removed.

Large thoracoabdominal cysts may be removed in a staged manner to avoid the morbidity of a thoracoabdominal incision. When undertaking a staged approach, the remaining portion of the duplication must have a mechanism for decompression (e.g., drainage into the intestine), avoiding postoperative sepsis due to leakage from an obstructed cyst. In cases in which the entire cyst cannot be removed, it is important to remove the entire mucosal lining so that the cyst cavity does not recur and potential ectopic gastric mucosa is removed. Curettage and gauze packing of the cyst cavity to promote sclerosis are discouraged because these forms of treatment have higher complication rates than complete removal or formal mucosal stripping.

## Abdominal Foregut Duplications

Gastric and duodenal duplications, most of which are cystic, can often be quite large (Fig. 90-6) and are frequently symptomatic. They cause symptoms due to mass effect and pressure on surrounding structures, resulting in gastric outlet obstruction, pancreatitis,[22] or ulcer-type symptoms from unbuffered hyperacidity with poor feeding and abdominal pain. In infants they may mimic hypertrophic pyloric stenosis.[37]

**FIGURE 90-5** Barium swallow study shows compression of the midesophagus from an esophageal duplication. This teenage boy presented with chest pain, and the duplication was resected thoracoscopically.

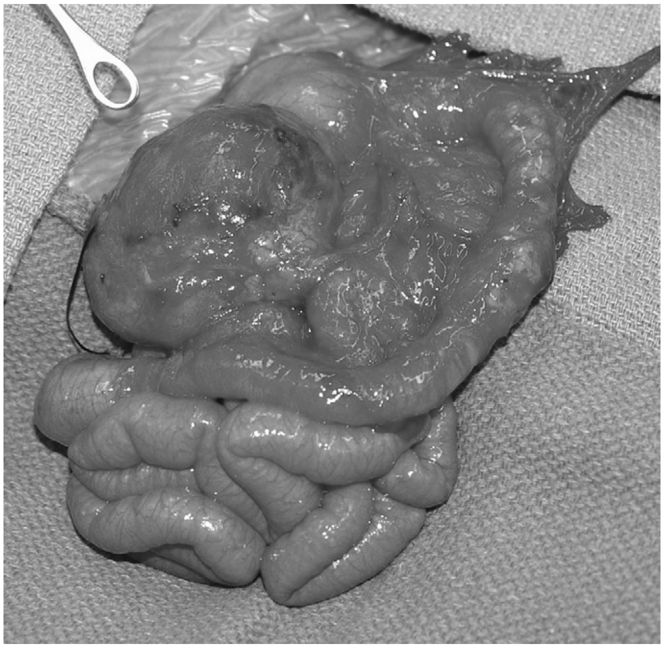

**FIGURE 90-6** This cystic mass occurred in an infant with vomiting and gastric outlet obstruction and was completely resected. The computed tomography scan of this giant duodenal duplication is shown in Figure 90-2. (Courtesy Dr. Aimen Shaaban.)

The term *gastric duplication* can be somewhat confusing because it is sometimes used to refer to lesions in association with the stomach, and some may use this term to refer to lesions containing ectopic gastric mucosa, regardless of their location. For purposes of this discussion, the term *gastric duplication* refers to those lesions associated with the stomach, which most often occur on the greater curvature. Patients typically present at a young age, and a palpable mass is frequently present. These lesions may be seen on antenatal ultrasonography.[38] Signs and symptoms may include failure to thrive, vomiting, anemia, gastroesophageal reflux, and abdominal pain. Such lesions may lead to perforation with pneumoperitoneum[39] or spontaneous hemoperitoneum.[40] Ultrasound evaluation is typically diagnostic of a large cystic mass in the upper abdomen and differentiates this lesion from hypertrophic pyloric stenosis. If the mass is in the right upper quadrant, it can be confused with a choledochal cyst, but foregut duplications are not usually associated with jaundice unless they obstruct the common bile duct. Upper gastrointestinal contrast studies may help delineate the extent of the lesion and its relationship to the stomach, duodenum, and pancreas.

The treatment of a gastric duplication is resection. Frequently, these lesions are large or may be intimately involved with either the gastroesophageal junction or the pylorus. Resection without violating the lumen of the stomach is ideal but often impossible. Segmental gastric resection or even partial cyst resection with mucosal stripping might be necessary. A gastrostomy or even a feeding jejunostomy may be beneficial if gastric emptying is likely to be prolonged after resection. Finally, the surgeon should be aware of the rare instance of communication of a gastric duplication cyst with the pancreatic ductal system, although this is more likely to occur with duplications arising in the duodenum.[41]

Duodenal duplications may present as biliary or pancreatic symptoms such as jaundice or pancreatitis. Symptoms are typically vague, consisting of upper abdominal pain with or without nausea and vomiting (80%),[21] early satiety, or failure to thrive. The lesions are most commonly located in the medial and posterior portions of the second and third portions of the duodenum. These cysts may be confused with choledochal cysts, especially if the major symptom is jaundice. Recurrent bouts of pancreatitis have also been reported. These lesions most commonly contain duodenal or small intestinal mucosa and may occasionally communicate with the lumen of the duodenum. A mass compressing the duodenum may be noted on upper gastrointestinal series or ultrasonography during an investigation of vague abdominal symptoms. It is especially important to have good imaging preoperatively with duodenal duplications. CT, endoscopic retrograde cholangiopancreatography, and MR cholangiography may all be helpful to determine the relationships of the cystic mass with the pancreas and the biliary tree.

Although endoscopic or percutaneous drainage of a duodenal duplication may be possible, the preferred treatment is resection. In certain cases in which resection would have the potential for significant morbidity, internal drainage may also be safe and efficacious. The treating surgeon must have command of a variety of techniques to perform such procedures because these cases can be challenging. For example, localized duodenal resection and reconstruction may suffice,[42] but marsupialization of the cyst to the duodenum or to a Roux-en-Y loop of intestine may be preferable depending on the anatomy of the lesion. Finally, a pancreaticoduodenectomy (Whipple procedure) may occasionally be necessary to adequately deal with the cyst.[22] Whatever procedure is chosen, it is safest to use intraoperative cholangiography to ensure that the biliary tree is intact and unobstructed after the cyst is treated. In cases in which the cyst contains gastric mucosa, it is wisest to remove all such ectopic gastric mucosa either by cyst excision or mucosal stripping.

## Duplications of the Small Intestine

Duplications found in proximity to the small intestine are the most common enteric duplications encountered, and the majority of these occur in the ileum. They may be either cystic or tubular, and most are located on the mesenteric side of the intestine, unlike Meckel diverticula, which occur on the antimesenteric side of the intestine. Frequently, the duplication shares its muscular wall and blood supply with the adjacent intestine such that the duplication resides in the leaves of the mesentery. This has implications for treatment of the duplication in that resection of the duplication may necessitate resection of the adjacent bowel. Communication with the lumen of the intestine may be variable. Increasingly, intestinal duplications are diagnosed as an intestinal anomaly on prenatal ultrasonography.

Signs and symptoms due to small intestinal duplications may vary as well, but abdominal pain and/or a mass are the most common. Small cystic duplications can act as a lead point for small bowel intussusception or result in localized volvulus. If the duplication enlarges or swells, it can lead to compression of the adjacent intestine and cause obstructive symptoms. This is more likely if the duplication is tubular and has a proximal communication with the bowel. Duplications that have a distal communication are less likely to become engorged or cause obstructive-type symptoms. Some duplications contain ectopic gastric mucosa that can cause peptic ulceration, bleeding, or perforation. Those with ectopic gastric mucosa can be diagnosed by technetium-99m pertechnetate scanning (Meckel scan), and patients who pass blood per rectum should be evaluated with this test. Frequently, the correct diagnosis of a duplication is not made until an operation is undertaken.

In a report from Beijing Children's Hospital, Li and colleagues[43] studied the blood supply of small intestinal duplications in 80 cases. They characterized two types of duplications on the basis of their blood supply. In type I lesions (parallel type), the duplication seemed to be more to one side of the mesentery with an artery supplying the duplication while the opposite vessel went directly to the native bowel. In type II lesions (intramesenteric type), the duplication was truly centered in the mesentery and vessels from both sides of the mesentery traversed the duplication to get to the native bowel. Li and colleagues[43] found that type II lesions represented the minority of lesions (24.6%), but more than 90% of these lesions were associated with thoracic vertebral anomalies, whereas only 5% of type I lesions had spinal anomalies. The authors cited these findings to argue that these two types of intestinal duplications must have different embryologic causes. They also suggested that knowledge of the vascular

anatomy of intestinal duplications allows for resection of these lesions without the need for resection of the adjacent bowel.[43]

Optimal treatment for small intestinal duplications is removal. In the case of cystic duplications, this is usually accomplished by excising the duplication with its adjacent bowel with primary reanastomosis (Fig. 90-7). This can be done either by open or by laparoscopic technique.[44–46] Laparoscopy may also be a useful adjunct to open operation to diagnose these lesions and to allow for decompression of large lesions in order to do an open resection through a much smaller incision. Limited resection should have no deleterious effect on the patient. If resection is not possible, one may drain the lesion into a Roux-en-Y loop of small intestine or create a large window to adjacent intestine. At the time of operation, it is wise to thoroughly inspect the length of the intestine because of the high incidence of multiple lesions in these patients. There have also been reports of duplications in association with intestinal atresia, which would present in the newborn period.[35] Infants who have duplications diagnosed on prenatal ultrasonography do not need to undergo resection in the neonatal period unless they present with bowel obstruction. However, resection should be undertaken within a few months to avoid complications such as obstruction or volvulus, and these patients should be followed closely. At least six cases of adenocarcinoma arising in small intestinal duplications, mainly later in life, have been reported, so these lesions should not be left indefinitely if they can be resected without much morbidity.[47]

Long tubular duplications of the small intestine represent a greater surgical challenge, particularly if resection of the adjacent intestine would lead to short-bowel syndrome. Ectopic gastric mucosa, if present, should be removed, either by limited resection or by mucosal stripping, because this can lead to bleeding or perforation. The duplication should be carefully inspected and the mesentery opened to ascertain if it is possible to resect only the duplication while leaving the adjacent intestine intact. The technique pioneered by Bianchi for longitudinal intestinal lengthening can be used for the mesenteric dissection.[48] Finally, creation of large windows (marsupialization) between the duplication and the adjacent intestine both proximally and distally may suffice so that the duplication is well drained. This can easily be accomplished with a linear gastrointestinal stapler. If marsupialization is chosen for treatment, these patients must be followed in case they later develop symptoms that may be secondary to retained gastric mucosa.

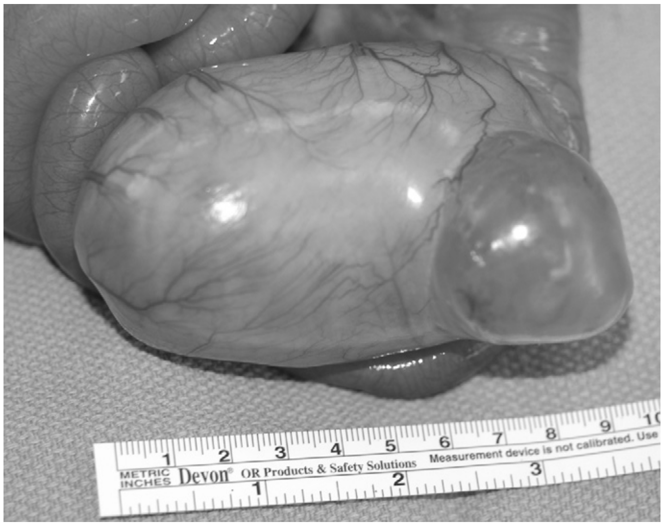


**FIGURE 90-7** This cystic duplication of the ileum with the adjacent 5 cm of bowel was resected from a 2-month-old girl. Intestinal continuity was reestablished with a primary anastomosis. This mass was diagnosed on prenatal ultrasonography.

## Hindgut Duplications

Duplications of the colon and rectum constitute about 17% of all enteric duplications. They can be simple cystic lesions in the wall or mesentery of the colon or quite extensive, running the entire length of the colon and emerging on the perineum as a separate opening, sometimes in the back wall of the vagina They also may be associated with abortive twinning anomalies and have been reported in conjoined twins[49] and with duplication or other anomalies of the urinary tract and the genitalia,[50] in which case these complex anomalies may also be associated with lower spinal anomalies. Colonic duplications usually contain colonic mucosa and rarely contain ectopic gastric mucosa. Rectal duplications typically are cystic masses of variable size that present in the presacral space behind the rectum, although occasional anterior masses are seen (see Fig. 90-3). They can present in the newborn period or any time later in childhood, and even occasionally in teenagers (Fig. 90-8).

There seem to be three general classes of hindgut duplications. The first are the cystic or short tubular masses that reside in the mesentery of the colon and are analogous to many midgut duplications. These tend to be rare. The second are the masses that reside in the midline, usually in front of the sacrum or coccyx and behind the rectum. These will sometimes be intimately involved in the blood supply of the rectum, especially if they extend upward into the abdomen,

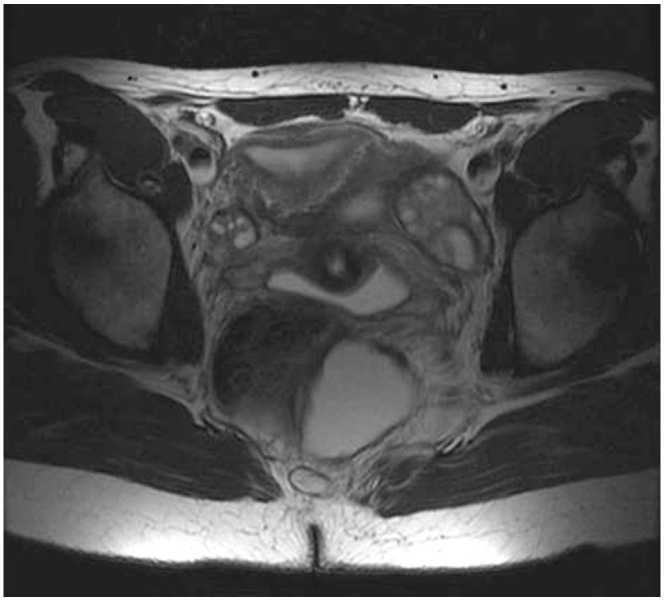

**FIGURE 90-8** Magnetic resonance image in a 17-year-old girl with a rectal duplication that became infected. It was initially treated with percutaneous external drainage followed by subsequent resection using a posterior sagittal approach.

and may require extensive resection and reconstruction. Other times, they are much more like cystic masses that can be excised without interfering with the blood supply of the rectum. Finally, there are side-to-side duplications of the colon and rectum that can vary in length and location. These tend to occur more frequently in females and may be associated with other lower abdominal and caudal anomalies such as genitourinary anomalies or spina bifida. Treatment of these lesions can be quite complex and frequently involves partial resection and/or fenestration of the extra lumen.

Given the myriad of duplications that occur in the hindgut, it is not surprising that there may be a wide variety of symptoms associated with them. A cystic mass may be present, or there may be distention and obstructive symptoms. Many are minimally symptomatic or may be associated with vague abdominal pain, constipation, or failure to thrive. Duplications that open into the vagina can present with signs and symptoms of rectovaginal fistula (Fig. 90-9), such as passing gas or stool through the vagina. Rectal duplications can present as pain or rectal obstruction. Rare cases can also be associated with urinary obstruction or retention. They can be confused with perirectal abscesses or fistulas if they become infected. Other presentations include rectal bleeding or prolapse.[51]

The diagnosis of hindgut duplications may be difficult. Accurate imaging and preoperative evaluation with CT, MRI, and sometimes a barium enema are essential to determine proper treatment. Second openings on the perineum may be studied by retrograde injection of contrast media. Rectal duplications should be evaluated by CT or MRI, which will show the extent of the lesion, as well as the relationship to the rectum, spine, and urinary tract. A triad of findings—presacral mass, rectal stenosis, and sacral bony anomalies—known as the Currarino triad is inherited in an autosomal dominant condition.[52] Just as with some small intestinal duplications, short or cystic hindgut duplications may sometimes only be diagnosed at the time of operation. Technetium scanning is rarely helpful because hindgut duplications rarely contain gastric mucosa.

As with most enteric duplications, surgical removal (when possible) is the optimal treatment. With short cystic duplications of the colon, this may be done with only a limited colon resection or simply by "shelling out" the lesion from the mesentery.

If a presacral duplication presents as an abscess, it is wise to drain it externally rather than through the rectum. Transrectal drainage leads to contamination of the lesion with fecal flora and recurrent abscess formation. Midline presacral rectal duplications can frequently be removed using a posterior sagittal approach,[53] sometimes with an associated limited rectal wall resection but often without. A nerve stimulator may be helpful to delineate the pelvic and sphincteric muscle during

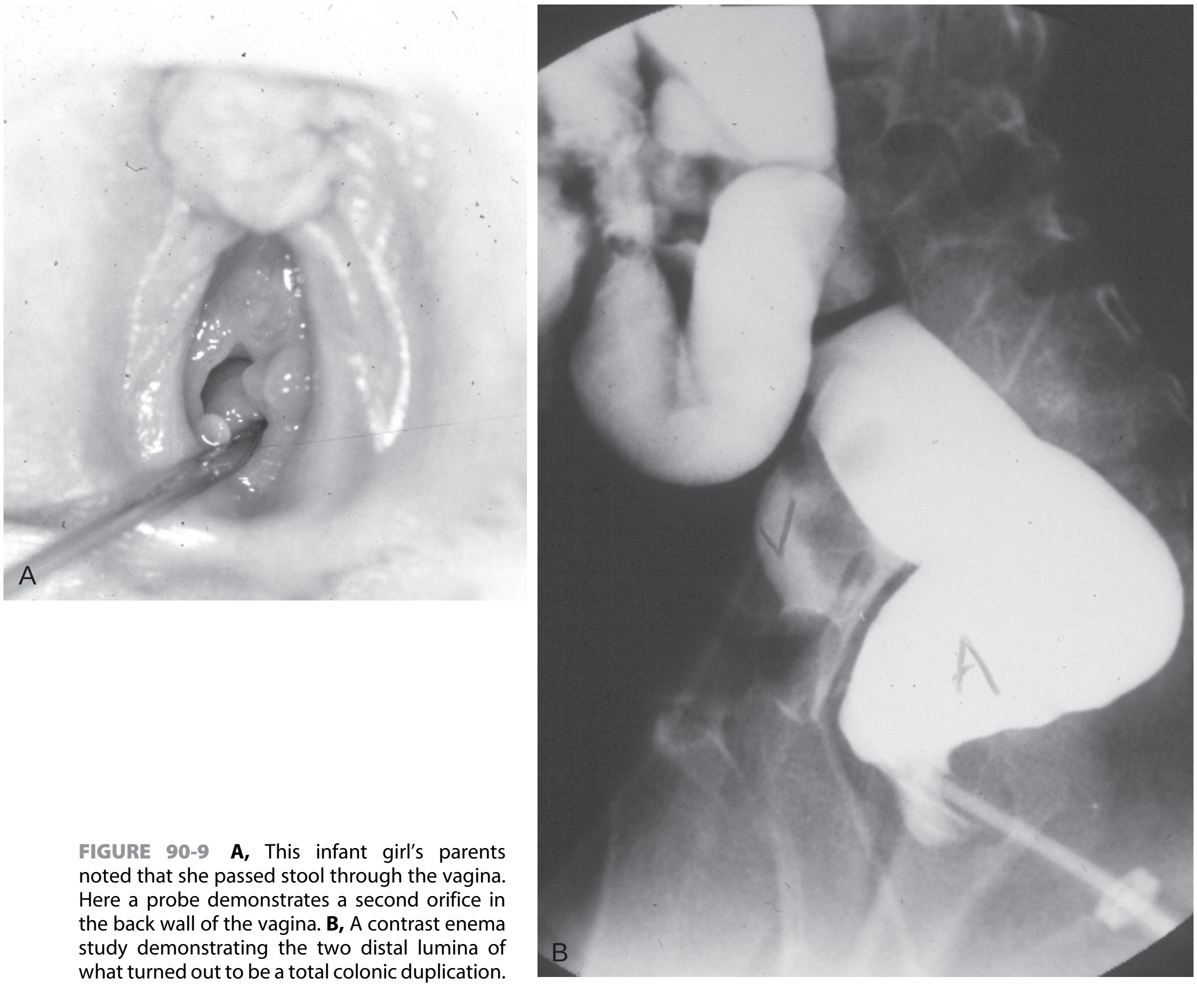

**FIGURE 90-9** **A,** This infant girl's parents noted that she passed stool through the vagina. Here a probe demonstrates a second orifice in the back wall of the vagina. **B,** A contrast enema study demonstrating the two distal lumina of what turned out to be a total colonic duplication.

the dissection and during the reconstruction. It is always wise to have the bowel prepared preoperatively if possible in case bowel resection is required. It is also wise to "prep" the patient in the operating room in such a way that a combined abdominal and perineal approach is available if necessary. Midline duplications in front of the rectum are fortunately rare but represent a formidable surgical challenge. Resection is difficult and dangerous because it may be necessary to move the rectum out of the way to resect the lesion, and there is risk to the bladder neck and sphincter. In some cases, these procedures may be approached from above with removal of the mucosa from the lesion while leaving the muscular wall in place. If anatomic distortion or extensive inflammation is anticipated, stenting the ureters immediately before laparotomy may aid in dissection. To avoid the risk of pelvic sepsis, the surgeon should always be prepared to use a temporary diverting colostomy when the resection and reconstruction become tenuous or complicated. The most common complication of resection of a rectal duplication is recurrence if all the mucosa of the duplication is not removed.

Long tubular duplications of the hindgut require a creative surgical approach. Resection often would require total or significant subtotal colectomy due to the shared blood supply of the native bowel and the duplication. This is not usually a desirable option in a small child. Also, there are frequently variations of the duplication in the region of the ileocecal valve; for example, there may be a cystic component in the distal ileum with a long tubular component adjacent to the colon.[23] Finally, if there is a portion of the duplication opening onto the perineum or into the genitourinary tract, that communication also must be treated. Cases of long side-by-side duplication of the colon may be treated by fenestrating the two lumina extensively both proximally and distally. This can be done through a colotomy at either end using a linear stapling device or a hand-sewn side-to-side anastomosis. If there is an opening to the perineum, the distal portion of the duplication that does not pass through the sphincter mechanism (e.g., a pathway that opens into the back wall of the vagina) should ideally be resected and the mucosa should be removed or at least be left so that it is well drained and separated from the fecal stream. To adequately treat such duplications, the surgeon may have to move the rectum or reconstruct the sphincter complex after resection.

## Conclusion

Intestinal duplications may present in diverse ways and encompass a wide variety of lesions from the neck to the anus. They can be simple and cystic, complex, multiple, or tubular. They can have other anomalies associated with them including spinal and genitourinary anomalies. Optimal treatment is resection, but in complex cases a variety of approaches may be required including fenestration or mucosal stripping. With proper treatment, children born with enteric duplications should do well and have excellent long-term outcomes and quality of life.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 91

# Mesenteric and Omental Cysts

Richard R. Ricketts

Mesenteric and omental cysts are rare; the incidence is approximately 1 per 105,000 admissions to general hospitals and 1 per 20,000 admissions to pediatric hospitals.[1,2] Modern series show that nearly one third of mesenteric cysts occur in children younger than 15 years and that one fourth occur in patients younger than 10 years.[3–5] These cysts are reportedly more common in females than in males and in white persons than in nonwhite persons.[4,6–10] In pediatric series, however, the age range is from birth to 18 years (mean, 4.35 years) and the cysts occur slightly more often in males (60%). The experience reported in this chapter is with 16 children admitted to Children's Healthcare of Atlanta at Egleston over 30 years.

## History

A mesenteric cyst was first recorded in an autopsy of an 8-year-old boy by the Florentine anatomist Benevieni in 1507.[11] In 1842 vonRokitansky[12] first described a chylous mesenteric cyst; Gairdner[13] reported an omental cyst in 1852. The first successful surgery for a cystic mass in the mesentery was performed by the French surgeon Tillaux[14] in 1880. Pean performed the first successful marsupialization of a mesenteric cyst in 1883.[9] In 1890 Carson presented the first U.S. report of a chylous cyst of the mesentery.[11] An estimated 600 cases of mesenteric cysts were recorded in the literature by 1950.[9] By 1994 that number had grown to 820 patients.[15,16] Since then there have been several series reported in children[3,17–19] and adults,[20] bringing the total to about 1000 cases.

## Embryology

Several mechanisms have been suggested to account for the development of mesenteric and omental cysts including failure of the embryonic lymphatic spaces to join with the venous system, deficiency of the normal lymphaticovenous shunts in perinodal tissue, failure of the leaves of the mesentery to fuse, occult trauma, neoplasia, and localized degeneration of lymph nodes.[11,21] The most commonly accepted theory, proposed by Gross,[22] is benign proliferation of ectopic lymphatics in the mesentery that lack communication with the remainder of the lymphatic system. These cysts are thought to arise from lymphatic spaces associated with the embryonic retroperitoneal lymph sac, analogous to cystic hygromas of the neck arising in association with the jugular lymph sac.[23] The role of lymphatic obstruction is questionable because experimental occlusion of lymph channels in animals fails to produce these cysts owing to the rich collaterals in the lymphatic system.[11,21,23] In addition, obstructed lymphatics have not been demonstrated with lymphangiography.[9] As of now, there is no conclusive evidence accounting for the embryologic events leading to the formation of these cysts.[24]

## Classification Systems

Beahrs and colleagues[11] classified cystic disease of the mesentery into four categories on the basis of possible etiology: embryonic and developmental cysts, traumatic cysts, neoplastic cysts, and infective cysts. In this system, mesenteric, omental, retroperitoneal, dermoid, urogenital, and enteric duplication cysts would be classified as "embryonic and developmental." Traumatic and infective cysts would have no endothelial lining. "Neoplastic" cysts would include cystic lymphangiomas.[24] This classification system creates confusion in terminology because most mesenteric and omental cysts in children are actually benign proliferation of lymphatic tissue and thus could be considered "neoplastic" or "embryonic."

Some authors differentiate between cystic lymphangiomas and mesenteric-omental cysts on the basis of histology.[3,21,25–27] Cystic lymphangiomas are simple cysts with an endothelial cell lining, foam cells, and thin walls that contain small lymphatic spaces, lymphoid tissue, and smooth muscle. The wall of a mesenteric cyst lacks smooth muscle and lymphatic spaces, and the lining cells are cuboidal or columnar.[21] Lymphangiomas occur in the mesentery or retroperitoneum and tend to present early in life with acute abdominal symptoms, whereas mesenteric cysts are limited to the mesentery and present in adulthood as asymptomatic masses.[21,25]

A more recent classification system, that of de Perrot,[28] is based on the origin of the cyst: lymphatic origin (lymphangioma); mesothelial origin (mesothelial cyst, cystic mesothelioma);

enteric origin (duplication cysts); and urogenital cysts, cystic teratomas (dermoid), and nonpancreatic pseudocysts (traumatic and infectious).

Because the evaluation and therapeutic objectives for mesenteric, omental, and retroperitoneal cysts are the same and because they are all anterior extensions of what were retroperitoneal structures during the embryonic stage,[29] they share common characteristics. In this chapter, a "mesenteric cyst" is defined as any cyst located in the mesentery; it may or may not extend into the retroperitoneum. It has a recognizable lining of endothelial or mesothelial cells.[3] An "omental cyst" has the same histologic characteristics but is confined to the greater or lesser omentum. Because mesenteric, omental, and retroperitoneal cysts are all of lymphatic origin, the term "cystic lymphatic malformations" may be more appropriate.[24]

## Spectrum of Disorders and Differential Diagnosis

Mesenteric cysts can occur in the mesentery anywhere along the gastrointestinal tract from the duodenum to the rectum.[11] They may extend from the base of the mesentery into the retroperitoneum. Omental cysts are located in the lesser or greater omentum. Mesenteric cysts are 4.5 times more common than omental cysts.[10] In a thorough review of 162 cases reported between 1950 and 1985, Kurtz and colleagues[2] found that 60% were located in the small bowel mesentery, 24% in the large bowel mesentery, and 14.5% in the retroperitoneum. The most common location is in the ileal mesentery. In the colonic mesentery, cysts occur most commonly in the sigmoid mesocolon.[4,9] Cyst location in several pediatric series is shown in Table 91-1.

The differential diagnosis of mesenteric and omental cysts is shown in Table 91-2. Modern imaging studies can usually determine the organ where cystic lesions within the abdominal cavity originate. The differentiation between intestinal duplication cysts and mesenteric cysts may be problematic because both are often intimately associated with the bowel wall. The former share a common blood supply and muscular layer with the adjacent bowel and have a well-defined mucosal layer that mesenteric cysts lack.[1,3,5,30,31] At the time of surgery, duplication cysts require resection of the involved bowel, whereas mesenteric cysts can often be enucleated from between the leaves of the mesentery.[32]

**TABLE 91-2**
**Differential Diagnosis of Mesenteric and Omental Cysts**

Intestinal duplication cyst
Ovarian cyst
Choledochal cyst
Pancreatic, splenic, or renal cyst
Hydronephrosis
Cystic teratoma, dermoid
Hydatid cyst
Ascites

The pathologic features of these cysts can vary considerably. They can be single or multiple, unilocular or multilocular; they can have serous, chylous, hemorrhagic, or mixed fluid contents; and their lining can vary from a flattened endothelial monolayer to a cuboidal or columnar epithelium to patchy fibrosis.[4,10,26,29,33] Rarely, the cyst wall contains calcium.[6,9,33] Unlike duplication cysts, mesenteric and omental cysts contain no mucus-producing cells.[4] Mesenteric cysts are most commonly single and multiloculated; the fluid is generally serous when the cyst involves the distal small bowel or colonic mesentery and chylous when it is located in the proximal small bowel mesentery.[5,9] Omental cysts almost always contain serous fluid.[33] The features of the cysts in this series are shown in Table 91-3.

## Clinical Presentation

The clinical presentation of mesenteric and omental cysts can vary from an incidental finding during laparotomy performed for another reason to an acute, life-threatening intra-abdominal catastrophe. In adults, these cysts are found incidentally in approximately 40% of patients[7,9,10] and present as acute abdominal emergencies in up to 60% of patients. The classic presentation is that of a low-grade, partial intestinal obstruction combined with a palpable, freely movable abdominal mass.[6] The most common mode of acute presentation in children is a small bowel obstruction, sometimes associated with volvulus and intestinal infarction.[5,25,33–35] In a series of

**TABLE 91-1**
**Location of Mesenteric and Omental Cysts**

| *Author* | *Date* | *No. of Patients* | *Mesentery* | *Omentum* | *Retroperitoneum* |
|---|---|---|---|---|---|
| Mollitt[5] | 1978 | 11 | 8 | 0 | 3 |
| Molander[30] | 1982 | 6 | 3 | 3 | 0 |
| Radhakrishma[35] | 1989 | 8 | 5 | 3 | 0 |
| Adejuyigbe[34] | 1990 | 5 | 3 | 2 | 0 |
| Kosir[25] | 1991 | 13 | 9 | 0 | 4 |
| Chung[1] | 1991 | 15 | 9 | 2 | 4 |
| Hebra[29] | 1993 | 22 | 13 | 6 | 3 |
| Bliss[3] | 1994 | 10 | 10 | 0 | 0 |
| Senocak[17] | 1994 | 19 | 14 | 5 | 0 |
| Okur[18] | 1997 | 10 | 7 | 1 | 2 |
| Egozi[19] | 1997 | 14 | 10 | 2 | 2 |
| Total | | 133 | 91 (68%) | 24 (18%) | 18 (14%) |

**TABLE 91-3**

**Cystic Lymphatic Malformations of the Abdomen ($N = 16$)**

| *Feature* | *Number (%)* |
|---|---|
| Age | |
| $<$ 5 yr | 12 (75) |
| $\geq$ 5 yr | 4 (25) |
| Sex | |
| Male | 10 (62.5) |
| Female | 6 (37.5) |
| No. cysts | |
| Single | 11 (69) |
| Multiple | 5 (31) |
| Type of cyst | |
| Multilocular | 14 (88) |
| Unilocular | 2 (12) |
| Fluid content | |
| Hemorrhagic | 7 (44) |
| Serous | 3 (19) |
| Chylous | 2 (12) |
| Infected | 1 (6) |
| Not specified | 3 (19) |
| Size (cm) | |
| Smallest | $4 \times 4.5 \times 1.7$ |
| Largest | $30 \times 40 \times 10$ |
| Location | |
| Mesentery | 11 (68.75) |
| Omentum | 3 (18.75) |
| Retroperitoneal | 2 (12.5) |

82 children operated on for volvulus, mesenteric cyst was the cause in 3.54% of cases.[36] Small bowel obstruction can also develop from acute enlargement of the cyst secondary to hemorrhage or from extrinsic compression of the bowel as it is stretched over an enlarging cyst (Fig. 91-1). The general mode of presentation of our 16 children is shown in Table 91-4. In no patient was the cyst found incidentally, although four patients were asymptomatic. In one of these four, a cystic intra-abdominal mass was identified by prenatal ultrasonography.

**TABLE 91-4**

**Mode of Presentation and Treatment ($N = 16$)**

| *Feature* | *Number (%)* |
|---|---|
| **Mode of Presentation** | |
| Asymptomatic mass, distention | 4 (25) |
| Acute (<48 hr) abdominal symptoms | 2 (12.5) |
| Subacute (<2 mo) abdominal symptoms | 5 (31.25) |
| Chronic (>2 mo) abdominal symptoms | 5 (31.25) |
| **Treatment** | |
| Enucleation, excision | 8 (50)* |
| Intestinal resection | 5 (31.25) |
| Excision with distal pancreatectomy | 1 (6.25) |
| Marsupialization, cautery | 2 (12.5) |
| **Drainage** | 0 |

*All three omental cysts excised.

In this series, 75% of the patients had abdominal symptoms and all patients had findings on abdominal examination. In only two patients (12.5%) did the condition present as an acute abdominal emergency.

The following case summaries illustrate the varying presentations of mesenteric and omental cysts:

1. A 7-day-old female infant presented with a 48-hour history of vomiting and diarrhea and was found to have fever, abdominal distention, and erythema of the abdominal wall. *Escherichia coli* sepsis was documented. The patient had multiple infected omental and mesenteric cysts involving the greater omentum and transverse mesocolon, all of which were excised. The patient recovered.
2. A 3-day-old male infant presented with signs and symptoms consistent with a small bowel obstruction. He was found to have one ileal multiloculated mesenteric cyst with volvulus that required small bowel resection with primary anastomosis.
3. A 2-year-old boy had an asymptomatic abdominal mass that was found to be a multilocular mesenteric cyst involving the transverse mesocolon and pancreas. Excision

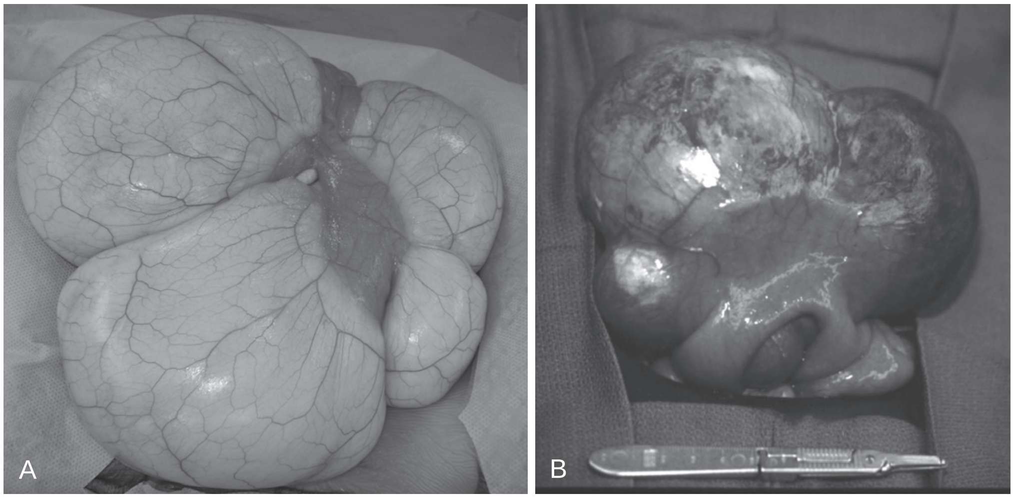


**FIGURE 91-1** **A,** Multiple mesenteric cysts filled with chylous fluid surrounding proximal small bowel. **B,** Large multilocular mesenteric cyst compressing overlying bowel and causing chronic partial intestinal obstruction.

of the cyst and distal pancreatectomy were performed for cure.

4. A 2-year-old girl presented with a 2-week history of asymptomatic abdominal distention. She was found to have a single 30- by 40- by 10-cm multilocular mesenteric cyst that extended along the base of the mesentery from the ligament of Treitz to the transverse mesocolon. Near-total excision of the cyst with marsupialization of the residual cyst into the peritoneal cavity and sclerosis of the wall with tincture of iodine resulted in long-term cure.
5. A female fetus was found to have an intraabdominal cystic mass on routine prenatal ultrasonography. After birth, the infant was jaundiced, which suggested a choledochal cyst; this was excluded by normal radionuclide scanning. After phototherapy, the patient remained asymptomatic but had a palpable, freely movable, nontender abdominal mass. She underwent elective resection of an omental cyst at the age of 6 months (Fig. 91-2).
6. A hydropic full-term female infant died from congestive heart failure. Autopsy revealed a 14-cm multiloculated cyst in the mesentery.
7. A 12-year-old girl with chronic abdominal pain was found to have a cystic mass on CT scan. Exploration revealed intestinal ischemia secondary to compression of the superior mesenteric artery by several mesenteric cysts. Subtotal intestinal resection resulted in short-bowel syndrome.
8. A 1-year-old boy with a right-sided reducible inguinoscrotal swelling since birth presented with irreducibility of the swelling of 3 days' duration. At laparotomy he was found to have a large mesenteric cyst of the terminal ileum, which communicated with the inguinoscrotal swelling.[37]

Complications associated with mesenteric and omental cysts include intestinal obstruction (most common), volvulus, hemorrhage into the cyst, infection,[38] rupture, torsion of the cyst,[10] obstruction of the urinary or biliary tract,[39] and malignancy.[2,5,8,9,11,40,41] The reported incidence of malignant conditions (sarcoma, lymphangioendothelioma, or, rarely, adenocarcinoma) is 3%,[2] although in a recent adult series of 16 patients (ages 12 to 68 years), there were three malignant cysts (18.8%).[20] No malignant mesenteric or omental cysts have been reported in children.

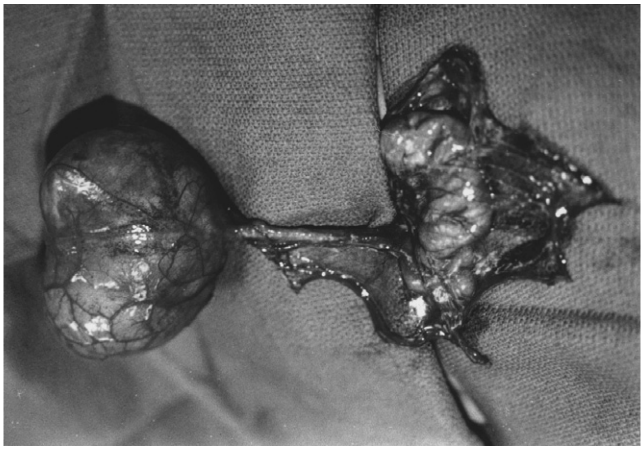

FIGURE 91-2 Asymptomatic but palpable, freely movable omental cyst first seen on prenatal ultrasound.

# Diagnosis

On physical examination, a majority of children with mesenteric and omental cysts have abdominal distention with or without a palpable mass. A definite mass may be difficult to palpate because of its large size, soft and fluid consistency, and great mobility. The mass may be huge, filling the abdominal cavity and simulating ascites.[17,38,42–45] It is dull to percussion. Omental cysts can sometimes be distinguished from ascites by the relative sparing of the flanks; ascites causes the flanks to bulge out, whereas omental cysts do not. If there is no other reason for ascites (e.g., liver or renal disease), a mesenteric or omental cyst should be considered.[32] If a definite mass is palpable, mesenteric cysts are generally movable in the transverse plane, whereas omental cysts are movable in the transverse and craniocaudal planes.[3,9]

Modern imaging studies can usually establish (or at least strongly suggest) the diagnosis of a mesenteric or omental cyst. A plain abdominal radiograph shows a gasless, homogeneous, water-dense mass that displaces bowel loops around it.[33] Omental cysts may compress bowel loops posteriorly, whereas mesenteric cysts may be surrounded by bowel loops.[31] Fine calcifications can sometimes be seen.[6,33] Abdominal ultrasonography and computed tomography (CT) have almost eliminated the need for contrast studies such as upper gastrointestinal series, barium enema, and intravenous pyelography. Abdominal ultrasonography is currently the imaging procedure of choice.[25,30,31] This test reveals a well-circumscribed, thin-walled, fluid-filled cystic structure that usually contains thin internal septi and sometimes contains internal echoes from hemorrhage, infection, or debris (Fig. 91-3).[3,30,31] Enteric duplication cysts are thick-walled structures that share a common muscular wall with the adjacent bowel.[31] They also have a clearly visible mucosal lining on ultrasonography. CT, with the administration of a gastrointestinal contrast

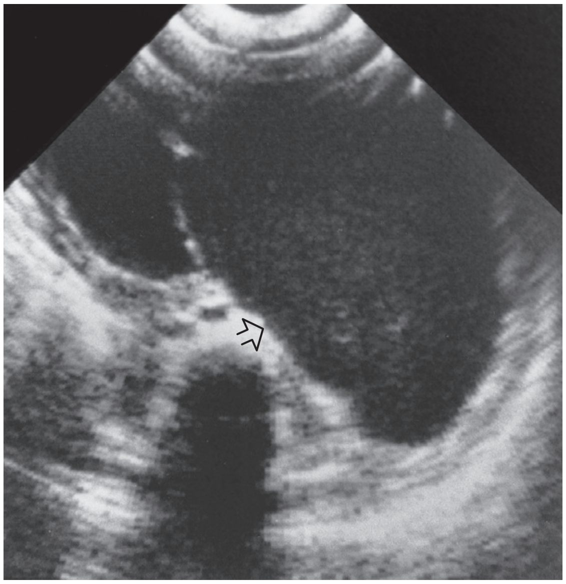

FIGURE 91-3 Ultrasonogram showing a large, multilocular cystic mass in the anterior abdomen, consistent with the diagnosis of a mesenteric cyst. Fine internal echoes represent hemorrhage within the cyst (*arrow*).

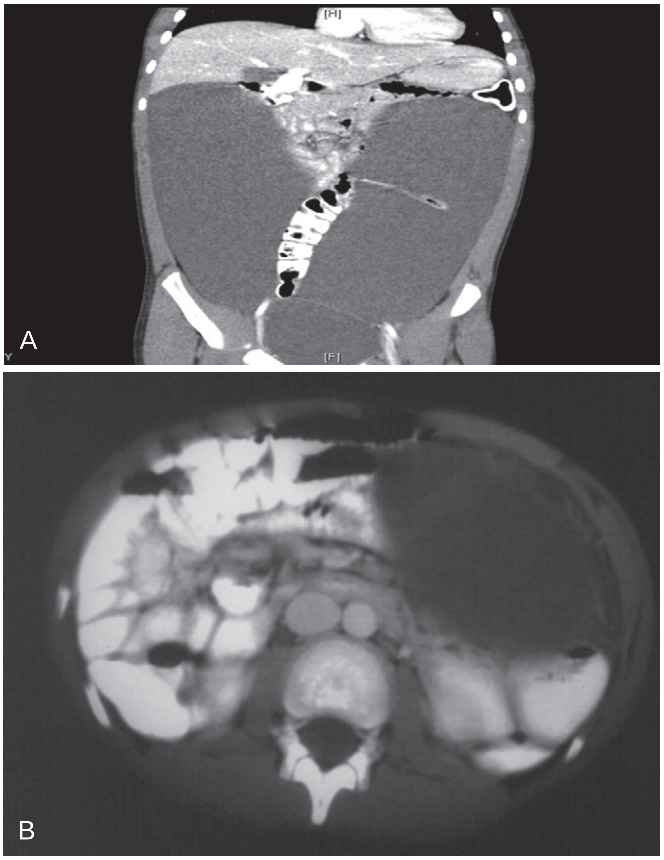


**FIGURE 91-4** **A,** Computed tomography scan with gastrointestinal contrast showing a large cystic mass surrounding a loop of colon. **B,** Computed tomography scan demonstrating a large unilocular cyst that is displacing bowel loops laterally and posteriorly.

agent, can show the relation of the bowel to the cystic mass (Fig. 91-4) and demonstrate that the cyst does not arise from any other organ such as the kidney, pancreas, or ovary.[9] A normal radionuclide scan of the biliary tract excludes choledochal cysts from diagnostic consideration.

## Treatment

The goal of surgery is complete excision of the mass. Omental cysts are easily removed and almost never require bowel resection.[29,33] Omental cysts can be excised using laparoscopic techniques.[42,46–48] Partial drainage of the cyst may be necessary to confirm the site of origin of the cyst and allow its removal through the umbilical port.[49] The preferred treatment of mesenteric cysts is enucleation.[2,9,29,32] In adults, the cyst can often be "shelled out" from between the leaves of the mesentery[32]; in children, however, bowel resection is frequently required to totally eradicate the mass and ensure that the blood supply to the bowel is not compromised. A bowel resection is necessary in only about 33% of adults, but 50% to 60% of children with mesenteric cysts require resection.[2,3,5,18,33,50] For this reason, a mechanical bowel preparation is recommended before surgery, if time permits.[1] If bowel resection is required, intestinal continuity can usually be reestablished primarily. The laparoscopic approach to resection of mesenteric cysts was first described by Mackenzie in 1993.[51] In many cases the cyst must be drained before it can be excised laparoscopically.[15,49,52–54] For those cases requiring a concomitant bowel resection, either an intracorporeal technique or a laparoscopic-assisted extracorporeal technique can be used.

If enucleation or resection is not possible, the third option is partial excision with marsupialization of the remaining cyst into the abdominal cavity. Approximately 10% of patients require this form of treatment.[2] If this procedure is done, the cyst lining should be sclerosed with 10% glucose solution,[4] electrocautery, or tincture of iodine in an attempt to minimize recurrence. Percutaneous injection of the lyophilized incubation mixture of group A *Streptococcus pyogenes* OK432 has been successful in the treatment of large, nonresectable lymphangiomas in children.[26] The mechanism of action of OK432 seems to be related to activation of the white cells (an increased number of natural killer cells and T cells) and an increase in cytokine-mediated endothelial permeability (increased activity of tumor necrosis factor and interleukin-6), resulting in shrinkage of the cystic spaces.[26] This agent may be useful to complement the surgical treatment of mesenteric cysts extending into the retroperitoneum. Partial excision and drainage are not indicated because of the high recurrence rate associated with these procedures.[2]

A simple and universal pathologic classification system that considers the different varieties of mesenteric cysts has been proposed by Losanoff and colleagues (Fig. 91-5).[26] Types 1 and 2 are easily cured with resection or enucleation, with or without concomitant bowel resection. Types 3 and 4, extending into the retroperitoneum, require complex surgical procedures and often sclerotherapy as well. Recurrence in types 3 and 4 is more common than in types 1 and 2.

The surgical treatment used for the current series is shown in Table 91-4. All three omental cysts were totally excised. Eleven of the 13 (85%) mesenteric cysts were completely excised; 2 (15%) were marsupialized into the peritoneal cavity and had the cyst lining sclerosed with electrocautery (1) or tincture of iodine (1). Of the completely excised cysts, 5 (45%) required concomitant bowel resection and 1 required distal pancreatectomy. None of the cysts was simply drained. No major short- or long-term complications, deaths, or recurrences occurred in this series.

## Outcome

The overall results of treatment in patients with mesenteric and omental cysts are favorable. The reported recurrence rate ranges from 0% to 13.6%, averaging about 6.1% in a series of 162 adults and children.[2] Most recurrences occur in patients with retroperitoneal cysts or those who had a partial excision.[2,10,25,29] The overall mortality rate in adults and children is 2%.[2] Only two deaths have been reported in children since 1950. One was a 26-month-old girl who presented with small bowel infarction from volvulus associated with a mesenteric cyst,[55] and the second was the baby with hydrops reported here.

## Summary

Mesenteric and omental cysts are rare, but they are more commonly encountered in children's hospitals than in adult general hospitals. Most cysts are developmental in origin and

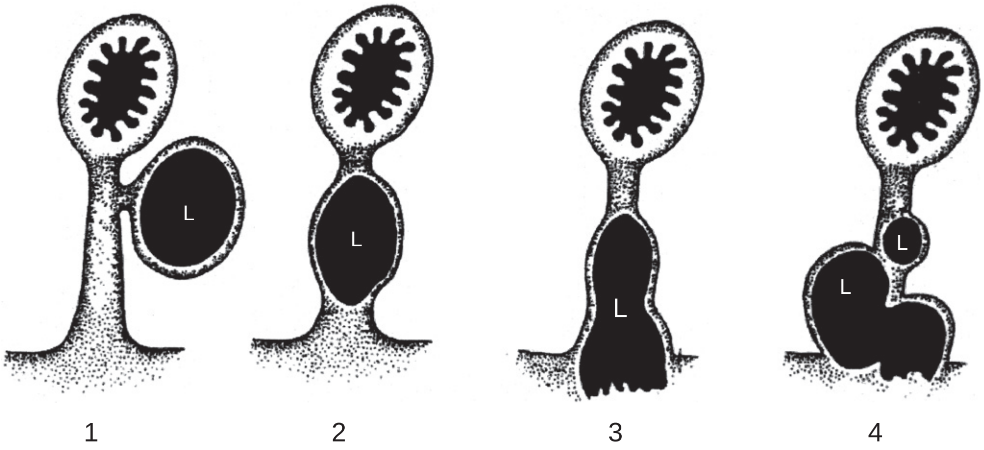


FIGURE 91-5 Classification of mesenteric cysts. Type 1—pedicled; easily resected. Type 2—sessile in leaves of mesentery; requires bowel resection. Type 3—extending into retroperitoneum; often incompletely resected. Type 4—multicentric; may require complex operations, sclerotherapy, or both. (From Losanoff JE, Richman BW, El-Sherif A, et al: Mesenteric cystic lymphangioma. J Am Coll Surg 2003;196:598.)

are related to a congenital abnormality of the lymphatic system. This leads to altered production and flow of lymph in ectopic lymphatic tissue, which lacks communication with central channels. The cysts can be located in the mesentery or omentum of any part of the gastrointestinal tract and may extend into the retroperitoneum. With modern imaging studies, these cysts can usually be differentiated from cystic lesions of other organs within the abdominal cavity. They may present incidentally, insidiously, or as an acute life-threatening emergency. In children, acute presentations from intestinal obstruction with or without volvulus are relatively common. In adults, less acute modes of presentation are the rule. The goal of treatment is complete removal of the cyst by either resection or enucleation. In children, concomitant bowel resection is often required. At times, a portion of the cyst wall must be left in situ and marsupialized into the peritoneal cavity and sclerosed. The short- and long-term prognosis of children with mesenteric and omental cysts is excellent, with a low recurrence rate, few complications related to treatment, and essentially no mortality.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 92

# Ascites

Eugene D. McGahren III

Ascites is the pathologic accumulation of excess fluid in the peritoneal cavity. The word "ascites" is derived from the Greek *askos* and *askites* meaning "bag," "bladder," or "belly."[1] Ascites has been recognized since the time of Hippocrates (400 BC), while modern descriptions of ascites in fetuses and infants date to the seventeenth century.[2–5] A wide variety of conditions, both congenital and acquired, cause ascites in infants and children (Table 92-1). The more common causes of ascites are addressed in this chapter.

## Anatomy and Pathophysiology

There are two major sources of abdominal lymph fluid. One is the flow of blood through the liver. Blood flow from the hepatic artery and portal vein perfuses the hepatic sinusoids and then exits via the hepatic veins. Pressure in the sinusoids is typically low because precapillary resistance is greater than postcapillary resistance. The space of Disse is a location in the liver defined by the hepatocytes on one side and the sinusoidal lining cells on the other side. Hepatic lymph is formed by the filtration of sinusoidal plasma into the space of Disse. It then drains from the liver via transdiaphragmatic lymphatics to the thoracic duct, which then empties into the subclavian vein. The sinusoidal endothelium is highly permeable to albumin, and the concentration of protein in hepatic lymph is close to that of plasma. Thus there is normally no significant osmotic gradient across the sinusoidal membrane.[1]

The second major source of abdominal lymph fluid is via the mesenteric venous system. The mean pressure of the mesenteric capillary is about 20 mm Hg. Intestinal lymph drains from regional lymphatics into the thoracic duct. The mesenteric capillary membrane is relatively impermeable to albumin. Because the concentration of protein in the mesenteric lymph is only about 20% that of plasma, there is a significant osmotic gradient that promotes the return of lymph fluid into the capillary under normal conditions. In an adult-sized patient, there is normally less than 150 mL of free fluid in the abdomen and the normal flow of lymph into the thoracic duct is about 800 to 1000 mL per day.[1]

Ascites occurs when there is an alteration in the normal hydrostatic, osmotic, and electrochemical forces that determine fluid balance. Increases in or aberrations of hydrostatic and/or osmotic pressures of the hepatic and mesenteric capillaries may cause a net transfer of fluid from blood vessels to lymph vessels that exceeds the drainage capacity of the lymph system. Such alterations in hydrostatic pressure may result from cardiac insufficiency or compromise of blood flow through the caval or portal venous systems. Changes in colloid pressure may result from hypoproteinemia secondary to liver compromise or from disturbances in capillary membrane permeability from a variety of inflammatory, metabolic, genetic, or neoplastic causes. Abnormalities in lymphatic drainage may result from trauma including surgery and child abuse or congenital or other anomalies that result in obstruction of the lymphatic system. Finally, ascites may be caused by direct communication between the urinary tract and the abdominal cavity. In this instance the ascites is partially the urine itself, as well as the fluid resulting from the inflammation caused by the urine.[1,6,7]

## Clinical Features

Abdominal distention is the most common physical finding associated with ascites.[5,8] Other physical signs may include bulging flanks, prominent abdominal wall vasculature, an everted or protuberant umbilicus if there is an umbilical hernia, or an inverted umbilicus if there is no hernia, inguinal hernias, scrotal or labial edema, a fluid wave, total body edema, and shifting dullness to percussion.[6–10] Other physical findings related to the underlying cause of the ascites such as a cardiac murmur, enlarged liver, spleen, or kidney, or an abdominal mass may be present. Urinary output may be diminished due to intravascular depletion, increased intra-abdominal pressure, or urinary leak.[11] Respiratory compromise may result from significant fluid accumulation and its pressure on the diaphragm.[2,12] Signs of peritoneal irritation suggest a primary inflammatory or infectious etiology of the ascites. Secondary infection of the ascitic fluid, otherwise known as *spontaneous bacterial peritonitis* (SBP) or *bacterial ascites* (BA), may also occur. Infected ascites may present with fever, nausea, vomiting, or encephalopathy. It is best diagnosed by a paracentesis that demonstrates an elevated polymorphonuclear neutrophil (PMN) count of greater than 250/μL. The sample may also identify the offending organism.[5,13]

**TABLE 92-1**
**Causes of Ascites**

| | |
|---|---|
| **Hepatocellular** | Glycogen storage disorders, lysosomal storage disorders, galactosemia, alpha-1 antitrypsin deficiency, viral hepatitis, neonatal hepatitis, congenital hepatic fibrosis, cirrhosis, hepatic or portal vein thrombosis, Budd-Chiari syndrome, malignancy, venoocclusive disease, biliary atresia |
| **Biliary** | Bile duct perforation, injury to bile ducts |
| **Chromosomal** | Trisomy 21, Turner syndrome |
| **Cardiac** | Congestive heart failure, arrhythmias |
| **Infection** | Appendicitis, tuberculosis and atypical aflatoxin B, cytomegalovirus, parvovirus, syphilis, varicella zoster, enterovirus, listeriosis, toxoplasmosis, hepatitis A, chlamydia, fungus |
| **Renal/Urinary** | Posterior urethral valves, ureteroceles, ureteral stenosis, urethral stenosis or atresia, neurogenic bladder, bladder perforation, nephrotic syndrome, urogenital sinus, cloacal malformation |
| **Gastrointestinal** | Atresia, malrotation, volvulus, necrotizing enterocolitis, intestinal perforation, enteropathy, meconium peritonitis, lymphangiectasia, trauma (including child abuse), congenital obstruction from peritoneal band, gastroschisis, omphalocele, postcardiac surgery, postabdominal surgery for tumor, other abdominal surgery, lymphangioma, intussusception |
| **Pancreatic** | Pancreatitis from any cause, pseudocysts, trauma |
| **Gynecologic** | Ruptured ovarian cyst, hydrometrocolpos |
| **Miscellaneous** | Ventriculoperitoneal shunt, peritoneal dialysis, pseudomyxoma peritonei, granulomatous peritonitis, myxedema, neoplasms (e.g., lymphoma, neuroblastoma, ovarian), metabolic storage diseases |

# Diagnosis

Beyond physical examination, plain radiographs of the abdomen typically show medial displacement of bowel, as well as diffuse abdominal opacification with ground-glass appearance. Separation of the properitoneal fat stripe from the colon and separation of air-filled bowel loops are two other nonspecific findings. The liver may have a rounded appearance and may appear pushed to the center. Calcifications may be present if the ascites is associated with bowel perforation and peritonitis, particularly in the prenatal period (Fig. 92-1).[6,7,14]

Ultrasonography is sensitive for detecting free fluid in the peritoneal cavity. Free fluid in the abdomen appears as shifting echo-free zones in dependent locations. Small amounts of fluid can be detected in the hepatorenal or splenorenal fossa, as well as in the pelvis. As little as 50 to 100 mL may be visible in the abdomen on ultrasound (see Fig. 92-1).[6] Repositioning the patient can help differentiate free from loculated fluid collections. Ultrasonography may also be helpful in identifying inciting causes of ascites and is particularly helpful in diagnosing urinary tract anomalies that are associated with ascites such as posterior urethral valves.[8] Ultrasound cannot distinguish between types of ascitic fluid, however. Prenatal ultrasound routinely detects fetal ascites and may aid in prenatal and postnatal strategies to aid the infant.[14,15] Computed tomography (CT) may be helpful in determining the cause of ascites, but it does not usually add any information about the fluid beyond what the ultrasound has obtained.

Ascitic fluid may be obtained by paracentesis and analyzed according to the clinical suspicion (Table 92-2). Ultrasound may be helpful in locating a site to be aspirated, especially if there are scars from previous surgery.[1] An aspirate of 10 to 20 mL should be sufficient for complete analysis. Macroscopic appearance is assessed and may appear straw colored, turbid, bloody, or chylous. Laboratory evaluation of ascitic fluid should include a cell count with differential, Gram stain and culture, cytology if indicated, and chemical analysis including pH, lactate dehydrogenase, albumin, protein, amylase, bilirubin, creatinine, and triglyceride levels.[6,7,16]

# Hepatocellular Ascites

Neonatal and viral hepatitis, biliary atresia, inborn errors of metabolism, congenital hepatic fibrosis, Budd-Chiari syndrome, and alpha−1 antitrypsin deficiency commonly lead to cirrhosis, portal hypertension and, subsequently, ascites in children. Hepatocellular ascitic fluid is a transudate that results from increased portal venous pressure, increased intraluminal pressure in the mesenteric capillaries, and loss of fluid into the peritoneal cavity. Loss of albumin potentiates this fluid loss and triggers renal absorption of sodium and water.[16–19] Diagnosis of each of these conditions is based on the results of various tests such as specific biochemical assays for inborn errors, viral cultures, tests for viral antibody titers, and liver histologic testing. Analysis of ascitic fluid should include a serum-ascites albumin gradient (SAAG). A gradient greater than 1.1 g/dL is 97% accurate in predicting portal hypertension.[19,20] The cell count should be low, and no bacteria should be visualized, although primary peritonitis can complicate preexisting ascites.

Guidelines of therapy for ascites of hepatic cause include salt and fluid restriction. Sodium intake should be limited to 1 to 2 mEq/kg day for infants and children and 1 to 2 g/day (44 to 88 mEq of sodium/day) for adolescents. Water intake should be no more than 75% of daily maintenance, although severe water restriction is unnecessary unless there is significant hyponatremia (<125 mg/dL).[8,16,19] Gentle diuresis is commonly undertaken with salt and fluid restrictions. The goal of diuresis is to attain an excretion of extracellular water and sodium. Spironolactone is a favored initial agent due to its potassium-sparing characteristic. Furosemide may be used temporarily with spironolactone at the start of diuretic therapy because spironolactone takes a few days to be effective.[7,16,19] Repeated large-volume paracentesis is required in patients for whom salt and fluid restriction fails, particularly if there are symptoms of respiratory insufficiency. Paracentesis in which the removed ascitic fluid is replaced with salt-poor albumin or dextran has been shown to be safe and effective, especially when combined with diuretic therapy and sodium restriction.[11,19,21–23]

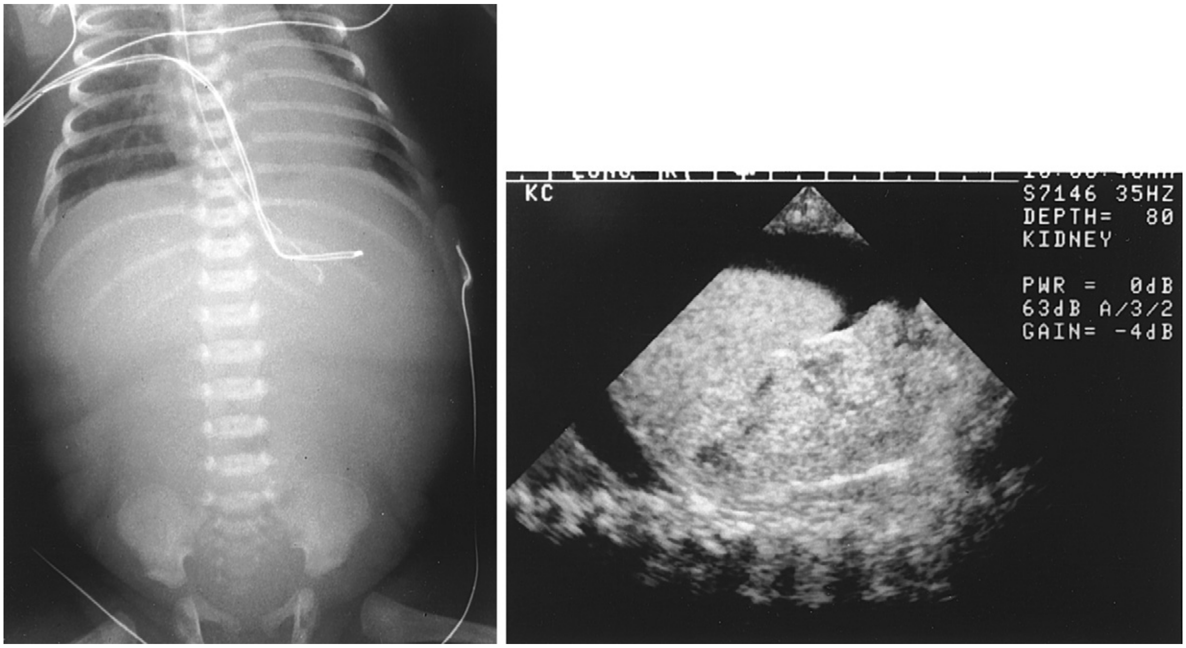


FIGURE 92-1 A newborn with hepatocellular ascites. The plain radiograph shows diffuse opacification with minimal bowel gas; the ultrasonogram shows fluid in the hepatorenal fossa.

**TABLE 92-2**
**Laboratory Analysis of Ascites**

| *Type of Ascites* | *Albumin Level* | *Bilirubin Level* | *Triglyceride Level* | *pH* | *Creatinine Level* |
|---|---|---|---|---|---|
| Hepatocellular | 2-3 g/dL | ≈Serum level | <50 mg/dL | 7.35 | <1 mg/dL |
| Biliary | ≈3 g/dL | 2-3 Times serum level | <50 mg/dL | >7.4 | <1 mg/dL |
| Chylous | <3 g/dL | <1 mg/dL | 1000-1500 mg/dL | 7.5 | <1 mg/dL |
| Urinary | <1 g/dL | <1 mg/dL | <50 mg/dL | <7 | ≈5-10 mg/dL |

Peritoneovenous shunting for intractable ascites of hepatic and other causes has been described in a few infants and children with good results.[24–26] Limitations attributable to the large size of the pump mechanism and venous tubing have made the use of such devices less common in pediatric applications. Modifications have been made by manufacturers to help customize Denver-type shunts for newborns.[25] An intraperitoneal vascular port has been successfully used for palliative relief of tense malignant ascites caused by hepatocellular carcinoma.[27] A newborn peritoneal dialysis catheter is also effective in draining ascitic fluid in a controlled manner. Transjugular intrahepatic portosystemic shunt therapy has been successful in managing ascites in a teenager and may have a role for therapy in selected children.[28]

## Biliary Ascites

Biliary ascites usually results from a spontaneous perforation of the common bile duct, most commonly at the junction with the cystic duct.[29–33] Rare instances of cystic duct perforation have been reported.[34,35] Spontaneous biliary duct perforation is a relatively rare condition with about 150 cases reported in the literature as of 2003,[36] with few reported since. Although many theories have been proposed, the cause of bile duct perforation is speculative. Distal duct obstruction, pancreatic fluid reflux up the common bile duct, congenital weakness of the common bile duct, or a localized mural malformation of the wall of the common duct and pancreaticobiliary maljunction have been proposed as possible causes.[31,37–39] It has been suggested that the proposed bile duct wall defects that may predispose to perforation may be part of a larger spectrum of defects that includes malformations such as choledochal cysts.[36] Perforation of the biliary tree in conjunction with choledochal cyst has been reported in case studies.[40–42] Biliary ascites may also result from perforation of the biliary tree due to trauma.[33,43]

Biliary ascites from spontaneous bile duct perforation typically occurs in infants and toddlers up to about age 2 years but may occur in older children as well.[33,39,44–48] It may also occur prenatally.[45] Most patients are otherwise healthy and have no predisposing conditions associated with the disorder. A typical presentation is the development of progressive painless abdominal distention with jaundice over a 1- to 4-week period. Vomiting, abdominal pain, and clay-colored stools may also be present. The condition is usually indolent in its presentation, although if biliary peritonitis is the initial presentation, the patient may be toxic appearing. However, most patients can tolerate large amounts of bile in the peritoneal cavity without evidence of infection or peritonitis.[33]

Physical examination is notable for abdominal distention, presence of fluid within the abdomen, and possibly inguinal hernias and bile-stained hydroceles.[33,36,39,44–47]

Biliary ascites should be suspected when the presentation and findings noted earlier occur in the absence of any liver disease. Ultrasound can confirm the presence of fluid within the abdomen, and nuclear scintigraphy and MRCP can aid in the identification and localization of a biliary leak.[36,46,47,49] Diagnosis can be definitively established by paracentesis. The fluid is bile stained with bilirubin levels of 100 to 400 mg/mL, although the level may be lower in more chronic presentations.[36]

The primary goal in the treatment of biliary ascites is typically external drainage.[33,36,44,45,47,50] The approach may involve exploration of the right upper quadrant with cholecystostomy and cholecystography to document the size and location of the perforation. If there is evidence of distal obstruction, some advocate giving consideration to a biliary-intestinal anastomosis but this is not commonly necessary.[44,50] If the perforation is confined to the cystic duct, cholecystectomy may provide definitive treatment.[35] Additional internal drainage procedures such as cholecystojejunostomy or duodenotomy with sphincteroplasty are usually unnecessary and fraught with difficulty because in most cases no intrinsic obstruction exists and inflammation tends to distort the anatomy.[31,51] The region is frequently densely scarred, and a sac filled with thick bile can be mistaken for a choledochal cyst.[36] External drainage can be accomplished by placing a Penrose or closed suction drain in the porta hepatis. A cholecystostomy tube or, less commonly, a T-tube may be useful to help with decompression and to further assess the biliary tree in the future.[44,52] External drainage has also been successfully accomplished using percutaneous technique, thus avoiding laparotomy.[47] Alternatively, laparoscopic technique may allow localization of the leak and precise drain placement.[44] There has been a recent report of endoscopic retrograde cholangiopancreatography assisted biliary stent placement facilitating treatment of spontaneous biliary leak.[48] Bile duct stenosis is the most common complication after external drainage. Portal vein thrombosis, bile leak, and cholangitis have also been reported.[36,47] If a choledochal cyst is the cause of the biliary leak, then excision of the cyst with appropriate enteric-biliary anastomosis is indicated.[40–42]

With adequate external drainage, most patients survive and need no additional surgical intervention. Eighty percent of perforations heal within 3 weeks.[29,31–33,44,47,51] Antibiotics and complete bowel rest with total parenteral nutrition (TPN) are important adjuncts in these patients. Fat-free enteral infant formulas are also used, but no studies have compared these two nutrition options in patients with biliary ascites. The cholecystostomy and peritoneal drains should remain in place until normal ductal anatomy has been demonstrated through the cholecystostomy.

# Chylous Ascites

Chylous ascites is the excessive collection of lymph fluid in the peritoneal cavity. In infants and children it is most commonly idiopathic (45% to 60% of cases) and is presumed to be due to congenital malformations of the lymphatic channels.[4,5,8,53,54] Known congenital lymphatic abnormalities that lead to chylous ascites include atresia or stenosis of the major lacteals at the base of the mesentery or the cisterna chyli, mesenteric cysts, generalized lymphangiomatosis, and lymphangioma.[5,8,55–57] The next most common cause of chylous ascites is thought to be obstruction of lymphatic channels by conditions such as intussusception, malrotation, incarcerated hernia, primary or metastatic cancer, tuberculosis, gastroschisis, omphalocele, or inflammatory lesions causing lymph node enlargement.[5,8,9,53,56–60] A large intraabdominal lymphangioma may mimic ascites.[61,62] Finally, injury to the lymphatics is responsible for an additional 15% to 20% of cases of chylous ascites. This may result from trauma, surgery for a variety of conditions, and child abuse. Ascites may not be noticed until days or weeks after the inciting event.[3,4,58,63–65]

Chylous ascites can occur in children of all age groups, although most are infants and toddlers.[5,8,53] Abdominal distention is the most common presenting sign. This may develop gradually or acutely and may be accompanied by abdominal pain and respiratory compromise.[*] Other signs and symptoms may include vomiting, diarrhea, inguinal hernia, and edema.[5,68]

The main confirmatory diagnostic study is abdominal paracentesis, which reveals a milky white fluid if the patient is receiving a fat-containing enteral diet. However, the fluid may appear less milky or amber if the child has not been receiving enteral feeds. The fluid is characterized by an elevated triglyceride concentration (often $> 1000$ mg/dL), a cell differential that is predominantly lymphocytes (70% to 90%), and elevated total protein and cholesterol concentrations.[4,5,6,8,20,53]

Determining the cause of the chylous ascites can be a challenge, especially if the child has no obvious conditions that may commonly predispose to a lymph leak. Studies such as ultrasonography, CT, and gastrointestinal contrast studies may be helpful in identifying predisposing conditions such as malrotation, lymphangioma, tumor, or mesenteric cysts. In newborns in whom ascites has no readily recognizable explanation, a congenital lymph channel malformation is the most likely diagnosis. Lymphangiography is described in older series, but it is difficult to perform in children and it has helped to direct treatment in only a minority of children in whom it has been used.[8,20]

Surgically correctable lesions such as malrotation, mesenteric cysts, intussusception, or incarcerated hernias should be corrected. In patients without a surgically correctable lesion, the initial treatment is aimed at reducing lymph flow through the damaged or obstructed lymph channels. This is accomplished by suspending enteral intake and initiating TPN. Some patients respond quickly to this intervention, with resolution of the ascites within 2 weeks. If the patient's nutritional and hydration status can be maintained, courses of TPN of up to 10 weeks can be considered.[63,67] Because medium-chain triglycerides (MCTs) are absorbed directly into the portal system, and therefore do not stimulate lymph flow, they have been traditionally advocated in the treatment of chylous ascites. Hard data confirming the benefit of MCT formula have been lacking. Nonetheless, the use of a low-fat, medium chain-enhanced formula such as Portagen has been reported

*References 3, 4, 5, 8, 53, 58, 66, 67.

in multiple successful nonoperative treatment courses and should be considered as an adjunct to TPN or as the initial enteral formula in patients who respond to TPN.[9,63–65,67] Prolonged use of low-fat infant formulas has been associated with poor neurologic development, possibly from fatty acid deficiency.[54] Treatment with low-fat formula should therefore be limited to 3 to 6 months. Administration of somatostatin has been reported to successfully resolve chylous ascites in some cases.[69,70] Paracentesis in addition to bowel rest should be reserved for patients with respiratory compromise.

Surgical intervention is warranted if nonoperative therapy is not successful after 6 to 10 weeks or if the patient becomes otherwise symptomatic.[8,53,54,63] Location of the leak may be facilitated by feeding the patient a high-fat diet (usually milk) up to 6 hours before surgical exploration. This results in a copious creamy lymph flow from the leak area. Addition of Sudan dye to the milk may further aid in identifying the leak.[66,71] The most common location of the lymph leak is at the base of the superior mesenteric vessels, although various retroperitoneal and mesenteric lymphatics may be involved.[8,12,53,54,66,71] Complete mobilization of the duodenum and the head of the pancreas and a thorough exploration of the entire retroperitoneum should be performed.[56] Ligation of an identified leaking lymphatic is curative in 85% of patients.[8,67] Recent reports also describe the potential usefulness of laparoscopy in localizing lymph leaks and the use of fibrin glue in the control of lymph leaks.[12,66,72] Peritoneovenous shunting may be a useful treatment strategy as a primary surgical intervention or as an intervention in those children in whom surgical exploration has failed to resolve the ascites.[26,63,68,73] In some older series, mortality from chylous ascites was significant, ranging from 24% to 30%.[5,8] However, with current nutritional support and surgical intervention capabilities, a successful outcome can now usually be expected.

# Urinary Ascites

Urinary ascites is a rare condition, though a common cause of ascites in newborns, accounting for up to one-third of cases of isolated ascites.[2,6] Males outnumber females by a ratio of 7:1.[74] Obstruction of the lower urinary tract, particularly from posterior urethral valves, accounts for approximately 70% of cases of urinary ascites. Other obstructive causes of urinary ascites include ureteroceles, ureteral stenosis, neurogenic bladder, and urethral stenosis or atresia.[2,6,74,75,76] Urinary extravasation from a discrete perforation is noted in approximately 65% of patients with an obstructive cause. The posterior fornix is the weakest part of the urinary system. Thus the site of perforation is most commonly located in the renal pelvis, although bladder perforation is also common.[2,76] Other causes of urinary ascites that are not obstructive in nature include trauma to the urachal remnant, often as a result of attempted umbilical arterial catheterization; spontaneous rupture of the bladder in infants, sometimes associated with connective tissue disorders; and, in females with persistent urogenital sinus or cloacal malformation, leakage of urine directly into the peritoneal cavity through the uterus and fallopian tubes.[2,6,74–83] A recent case of urinary ascites was reported with only the presence of vesicoureteral reflux.[84]

Most patients with urinary ascites present soon after birth. However, prenatal ultrasound may also detect ascites.[85–89] On physical examination, abdominal distention, frequently with palpable flank masses, is the most common presentation. Respiratory distress and acidosis (absorption of urine from the peritoneal cavity) may be present. Potter syndrome (maternal oligohydramnios, renal, pulmonary, and chest wall hypoplasia) may be present. Prune-belly syndrome may also be a physical finding.[2,89,90] Hyponatremia, hyperkalemia, and an elevated serum blood urea nitrogen (BUN) level and creatinine level are also common.[2,74,91]

Workup should begin with abdominal ultrasonography, which will demonstrate the ascitic fluid. It will also identify most common urinary tract abnormalities that are associated with urinary ascites such as hydronephrosis, dilated ureters, and a dilated or thickened bladder.[6] Voiding cystourethrography (VCUG) demonstrates any obstructing lesions and may show the point of extravasation.[75,76,78] Intravenous pyelography (IVP) or renal scanning with diethylenetriamine pentaacetic acid (DTPA) or mercaptoacetyltriglycine (MAG 3) may provide information about the degree of renal parenchymal damage caused by long-standing obstruction and may show the point of extravasation.

Treatment ultimately addresses the underlying urinary tract obstruction if present. However, fluid resuscitation, antibiotics, and distal urinary tract drainage constitute the initial treatment in these patients.[75,76,78] Prenatal intervention for significant urinary obstruction may also be considered.[92] Urinary tract decompression may be accomplished by Foley catheterization, particularly in the case of posterior urethral valves. Cystoscopy with valve ablation is then performed electively. Other decompression strategies may include percutaneous nephrostomy or surgical vesicostomy or pyelostomy depending on the offending lesion and the condition of the patient.[75,76] Although there are some who advocate routine drainage of the ascites, typically drainage of the ascites or repair of the perforation is not necessary because the urinary ascites is reabsorbed once urinary drainage has been achieved and the perforation heals quickly.[2,74,76] Drainage of the ascites is necessary in the presence of respiratory compromise or infection.[2] Once the previously mentioned measures have been successfully completed, definitive operation can be undertaken to address the offending lesion. There is a risk of compromised long-term renal function due to the chronic obstruction. However, the spontaneous decompression of the obstruction that results in urinary ascites is felt to be protective of renal function. Thus a significant number of patients retain good renal function, although this must be monitored on a long-term basis.[2,6,74,85,87] With improvements in neonatal care and early recognition of these conditions, the mortality rate from urinary ascites has decreased from 70% to 0%.[76]

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 93

# Polypoid Diseases of the Gastrointestinal Tract

Joseph L. Lelli, Jr.

Polyps are any masses that project into the lumen of the gastrointestinal tract. Some masses that appear to be polyps are subepithelial. True intestinal polyps, however, are of an epithelial origin. Polyps in children most commonly occur as an isolated lesion referred to as a *juvenile polyp*. However, more rarely, polyps in children can occur as a genetically related disease with features including multiple polyps (polyposis) in the gastrointestinal tract, heritability within a family, and an increased lifetime risk of developing a related cancer in the gastrointestinal tract or in other organ systems. Children with these features are considered to have a "polyposis syndrome." Polyposis syndromes in children are classified into two groups, namely adenomatous polyposis syndromes or hamartomatous polyposis syndromes (Table 93-1).

Polyps are common during childhood, occurring in approximately 1% of preschool and school-aged children.[1] Because of their high incidence, polyps of the gastrointestinal tract represent the most frequent cause of rectal bleeding in toddlers and preschoolers aged 2 to 5 years of age. Juvenile polyps are most common (80%) and are followed by lymphoid polyps (15%).[2] Adenomatous polyps occur in less than 3% of all children with polyps.

## Juvenile Polyps

Juvenile polyps were first described by Verse in 1908.[3] For many years, all polyps in children were considered adenomas[4] and were often treated with radical procedures. Horrilleno[5] first used the term *"juvenile polyp"* in 1957 to describe a histologically distinctive colorectal polyp that occurred predominately during childhood. In 1962 Morson[6] made an important contribution when he demonstrated that juvenile polyps were benign hamartomas, thereby distinguishing them from potentially malignant adenomas. Less radical treatment of these polyps, however, was slow to follow. The distinction between isolated juvenile polyps and juvenile polyposis was first made by McColl and colleagues in 1964,[7] and three distinct forms of juvenile polyposis were further defined by Sachatello in 1972.[8] Kaschula in 1971[9] followed by Enterline in 1976[10] reported cases of children with both juvenile and adenomatous polyps. Billingham[11] reported the presence of solitary adenomas in children with juvenile polyps in 1980. These early reports of the coexistence of juvenile and adenomatous polyps led to the identification of adenomatous and malignant changes in juvenile polyps.[12–14] However, only polyps associated with juvenile polyposis have malignant potential in children.[15–17] The distinction between the commonly occurring isolated juvenile polyps, which are benign, and the rare juvenile polyposis syndromes, which may be malignant, has become increasingly important.[15,16,18,19]

Jass[20] has proposed the following criteria for increased risk for cancer in children with polyps: (1) more than five juvenile polyps in the colon, (2) polyps throughout the gastrointestinal tract, and (3) any number of polyps associated with a family history of juvenile polyposis. Jass's criteria clarify the three distinct juvenile polyposis syndromes originally described by Sachatello in 1972.[8] On the basis of Jass's and Sachatello's studies, the following classification of juvenile polyps is most commonly used:

I. *Isolated Juvenile Polyps* (nonmalignant): fewer than five polyps confined to the colon without a family history of juvenile polyposis.

II. *Juvenile Polyposis Syndromes* (malignant potential):
   1. *Diffuse juvenile polyposis of infancy:* widespread polyposis of entire gastrointestinal (GI) tract in patients younger than 6 months of age.
   2. *Diffuse juvenile polyposis:* multiple polyps throughout the GI tract, but mostly in the stomach, distal colon, and rectum, usually occurring in patients 6 months to 5 years of age.
   3. *Juvenile polyposis coli:* multiple juvenile polyps confined to the distal colon and rectum in patients 5 to 15 years of age.

Juvenile polyposis syndromes, Cowden disease, and Peutz-Jeghers syndrome are all classified as hamartomatous polyposis syndromes (see Table 93-1).

TABLE 93-1
**Classification of Polyposis Syndromes**

| *Classification* | |
|---|---|
| Adenomatous polyposis syndromes | 1. Familial adenomatous polyposis (FAP)<br>2. Gardner syndrome<br>3. Turcot syndrome |
| Hamartomatous polyposis syndromes | 1. Juvenile polyposis<br>2. Cowden disease<br>3. Peutz-Jeghers syndrome |

## ISOLATED JUVENILE POLYPS

### Pathology

Juvenile polyps, which are also known as *retention, inflammatory* or *cystic polyps,* are the most common type of polyp found in the GI tract and account for 80% of polyps in children. Such polyps are generally considered hamartomas[6] or a malformation in which normal colonic tissue has become arranged in a haphazard manner.[20]

Grossly, the typical polyp has a glistening, smooth, spherical, reddish head and ranges from 2 mm to several centimeters in diameter (Fig. 93-1). Polyps will often have an ulcerated surface, which accounts for the rectal bleeding. A cross section shows cystic spaces filled with mucus (Fig. 93-2). Juvenile polyps are typically attached by a long, narrow stalk covered by colonic mucosa. This stalk predisposes the polyp to torsion, which results in venous congestion, surface ulceration, bleeding, and auto amputation.

Microscopically, the surface of the polyp has a single layer of colonic epithelium. This epithelial layer is often ulcerated or replaced with granulation tissue. When inflammation occurs, the epithelium may show a reactive hyperplasia that can mimic dysplasia or adenomatous changes.[21] The main body of the polyp consists of dilated or cystic epithelial tubules that are lined by normal colonic epithelium. These tubules and cystic lakes are embedded in a lamina propria and an abundant, loose, vascular, and fibrous stroma (Fig. 93-3). The stroma is usually heavily infiltrated with neutrophils, eosinophils, lymphocytes, and monocytes. Mitotic figures are rarely seen. Only two descriptions of malignant changes in a solitary juvenile polyp are present in the literature,[22,23] and according to Jass,[20] only one of these may be a true malignant condition. In a longitudinal study of patients with solitary polyps, no increased risk for developing colorectal cancer could be found.[24]

FIGURE 93-1 Typical juvenile polyp with its stalk attached.

FIGURE 93-2 Gross cross section of juvenile polyp with typical cystic "lakes" filled with mucus.

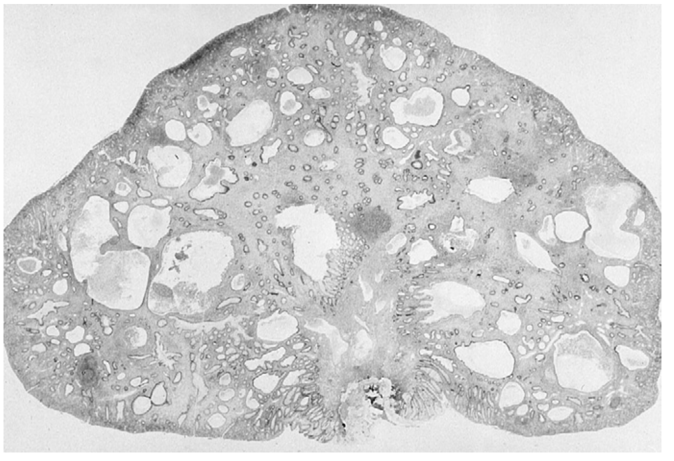
FIGURE 93-3 Photomicrograph of typical juvenile polyp. The surface shows a smooth, flattened, colonic epithelium. Large tubular and cystic lakes are present, embedded in an abundant, loose stoma.

### Etiology

The etiology of juvenile polyps is unknown, but several authors have suggested hereditary,[25] genetic,[26] hamartomatous malformation,[6] and inflammation.[27] Recent data suggest that juvenile polyps result from a structural rearrangement of the mucosa secondary to an inflammatory process.[28] The initial event is probably ulceration and subsequent inflammation of the mucosa, leading to obstruction of regional, small colonic glands of the mucosa. The obstructed glands proliferate, branch, and dilate, forming a cystic structure. The cystic structure pushes up the mucosa, leading to further ulceration, inflammation, and formation of granulation tissue. As the

cycle continues, an increasingly larger and larger mass pushes into the lumen. The fecal stream and peristalsis push the mass down the lumen, causing the stalk to elongate and resulting in the typical pedunculated appearance of the juvenile polyp.

### Incidence

Although the incidence of juvenile polyps is unknown, they are believed to occur in approximately 1% of all preschool children.[1] Most juvenile polyps appear in the first decade of life, with the peak incidence between 3 and 5 years of age.[1] The polyps are solitary in 50% of cases, with the remainder having 2 to 10 polyps. The location of these polyps has changed over the past 10 years. Historically, 70% of the polyps were found in the rectum. Today, only 40% are found in the rectum or sigmoid colon, whereas 60% are found evenly distributed throughout the proximal colon.[1] Juvenile polyps are rarely seen after adolescence.

### Clinical Presentation

The most common presenting symptom of a juvenile polyp is bleeding (93%) that results from ulceration of the polyp surface. Blood loss is usually minimal and appears as bright red streaks of blood over the surface of the stool. Abdominal pain (10%), which is believed to be caused by traction on the polyp from peristaltic activity, and prolapse of the polyp (4%) are other less common presenting symptoms. Prolapse of the rectum and encopresis have also been reported.[1] Many juvenile polyps will autoamputate, resulting in spontaneous cessation of rectal bleeding.[29]

The differential diagnosis of juvenile polyps encompasses all of the causes of rectal bleeding in toddlers through children who are 6 years of age. Anal fissures and rectal prolapse cause rectal bleeding but are easily distinguished from polyps on physical examination. Bleeding from Meckel diverticulum or duplication of the intestine usually causes more substantial blood loss than that from a polyp, and the blood usually commingles with the stool rather than coating it. Bleeding from an intussusception is accompanied by abdominal pain that is substantially worse than that seen with polyps. Inflammatory bowel disease is usually accompanied by diarrhea, which is not seen with polyps. Blood dyscrasias, such as Henoch-Schönlein purpura, should also be considered in the differential diagnosis.

### Treatment

The diagnosis and treatment of juvenile polyps requires a combination of history, digital rectal examination, and colonoscopy. The shift of juvenile polyps to the more proximal colon[29] and the concern for the presence of juvenile polyposis (>5 polyps), with its increased risk of malignancy, mandates that the entire colon be surveyed. Children with suspected polyps should have a digital rectal examination initially. Polyps in the rectum can be easily removed during anoscopy. Following removal of a rectal juvenile polyp, pancolonoscopy, in a well-prepared bowel, should be performed to determine if additional, more proximal polyps are present.[30] Children with juvenile polyposis and adenomatous changes are more likely to have right-sided polyps[31]; therefore all polyps should be removed and undergo histologic evaluation. Complications following endoscopic removal of polyps are rare.

## Polyposis Syndromes

Gastrointestinal polyps are the result of a defect in the balance between cellular growth promotion and cellular growth inhibition. The defect results from either an activated oncogene that has upregulated a growth-promoting protein or the loss of function of a growth-inhibiting protein, usually by the inactivation of a tumor suppressor gene. In the polyposis syndromes there has been inactivation of a tumor suppressor gene.[32,33] A resulting gastrointestinal cancer occurs when there are additional genetic defects. Polyposis syndromes can be classified into adenomatous polyposis syndromes and hamartomatous polyposis syndromes.

## Adenomatous Polyposis Syndromes

All of the adenomatous polyposis syndromes are distinguished by the development of a large number of adenomas in the colon. Additionally, these syndromes are associated with extracolonic manifestations such as duodenal polyps; benign soft tissue tumors such as osteomas of the mandible, long bones, and skull; and congenital hypertrophy of the retinal pigmented epithelium (CHRPE) (Table 93-2). Adenomatous polyposis syndromes include familial adenomatous polyposis (FAP), most common in children; Gardner syndrome; and Turcot syndrome.

## Familial Adenomatous Polyposis

FAP is distinguished by the progressive development of hundreds to thousands of adenomatous polyps in the colon. By 15 years of age 50% of those that carry the FAP gene will have polyps. The lifetime risk for developing a colorectal cancer is 100%; however, the average age for developing an adenoma in FAP is 16 years and 39 years for developing a colorectal cancer.[34]

**TABLE 93-2**
**Extracolonic Features in Familial Adenomatous Polyposis**

| *Cancer (Lifetime Risk)* | *Other Lesions* |
|---|---|
| Duodenal (1%-5%) | CHRPE |
| Pancreatic (2%) | Nasopharyngeal angiofibromas |
| Thyroid (2%) | Osteomas |
| Brain (medulloblastoma) (<1%) | Radiopaque jaw lesions |
| Hepatoblastoma (0.7% of children < 5 yr old) | Dental abnormalities |
| | Lipomas, fibromas, epidermoid cysts |
| | Desmoid tumors |
| | Gastric adenomas/fundic gland polyps |
| | Duodenal, jejunal, ileal adenomas |

CHRPE, congenital hypertrophy of the retinal pigment epithelium.
Modified from Cruz-Correa M, Giardello FM: Diagnosis and management of hereditary colon cancer. Gasroenterol Clin North Am 2002;31:537-549.

## HISTORY

The first case of adenomatous polyposis was recorded by Covisart in 1847,[35] but it was Chargelaigue,[36] who, 12 years later, gave the first definitive account of the disease in a 16-year-old girl and a 21-year-old man. The first pathologic description of these colonic polyps was reported by Virchow in 1867,[37] with Woodward in 1881[38] being the first to distinguish between neoplastic and inflammatory polyps. The first familial association of these polyps was described by Cripps in 1882[39] between a 9-year-old boy and his 17-year-old sister. However, the malignant potential of these polyps was not recognized until 1890 by Handford.[4]

The first recorded operations for polyposis are credited to Lilienthal[21] in North America and subsequently to Lockhart-Mummery at St. Mark's Hospital in London, as reported by Thompson and Watne.[40,41] Lockhart-Mummery, in 1925,[42] concluded that (1) multiple adenomatous polyps develop in succeeding generations, (2) afflicted individuals develop cancer at an early age, and (3) the adenomas are an antecedent to cancer. In 1927 Cockayne[43] described the mode of inheritance as Mendelian dominant, which was later confirmed by Dukes in 1930[44] and Lockhart-Mummery in 1939.[45] Since then, FAP has become a model for understanding the adenoma-carcinoma sequence.[46]

The detection of a deletion in chromosome 5q[47] in a patient with Gardner syndrome has led to characterization of the gene responsible for FAP, the *APC* gene.[48–57] The 5q deletion or alteration in the *APC* gene results in a gene product with a truncated protein, which subsequently causes the *APC* gene to act as a tumor suppressor gene.[32,33] Mouse models for FAP have been developed,[58] and these will facilitate research in gene therapy.

**FIGURE 93-4** Gross specimen of the total colon in a patient with familial adenomatous polyposis demonstrating thousands of adenomatous polyps. Note the large adenoma in the ascending portion of the colon.

**FIGURE 93-5** Close-up view of colonic mucosa demonstrating a "carpet" of small 1- to 2-mm adenomas in a patient with familial adenomatous polyposis.

## PATHOLOGY

FAP is defined as the presence of at least 100 visible adenomatous polyps in the large intestine.[59] However, patients with fewer polyps have been diagnosed as having FAP, and one patient who had early onset of colorectal cancer and had a 5q gene deletion had only one endoscopically detectable polyp.[60]

Colorectal polyps are the hallmark of FAP. Although 100 polyps is the usual threshold for diagnosing this disorder, patients coming to colectomy in their teenage years typically have thousands of polyps (Fig. 93-4). Two types of FAP seem to exist: the sparse type, which is characterized by hundreds of polyps, and the profuse type, which is characterized by thousands of polyps. Utsunomiya and colleagues[61] have shown that the history of the two types is different—patients with the profuse type tend to develop adenocarcinoma at an earlier age.

In FAP the polyps are typically scattered throughout the colon, which allows diagnosis by sigmoidoscopy. The polyps vary in size from 1 to 2 mm in diameter, and when present, pedunculated polyps can be 1 cm in diameter or larger (Fig. 93-5). During duodenoscopy, biopsy of normal-appearing duodenal mucosa may reveal microscopic adenomas too small to be seen macroscopically. These microadenomas may consist of only three or four dysplastic crypts that usually have a tubular adenomatous structure.[62]

Adenomatous polyps result from a neoplastic transformation of at least one epithelial cell that is in the proliferative portion of a crypt.[63] The transformed clone then populates the upper part of the crypt, which divides by budding.[63] Crypt fusion is then responsible for further growth of the adenoma. This neoplastic transformation, called *dysplasia,* implies atypical morphologic characteristics, with nuclear enlargement and stratification. Adenomas seem to pass through gradations of dysplasia until invasive adenocarcinoma develops.[64] Extension of neoplastic cells into the basement membrane of the colonic epithelium represents carcinoma in situ. As the neoplastic cells extend beyond the basement membrane, the tumor becomes microscopically invasive. Because the colonic mucosa does not contain lymphatics, metastasis does not usually occur until the tumor invades through the muscularis mucosa into the submucosa.

Small intestinal mucosa can also be involved with adenomatous polyps. Polyps of the small intestine are frequently found around the orifice of the common bile duct.[65] Polyps in this region are variable in size, are often microscopic, and involve only a few crypts. Adenocarcinoma of the duodenal papilla and periampullary regions occurs in 2.9% of patients with FAP[65] and has been found in the common bile duct of these patients.[66]

Gastric polyps occur in patients with FAP, but they are usually benign polyps of the fundic gland.[67] These polyps result from cystic dilation of specialized gastric glands rather than from dysplasia. No evidence that neoplastic transformation occurs in polyps of the fundic gland exists.[68]

## ETIOLOGY

The incidence of FAP ranges from 1 in 6000 to 1 in 12,000 births.[69–71] FAP is inherited as an autosomal dominant trait with a moderate incidence (10%) of new mutations.[72] The manifestations of FAP differ greatly, probably as a result of variation in the mutation of the *APC* gene. Although the occurrence of polyps is strongly related to genetics, the phenomenon of regression of rectal polyps after colectomy and ileorectal anastomosis was recognized in 1988[73,74] and points to the fact that the luminal environment also plays a role in the development of polyps.

FAP is caused by a mutation in the *APC* gene on the long arm of chromosome 5, where a variable deletion or alteration of the gene is associated with the disease. The *APC* gene codes for a protein product that acts as a tumor suppressor.[72] Because of this gene deletion, the probability of cancer (as diagnosed by biopsy during sigmoidoscopy) by 25 years of age is 90%.[4] In colorectal cancer cell lines that have an intact chromosome 5 introduced into the cells, the ability of the cells to induce tumor growth in mice is considerably reduced.[58,75] Similar results have been found for other tumor suppressor genes, namely the *TP53* gene on chromosome 17p and the deleted colorectal cancer gene (*DCC*) on chromosome 18q.[72] It has become apparent there is genetic heterogeneity in FAP. Certain germline mutations of the *APC* gene predispose to attenuated disease expression.[77,78] Further evidence indicates that additional modifier genes influence the severity of FAP.[79]

## CLINICAL PRESENTATION

Although FAP has been recognized in infancy and early childhood, it is most frequently identified in early adolescence. Most patients are asymptomatic, but some present with increased frequency of defecation, rectal bleeding, anemia, and abdominal pain. Most (90%) are identified by routine surveillance because of a familial history of adenomatous polyposis.

Diagnosis is established by sigmoidoscopy and occasionally by air contrast barium enema. Sigmoidoscopy usually reveals a carpet of polyps that cover the entire surface of the colon. Biopsy of at least 10 polyps will confirm the diagnosis. In some patients with FAP, most of the polyps will be located in the proximal colon. If the diagnosis of FAP represents a new mutation (no other family members are known to have the disease), a careful examination of all family members is required.

Polyps are found in the stomach in up to 50% of patients with FAP, but only 6% of the polyps are adenomatous,[67] with the rest being fundic gland polyps (hamartomas). Polyps occur in the duodenum less often than in the stomach; however, duodenal polyps are much more likely to be adenomatous. Several series have demonstrated that up to 98% of FAP patients have visible duodenal polyps or at least a histologic abnormality with dysplasia, unicrypt adenomas, or hyperplasia in the duodenal mucosa.[65,67,80] Adenocarcinoma of the duodenal papilla or periampullary region eventually develops in 2.9% of patients with FAP.[65] For these reasons, upper endoscopy is necessary in all patients with this disorder.

## TREATMENT

Malignant conditions of the colon will occur in all patients with FAP if left untreated. The average age for developing cancer is 39, with 7% developing cancer by age 20 and 15% by age 25.[81] Surgical removal of the entire colonic mucosa will prevent colorectal carcinoma. Most patients who present with symptomatic polyps already have a malignant condition.[81] Therefore colectomy is recommended at any age, if the child is symptomatic.

A wide range of surgical options exists. Total proctocolectomy with a permanent ileostomy prevents cancer but leaves a young patient with a permanent abdominal wall stoma. The physiologic and psychologic impact of a permanent ileostomy is substantial in adolescence. This operation can cause substantial sequelae because of the extensive pelvic dissection, namely, damage to the nervi erigentes with resultant bladder atony and in males, impotence. For these reasons, total proctocolectomy is not the treatment of choice for FAP in a pediatric patient.

Total abdominal colectomy with an ileorectal anastomosis and continued surveillance of the retained rectum has probably been the most common operation for FAP performed in the past. St. Mark's Hospital in London reported results with 215 patients undergoing this procedure.[40] Immediate postoperative complications included prolonged ileus (7%), anastomotic breakdown (2%), and bleeding (<1%), for a total complication rate of 10%. Frequency of defecation at late follow-up (6.5 years) was three stools per day, and less than 10% reported nighttime soiling. Continence was considered completely normal in 72%. Forty-four percent (44%) of the patients, however, required subsequent treatment for their rectal polyps. Depending on the density of the rectal polyps, the patients were evaluated every 3 to 6 months, with sigmoidoscopy and fulguration of any polyps greater than 5mm in diameter. Ten percent developed carcinoma in their rectal stump. The cumulative risk for rectal cancer was 10% at 50 years of age and 29% by 60 years of age.[81]

In more recent years, total colectomy with a rectal mucosectomy and an ileoanal pouch procedure has become the preferred operation for children with FAP. The J pouch is the preferred technique because of simplicity of construction and sparsity of complications.[82] Geiger and colleagues[83] reported a novel technique of a double-stapled, ileoanal, J pouch anastomosis with excellent outcomes. An inverse relationship exists between the size of the reservoir and the frequency of defecation.[84–87] Other factors that influence frequency of defecation include inflammation, sphincter function, and small intestinal motility. Larger reservoirs allow less frequent defecation but tend to be associated with more frequent bouts of inflammation of the reservoir ("pouchitis"), which probably results from stool stasis. In several recent series that studied 450 patients with reservoirs, the frequency of defecation ranged from 3.3 to 7.2 with an average of 5.8 stools per day.[88–93] Large series of patients with reservoirs, however, report an average rate of pouchitis of 23% and a pelvic sepsis rate of 8%.

### FOLLOW-UP

In addition to colonic polyps, patients with FAP can develop a large assortment of benign extracolonic manifestations and occasionally other cancers (see Table 93–1). Endoscopy of the upper gastrointestinal tract and sigmoidoscopy should be performed annually in all patients. Removal of polyps in the duodenum can be done by endoscopic snaring or by open duodenotomy. Size larger than 1 cm in diameter, rapid growth, polyp induration, severe dysplasia, or villous change suggests the need for a more aggressive intervention. Recent data have shown that 42% of adenomas of the ampulla of Vater that are larger than 1 cm in diameter contain a foci of cancer compared with only 13% of those smaller than 1 cm.[94] The incidence of duodenal cancer, however, remains low at 1% to 5%. Sigmoidoscopy can be done easily in patients with an ileoanal pull-through. The anal canal and any short segment of rectal mucosa left behind must be carefully evaluated.

### OTHER TREATMENTS

Drugs and several dietary supplements have been used to treat polyps. These include vitamin C,[95,96] sulindac,[96] dietary fiber,[97] and calcium.[98,99] In a randomized, double-blinded study of the use of sulindac, inhibition of both rectal and duodenal polyp growth was observed[100] and other studies have confirmed this finding.[71,101] In a randomized, double-blind, placebo-controlled study, however, standard doses of sulindac did not prevent the development of adenomas in subjects with FAP. Rectal cancer has been reported after prolonged sulindac treatment.

### GARDNER SYNDROME

Between 1951 and 1955, Gardner and colleagues[102–105] established the association of colonic familial adenomatous polyposis and the extracolonic findings of multiple osteomas, fibromas, and epidermoid cysts. They also demonstrated that the syndrome was inherited in an autosomal dominant pattern.[102,104] The natural history and treatment of the colonic polyps is the same as for those patients with FAP. The osteomas are most frequently found in the skull and facial bones, and abnormal dentition with impaction and early tooth decay and supernumerary teeth are seen.[106] Sebaceous cysts are most commonly found on the legs, followed by the face, scalp, and arms. Lipomas and fibromas are also seen.

Periampullary cancer was thought to be more prevalent in Gardner syndrome than in those with FAP, but surveillance of the duodenum in patients with FAP has shown a high incidence of duodenal abnormalities in all patients. Because detailed surveillance of all patients with familial polyposis has revealed many subtle extracolonic manifestations, the distinction between Gardner syndrome and FAP is becoming less clear. FAP is probably an all-encompassing syndrome, in which patients manifest different signs as the condition evolves.[107]

Desmoid tumors of the abdominal wall and mesentery of the small intestine occur in approximately 20% of patients with Gardner syndrome. These tumors also occur in patients who only have the colonic manifestations of FAP and are the leading cause of death in those who have undergone a prophylactic colectomy. Desmoid tumors are a dense, fibroplastic proliferation that may remain localized or may become widespread throughout the mesentery or the abdominal wall. All stages of fibrous dysplasia including fibrosarcoma have been seen. Most desmoid tumors appear after surgery, usually within 6 to 30 months.[108] Desmoid tumors of the body wall may be observed initially because many of them remain static or even regress over several years.[108] For those that continue to grow or reach 10 cm in diameter, complete local excision is met with a recurrence rate of less than 10%, which is satisfactory. Most intraabdominal desmoid tumors do not become evident until they have reached a nonresectable size. Because of the difficulty in resecting intraabdominal desmoid tumors, several drugs have been tried with varied rates of success. Such drugs include steroids; antiestrogen agents (progesterone, tamoxifen, and toremifene); and nonsteroidal anti-inflammatory agents.[109–115]

### TURCOT SYNDROME

Turcot, Despres, and St. Pierre[116] described two siblings who initially presented with colonic familial adenomatous polyposis and eventually died of intracranial brain tumors (glioblastoma and a medulloblastoma). Turcot believed that the brain tumors were extracolonic manifestations of FAP. Ependymomas and carcinoma of the thyroid (which are usually papillary in origin)[107] have also been described to occur in Turcot syndrome.

## Hamartomatous Polyposis Syndromes

Hamartomatous polyposis syndromes are distinguished by an overgrowth of cells that are native to the area in which they normally occur. The overgrowth is in general not considered to have malignant potential. Several of the syndromes in this category, however, have an increased lifetime risk of developing either intestinal or extraintestinal cancers. The hamartomatous polyposis syndromes include juvenile polyposis syndrome, Cowden disease, and Peutz-Jegher syndrome.

### JUVENILE POLYPOSIS SYNDROME

Juvenile polyposis syndromes are uncommon. These syndromes can be separated into three distinct clinical entities: diffuse juvenile polyposis of infancy, diffuse juvenile polyposis, and juvenile polyposis coli.[8]

#### Diffuse Juvenile Polyposis of Infancy

Diffuse juvenile polyposis of infancy presents within the first few months of life,[15] usually without any family history.[20] Presenting signs include diarrhea, rectal bleeding, intussusception, protein-losing enteropathy, macrocephaly, clubbing of fingers and toes, and hypotonia.[117–121] The extent of diarrhea, rectal bleeding, and protein-losing enteropathy is directly related to the number of polyps present. The entire GI tract is frequently involved. Treatment for this syndrome is usually aggressive, starting with total parenteral nutrition and intestinal rest. The latter measure reduces the protein and blood loss and decreases the incidence of intussusception.[122] When the nutritional status of the patient has been stabilized, portions of the intestine with the most polyps are

removed. Despite appropriate treatment, this disease is almost universally fatal; only 2 of 12 patients are reported as surviving beyond 2 years of age.[7,17,117–121,123–126]

### Diffuse Juvenile Polyposis

Children with diffuse juvenile polyposis are usually 6 months to 5 years of age and present with mild rectal bleeding and prolapse but may also have protein-losing enteropathy, intussusception, and malnutrition.[15] For this age group it is important to distinguish juvenile polyposis from familial adenomatous polyposis. Polyps associated with diffuse polyposis are found throughout the bowel, most often in the stomach, distal colon, and rectum.[15] Endoscopic polypectomies and segmental bowel resection are used in the treatment of this disease. These children usually do well, although the need for recurrent therapy is common.

### Juvenile Polyposis Coli

Juvenile polyposis coli occurs in children between the ages of 5 and 15 years of age. This disorder is usually characterized by bleeding of bright red blood from the rectum, anemia, rectal prolapse, or all of these disorders. Polyps are usually limited to the distal colon and rectum.[15] Approximately 50% of the patients will have a family history, indicating an autosomal dominant pattern of inheritance.[17] Associated congenital defects including cleft palate, malrotation, polydactyly, and abnormalities of the heart and cranium have been described.[20]

***Pathology*** Any child with five or more polyps, polyps throughout the GI tract, or even one polyp if the child has a family history of juvenile polyposis is considered to have a juvenile polyposis syndrome.[20] Most patients with such syndromes will have approximately 50 to 100 colorectal polyps. Patients with diffuse juvenile polyposis of infancy and diffuse juvenile polyposis will also have polyps in the stomach, small intestine, or both. The importance of identifying children with a polyposis syndrome lies in the need for long-term surveillance due to the high risk of carcinoma (17%) occurring at an early age (mean age at diagnosis of carcinoma is 35.5 years).[15]

The gross appearance of a polyp in juvenile polyposis is the same as one in isolated juvenile polyps. Approximately 20% of the polyps in juvenile polyposis, however, present grossly as a multilobular mass resembling a cluster of polyps attached to a stalk (Fig. 93-6).[18] Histologically, these polyps demonstrate more epithelium with a villous or papillary configuration. Epithelial dysplasia can occur in juvenile polyps[*] and in coexisting adenomas found in conjunction with juvenile polyps.[9,14,16,18,131–136] Severe dysplasia, which could be considered carcinoma in situ, has been found in patients with juvenile polyps associated with juvenile polyposis syndrome.[137] Lobular polyps have a higher propensity for more severe dysplasia (47%) than the nonlobular polyps (10%).[18] Several reports of infiltrating adenocarcinoma of the colon and rectum in association with juvenile polyposis exist.[8,12,129,131,138–140] According to the St. Mark's Polyposis Registry in London, the cumulative risk for cancer in patients with a juvenile polyposis syndrome by age 60 is 68%.[19,128]

*References 9, 12–14, 16, 18, 25, 127–132.

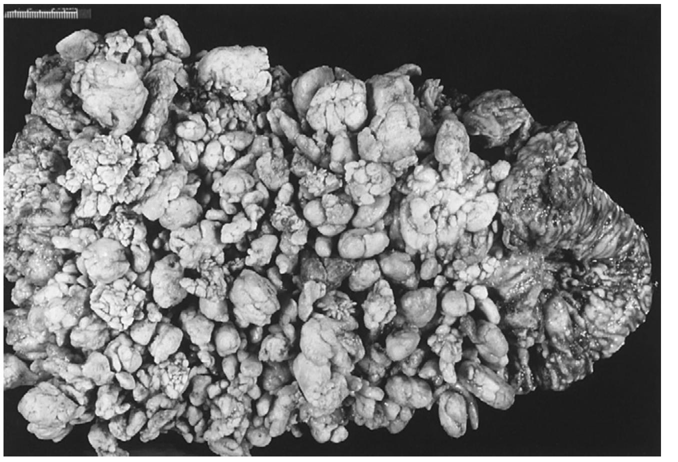

**FIGURE 93-6** Gross specimen of colon in a patient with juvenile polyposis syndrome. Note small adenomas and multilobular clusters of polyps attached to stalks.

***Treatment*** The autosomal dominant pattern of inheritance and the 68% cumulative risk for cancer by age 60 means that treatment must include long-term follow-up of patients with polyposis and their family members. Some advocate prophylactic colectomy and rectal mucosectomy with endorectal ileal pull-through as a primary treatment.[129] Others recommend regular screening (every 2 years) with colonoscopy and random biopsy[141] and subsequent colectomy if severe dysplasia, rapid polyp formation, or bleeding occurs.[16] One patient had a colectomy and ileosigmoidostomy at 4 years of age only to develop inoperable cancer of the sigmoid colon at 27 years of age.[18] First-degree relatives should be screened because of the familial nature of the disease. The approach to patients with juvenile polyposis should be similar to that taken for patients with familial adenomatous polyposis.

## PEUTZ-JEGHER SYNDROME

### History

The association of intestinal polyps with mucocutaneous pigmentation spots of the mouth, hands, and feet was first reported by Peutz in 1921.[142] In 1944[143] Jegher first reported two cases. In 1949[144] he and his colleagues added 8 more to 12 other cases he had collected from personal communications. Jegher and colleagues[144] subsequently defined the two main features of the syndrome: melanin spots on the buccal mucosa and lips, with variable melanin pigmentation on the face and digits, and polyposis of the intestinal tract. In 1954 Bruwer, Bargen and Kierland[145] were the first to use the term *Peutz-Jeghers syndrome*. In recent years, reports of intestinal and extraintestinal cancers have led to a reassessment of the management of these patients.[146]

### Pathology

Peutz-Jeghers syndrome is characterized by melanotic spots, ranging in color from brown to black, occurring on the lips, around the mouth, and on the buccal mucosa. These spots can also be found on the hands, feet, nasal mucosa, and conjunctivae and in the rectum.[146] The pigmented spots are usually present at infancy and usually fade at puberty.

Although the polyps associated with Peutz-Jeghers syndrome can be found anywhere from the stomach to the rectum, they occur most commonly in the small intestine (55%). Approximately 30% of these polyps are found in the stomach and duodenum, and 15% are found in the colon and rectum.[147] Grossly, the polyps range from a few millimeters to several centimeters and present as smooth, firm, pedunculated lesions that are lobulated, in contrast to juvenile polyps, which are not lobulated. Peutz-Jeghers polyps are classified histologically as hamartomas of the muscularis mucosa[146] and demonstrate strands of smooth muscle fibers that divide the polyp into sectors (Fig. 93-7).[148–150] Adenomas can occur concurrently with Peutz-Jeghers polyps.

### Etiology/Incidence

Peutz-Jeghers syndrome is rare and has an equal sex distribution; it has been described in all ethnic groups. Most cases of Peutz-Jeghers syndrome are inherited in an autosomal dominant pattern, but some develop de novo, most likely representing new, spontaneous mutations. Recently two groups of investigators have defined the genetic mutation associated with Peutz-Jeghers syndrome. In Peutz-Jeghers–affected individuals many (but not all) have a mutation of a novel serine/threonine kinase (LKB1 or STK11) with loss of kinase activity.[151,152] Routine genetic testing and gene therapy for this disease is under investigation but currently not available.[153]

### Clinical Presentation

Because of the familial association of Peutz-Jeghers syndrome, the syndrome is often revealed in patients through screening programs. If there is no family history, patients usually present with crampy abdominal pain related to transient intussusception of a polyp. Abdominal radiographs will often demonstrate dilated or partially obstructed small intestine but rarely complete obstruction. Anemia resulting from occult blood loss and malignant conditions are other presenting signs. Thirty percent of patients present with signs and symptoms in the first 10 years of life, with 50% presenting by 20 years of age.[154,147]

Several reports of intestinal tumors in association with Peutz-Jeghers syndrome have been published.[155–160] Malignant changes in hamartomatous polyps of Peutz-Jeghers syndrome have been commonly reported.[101,159,161–167] Separate adenomatous and carcinomatous changes in hamartomas have also been reported, which suggests that the adenoma-carcinoma sequence occurs in the small intestine of patients with Peutz-Jeghers syndrome.[161] A review of 72 patients with the syndrome[159] showed that 22% developed cancer. Nine cases were gastrointestinal or pancreatic in origin, and seven were extraintestinal. Compared with an age-matched general population, patients with Peutz-Jeghers syndrome had a relative risk for death from gastrointestinal cancer alone that was 13 times greater, and the risk for death from all cancers was 9 times greater. The chance of dying from cancer by the age of 60 is approximately 50% in patients with Peutz-Jeghers syndrome.[146]

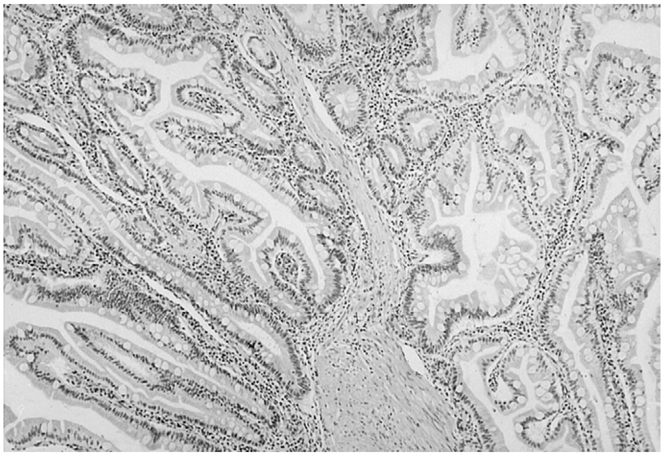

FIGURE 93-7 Photomicrograph of a Peutz-Jeghers polyp demonstrating a hamartomatous alteration of the muscularis mucosa. Smooth muscle fibers divide the polyp into sectors.

Extraintestinal tumors associated with Peutz-Jeghers syndrome include ovarian, cervical, and testicular neoplasms. Reported ovarian tumors include cystadenomas,[154,168,169] granulosa cell tumors,[135] and sex-cord tumors.[170–172] Adenocarcinoma of the cervix can occur and is usually associated with an ovarian tumor.[174] Sertoli cell tumors of the testicle have been found and cause gynecomastia in 50% of cases. These tumors are usually benign but have malignant potential[175–177]; thus an orchiectomy is recommended. Cancer of the breast, thyroid, bile duct, pancreatic, and gallbladder have all been described in association with Peutz-Jeghers syndrome.[146]

### Treatment

Peutz-Jeghers syndrome should be suspected in any child who presents with colicky abdominal pain or occult anemia and melanotic pigmented spots. Recommendations for treatment have changed over the past decade because of the increasing concern of malignancy. The management protocol proposed by Phillips and Spigelman[146] includes the following annual evaluations: (1) symptoms related to polyps, (2) blood count to detect anemia caused by blood loss, (3) breast and pelvic examinations with cervical smears and pelvic ultrasonography in girls, (4) testicular examination with ultrasonography in boys, and (5) pancreatic ultrasonography. In addition, esophagogastroduodenoscopy and colonoscopy are recommended on a biennial basis, along with small intestine contrast studies. Recently magnetic resonance imaging (MRI) has shown promise as a surveillance modality for small intestinal screening.[178] Mammography is recommended at 25, 30, 35, and 38 years of age, biennially until 50 years of age, and then annually.

All polyps larger than 0.5 mm found at endoscopy should be removed. Laparotomy with intraoperative enteroscopy is recommended for removal of all small bowel polyps greater than 15 mm in diameter. The previous practice of radical intestinal resections should be avoided because of the recurrent nature of the polyps and the ensuing short-bowel syndrome that can occur. Any intestinal or extraintestinal tumors should be treated aggressively. Historical data indicate that the chance of patients with Peutz-Jeghers syndrome dying by the age of 60 is close to 60% compared with 25% in an age-matched general population.[146]

## COWDEN DISEASE

Cowden disease is an autosomal dominant condition distinguished by multiple hamartomas that affects all three of the germ layers. Patients with Cowden disease are at an increased

risk of developing breast, thyroid, and endometrial neoplasias.[179,180] Eighty percent of patients present with dermatologic lesions including facial trichilemmomas, acral keratoses, papillomatous papules, or mucosal lesions. Other major but not necessarily pathognomonic criteria include breast carcinoma, thyroid carcinoma, macrocephaly, and endometrial carcinoma. Only 35% of patients who meet the criteria for Cowden disease will have gastrointestinal polyposis.[7] The polyps are typically juvenile polyps without any increased risk of developing a gastrointestinal cancer.

# Nonepithelial Polyps

## LYMPHOID POLYPS

### History

The first case of lymphoid hyperplasia of the terminal ileum was described by Marina-Fiol and Rof-Carballo in 1941 as reported by Patel and Awen.[181] Fieber and Schaefer[182] reviewed eight cases previously described in the literature and added four of their own in 1966. Byrne and colleagues[183] reported only 44 cases in the world literature; however, lymphoid polyps were identified in 60% of children studied by Franken for remote abdominal complaints.[184] Thus the incidence of lymphoid polyps is probably higher than reported, but clearly most of them are asymptomatic, and, therefore, never identified.

### Pathology

Lymphoid polyps vary in size from a few millimeters to 3 centimeters in diameter and are usually sessile in form. The polyps are caused by elevation of hyperplastic submucosal lymphoid aggregates. The overlying mucosa often becomes ulcerated, which gives the polyp the volcano-like appearance. Ulceration of the mucosa leads to occult blood loss. Hyperplasia of the submucosal lymphoid tissue is believed to be caused by nonspecific infections of childhood.[1,2,4,108]

### Incidence

Lymphoid polyps tend to develop in young children within the first few years of life as a result of exposure to new bacteria and viruses.[122] The peak incidence is at 4 years of age and significantly diminishes by 5 years of age.

### Clinical Presentation

Anemia resulting from blood loss and occasionally substantial rectal bleeding are the usual presenting signs of lymphoid polyps. Colonoscopy, air contrast barium enema, or both are the diagnostic methods of choice for diagnosing lymphoid polyps of the colon. An air-contrast barium enema will show small, uniform, umbilicated, polypoid filling defects that are distinct from juvenile or adenomatous polyps (Figs. 93-8 and 93-9).[183,184] Small elevations of otherwise-normal mucosa are seen on endoscopy, and biopsy will confirm the diagnosis. Histologic evaluation reveals lymphoid aggregates with large germinal follicles.[122]

### Treatment

Lymphoid polyps are benign, are self-limiting, and tend to regress spontaneously.[42,185] Once a histologic diagnosis is made, expectant measures will usually be rewarded by regression of

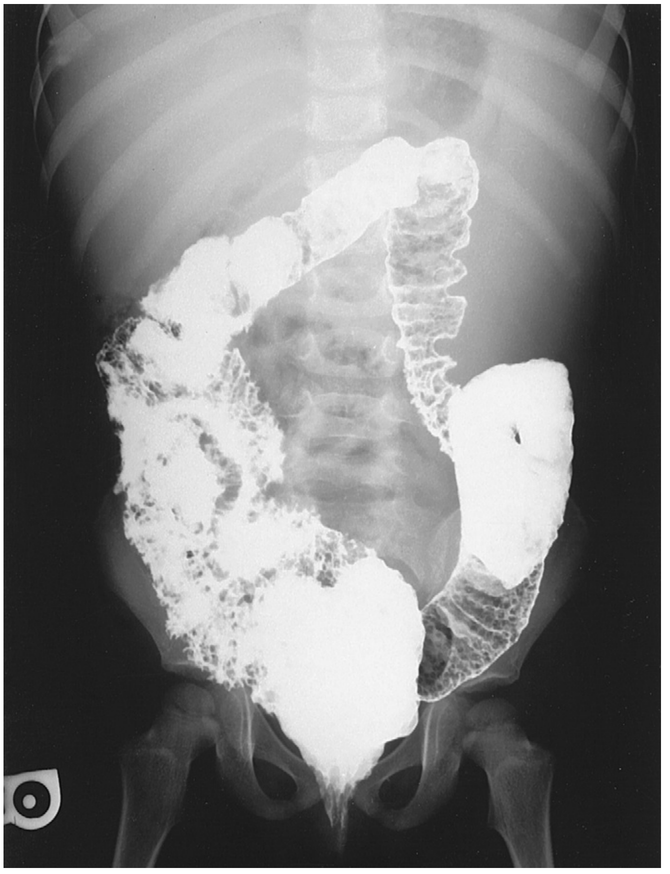

**FIGURE 93-8** Barium enema showing multiple, small 1- to 2-mm mucosal nodules throughout the entire colon and terminal ileum. The central umbilication within these nodules seen on this postevacuation film is diagnostic of diffuse lymphoid hyperplasia.

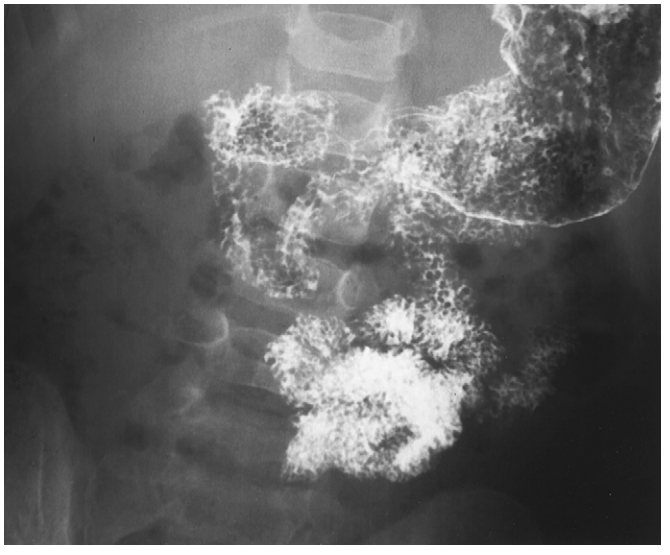

**FIGURE 93-9** An upper gastrointestinal series showing diffuse lymphoid hyperplasia throughout the stomach and small intestine.

the lesions. Substantial uncontrolled bleeding and intussusception may require a more aggressive surgical approach.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 94

# Necrotizing Enterocolitis

Karl G. Sylvester, Gigi Y. Liu, and Craig T. Albanese

Necrotizing enterocolitis (NEC) is an acquired inflammatory disease that affects the gut of newborn infants nearly exclusively. Despite decades of research, NEC remains a leading cause of infant morbidity and mortality in neonatal intensive care units (NICUs). Increased rates of preterm birth and advances in neonatal care have contributed to a growing population of infants at risk for NEC. It is now the most common newborn surgical emergency and is associated with significant morbidity and mortality that exceeds all other gastrointestinal (GI) conditions requiring surgical intervention. Although the precise pathogenesis remains incompletely understood, clinical progress in recent years portends a shift in focus to prevention and the earlier identification of those infants most at risk or with progressive disease. Despite the recent completion of two successful prospective trials, the optimum surgical management of advanced disease with perforation remains controversial.

## Historical Perspective

Dating to at least 1888, there are several reports describing pathologic findings of intestinal perforation in neonates as the cause of death suggestive of NEC.[1–3] The first report of a successfully treated infant with a localized ileal perforation that was described as a disease resembling NEC is attributed to Agerty[4] in 1943. Subsequently, in 1953 Schmid and Quaiser[5] first used the term *necrotizing enterocolitis*. In 1964 Berdon[6] reported the clinical and radiographic findings of 21 patients with NEC. Then in 1975 Santulli[7] first hypothesized that the development of NEC had three essential components: injury to the intestinal mucosa, the presence of bacteria, and the availability of a metabolic substrate (to be taken as the presence of enteral feedings). This characterization remains a central tenet of our understanding of the overall pathophysiology of NEC (discussed later). Over the past several decades the management of infants with NEC has evolved from aggressive early operation to supportive care with the increasing realization that most infants can be managed, at least initially, nonoperatively.

The subsequent seminal work of Bell and colleagues[8] codified a severity-based classification scheme that is widely accepted due to its simplicity and clinical utility in suggesting therapy on the basis of likely outcomes. Bell's criteria (Table 94-1) can be summarized as indicating clinical findings suspicious for NEC (Bell's stage I), definitive NEC (Bell's stage II), and advanced NEC (Bell's stage III). In general, a stage I infant manifests clinical criteria that raise suspicion without definitive evidence such as pneumatosis intestinalis or bloody stool. In stage II, or definitive disease, there is nearly always evidence for pneumatosis intestinalis (Fig. 94-1). The hallmark of advanced disease is the appearance of pneumoperitoneum or other clinical findings to suggest irreversible tissue damage with perforation. In 1979 the International Classification of Diseases established a code for death from NEC, thereby allowing more precise epidemiologic and outcome analyses. Currently, the optimum surgical approach in order to realize the best short- and long-term outcomes in infants with intestinal perforation secondary to NEC remains the subject of intense scrutiny via ongoing clinical trials.

## Incidence

Although the overall reported incidence of NEC among newborn infants is relatively low and reported to fall between 5% and 10%.[9–11] The true incidence is unknown given a number of either early or suspicious cases of NEC that cannot be accurately tabulated. Conversely, the number of infants that are under consideration for either having or developing NEC can be quite high and is directly related to degree of prematurity. Perhaps more puzzling, the incidence of NEC varies significantly within the United States and throughout the developed world. For example, the worldwide incidence of NEC in very-low-birth-weight (VLBW, <1500 g) infants varies from 1% to 2% in Japan, 7% in Austria, 10% in Greece, 14% in Argentina, and 28% in Hong Kong.[12–16] The reasons for these disparities are unclear but are likely multifactorial including biologic (e.g., genetic) and environmental (e.g., variation in practice patterns). Irrespective of geographic reporting location, it is clear the incidence of NEC varies according to degree of prematurity and birth weight. NEC accounts for 1% to 7% of all NICU admissions in the United States, or 1 to 3 cases per 1000 live births.[9,17,18] In VLBW infants, the disease occurs in approximately 10% to 12%, but ranges between 2% and 22%, depending on the center of inquiry.[11,15,19]

**TABLE 94-1**
**Modified Bell Staging Criteria for Necrotizing Enterocolitis**

| *Stage* | *Systemic Signs* | *Abdominal Signs* | *Radiographic Signs* |
|---|---|---|---|
| IA<br>Suspected | Temperature instability, apnea, bradycardia, lethargy | Gastric retention, abdominal distention, emesis, heme-positive stool | Normal or intestinal dilation, mild ileus |
| IB<br>Suspected | Same as above | Grossly bloody stool | Same as above |
| IIA<br>Definite, mildly ill | Same as above | Same as above, plus absent bowel sounds with or without abdominal tenderness | Intestinal dilation, ileus, pneumatosis intestinalis |
| IIB<br>Definite, moderately ill | Same as above, plus mild metabolic acidosis and thrombocytopenia | Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass | Same as IIA, plus ascites |
| IIIA<br>Advanced, severely ill, intact bowel | Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, and neutropenia | Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention | Same as IIA, plus ascites |
| IIIB<br>Advanced, severely ill, perforated bowel | Same as IIIA | Same as IIIA | Same as above, plus pneumoperitoneum |

Modified from Neu J: Necrotizing enterocolitis: The search for a unifying pathogenic theory leading to prevention. Pediatr Clin North Am 1996;43:409-432 and Caplan MS, Jilling T: New concepts in necrotizing enterocolitis. Curr Opin Pediatr 2001;13:111-115.

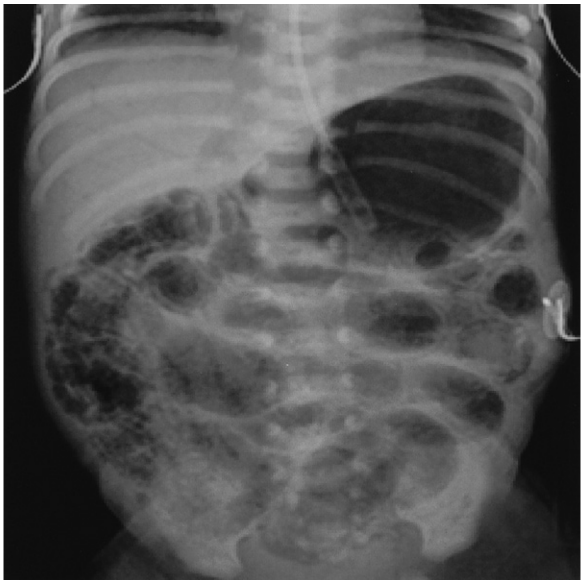

**FIGURE 94-1** Plain abdominal radiograph demonstrating extensive pneumatosis intestinalis (cystic and linear) and an arborizing pattern of air over the liver shadow representing gas dispersed within the radicles of the portal venous system.

Several confounding factors may account for the variability in incidence reporting including the number and survival of low-birth-weight (LBW) infants, the source of patient referrals (inborn or outborn), and the diagnostic criteria used to establish definitive NEC. A relatively large multicenter survey of VLBW infants noted an incidence of 10.1% for definite NEC (stage II) and 17.2% for suspected NEC (stage I), although there was considerable intercenter variability.[20] In another study, the incidence of definite NEC versus suspected NEC was 8.6% and 18.6%, respectively.[18] The observed variability in these and many other series may be underestimating the true frequency of NEC because the incidence is often defined as the total number of cases of NEC divided by the total number of patients admitted to the NICU. Thus these figures may include many premature infants who die within the first several days of life and before enteric feedings and therefore are unlikely attributable to NEC. In consideration of this, a notable historical study that excluded early neonatal deaths and included only infants who had been fed reported an incidence of 15%.[21]

# Epidemiology and Pathogenesis

## EPIDEMIOLOGY

### Age and Maturity

NEC is predominantly a disease of premature LBW infants rather than those who are small for gestational age. It is estimated that only 7% to 13% of all NEC cases occur in full-term infants.[22,23] Kliegman and Fanaroff[24] reported that the mean gestational age of 123 patients with NEC was 31 weeks (average birth weight, 1460 g). Infants with extremely low birth weight (ELBW) (<1000 g) and those 28 weeks' gestational age or younger are at greatest risk.[25,26] In a large multicenter prospective study from the NICHD Neonatal Research Network involving 4438 infants weighing between 501 and 1500 g, Lemons[11] demonstrated an inverse relationship between the incidence of NEC and birth weight. Specifically, the incidence of NEC was highest in infants weighing between 501 and 750 g (14%) and declined with increasing weight: 751 to 1000 g (9%), 1001 to 1250 g (5%), and 1251 to 1500 g (3%). These findings have been confirmed by others[23,27,28] and extended to document an inverse relationship between the age at onset of NEC and gestational age. Infants in whom NEC developed in the first week of life were more mature (average gestational age, 36.1 weeks) than those in whom NEC developed after

1 week of age (average gestational age, 33.4 weeks). Complications were more common, and the mortality rate was higher in patients with early-onset disease. Wilson[29] calculated the birth weight–specific, weekly attack rate in patients with NEC and found the risk period for NEC decreased as birth weight increased. They found a consistent pattern of sharply declining risk with attainment of age equivalent to 35 to 36 weeks' gestation. From these observations the authors speculated that functional maturation of the GI tract may play a principal role in determining the risk for NEC.

### Feedings

Approximately 90% of NEC cases develop in infants after feedings are initiated.[30–32] In a longitudinal cohort study reviewing the incidence of NEC for a 3-year period before and after implementing a "standardized feeding schedule" for infants weighing between 1250 and 2500 g and less than 35 weeks' gestation, Kamitsuka[33] reported an 84% reduction in the risk for NEC. Other studies have also suggested an association between an increase in the incidence of NEC and advancement of formula feedings at rates greater than 20 kcal/kg/day.[34,35] Despite these reports, randomized trials failed to demonstrate any difference in the incidence of NEC related to fast versus slow, early versus delayed, or continuous versus intermittent bolus feedings.[36–39] In a randomized trial involving 185 VLBW infants in which slow (15-mL/kg/day increments; 10-day schedule to full feeding) and fast (35-mL/kg/day increments; 5-day schedule to full feeding) feeding advancements were compared, Rayyis[39] demonstrated no significant difference in the incidence of NEC (13% vs. 9%), perforation (4% vs. 2%), and mortality (2% vs. 3%) between groups. In a review of randomized trials comparing continuous versus intermittent bolus tube feeding for premature infants weighing less than 1500 g, Premji and Chessell[38] found no significant differences in the incidence of NEC between the two groups.

In a randomized trial investigating the incidence of NEC in VLBW infants assigned to receive either minimal-volume feeding (20 mL/kg/day) for 10 days before advancing to full-volume feeding or a standard feeding advancement protocol (starting at 20 mL/kg and increasing by 20 mL/kg/day to full-volume feeding), Berseth[40] reported a significantly lower incidence of NEC in the minimal-volume group than in the standard group (1.4% vs. 10%). The prolonged use of "trophic feeding" volumes is thought to trigger maturation of GI structure and function. This study reinforces previous studies that gut stimulation protocols are beneficial to VLBW infants[41] and that initiation of a minimal-volume feeding protocol for 7 to 10 days followed by modest advancement of feeding may greatly reduce the incidence of NEC.[42] However, there are no contemporary studies that specifically address this issue.

### Pharmacologic Agents

Indomethacin is commonly used in premature infants to treat a hemodynamically significant patent ductus arteriosus (PDA). Indomethacin blocks prostaglandin synthetase, thus causing vasoconstriction. Spontaneous gastrointestinal perforation (SIP) and NEC have been noted in LBW infants treated with high-dose indomethacin.[43,44] It has been postulated that indomethacin increases mesenteric vascular resistance and reduces mesenteric blood flow by 16% to 20%.[45] Norton[46] demonstrated that the use of indomethacin as a tocolytic agent was associated with an increased incidence of NEC in babies delivered before 30 weeks' gestation (mean age at delivery, 27.6 weeks), although indomethacin did not increase the incidence of NEC in babies born after 32 weeks' gestation. Two randomized controlled trials involving more than 500 LBW premature infants receiving early low-dose indomethacin versus placebo for closure of a PDA demonstrated no difference in the subsequent incidence of NEC.[47,48] According to several recent Cochrane Reviews, ibuprofen appears to be as effective as indomethacin in leading to a PDA closure and with fewer reported cases of NEC or SIP.[49] Interestingly, although the continuous infusion of indomethacin for a PDA leads to fewer alterations in cerebral, renal, and mesenteric blood flow compared with bolus infusion, to date, insufficient evidence exists to demonstrate that this results in a lowered risk of NEC or SIP.[50] Earlier indomethacin may be associated with increased incidence of SIP but protection from NEC. Moreover, a PDA itself may predispose to NEC, independent of indomethacin.

### Cytokines and Growth Factors

Cytokines and growth factors play a critical role in mediating the interaction among enterocytes, endothelial cells, fibroblasts, and inflammatory cells that together are critical to the overall cellular pathophysiology of NEC. These soluble factors direct cellular proliferation, maturation, chemotaxis, and activation in both the local gastrointestinal milieu and systemically to effect the onset and progression of NEC (Table 94-2).[51–56]

### Growth Factors

Epidermal growth factor (EGF) is known to be an important trophic factor for the developing GI tract and has been shown to be present in high concentration in human breast milk.[57,58] Typically, EGF is secreted into the gut lumen primarily by the salivary and Brunner glands of the duodenum and binds to EGF receptors that have been demonstrated throughout the fetal and neonatal intestine, especially on the basolateral membrane of enterocytes.[59–64] EGF enhances proliferation and differentiation of epithelial cells but also has significant effects on healing of damaged mucosa and on intestinal adaptation after injury.[62,65–67] Significantly reduced levels of salivary and serum EGF have been demonstrated in premature infants in whom NEC developed versus age-matched controls.[68,69] Furthermore, lower levels of salivary EGF during the first week of life were associated with an increased incidence of NEC in a recent clinical trial[70] involving 327 premature and term neonates. Similarly, inactivation of the EGF receptor in knockout mice has been shown to result in hemorrhagic enteritis that is histologically similar to NEC.[71]

Several animal studies that administered EGF provide insight to the molecular mechanism underlying EGF-mediated protection against NEC. In studies using a neonatal rat model of NEC that involved asphyxia and cold stress, enterally administered supplements of EGF have been shown to significantly decrease the incidence and severity of NEC in rat pups[72] through down-regulation of the proinflammatory interleukin-18 (IL-18) and increased production of the anti-inflammatory cytokine IL-10.[73] Supplement of EGF in two rat models has successfully reduced intestinal epithelial cell apoptosis in the ileum, decreased intestinal permeability,

**TABLE 94-2**
**Summary of Important Growth Factors and Cytokines Contributing to the Pathogenesis of NEC**

| *Cytokines* | *Functions* | *Proinflammatory* | *Antiinflammatory* | *Protective Effects in Guts* | *Trophic Effects in Enterocytes* |
|---|---|---|---|---|---|
| EGF and HB-EGF | • Proliferation and differentiation of epithelial cells<br>• Healing of damaged mucosa | No | Yes | Yes | Yes |
| Epo | • RBC proliferation | No | No | Yes | Yes |
| IL-1β | • Macrophage activation, neutrophil recruitment, expression of endothelium adhesion molecules<br>• Production of IL-6, IL-8, PGE2 | Yes | No | Unknown | Yes |
| IL-4 | • T- and B-cell and macrophage regulation<br>• Differentiation of CD4 T cell into Th2 cells | Yes | Yes | Yes | Unknown |
| IL-6 | • Production of acute phase proteins, B-cell growth, T-cell proliferation, metalloproteinases, and GM-CSF | Yes | Unknown | Unknown | Unknown |
| IL-8 | • Attraction of neutrophils and basophils to site of inflammation | Yes | No | No | Unknown |
| IL-10 | • Decreases macrophage activation<br>• Inhibition of proinflammatory cytokine production | No | Yes | Yes | Unknown |
| IL-11 | • Increases megakaryocyte and macrophage production | No | Yes | Yes | Yes |
| IL-12 | • Production of IFN-γ, Th1 and NK cell proliferation<br>• Cytotoxic T lymphocyte and Th1 cell differentiation<br>• Macrophage activation and production of complement-fixing antibodies<br>• Up-regulation of IL-18 receptor | Yes | Unknown | Unknown | Unknown |
| IL-18 | • IFN-γ and B-cell antibody production<br>• Enhanced NK cell cytotoxic activity<br>• Activation and migration of neutrophils, phagocytosis, and integrin expression | Yes | No | Unknown | Unknown |
| NO | • Regulation of leukocyte-endothelial interaction and platelet aggregation and adhesion<br>• Apoptosis from peroxynitrite when NO reacts with superoxide | Yes | Yes | Yes | No |
| TNF-α | • Cytokine release of IL-1β, IL-6, IL-8, NO, PGE2, matrix metalloproteases, PAF, and TXA2<br>• Inhibition of the release of glucocorticoids, TGF-β, and IL-10<br>• Apoptosis induction<br>• Neutrophil activation and recruitment | Yes | Unknown | Unknown | Unknown |
| PAF | • Mesenteric vasoconstriction<br>• Capillary leakage and increased intestinal mucosal permeability<br>• Neutrophils and platelet activation | Yes | Unknown | Unknown | Unknown |
| COX2 | • Synthesis of proinflammatory prostaglandins | Yes | Unknown | Unknown | Unknown |

Modified from Ledbetter DJ, Juul SE: Necrotizing enterocolitis and hematopoietic cytokines. Clin Perinatol 2000;27:697.

increased mucin production by goblet cells, and improved overall intestinal structure.[74,75]

Heparin-binding epidermal-like growth factor (HB-EGF) is a member of the EGF family of growth factors. HB-EGF initially was identified in conditioned medium of macrophage-like cells as a mitogen for fibroblasts and smooth muscle cells.[76] The presence of HB-EGF has been reported in both human amniotic fluid and milk.[77,78] An HB-EGF knockout mouse model has shown significantly increased intestinal permeability, delayed onset of angiogenesis, and increased incidence and severity of NEC.[79,80] According to several animal studies,[78,81–84] HB-EGF has been demonstrated to protect developing intestinal epithelium from hypoxic necrosis and cytokine-induced apoptosis, as well as to exert its cytoprotective effects via decreased reactive oxygen and nitrogen species production. Interestingly, simultaneous administration of both EGF and HB-EGF did not result in any additional protective effect against NEC.[83]

Erythropoietin (Epo) is a peptide produced by the kidneys that regulates red blood cell production in response to anemia. Since development of the recombinant protein, rEpo has become widely used in the NICU.[85,86] Epo has been found in human breast milk, and functional Epo receptors have been demonstrated in fetal and neonatal small intestine, thus

suggesting a possible role in GI development.[87–89] In a retrospective study comparing 260 VLBW infants who received recombinant Epo (rEpo) with 233 matched controls, Ledbetter and Juul[90] demonstrated a significantly lower incidence of NEC in the rEpo group (4.6%) than in the control group (10.8%). Studies in neonatal rats given rEpo enterally have demonstrated a dose-dependent increase in intestinal mucosa villus surface area and increased cellular proliferation, thus suggesting a role of rEpo as a trophic factor in the developing small intestine.[91] In a neonatal rat model of NEC involving exposure to hypoxia and reoxygenation, pretreatment with intraperitoneal injections of rEpo resulted in significantly decreased mucosal inflammation and necrosis, which was suggested to be mediated by decreased production of nitric oxide (NO).[92]

## Cytokines

Cytokines are endogenous mediators of the inflammatory cascade. Proinflammatory and antiinflammatory cytokine production is tightly regulated by complex feedback mechanisms to maintain homeostasis.[93,94] Overproduction of either may have significant untoward effects. Overproduction of proinflammatory cytokines (IL-1, IL-2, IL-6, IL-8, IL-12, tumor necrosis factor-alpha [TNF-α], interferon) and platelet-activating factor (PAF) may lead to shock, multiorgan failure, and death.[95,96] Overproduction of antiinflammatory cytokines (IL-4, IL-10, IL-11) may result in excessive suppression of immune function.[97,98] A number of different inflammatory mediators have been implicated in the pathogenesis of NEC, several of which are highlighted later.[99,100]

IL-1β in the gut can be found in macrophages, neutrophils, intestinal epithelial cells, endothelial cells, fibroblasts, dendritic cells, smooth muscle cells, and enteric glia.[101,102] Microbial products, inflammation, and TNF-α trigger its release.[101,102] Upon binding to the IL-1 receptor, IL-1β and its receptor activate the transcription factor NF-κB, which triggers release of acute phase proteins, IL-6, IL-8, and $PGE_2$.[101,102] Elevated IL-1β has been detected in full-thickness specimens of NEC intestine.[103] Edelson[104] detected a greater level of IL-1 receptors late in the course of severe NEC. Both IL-1β and IL-1 receptor may serve as markers for progressive disease.

Levels of IL-6 increase in the presence of microbes, microbial products, TNF-α, and IL-1β.[101,105] Upon binding to IL-6 receptors, which are only expressed on hepatocytes and some leukocytes, IL-6 triggers the STAT-4 pathway, resulting in production of acute phase proteins, B cell growth, antibody production, T-cell proliferation, and enhanced activity of hematopoietic growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF).[101,105] Furthermore, it leads to the production of tissue inhibitors of metalloproteinases and inhibition of superoxide production.[106] Elevated IL-6 has been reported in the plasma and stool of babies with NEC,[107] but its mRNA expression in surgical intestinal specimens is not any higher than the controls.[105]

IL-8 is released in response to LPS, TNF-α, and IL-1β.[108] After binding to the chemokine receptors CXCR1 and CXCR2, which signal through phospholipase C and PI3-kinase, respectively, IL-8 is responsible for neutrophil activation and migration into tissues, as well as the production of acute phase proteins.[108] In a study evaluating serial serum levels of two proinflammatory cytokines (IL-1β, IL-8) and two antiinflammatory cytokines (IL-1 receptor antagonist [IL-ra], IL-10) in infants with NEC, Edelson and colleagues[104] demonstrated significantly higher levels of IL-8 and IL-10 in infants with severe NEC from the onset of disease through 24 hours than in infants with less severe NEC. Nadler[109] investigated the pattern of cytokine expression in infants undergoing resection for severe NEC and infants undergoing intestinal resection for other inflammatory conditions. Significant up-regulation of IL-8 mRNA was seen in the specimens from infants with NEC as compared with controls.

IL-12 is released in response to bacteria, bacterial products, and viruses and exerts its effect on T cells and NK cells upon binding to its receptor.[110] Its immunologic functions include the following: IFN-γ production, Th1 and NK cell proliferation, cytotoxic T lymphocyte and Th1 cell differentiation, macrophage activation, and production of complement-fixing antibodies.[110] Halpern[111] localized IL-12 via immunohistochemistry to monocytes in the intestinal mucosa and lamina propria in a neonatal rat model of NEC.

Tissue IL-18 levels peak in response to lipopolysaccharide (LPS or endotoxin), Fas ligand, gram-positive bacteria exotoxins, and IL-12 and subsequently induce the production of TNF-α and IL-1β.[112] Binding to the IL-18 receptor results in NF-κB activation and promotes Th1 or Th2 lineage maturation depending on the underlying genetic influence and cytokine environment.[113] Heninger[114] discovered infants with stage III NEC or above to have a higher frequency of the IL-18607 AA genotype, thus suggesting that this variation may be used for predicting the outcome of NEC.

IL-4, produced by Th2 cells, mast cells, B cells, and stroma cells, is a key regulator in humoral and adaptive immunity.[100,120] It has been demonstrated to possess cytoprotective effects in human intestinal epithelial cells by reducing bacterial translocation, increasing leukocyte superoxide production, and inducing decay-accelerating factor, which protects the host from the attack of autologous complement activation.[115,116] Genetic studies by Treszl[117] revealed that infants with NEC were less likely to possess the IL-4 receptor α-chain mutant allele compared with infants without NEC. Treszl[117] speculated that this mutant allele is associated with enhanced transduction of IL-4 signals, which shifts the development of lymphocytes to a more pronounced Th2 state.

IL-10, produced by Th2 cells, monocytes, and B cells, is an inhibitor of proinflammatory cytokine production and of several accessory cell functions of the macrophage, T cell, and natural killer (NK) cell lines.[118] Furthermore, IL-10 has also been shown to decrease the production of metalloproteinases[119] and suppress iNOS mRNA and NO expression in small bowel, liver, and serum.[120] It is postulated that diminished production of IL-10 in preterm infants resulted in persistent up-regulation of the inflammatory response and therefore increased susceptibility in the preterm neonate to long-term tissue damage after acute inflammatory conditions.[121] Although Edelson and colleagues[104] found significantly higher levels of IL-10 in infants with severe NEC from the onset of disease through 24 hours than in infants with less severe NEC, in a neonatal rat hypoxia-reoxygenation model of NEC, recombinant IL-10 administered subcutaneously was found to significantly attenuate the extent of intestinal injury when compared with control animals, thus suggesting a protective effect of its antiinflammatory properties.[122] Taken together, these findings indicate that IL-10 has the potential to be a marker of severe disease and may

be considered a therapeutic target to function as a strong cytokine inhibitor. The high level of IL-10 in severe NEC, in contradistinction to less progressive NEC, suggests a significant role for antiinflammatory mediators in the pathophysiology of NEC to dampen the inflammatory response.

IL-11 or adipogenesis inhibitory factor is a member of the IL-6 type cytokine family that uses the gp130 receptor subunit for intracellular signal transduction. IL-11 has been shown to be a pleiotropic cytokine that promotes epithelial regeneration and enhances adaptation after bowel resection.[123] Subcutaneous administration of recombinant IL-11 in rats undergoing placement of a defunctionalized (Thiry-Vella) loop of intestine or massive small bowel resection has resulted in prevention of mucosal atrophy in the defunctionalized loop and enhanced mucosal adaptation and absorptive function in the remaining intestine after resection.[124,125] In addition, Nadler[109] noted significant up-regulation of IL-11 mRNA in infants undergoing resection for severe NEC and found an inverse correlation between IL-11 expression and the likelihood of pan-necrosis, thus suggesting that IL-11 secretion may be an adaptive response to limit the extent of intestinal damage.

TNF-α has many proinflammatory effects including neutrophil activation, induction of leukocyte and endothelial adhesion molecules, and induction of other cytokines such as PAF.[126] TNF-α has been demonstrated to produce profound hypotension and severe intestinal necrosis similar to NEC in animals. This effect has been shown to be mediated by PAF and attenuated by PAF receptor antagonists.[127] Confirmatory studies in human neonates with NEC identified significantly elevated plasma levels of TNF-α compared with controls.[99] Pentoxifylline, a drug that has multiple effects including inhibition of production of TNF-α, was shown to reduce bowel necrosis in an adult rat ischemia-reperfusion model of bowel injury, as well as the incidence of NEC in a neonatal rat model.[128] Furthermore, two separate studies[129,130] have demonstrated a significant reduction in the severity of NEC in neonatal rats after intraperitoneal TNF-α antibody prophylaxis. However, the A(-308) and A(-238) allele variants of the promoter region of the TNF-α gene, which were reportedly associated with higher TNF-α production, fail to show any influence on the risk and course of NEC in VLBW infants.[131]

A tremendous amount of investigation has been performed to define the role of nitric oxide (NO) in the pathogenesis of a number of different inflammatory processes. Evidence supports a possible dichotomous function of NO as both a beneficial and a detrimental molecule, especially with regard to the GI tract.[132,133] NO is produced from arginine by three isoforms of nitric oxide synthase (NOS). NOS-1 (neuronal, nNOS) and NOS-3 (endothelial, eNOS) are constitutively present at low levels in the small intestine. NOS-2 (inducible, iNOS), which is expressed in the myenteric plexus, endothelial cells, gastric epithelial cells, and enterocytes,[134,135] is a form that can be induced in response to inflammatory cytokines.[136,137] The constitutive forms of NOS and constitutive levels of NO have been demonstrated to modulate a number of important functions in the GI tract including maintenance of mucosal integrity, regulation of mucosal permeability, modulation of water and electrolyte transport, regulation of blood flow, regulation of motility, and inhibition of leukocyte adhesion and activation.[138–142]

Inhibition of NO synthesis in a variety of animal models of intestinal injury induced by ischemia-reperfusion, LPS, or PAF has resulted in marked exacerbation of mucosal injury.[143–148] Administration of exogenous sources of NO including L-arginine, sodium nitroprusside, and nitroglycerin greatly attenuates these detrimental effects.[149–152] In a prospective study of 53 premature infants, Zamora[153] demonstrated a significantly lower plasma arginine level at the time of diagnosis in infants in whom NEC developed compared with controls. In the only randomized, prospective, placebo-controlled study of VLBW infants assigned to receive either daily L-arginine supplements (261 mg/kg) or placebo for the first 28 days of life, Amin[154,155] found a significantly lower incidence of NEC in the supplement group (6.7%) than in the control group (27.3%). Throughout the study, the group that received arginine supplementation had significantly higher mean plasma arginine levels than the control group did. Interestingly, in both groups the infants in whom NEC developed had significantly lower plasma arginine levels at the time of diagnosis than their respective peers did. It is not known whether the decreased arginine levels represent increased utilization for NO production, consumption for the synthesis of other proteins, or decreased enteral absorption. This study suggests the possible benefits of arginine supplementation and potentially other NO donors in the prevention of NEC.

The inducible form of NO synthase (NOS-2, iNOS) is induced in response to inflammatory cytokines. Within several hours of stimulation, NOS-2 expression and activity within the intestinal epithelium increase up to 15-fold and result in the production of large amounts of NO.[135] Although the low levels of NO produced by the constitutive isoforms of NOS may play a homeostatic role in the GI tract, sustained release of NO as a result of up-regulation of NOS-2 has been suggested to have deleterious effects by inducing cellular injury and failure of the mucosal barrier.[135,156,157] This is thought to occur by the reaction of excess NO with superoxide (O2−) to produce peroxynitrite (ONOO−), a potent reactive nitrogen intermediate that may trigger cytotoxic processes including lipid peroxidation and DNA damage.[157–159] In a prospective study investigating NOS-2 expression in the intestine of infants undergoing resection for NEC, Ford[160] demonstrated marked up-regulation of NOS-2 gene expression in the intestinal epithelium and increased apoptosis of enterocytes in the apical villi. In addition, increased levels of nitrotyrosine residues were detected in the apical villi, thus suggesting that the mucosal injury and increased apoptosis were mediated through the formation of NO and peroxynitrite. In a neonatal rat hypoxia model of NEC in which breast milk–fed animals were compared with formula-fed animals, Nadler and colleagues[161] demonstrated a significantly higher incidence of NEC, NOS-2 expression, and enterocyte apoptosis along with decreased IL-12 mRNA in the formula-fed group than in the breast milk–fed group. The decreased IL-12 expression is thought to be mediated by NO and theorized to contribute to intestinal injury by attenuating bacterial clearance. Furthermore, Whithouse has shown in a rat model that the progression of NEC to intestinal ischemia is associated with a shift from nitric oxide to superoxide production by the intestinal vascular endothelium.[162]

PAF, an endogenous phospholipid inflammatory mediator, has been shown to play an important role in the pathophysiology of intestinal injury in both animal and human studies.[12] PAF has diverse biologic effects including

mesenteric vasoconstriction, capillary leakage, increased intestinal mucosal permeability, and neutrophil and platelet activation.[163–165] Clinically, increased PAF levels have been demonstrated in formula-fed premature infants, as well as in those in whom NEC developed.[100,166] In a neonatal rat model of NEC, Caplan[167] showed that intestinal PAF concentrations, intestinal phospholipase A2 (PAF-synthesizing enzyme) mRNA expression, and intestinal PAF receptor mRNA expression are all elevated. In other animal experiments, exogenous PAF administration results in severe bowel necrosis[168]; endogenous intestinal production of PAF is up-regulated in response to various stimuli including LPS, hypoxia, and TNF-α[127,169–171]; and administration of PAF receptor antagonist, or PAF acetylhydrolase (PAF-degrading enzyme), reduces the risk for NEC.[170,172,173] In human studies, PAF acetylhydrolase activity has been demonstrated to be present in human breast milk; it has also been shown to be decreased in neonates, with levels approaching adult enzyme activity at around 6 weeks of life, and has been found to be deficient in infants with NEC.[99,174,175] In a prospective study of 164 infants at risk for NEC, Rabinowitz[176] monitored serial plasma levels of PAF and PAF-related lipids (PAF-LL) to investigate the changes that occur with NEC. There was a significantly higher peak in PAF-LL levels in infants in whom NEC developed than in controls. In addition, rising PAF-LL levels were positively correlated with progression of the severity of NEC; these levels returned to baseline levels during recovery. With the studies mentioned, a systematic review[56] of serologic tests in diagnosing NEC suggested that PAF is one of the better performing markers for NEC with a sensitivity of 92% and specificity of 84% despite the considerable heterogeneity between the studies.

Cyclooxygenase (COX) catalyzes the rate-limiting step of arachidonic acid metabolism into prostaglandins, leukotrienes, and thromboxanes.[177] Two isoforms of the COX enzyme have been identified. COX-1 is constitutively expressed in many tissues including the GI tract.[178] COX-2 is the inducible form that is expressed in inflammatory conditions of the GI tract such as inflammatory bowel disease.[179,180] Proinflammatory cytokines (IL-1, IL-6, TNF-α), as well as the proinflammatory transcription NF-κB, have been shown to increase COX-2 expression.[181] NF-κB is an important protein in the activation of a number of inflammatory mediators and cytokines.[182] A marked increase in COX-2 expression has been demonstrated in intestine resected from infants with severe NEC.[183] To elucidate the mechanisms involved in COX-2 expression in NEC,[183] Chung demonstrated a coordinated induction of NF-κB activation and COX-2 expression during the early phases of injury in a neonatal rat model of NEC.

LPS (endotoxin) is a bacterial product that has the capacity to produce potent inflammatory responses through the induction of various proinflammatory cytokines such as PAF and TNF. Recent studies suggest that LPS binds with pattern recognition receptors on the intestinal epithelial barrier, such as Toll-like receptors (TLRs), formylated peptide receptors (FPRs), or nucleotide-binding oligomerization domain-like receptors (NODs), to trigger mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), and caspase-dependent pathways, thus leading to various inflammatory responses (Fig. 94-2).[184] Furthermore, Grishin[185] has demonstrated that LPS stimulates p38 MAPK-dependent expression of cyclooxygenase-2 (COX-2) in a rat model of NEC. Systemic injection of LPS has been shown to produce hypotension, shock, and severe intestinal necrosis.[25] It has been used in animal models of NEC to reliably generate intestinal injury that resembles NEC.[186]

## PATHOGENESIS

Despite many years of extensive investigation and the identification of several key risk factors, the precise pathogenesis of NEC remains elusive. The etiology is likely multifactorial and involves a combination of mucosal compromise, pathogenic bacteria, and enteral feedings that in a susceptible host results in bowel injury and an inflammatory cascade (see Fig. 94-2). Of the risk factors, prematurity is the most

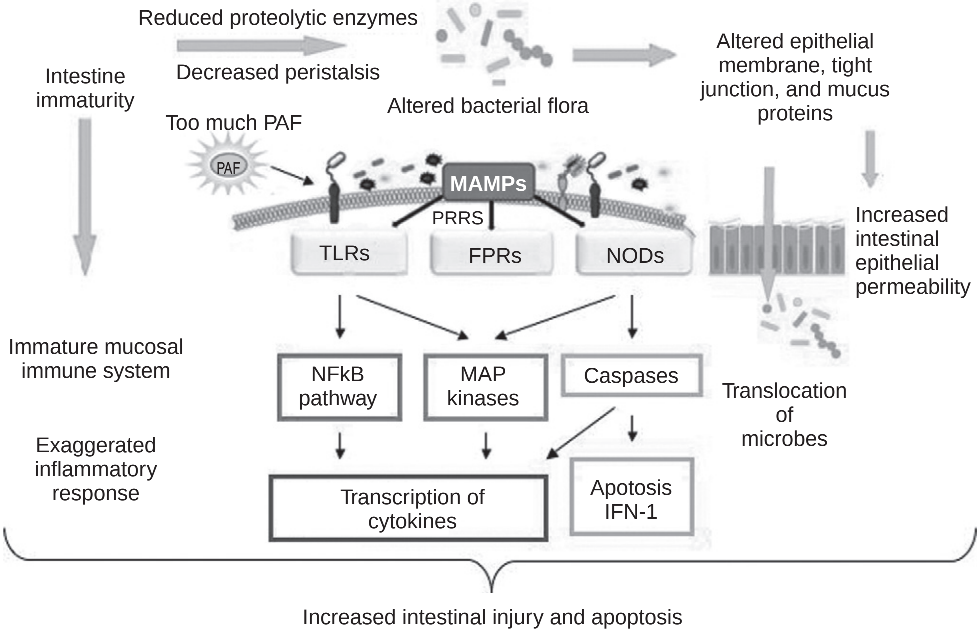


**FIGURE 94-2** Schematic summarizing the pathologic features that contribute to the pathogenesis of necrotizing enterocolitis.

consistent along with the enteral feeding of formula. Commercially available formulas lack many of the beneficial properties present in breast milk. These protective agents include gut trophic hormones, factors that induce intestinal maturation, factors that enhance colonization by nonvirulent bacteria, antiinflammatory mediators, vitamins, antioxidants, and components that support cellular and humoral immunity.[187–190]

### Evidence for an Impaired Gut Barrier

The preterm GI tract is characterized by an immaturity of cellular and humoral immunity,[191,192] increased permeability,[193] reduced gastric acid secretion,[194] reduced concentration of proteolytic enzymes,[195] incomplete innervation and decreased motility,[196,197] and immaturity of the intestinal epithelium and microvilli barrier function.[198] Decreased barrier function is evident in otherwise healthy preterm infants by their ability to systemically absorb and deliver undigested macromolecules, whole bacteria, and LPS.[199–201] Compromise of the intestinal epithelial barrier appears to be the first event leading to activation of the inflammatory cascade.

Reduced mucosal blood flow leading to cellular hypoxia and injury is one of the most frequently cited etiologic factors for NEC. Touloukian[202] emphasized the high incidence of perinatal physiologic stressors that may primarily or secondarily cause intestinal ischemia. Chief among these factors are hypoxic and hypotensive episodes, exchange transfusions through the umbilical vein, umbilical artery catheters, cardiovascular lesions, and serum hyperviscosity. The "diving reflex" in which blood is preferentially diverted away from the splanchnic circulation in order to maintain adequate perfusion of the heart and brain has been hypothesized to occur during these episodes.[203] During periods of low blood flow and subsequent reperfusion, Parks[204] found that a reaction among xanthine oxidase, hypoxanthine, and molecular oxygen results in a burst of superoxide radical production. These free radicals may cause damage to cellular and mitochondrial membranes and alter the permeability of the intestinal mucosal barrier. Although animal studies provide support for this theory, clinical correlation has been lacking, and prospective clinical trials have not been able to consistently establish an association between a hypoxic event and the development of NEC.[205]

Extensive investigation into the critical role of various inflammatory mediators in the pathogenesis of NEC has been conducted. Studies in animal models and human specimens have identified PAF, LPS, NO, and TNF-α as leading potential mediators of NEC.[160,168,169] Increased mucosal permeability and susceptibility allowing translocation of bacteria or bacterial toxin and activation of the inflammatory cascade are thought to be the critical steps leading to the final collapse of intestinal epithelial integrity.[206] Recent studies have suggested that the disruption in the intestinal mucosal barrier results from accelerated apoptosis. All of the key mediators identified in NEC (PAF, NO, LPS, TNF-α) have been shown to cause apoptosis of intestinal epithelial cells.[160,207–209] In a neonatal rat model of NEC involving formula-fed animals exposed to hypoxia and cold stress, Jilling[210] demonstrated a marked increase in apoptosis in the epithelial layer of the NEC group in comparison with mother-fed controls. The accelerated apoptosis was shown to precede gross morphologic changes in the intestinal epithelium. Administration of a pan-caspase inhibitor to inhibit intestinal apoptosis resulted in a significantly reduced rate of epithelial apoptosis, as well as a decreased incidence of NEC, thus suggesting that apoptosis was the underlying cause of the subsequent mucosal damage, ultimately leading to NEC.

Sustained overproduction of NO secondary to up-regulation of NOS-2 in the GI tract in response to an inflammatory stimulus has been suggested to induce cellular injury and disruption of the intestinal epithelial barrier through a variety of mechanisms.[156] Ford[160] demonstrated up-regulation of NOS-2 and NO in the intestinal wall of infants with NEC and increased apoptosis of enterocytes mediated by the potent oxidant peroxynitrite. This accelerated apoptosis is thought to result in a break in the villus tip of the intestinal mucosal barrier where bacteria may attach, translocate, and initiate an inflammatory cascade.[211] In addition, peroxynitrite has also been shown to inhibit the proliferation of intestinal epithelial cells in a rat model of NEC.[212] The data suggest that in conditions associated with sustained overproduction of NO or peroxynitrite (e.g., NEC), intestinal epithelial barrier dysfunction may result from an imbalance caused by accelerated epithelial injury and blunted tissue repair mechanisms.

### Role of Infectious Agents

The type of feeding and pattern of intestinal colonization may determine the risk for development of NEC. Breast-fed infants become colonized predominantly with bifidobacteria (gram-positive bacteria) that help control the growth of gram-negative bacteria.[213,214] In contrast, formula-fed infants become colonized predominantly by coliforms, enterococci, and *Bacteroides* species.[215]

The intestinal mucosa serves as a barrier to the largest microbial challenge to the human body. Beyond serving as a simple physical barrier, the dynamic interaction between the intestinal mucosa and colonizing microbes is an integral part of the innate immune system and is regulated by a system of pattern recognition receptors (PRR). During gut colonization, crosstalk between the system of PRR and commensal bacteria occurs, resulting in intestinal mucosal tolerance or hyporesponsiveness toward the enteric microbes in order to establish a symbiotic relationship. The PRR respond to microbial associated molecular patterns (MAMP) (i.e., LPS, flagellin, peptidoglycans) in order to modulate the cellular response through a variety of downstream signaling pathways (see Fig. 94-2). The PRR system includes the TLRs, which are largely responsible for sampling and interpreting the extracellular environment, and in this capacity, the TLRs have been implicated as an integral mechanism to the pathogenesis of NEC.[184] Hackam and colleagues have shown that the LPS receptor, TLR4, is integral to intestinal mucosal repair in rodent models of NEC through its effects on enterocyte apoptosis and migration.[216] Work by this same group has demonstrated increased expression of TLR4 in the human intestine that develops NEC. There is an intense and ongoing interest in this line of investigation as a primary determinant in establishing a symbiotic gut-microbe axis, which may provide protection against the development of NEC.

The importance of bacteria in the pathogenesis of NEC is supported by the following evidence: (1) NEC occurs in episodic and epidemic waves in which affected patients are

related in place and time or had the same infectious agent[217,218]; (2) during clustered occurrences, the identical microorganisms can be isolated from both afflicted babies and their caretakers[219]; (3) NEC can occur in infants with no known risk factors; (4) NEC can develop several weeks or months after a perinatal insult, when the GI tract is fully colonized and has had sufficient time to recover from any perinatal insult[220,221]; (5) administration of large doses of vitamin E (interferes with intracellular killing of bacteria by leukocytes) to premature infants has been linked with an increase in the incidence of NEC[222]; (6) a NEC-like disease occurs in vulnerable hosts after the ingestion of *Clostridium* species[223]; (7) lesions resembling NEC can be reproduced experimentally with the administration of LPS[169]; (8) endotoxemia is demonstrated in 80% of those with NEC and positive blood cultures for gram-negative bacteria[224]; and (9) pneumatosis intestinalis is a common radiographic finding and represents submucosal gas collections produced by bacterial fermentation.[225,226]

**FIGURE 94-3** Intraoperative photograph of intestine with necrotizing enterocolitis demonstrating areas of hemorrhagic necrosis and gangrene.

## Unifying Hypothesis for Necrotizing Enterocolitis

Taken together, empiric and experimental data suggest that NEC occurs in a vulnerable host that has become further compromised at the level of the gastrointestinal tract. Infant prematurity and care in the NICU conspire to result in the initiation of bacterial insult or invasion of the immature GI tract, whose key functions including barrier function and immune modulation are altered. As a result, the interaction among the enterocyte, immune effector cells, and resident microbiota initiates an inflammatory cascade that becomes unbalanced, resulting in progressive enteric mucosal injury and increased permeability. In recent years the key role of the gastrointestinal tract as an immune system organ has been increasingly documented.[227,228] Because the microbiota of the human GI tract has increasingly been identified as playing a key role in overall human health through this symbiotic relationship, gut colonization during the newborn period likely presents a particularly vulnerable time for innate immune system, human gut, and gut microbial community dysfunction to occur when this process is disrupted or delayed. The process of gut colonization has been elegantly documented to involve both environmental and genetic factors as evidenced by the findings in twins of similarities in gut microbiota.[229] Moreover, the process is active and dynamic, undergoing a significant shift even in well newborns and infants throughout the first year of life.

## Pathology

NEC may involve single (50%) or multiple (discontinuous) segments of intestine, most commonly in the terminal ileum, followed by the colon.[230] Involvement of both the large and small intestine occurs in 44% of cases. Pan involvement (pannecrosis, NEC totalis) is a fulminant form of NEC characterized by necrosis of at least 75% of the gut, and it accounts for 19% of all cases of surgically treated NEC and most of the deaths.[26]

At surgery, the gross appearance of NEC is fairly constant. The bowel is markedly distended with patchy areas of thinning (Fig. 94-3). The serosal surfaces are typically red to gray and may be covered by a fibrinous exudate. With frank gangrene, the serosal surface is black or, in the most advanced cases, bland gray to white, given the complete loss of perfusion. Subserosal gas collections are frequently encountered. The mucosal surface may be ulcerated with wide areas of epithelial sloughing. Bloody peritoneal fluid is seen when bowel necrosis is present, and brown and turbid fluid is seen when perforation has occurred.

Histologically, enteric inflammation is nearly ubiquitous in NEC (Fig. 94-4). The degree and nature, however, vary from one area to another. Acute and chronic inflammatory changes coexist in 60% of cases. The most common microscopic lesion is bland or coagulation necrosis of the superficial mucosa (89%).[231] Edema and hemorrhage of the submucosa follow complete mucosal necrosis (see Fig. 94-4). Pneumatosis intestinalis is initially seen in the submucosa and later in the muscularis and subserosa. Bacteria in the bowel lumen and wall are present in up to 40% of cases and are occasionally found in gas cysts. Transmural necrosis, characterized by hyaline eosinophilia and loss of nuclear detail in the muscular layers, is present in advanced disease. Epithelial regeneration, formation of granulation tissue, and early fibrosis are often present during the resolution of NEC. This suggests a suppurative process lasting at least several days. Granulation tissue with mucosal and submucosal fibrosis may be seen adjacent to areas of active mucosal and submucosal necrosis and may account, in part, for late stricture formation. Thrombi are sometimes noted in small mesenteric vessels and in small arterioles of the submucosa. Small-vessel thrombosis within necrotic tissue is considered a secondary change. Large-vessel thrombosis is a relatively rare finding at autopsy.

## Diagnosis

### CLINICAL FEATURES

NEC is commonly heralded by nonspecific clinical findings that simply represent physiologic instability.[231,232] These findings include lethargy, temperature instability, recurrent

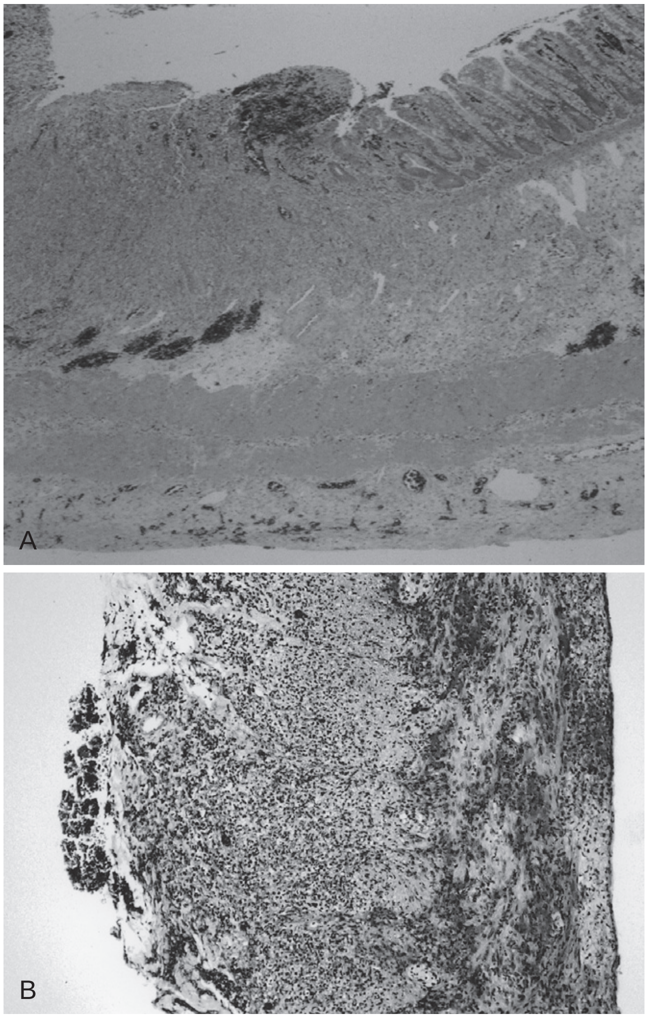

**FIGURE 94-4** **A,** Histologic section demonstrating early necrotizing enterocolitis with inflammation and pneumatosis intestinalis in the submucosa (hematoxylin-eosin stain, ×150). **B,** Histologic section demonstrating advanced necrotizing enterocolitis with transmural necrosis and loss of villus and crypt architecture (hematoxylin-eosin stain, ×150).

apnea, bradycardia, hypoglycemia, and shock. More specific symptoms related to the GI tract include abdominal distention (70% to 98%), blood per rectum (79% to 86%), high gastric residuals after feeding (>70%), vomiting (>70%), and diarrhea (4% to 26%). Gross blood in the stool is present in 25% to 63% of cases and occult blood in 22% to 59%. Rectal bleeding is seldom massive. Because the spectrum of disease severity varies, physical examination may initially demonstrate only subtle abdominal distention and minimal tenderness. As the disease progresses, abdominal palpation may elicit tenderness and demonstrate palpable bowel loops, a fixed or mobile mass, or abdominal wall crepitus. Edema and erythema of the abdominal wall as a result of the underlying peritonitis are present initially in approximately 4% of cases but are more common later in the course of the disease. In males, there may be discoloration of the scrotum, indicative of perforation. In a small subset of patients, the disease is rapidly progressive and the initial manifestation is heralded by florid clinical findings and death within 24 hours.

## LABORATORY FINDINGS

Infants with NEC usually have neutropenia, thrombocytopenia, and metabolic acidosis. The total leukocyte count may be elevated, but it is generally low. In one study, 37% of infants had absolute neutrophil counts less than 1500 cells/mm$^3$.[233] Infants with the lowest counts in this study had the worst prognosis. Neutrophil counts less than 6000 cells/mm$^3$ are most commonly associated with concomitant gram-negative septicemia. Some authors[234] have advocated that surgical treatment should be considered in infants older than 34 weeks' gestation if they have lower total neutrophil counts, a higher immature neutrophil number, and a greater immature-to–total neutrophil ratio at first presentation of NEC.

Thrombocytopenia is nearly universally present and seems to be associated with gram-negative sepsis and platelet binding by endotoxin. The incidence of thrombocytopenia in NEC is 65% to 90% and essentially unchanged from the earliest reports from the 1970s.[233,235] O'Neill[236] demonstrated that in a cohort of 40 infants who underwent surgery for NEC, 95% had platelet counts less than 150,000 cells/mm$^3$. Rowe and colleagues[237,238] found that platelet counts less than 150,000 cells/mm$^3$ were present in patients who had positive cultures for gram-negative organisms. The nadir platelet count during the course of the disease was noted to be lower in patients with more severe disease and in those who died.[239] A platelet count less than 104/L or a rapid fall is a poor prognostic indicator. A retrospective single-center study of 91 infants by Kenton[240] suggests that a platelet count less than 104/L within 3 days of the diagnosis of NEC should warrant surgical intervention to decrease the likelihood of bowel gangrene and its attendant morbidity and mortality.

## EMPIRIC AND EXPERIMENTAL INDICATORS OF NEC AND ITS SEVERITY

Metabolic acidosis is common (40% to 85% of patients with NEC) and is believed to result from hypovolemia and sepsis. It is not a specific indicator of intestinal necrosis. Stool samples are commonly positive for occult blood and reducing substances. Book[241] reasoned that intestinal mucosal damage from NEC leads to carbohydrate malabsorption. Poorly digested carbohydrates pass into the colon, where they are fermented and excreted in stool. The authors tested the stool of formula-fed infants for reducing substances with reagent (Clinitest) tablets and found that 71% of formula-fed infants in whom NEC developed had greater than 2+ reducing substances in their stool. Colonic bacterial fermentation increases the local production of D-lactate, which is absorbed and excreted by the kidneys. Garcia[242] could show elevated urinary D-lactate levels in infants with NEC but not in control infants. With recovery from NEC or administration of enteral antibiotics, D-lactate excretion decreased. Similarly, hydrogen excretion in the breath is elevated when fermentation is increased. This test is helpful in ruling out NEC. A negative result on a breath hydrogen test is 99% accurate in ruling out NEC.[243] Abubacker[244] indicated via a study of 24 infants with NEC that a preoperative blood lactate level of greater than 1.6 mmol/L carries a poor prognosis with mortality odds ratio of 22 (CI 1.54 to 314.3, $P = 0.04$). Finally, a multicenter study of 473 infants with NEC by Moss and colleagues[245] identified metabolic acidosis

at diagnosis (pH < 7.3 or bicarbonate < 16) as one of the 12 parameters that may assist in predicting the progression of NEC.

In an uncontrolled retrospective study comparing two centers' criteria for surgical intervention, Tepas[246,247] found that if three of seven critical metabolic derangements (positive blood culture within 96 hours of diagnosis, pH < 7.25 or receiving bicarbonate, bandemia > 20%, serum sodium < 130 mEq/L, platelet count < 50,000 cells/mm$^3$, MAP < gestational age or on any pressors, and absolute neutrophil count < 2000) were identified, this permitted earlier identification of infants needing exploration and resulted in better surgical outcomes (mortality and the need for postoperative parental nutrition) than did delaying operation until radiographic proven evidence of perforation by pneumoperitoneum.

C-reactive protein (CRP), an acute phase reactant, has been measured in an attempt to correlate its level with the presence, absence, or resolution of the disease.[248] CRP may serve as an early indicator of NEC when levels rise more than 10 mg/L within 48 hours of the suspected diagnosis (reported sensitivity, 92%; specificity, 81%). Failure of CRP to return to normal within 10 days was an indicator of abscess, stricture, or septicemia. A systematic review of various biomarkers for NEC[56] selected six qualified studies[248–253] on CRP that together indicated CRP is a relatively sensitive but nonspecific marker for NEC, yielding a combined diagnostic odds ratio (DOR) of 5.82 and an area under the curve (AUC) of 0.70. The diagnostic odds ratio expresses how much greater the odds of having the disease are for people with a positive test result rather than for the people with a negative test result. In this case, although the DOR is high, its AUC is only 70%, implying a weaker diagnostic performance.

*Intestinal fatty acid–binding protein* (I-FABP) is a small (14 to 15 kd) cytoplasmic protein of mature enterocytes. It is released into the circulation upon death of enterocytes, thus representing intestinal injury when detected in high concentration. Lieberman,[254] Edelson,[255] and Guthmann[256] have demonstrated an elevated level of I-FABP in the serum of neonates with NEC. Given its small size and its ability to pass through the glomerulus, urinary I-FABP has been detected as potential marker of NEC by Derikx.[257] Evennett[258] further characterized the release of urinary I-FABP by correlating its I-FABP-to-creatinine concentration with the severity of NEC. The I-FABP-to-creatinine concentration was significantly higher in infants with extensive disease than in those with focal disease (7.4 pg/mmol [2.1 to 35 pg/mmol] vs. 1.1 pg/mmol [0.3 to 1.7 pg/mmol], respectively, $P = .002$). Although studies have shown higher concentrations of I-FABP in infants with severe NEC, Thuijls[259] concluded urinary I-FABP not to be an effective screening tool for NEC given its ability to identify merely one third of neonates with NEC in a group of 226 neonates with no clinical suspicion of NEC originally. This study was performed on the basis of a cutoff point of 2.20 pg/nmol creatinine derived from testing urinary I-FABP on 35 neonates suspected of NEC. However, Thuijls[259] repeated the conclusion by Evennett[258] that urinary I-FABP is a promising prognostic marker for NEC.

Calprotectin, a calcium-binding protein found in neutrophils and macrophages, is a marker of inflammation of the gastrointestinal tract. It has been found in stool due to transepithelial migration of myeloid cells and has been a useful marker for exacerbation of inflammatory bowel disease in children.[260] Josefsson found fecal calprotectin to be elevated greater than 2000 μg/g feces in NEC with perforation with microscopic bowel inflammation but less than 2000 in cases with focal disease. Thus similar to I-FABP, it may be a useful marker for disease severity but not a strong screening tool.

# Microbiology

It has proven extremely difficult to identify common offending infectious agents in infants with NEC. Organisms recovered from the blood and stool of patients with NEC vary depending on the GI tract flora, the nosocomial flora, the site cultured, and the duration of previous antibiotic therapy. It is unclear whether the bacteria cultured represent pathogens causing NEC or, instead, secondary opportunistic invaders selected by the antibiotic regimen. Furthermore, lack of sufficiently matched controls and incomplete bacteriology data on other patients in similar environments makes study of the microbiology of NEC difficult.

## BACTERIOLOGY

Bacteriologic data for NEC have primarily been based on cultures obtained from the blood, stool, and peritoneal cavity. Blood cultures are positive in 30% to 35% of patients.[215] Cultures commonly grow *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Staphylococcus aureus, Staphylococcus epidermidis,* enterococci, *Clostridium perfringens,* and *Pseudomonas aeruginosa. K. pneumoniae* and *E. coli* cause the majority of positive blood cultures. The organisms most frequently cultured from stool specimens are *E. coli, K. pneumoniae, Enterococcus cloacae, P. aeruginosa, Salmonella species, coagulase-negative staphylococci (S. epidermidis), C. perfringens, Clostridium difficile,* and *Clostridium butyricum.*[261–263] Peritoneal cultures most commonly grow *Klebsiella species, E. coli,* coagulase-negative staphylococci, *Enterobacter* species, and yeast.[264]

## FUNGAL CULTURES

In contrast to bacteria, no data implicate a fungus as an initiating organism in the pathogenesis of NEC. Fungi are believed to be secondary invaders. Fungal septicemia with *Candida* species has been implicated in many late NEC deaths.[265,266] In a retrospective premortem and postmortem examination of body fluid and tissue cultures from 30 patients who died of NEC by Smith and colleagues,[265] 47% of patients had evidence of fungal infection and colonization was found in 20%.

## CLUSTERED EPIDEMICS

In most large series, sporadic cases have been followed by the sudden appearance of a cluster of a relatively large number of cases. In many of the epidemics, no specific pathogen has been identified. During these episodes, nursery personnel experienced concomitant acute GI illnesses.[21,267] In those few studies in which a specific pathogen is identified, it was in association with documented contamination of milk formula or milk fortifier that was used in the NICU.[268] Identified species have

included *E. coli, Salmonella species, C. difficile,* rotavirus, norovirus, torovirus, and a coronavirus-like organism.[217,268–274]

# Imaging

The cornerstone of the diagnosis of NEC remains plain anteroposterior and left lateral decubitus radiographs. Any or all of the following findings are associated with NEC: ileus pattern (nonspecific bowel distention), pneumatosis intestinalis (linear or cystic) (see Fig. 94-1), portal vein gas, pneumoperitoneum, intraperitoneal fluid, and persistently dilated, fixed loops.[275] Both pneumatosis and portal vein gas are often fleeting signs but are considered pathognomonic in the appropriate clinical setting of prematurity. In more recent years, there has been a trend and tendency toward the increased use of bedside ultrasound with Doppler imaging of the GI tract in an effort to identify more subtle findings like abdominal fluid, hyperemia, decreased blood flow to the gut, and pneumatosis intestinalis, all of which may not be well seen by plain radiograph.[276–291] Despite this trend, to date there have been few good comparative studies documenting the clinical utility of ultrasound in the diagnosis of NEC.

## BOWEL DISTENTION

Multiple gas-filled loops of intestine are the earliest and most common radiologic finding in patients with NEC (55% to 100% of cases).[292] As fluid and air accumulate, air-fluid levels are visible on the decubitus view. The degree of dilatation and the distribution of bowel loops are related to the clinical severity and progression of the disease. In some cases, nonspecific intestinal dilatation precedes clinical symptoms suggestive of NEC by several hours.

## PNEUMATOSIS INTESTINALIS

Demonstration of pneumatosis intestinalis (intramural gas) in the appropriate clinical setting is diagnostic of NEC (see Fig. 94-1). The air mainly comprises hydrogen, a byproduct of bacterial metabolism. The frequency of pneumatosis intestinalis ranges from 19% to 98%, although it may be absent in up to 14% of patients with NEC (even severe disease).[205] Conversely, extensive pneumatosis may be present with minimal signs; it often responds promptly to medical management. Pneumatosis is fleeting, may appear before the onset of clinical symptoms, and is commonly an early rather than a late finding. Pneumatosis is most frequently noted when infants have been fed (84%), in contrast to unfed babies (14%).[31] Pneumatosis intestinalis is not specific for NEC and has been noted in infants with enterocolitis of Hirschsprung disease, inspissated milk syndrome, pyloric stenosis, severe diarrhea, carbohydrate intolerance, and other disorders. Two forms of pneumatosis intestinalis are recognized radiographically: cystic and linear. The cystic form has a granular or foamy appearance and represents gas in the submucosa. It is often confused with fecal material in the large intestine. Linear pneumatosis consists of small bubbles collected within the muscularis and subserosa to form a thin linear or curvilinear gas pattern outlining the wall of a segment of the intestine.

## PORTAL VEIN GAS

Portal vein gas (PVG) appears as linear branching radiolucencies overlying the liver and often extending to its periphery (see Fig. 94-1). It represents gas dispersed through the fine radicles of the portal venous system. The presence of portal vein gas is fleeting, which perhaps accounts for the low reported incidence of 10% to 30%.[293] In most series the presence of portal vein gas is associated with a poor prognosis.[205] In cases with pan-intestinal involvement, PVG is present in 61% of patients. The genesis of portal vein gas may involve accumulation of gas in the bowel wall as a result of bacterial invasion, dissection into the venous system, and migration to the radicles of the portal vein. Alternatively, it may represent the action of gas-forming bacteria within the portal venous system itself.

## PNEUMOPERITONEUM

Free air in the peritoneal cavity associated with perforation of the intestine can be demonstrated in 12% to 30% of patients. It is best noted on the left lateral decubitus or cross-table lateral view. Upright radiography is unnecessary. A supine view of the abdomen can demonstrate free air by outlining the falciform ligament ("football sign"), the umbilical artery, or urachal remnants or by revealing the "double-wall" sign. This sign refers to visualization of air on both sides of the wall (lumen and peritoneal cavity). In patients who have intestinal perforation proven by surgery, radiographic evidence shows free air in only 63%, thus demonstrating that perforation can occur in a surprisingly high number of patients without evidence of pneumoperitoneum. One must also recall that pneumoperitoneum may occur without intestinal perforation from mechanical ventilation for severe lung disease. In this clinical situation, barotrauma may produce alveolar rupture with air dissection into the abdomen through the mediastinum. The patient's signs, symptoms, and laboratory findings will often differentiate the cause of the air. If one is unsure, abdominal paracentesis may be performed and any aspirated fluid analyzed. If there is no ascites, a water-soluble contrast study via the gastric tube may be performed to rule out gastric perforation.

## INTRAPERITONEAL FLUID

Several plain radiographic findings suggest free fluid in the peritoneal cavity that is amenable to paracentesis: (1) a grossly distended abdomen devoid of gas, (2) gas-filled loops of bowel in the center of the abdomen surrounded by opacity out to the flanks, (3) increased haziness within the abdomen, and (4) separation of bowel loops. These findings have been reported in 11% of cases. Both ascites and portal vein gas are radiographic findings associated with high mortality rates. Twenty-one percent of patients with surgically proven intestinal perforation have ascites. However, 16% of all patients with proven intestinal perforation have neither ascites nor pneumoperitoneum on plain radiographs.

## PERSISTENT DILATED LOOPS

The "persistent dilated loop sign" is a plain radiographic finding that was described by Wexler[294] in a study of five babies with NEC in whom a single loop or several loops of dilated bowel remained unchanged in position and configuration for 24 to 36 hours. Full-thickness necrosis subsequently developed in these patients. This finding, however, does not

always indicate bowel necrosis. Leonard[295] found a persistent loop in 33% of 21 patients with proven NEC. Fifty-seven percent of infants with a persistent loop had necrotic intestine at surgery or autopsy, but necrosis never developed in 43% and they recovered with nonoperative treatment.

### CONTRAST STUDIES

Radiopaque contrast studies of the upper GI tract may occasionally be useful to improve diagnostic accuracy in patients with equivocal clinical and radiologic signs of NEC. However, overdiagnosis by contrast radiography is possible and may lead to unwarranted treatment. Careful attention to the type of contrast agent used for the study is critical.[294] Barium should never be used because extravasation of a barium and stool mixture through a perforation may intensify the peritonitis. Unlike barium, water-soluble contrast agents are absorbed by both the bowel and the peritoneal cavity. The practical implication of this absorption is a transient (6 to 12 hours) increase in urinary specific gravity. Historically, water-soluble agents were hyperosmolar and caused dangerously large intraluminal fluid shifts, especially in premature patients. Current water-soluble agents are nonionic, have much lower osmolarity, and produce excellent opacification of the GI tract. NEC is suspected when intestinal contrast enhancement demonstrates bowel wall loops separated by edematous walls, an irregular mucosa with ill-defined margins, mucosal ulceration, bowel wall spiculation, or pneumatosis intestinalis. Currently, the use of contrast studies is usually reserved for interrogation of the GI tract after the acuity of NEC has resolved and in order to examine for stricture formation during or after recovery. Though advocated by some,[296] contrast enemas should not be performed because of the risk for rectosigmoid perforation. Unless there is colonic disease or reflux of contrast into a diseased distal ileum, the contrast enema will not be diagnostic of NEC. It may, in fact, overdiagnose NEC because contrast enemas have been shown to produce pneumatosis and transient portal venous air. In an infant who has recently completed a course of therapy for NEC but has persistent signs of partial small bowel obstruction or blood-tinged stools, contrast enemas may be useful in identifying strictures.

### ULTRASONOGRAPHY

Ultrasonography (US) has been used to identify necrotic bowel, intraperitoneal fluid, and portal venous air. However, abdominal sonography can depict the following findings highly suggestive of nonviable bowel over plain abdominal radiography: presence of intra-abdominal fluid, thinning of the bowel wall, reduction of bowel wall perfusion, abnormal bowel loops, and intermittent gas bubbles in liver parenchyma and the portal venous system.[297] The abnormal bowel loops on US are characterized by a hypoechoic rim with a central echogenic focus (“target sign”).[278] Appearing as pericholecystic hyperechogenicity, the intermittent gas bubbles in liver parenchyma and the portal venous system are believed to represent either pericholecystic venous gas or extension of the foamy inflammatory infiltrate of NEC into the pericholecystic space.[298,299]

Theoretically, US may have significant value if it can identify patients who require operation in a more sensitive and timely manner than is otherwise possible with conventional clinical and radiographic methods. Although Silver[299] has correlated seven sonographic findings with adverse outcomes needing surgical intervention, more studies are necessary to compare the sensitivity and specificity, as well as intraobservable and interobservable agreements between sonographic and radiographic findings. Thus at this time, the use of US for the diagnosis of NEC is most applicable to patients with questionable clinical and radiologic findings or to localize intra-abdominal fluid for paracentesis.

### MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is a noninvasive modality that has recently been used to identify infants with ischemic bowel secondary to NEC. Although MRI is capable of demonstrating the cardinal findings of NEC, its utility is limited.[300]

## Classification

To select the appropriate treatment (nonoperative vs. operative) and to determine the impact of therapy on survival and late outcomes, it is essential that investigators use comparable criteria for classifying the stages of NEC. Several classification schemes have been proposed. In 1978 Bell[8] introduced the now most commonly used three-stage classification system (suspected, definite, and advanced) that categorizes patients by historical factors, GI manifestations, radiologic findings, and systemic signs (see Table 94-1). The Bell staging criteria have been modified[220]; the three stages are still used, but subsets are included in an effort to identify specific prognostic factors. Infants with stage I disease have features suggestive of NEC, patients with stage II disease have definitive NEC without an indication for surgical intervention, and patients with stage III disease have advanced NEC with evidence of bowel necrosis or perforation.

## Management

### NONOPERATIVE

In the absence of intestinal necrosis or perforation, the mainstay of treatment for patients with NEC is supportive. Feedings are discontinued, the GI tract is decompressed through a sump gastric tube, and intravenous fluid resuscitation is initiated. A complete blood count, platelet count, blood gas analysis, and CRP and serum electrolyte levels are obtained. Blood and urine samples are sent for culture, and broad-spectrum intravenous antibiotic therapy is initiated. Until recently, most antibiotic regimens included a penicillin, an aminoglycoside, and an agent effective against anaerobic organisms. It seems logical that coverage for anaerobic organisms be included because these infants are usually 1 to 2 weeks old and have or are undergoing colonization by coliforms. To date, no controlled study has shown the efficacy of this regimen. The antibiotic regimen is best tailored not only to the most common organisms found with NEC but also to the nosocomial nursery flora. Because of recent reports of patients with stool and blood cultures positive for coagulase-negative staphylococci, some groups now empirically treat patients with a combination of vancomycin and gentamicin or vancomycin and a third-generation cephalosporin.[301] The incidence of fungal sepsis in infants who die of NEC is high, so a strong index of suspicion must be maintained and empirical antifungal therapy should be considered if the patient’s clinical course is prolonged. Historically, close clinical observation consists of frequent physical examination, two-view abdominal radiography

performed every 6 to 8 hours, serum platelet and leukocyte counts, and blood gas analysis. However, one could question the utility of the frequent use of plain radiographs at this interval, given the number of cases that have progressive NEC without pneumoperitoneum and depending on the individual practitioners' trigger for operative intervention.

Patients with definite disease of moderate severity (Bell stage II) are normally treated by bowel rest, decompression, and antibiotic therapy for at least 7 to 14 days. A central venous catheter may be placed for total parenteral nutrition. If the patient is clinically well, small amounts of formula may be restarted. The infant is constantly and carefully monitored for abdominal distention, vomiting, or nonspecific signs or symptoms of NEC. Once feedings resume, stools are tested for reducing substances and occult blood. Feedings are discontinued if the result of either test becomes positive. Infants who have undergone surgery receive 1 to 2 weeks of postoperative intravenous antibiotics. Feedings are initiated when the patient is clinically well and return of bowel function has been established.

## INDICATIONS FOR OPERATION

The principal goals of surgical intervention in the setting of NEC are to remove gangrenous bowel and preserve intestinal length.[302,303] On the basis of historical clinical experience, many argue that exploration should not be undertaken until gangrene is present but should be performed before perforation occurs. Unfortunately, no combination of clinical examination or adjunct testing has been shown to have high sensitivity for intestinal gangrene.[304,305] Thus there remains controversy regarding the indications for operation, the most appropriate timing of intervention, and the optimal surgical treatment strategy. The most widely accepted indication is the presence of pneumoperitoneum. Relative indications include a positive paracentesis, palpable abdominal mass, abdominal wall erythema, portal venous gas, fixed intestinal loop, and clinical deterioration despite maximal medical therapy.

In an attempt to identify characteristics that may serve as predictors of intestinal gangrene, Kosloske[304] reviewed 12 criteria used as indications for operation in 147 patients with NEC and stratified these criteria according to sensitivity, specificity, positive/negative predictive value, and prevalence. The "best" indicators (specificity and positive predictive value [PPV] approaching 100%, prevalence $> 10\%$) were pneumoperitoneum, positive paracentesis (aspiration of $> 0.5$ mL brown or yellow fluid containing bacteria on Gram stain), and portal venous gas. "Good" indicators (specificity and PPV approaching 100%, prevalence $< 10\%$) were a fixed intestinal loop, erythema of the abdominal wall, and a palpable abdominal mass. A "fair" indicator (specificity of 91%, PPV of 94%, prevalence of 20%) was "severe" pneumatosis intestinalis as graded by a radiographic system. "Poorer" indicators were clinical deterioration (PPV of 78%), platelet count lower than 100,000/mm$^3$ (PPV of 50%), abdominal tenderness (PPV of 58%), severe GI hemorrhage (PPV of 50%), and gasless abdomen with ascites (0%). Unfortunately, none of the indicators had sensitivity greater than 48%.

Instead of looking at indicators separately, Coursey[306] combined various radiologic findings into a 10-point Duke Abdominal Assessment Scale (DAAS) to improve intraobserver and interobserver agreement on diagnosing severe NEC. A subsequent validation study by the same authors[307] demonstrated that for every one-point increase in the DAAS score (AUC = 0.83), infants with NEC were significantly more likely to need surgical intervention. Although the study did not define a specific score cutoff for surgical intervention, 93% of the operated infants in this study had a score of 7 or above.

### Pneumoperitoneum

Infants in whom pneumoperitoneum develops during the management of NEC should undergo either laparotomy or peritoneal drain placement. Unfortunately, pneumoperitoneum is not always demonstrable in neonates with gut perforation, with one study reporting that only 63% of infants with perforation demonstrated free air.[308]

### Paracentesis

A positive result on paracentesis, defined as free-flowing aspiration of more than 0.5 mL of brown or yellow-brown fluid that contains bacteria on Gram stain,[156] is highly specific for intestinal necrosis. A negative result on paracentesis is rare with intestinal necrosis but can occur when a localized, walled-off perforation is present or a segment of bowel is injured but not perforated.[309] Currently, there is no absolute indication for paracentesis. Kosloske[304] recommends abdominal paracentesis for patients with extensive pneumatosis intestinalis or for those who do not improve with nonoperative management. If no peritoneal fluid is aspirated, peritoneal lavage is performed by instilling up to 30 mL/kg of normal saline solution into the peritoneal cavity, turning the patient from side to side, and then withdrawing the fluid. Ricketts and Jerles[309] reported a greater than 70% survival rate when a positive result on abdominal paracentesis was used as the indication for exploration in 51% of their patients; three false-negatives occurred. They performed paracentesis when there was erythema and edema of the abdominal wall, portal vein gas, a fixed and dilated loop on sequential abdominal radiography, a fixed and tender abdominal mass, or persistent clinical deterioration. The indications used for paracentesis in this report are considered indications for operation by many surgeons.

### Portal Venous Gas

To determine the significance of portal vein gas in relation to the presence and extent of bowel necrosis and mortality, Kurkchubasche[310] reviewed the experience of Children's Hospital of Pittsburgh, as well as the world literature. Of the 616 patients collected, 118 (19%) had portal vein gas on plain radiography. Of these 118 patients, 102 underwent operation, usually 24 hours after the radiographic appearance of portal vein gas. All 102 patients had full-thickness bowel necrosis, and 52% had necrosis of more than 75% of the length of the entire small intestine. The overall surgical mortality rate for patients with portal vein gas was 52%, and more than 90% of those with pan involvement died. Of the 15 patients who had portal vein gas and did not undergo immediate exploration, bowel necrosis requiring subsequent operation developed in 6 (40%) and 5 of the 6 died. In a separate study, Rowe[26] suggested that intestinal necrosis will develop in more than 90% of infants with portal venous gas, with pan involvement developing in 52%. More recently, in a review of 40 infants with NEC and portal venous gas,

Molik[311] reported a 54% overall operative mortality and pan involvement in 25%.

### Fixed Persistent Intestinal Loop

A fixed dilated intestinal loop is defined by persistent location and configuration for more than 24 hours. In a recent study, approximately half the patients with evidence of a fixed dilated loop recover without an operation.[312] The finding of a fixed loop is considered concerning by most observers as indicating a pregangrenous or severely compromised intestinal loop, yet to date there is little objective evidence to support that assumption. Moreover, at this time there is no general consensus on the utility of fixed loop in guiding operative management.

### Clinical Deterioration

Many criteria for operating on children who show continued clinical deterioration despite adequate supportive therapy exist,[313] but none by themselves are absolute indications. These criteria include abdominal wall erythema, peritonitis on physical examination, persistent/increasing acidosis, and persistent/progressive thrombocytopenia.

### Ascites

As mentioned, pneumoperitoneum may not always be evident with intestinal perforation. A gasless abdomen, suggestive of a fluid-filled abdominal cavity, may be the only indication of perforation. Frey[308] reported that in 21% of infants with intestinal perforation, the only radiographic evidence was ascites. They noted that radiographs are imprecise and that evidence of ascites in the appropriate clinical setting of NEC mandates paracentesis for further evaluation.

## OPERATIVE MANAGEMENT

Advanced disease requiring surgical intervention develops in up to 50% of infants with NEC.[314,315] Until recently, given the lack of quality prospective randomized trials, the optimal surgical treatment strategy for NEC remained controversial. Surgical goals are to remove gangrenous bowel and preserve intestinal length. Within this context, a number of different options exist, but most agree that the surgical approach should be determined by the extent of intestinal involvement. The patient's general condition should be optimized before operation with aggressive ventilatory support, treatment of shock, administration of broad-spectrum antibiotics, and correction of anemia and coagulopathy. Operative procedures may be performed in the NICU under appropriate conditions without an increase in complications.[316]

### Primary Peritoneal Drainage

Treatment of intestinal perforation in VLBW infants remains controversial. In 1977 Ein[317] reported the use of peritoneal drainage (PD) as a means of stabilizing and improving the systemic status of premature infants with perforation before laparotomy. Since then, primary treatment with PD has been used in a variety of settings, and some investigators have suggested that it may serve as definitive therapy. More recently, several studies have attempted to address this issue more rigorously.[318–333] Currently, most surgeons propose PD as the initial treatment in ELBW infants (<1000 g at birth) with perforated NEC to allow resuscitation and stabilization before definitive laparotomy. In an attempt to address this issue, two multicenter prospective randomized controlled trials were conducted. In the NECSTEPS trial of 117 infants (<34 weeks' gestation and < 1500 g) by Moss,[324] 19 of 55 infants with PD died (34.5%), as compared with 22 of 62 infants with laparotomy (LAP) (35.5%, $P = 0.92$) by 90 days postoperatively. The percentages of infants who became dependent on total parenteral nutrition were 17 of 36 (47.2%) in the PD group and 16 of 40 (40%) in the laparotomy group ($P = 0.53$). Although this study was originally designed to detect a reduction in 90-day mortality from 50% to 25% with a statistical power of 82%, it failed to enroll the desired number of study subjects in the time allotted to the study, thus reducing the power to 77% or less.

Three primary conclusions were drawn from this prospective randomized trial. The trial found that the type of operation performed for intestinal perforation in infants with NEC (1) does not significantly affect 90-day mortality, (2) does not affect rate of dependence on total parenteral nutrition at 90 days postintervention, and (3) did not affect the total length of hospital stay. The results of this trial have led to a follow-up study that seeks to determine the difference in median to long-term outcomes comparing the two surgical procedures with an emphasis on neurodevelopmental outcomes. Two years following the publication of the NECSTEPS trial results, Rees[323] published the results from the European NET trial that included 69 patients. Similar to the results in the NECSTEPS trial, there was no significant difference in the 6-month survival rate between infants undergoing either laparotomy or PD as primary treatment for perforated NEC. Six-month survival was 18 of 35 (51.4%) with PD and 21 of 33 (63.6%) with LAP ($P = 0.3$; Fisher exact text, difference 12%, Cl, (11, 34%). Cox regression analysis showed no significant difference between groups (hazard ratio for PD 1.6; $P = 0.3$; 95% CI, 0.7 to 3.4). However, in the PD group, delayed laparotomy was performed in 26 of 35 (74%) patients after a median of 2.5 days (range, 0.4 to 21) and did not improve 6-month survival compared with primary laparotomy (relative risk of mortality 1.4; $P = 0.4$; 95% CI, 0.6 to 3.4). Unlike the conclusion derived by the NECSTEPS trial, Rees concluded that PD is ineffective as either a temporizing measure or definitive treatment because of the high percentage of infants requiring "rescue" laparotomy.

Even though the two prospective studies did not demonstrate statistically significant differences in mortality between PD and LAP, the most recent meta-analysis by Sola[334] (273 PD, 250 LAP), which selected two clinical trials and three prospective cohort studies[325,326] out of the 12 studies reviewed, indicated an increased mortality of 55% with PD (OR 1.55, 95% CI, 1.08 to .22, $P = 0.02$) without statistical heterogeneity. Upon careful review, four of the five studies showed mortality rates of PD to be higher than LAP and the authors attributed the higher rates to more premature and smaller infants selected for the PD group. Thus controversies persist in initiating PD for stabilization before laparotomy. Currently, in an effort to address intermediate and long-term morbidity, a multicenter trial sponsored by the NICHD Neonatal Research Network was initiated in 2010. The primary objective of this trial is to determine the rate of primarily neurodevelopmental impairment at 2 years of age in ELBW infants with NEC who undergo either PD or laparotomy as primary treatment of perforated NEC.

### Laparotomy

At laparotomy, the extent of NEC may be classified as focal, multifocal, or pan-intestinal (<25% viable bowel). Depending on the extent of disease and patient characteristics at the time of surgery, a number of different surgical options may be undertaken including resection with enterostomy, resection with anastomosis, proximal enterostomy, the "clip-and-drop" technique, and the "patch, drain, and wait" technique. The abdomen is entered via a transverse supraumbilical incision with precautions taken to not injure the liver. Optionally, samples of peritoneal fluid may be harvested for culture of aerobic, anaerobic, and fungal organisms. The entire GI tract is systematically examined to assess the extent of disease and viability of the bowel. If clear demarcation of gangrenous bowel is encountered, it is resected. Marginally viable bowel can be preserved yet defunctionalized either through a proximal diversion (enterostomy) or clip-and-drop technique wherein the intestine is closed at either end using hemoclips in an effort to prevent further passage or leakage of the fecal stream. These latter techniques are particularly useful if the overall length of involved intestine is such that the infant would be rendered "short-gut" if all marginally involved intestinal length is removed. A second-look operative approach to extensive NEC involvement is currently not widely practiced. Infants tend to be quite ill with significant ongoing physiologic instability following most operative interventions for NEC. At the conclusion of the procedure, one should record the length of viable intestine remaining and note the presence or absence of the ileocecal valve.

A rarely cited complication of laparotomy for NEC is spontaneous intraoperative liver hemorrhage from injury caused by retractors or finger dissection. VanderKolk[335] reported this complication in 11.8% of operations for NEC over a 5-year period. The mean gestational age of those with liver hemorrhage was 28 weeks (mean weight, 1262 g). Only one of these patients survived. The authors identified low mean preoperative arterial pressure and high preoperative fluid administration over the preceding 24 hours as significant predisposing factors. This complication occurred shortly after the abdomen was opened, and the intestine was eviscerated. Liver congestion was followed by subcapsular hematoma and then free rupture.

### Focal Disease

When a single area of bowel is necrotic or perforated, only limited resection is necessary. Creation of a proximal enterostomy and distal mucus fistula has been the standard of care. Stomas can be created either through the ends of the incision or through a separate exit site on the abdomen. Factors to be considered when deciding on optimized stoma sites include mesentery that has been shortened by inflammation that may impede exteriorization, placement and fitting of future stoma bags without leakage, ease of future closure if diverting ends are placed in close proximity or remotely, and incidence of additional complications including wound infection and stoma prolapse. Most enterostomies are created by suturing the intestine to the fascia with interrupted sutures. About 2 cm of bowel are left protruding from the abdominal wall, and no attempt is made to "mature" the end of the intestine. If stoma viability is in question postoperatively, a small portion of the full thickness of the intestine is excised at the bedside and the cut ends are observed for bleeding.

Resection with primary anastomosis for isolated disease may be performed in carefully selected patients. Proponents of primary anastomosis cite the high morbidity associated with enterostomies in infants and no need for a second operation.[336] To safely perform this technique, the following criteria must be met: (1) a sharply localized, usually proximal segment of disease; (2) undamaged appearance of the remaining intestine; and (3) stable overall patient physiology without evidence of rapidly progressive sepsis or coagulopathy.

### Multisegmental Disease (>50% Viable)

If the patient has multiple areas of necrosis separated by viable bowel, several options are available. Historically, the surgeon excises each diseased segment individually and creates multiple stomas rather than performing a massive resection. Conversely, a single high stoma (proximal jejunum) may be created and the distal bowel "spliced" together, thereby avoiding multiple stomas. A proximal jejunostomy can cause significant fluid and electrolyte loss and peristomal skin complications, although aggressive skin care with measurement and replacement of stoma losses can avoid these potential complications. Anastomotic strictures are not uncommon and are addressed at the time of jejunostomy closure. Resection plus anastomosis has also gained increased acceptance as a valid treatment option for severe NEC and for multifocal disease.[303] In a study involving 46 infants with multifocal NEC, Fasoli[302] reported a higher survival rate after resection and primary anastomosis (85%) versus enterostomy (50%).

Moore[337] described a controversial approach termed the "patch, drain, and wait" procedure in 1989. The principles of this potentially bowel length–preserving method are transverse single-layer suture approximation of perforations (patch), insertion of two Penrose drains that exit in the lower quadrants (drain), and a commitment to long-term parenteral nutrition (wait). The Penrose drains capture fecal fistulas and function as de facto enterostomies as the peritoneal cavity is rapidly obliterated by adhesions.[338] This procedure does not address the issue of ongoing sepsis because necrotic bowel is not resected, the general peritoneal cavity is difficult to drain, and the thin-walled perforated bowel often cannot handle suture.

Vaughan[339] described a promising novel technique aimed at avoiding multiple enterostomies, circumventing the complications of a high jejunostomy, and preserving bowel length. The authors performed the "clip-and-drop-back" technique in three patients with NEC. In this procedure the obviously necrotic bowel is removed, and the cut ends are closed with titanium clips or staples. Reexploration is performed 48 to 72 hours later, the clips are removed, and all segments are reanastomosed without any stomas. In one of the three patients, reresection was required during the second-look operation, the bowel ends were clipped again, and a successful primary anastomosis was performed during a third operation. Follow-up for this small series was 6 months to 7 years with no anastomotic complications or delayed reoperations.

### Pan Involvement (NEC Totalis, <25% Viable)

Pan involvement develops in 19% of patients[310]; it poses an enormous treatment problem and remains a highly controversial management issue. The overriding consideration is to

spare as much intestine as possible. Treatment options include resection of all necrotic bowel with placement of proximal or multiple stomas or proximal diversion without bowel resection, with plans for a second-look procedure. The decision to forego any treatment is supported by studies that demonstrate a 42% to 100% mortality rate in patients with pan involvement, with almost all survivors left with short-bowel syndrome. The mortality rate is nearly 100% for infants who weigh less than 1000 g.

Diverting the intestinal stream by high proximal jejunostomy (without bowel resection) may facilitate healing of injured bowel through distal intestinal decompression, a reduction in its metabolic demands, and a decrease in the number of bacteria and possibly their byproducts. This technique was initially reported by Martin and Neblett[340] and involves performing a high jejunostomy without resection, with plans for a second-look operation after 6 to 8 weeks. In a series of 10 patients with pan involvement, Sugarman and Kiely[341] reported 8 infants surviving to undergo a second procedure. Resection of necrotic segments plus anastomosis was performed successfully, but the long-term survival rate was only 50%.

### Stoma Closure and Complications

There is neither an ideal weight and age nor a universally agreed-upon time at which intestinal continuity should be restored. The principal determinants are time since surgery, weight gain, and stoma output and need or effects of TPN on overall metabolic function (i.e., liver). In general, the enterostomy may be safely closed anytime after 4 weeks since the last operation. Attempted closure at less than 4 weeks postoperatively may be met with a peritoneal cavity that is obliterated by vascular adhesions and resolving inflammation. Before enterostomy closure, patency of the distal end of the bowel (i.e., colon) should be confirmed by either a retrograde or antegrade contrast study to rule out a stricture or strictures in the distal defunctionalized bowel. A study by Musemeche[342] examined the complication rate after stomas were closed less than 3 months after surgery, 3 to 5 months after surgery, and more than 5 months after surgery; no differences were found. They also noted no difference in complications between patients who underwent closure at a body weight less than 2.5 kg, 2.5 to 5 kg, or greater than 5 kg.

Although enterostomy in neonates may be lifesaving, it is also a major cause of morbidity. In recent studies, enterostomies in newborns had an associated complication rate ranging from 34% to 68%.[343,344] Complications included wound infections, wound dehiscence, stoma stenosis requiring revision, incisional hernia, parastomal hernia, prolapse or intussusception, and small bowel obstruction.

# Survival

Over the past decades, the survival of infants with NEC has progressively improved. This improvement has been attributed to earlier diagnosis and more effective supportive treatment for premature infants. Effective supportive treatment includes improved ventilatory strategies, surfactant therapy, total parenteral nutrition, improved understanding of the pathophysiology and management of critically ill newborns, and advancements in pediatric anesthesia. The increased survival has been most noticeable in infants who weigh less than 1000 g and are less than 28 weeks' gestational age. In a recent review of 754 premature infants born between 22 and 25 weeks' gestation, the overall survival rate was 63%, with a range of 14% at 22 weeks' gestation to 76% at 25 weeks' gestation.[19] Mortality was still significantly higher in VLBW infants than in larger patients. This is highlighted by studies that examined the outcome of VLBW infants in comparison with "standard" premature infants (>1000 g) with pan involvement NEC. Snyder[345] found that infants weighing less than 1000 g are more likely to require laparotomy (51% vs. 34%) and to eventually have pan involvement (10% vs. 4%) than infants greater than 1000 g. Pan involvement was associated with 100% mortality in both groups. In a retrospective study of 70 infants weighing less than 1000 g with perforated NEC, Erhlich[331] demonstrated that infant survival was independent of the type of surgical treatment (PD vs. laparotomy), but instead was inversely related to the number of comorbid conditions associated with the patient.

Taken together, it seems unlikely that the significant differences in mortality rates observed in various series are attributable to differences in the effectiveness of the treatment programs used. In different groups of patients, the disease varies from predominantly localized disease to extensive necrosis. The patient population differs between the various series. The mortality rate can vary considerably, depending on birth weight, coexisting disease, virulence of the disease process, and whether the patient is inborn locally versus transferred from another facility that has initiated therapy. The precarious state of patients at risk for NEC is emphasized by one series that compared patients who had NEC with matched controls, in which the mortality rate in controls was 33%.[346]

# Complications

## GASTROINTESTINAL

### Intestinal Strictures

The first clinical and radiologic description of intestinal stricture after recovery from acute NEC was reported in 1968 by Rabinowitz.[347] The reported overall incidence varies from 9% to 36%,[348,349] and stricture formation is more frequent after nonoperative treatment. The incidence of strictures after NEC is increasing as the mortality rate from the disease decreases. Strictures result from fibrotic healing of an area of severe ischemic injury. Regardless of whether the stricture follows operative or nonoperative therapy, the most common site of involvement has been the colon (80%). The next most common site is the terminal ileum (15%). Sixty percent of colonic strictures involve the left colon, and the most common colonic site is the splenic flexure (21%). Most patients have single strictures, but multiple strictures can occur (15%).[350] An intestinal stricture should be suspected after nonoperative management of NEC in an infant with failure to thrive, rectal bleeding, or bowel obstruction. These signs and symptoms occur in 50% of patients with strictures and should be evaluated with a contrast enema. If the study demonstrates a stricture in a symptomatic patient, elective resection with anastomosis is usually indicated.

### Intestinal Malabsorption and Short-Bowel Syndrome

Malabsorption may result from a variety of factors including decreased bowel length, decreased mucosal absorptive area, enzyme depletion, gut hypermotility, hypersecretion of gastric acid, bacterial overgrowth, decreased intestinal transit time, vitamin $B_{12}$ deficiency, and bile salt deficiency. Short-bowel syndrome (see Chapter 86) is the most serious long-term GI complication associated with surgically treated NEC. It occurs in up to 23% of NEC survivors who undergo surgical resection.[313]

### Cholestatic Liver Disease

Cholestatic liver disease results from a number of factors but primarily from prolonged administration of total parenteral nutrition. It is characterized by direct hyperbilirubinemia, hepatomegaly, and elevated aminotransferase levels. Although the condition is multifactorial, the most important contributing factor is probably prolonged fasting. It has been shown that the most effective treatment is establishment of early, small-volume enteral feeding that aids in bowel adaptation by conferring a trophic effect on the intestinal mucosa and by stimulating bile flow.

### Recurrent Necrotizing Enterocolitis

NEC can recur after operative and nonoperative management. The incidence of recurrence has been reported to be 4% to 6%.[309,351] No consistent association has been noted between recurrent NEC and the type or timing of enteral feeding, the anatomic site, or the method of initial management. Various case reports suggest supraventricular tachycardia, percutaneous transluminal angioplasty, and allergic enterocolitis to be associated with recurrent necrotizing enterocolitis.[352–354] Interestingly, Pickard[355] proposes that infants with congenital heart diseases and NEC have a decreased risk of having recurrent NEC (OR for CHD 0.58 [95% CI, 0.18 to 1.89], OR for PDA 0.49 [95% CI, 0.10 to 2.28], OR for all other congenital cardiac diseases 0.72 [95% CI, 0.15 to 3.34]) through a retrospective study of 202 infants with NEC. More than 70% of patients were successfully treated nonoperatively for recurrence by Stringer and colleagues.[351]

### Anastomotic Ulceration

A late complication that may occur many years after resection for NEC is the development of anastomotic ulceration. Sondheimer[356] reported six children who underwent ileocolonic resection and anastomosis in the neonatal period in whom lower GI bleeding developed at 5 to 13 years of age. Anastomotic ulceration was diagnosed by colonoscopy, and treatment entailed ulcer resection in five of six patients. Recurrence of marginal ulcers developed in four of five patients who underwent resection. Histologic examination revealed shallow ulcers penetrating only to the muscularis. The cause of the ulcers is unknown.

## NEURODEVELOPMENTAL COMPLICATIONS

The length of hospitalization of infants has been strongly associated with developmental progress at 1 to 2 years of age.[349] This probably reflects the adverse effects of medical and social factors on the developing brain. It is recommended that developmental screening be performed every 4 months during the first year and every 6 months during the second year of life as long-term follow-up data suggest that normal premature infants and survivors of severe NEC remain at high risk for neurologic developmental morbidity.

Approximately 50% of infants surviving NEC are neurodevelopmentally normal.[309,346] Historically, it was believed that any adverse neurodevelopmental outcome in a patient treated for NEC was due to underlying prematurity and comorbid conditions rather than NEC itself, but recent evaluations of surviving infants contest this assumption. Vohr[357] studied the neurodevelopmental, neurosensory, and functional outcomes of 1151 ELBW (401 to 1000 g) survivors at 18 to 22 months' corrected age and reported significant deficits in neurologic development (25%), a Bayley II Mental Developmental Index less than 70 (37%), a Psychomotor Development Index less than 70 (29%), vision impairment (9%), and hearing impairment (11%). NEC was specifically associated as a risk factor for both an abnormal neurologic examination and a low Bayley Psychomotor Development Index. In a study assessing the effect of NEC on neurodevelopment, Sonntag[358] compared VLBW infants with NEC with matched infants without NEC at 12 and 20 months' corrected age. Despite normal somatic growth in infants with NEC not complicated by short bowel syndrome, the authors demonstrated significant neurodevelopmental delay at both 12 and 20 months of age. Fifty-five percent of infants with NEC were noted to be severely impaired versus only 22.5% of infants without NEC. Furthermore, Hintz[359,360] demonstrated through the National Institute of Child Health and Human Development Neonatal Research Network Registry that among the ELBW infants (weight $<$ 10th percentile for gestational age), infants with surgical intervention but not medical treatment for NEC are at significant risk for Mental Developmental Index less than 70 (OR: 1.61, 95% CI, 1.05 to 2.50), Psychomotor Developmental Index less than 70 (OR: 1.95, 95% CI, 1.25 to 3.04), and neurodevelopment impairment (OR: 1.78, 95% CI, 1.17 to 2.73) compared with infants without NEC.

# Prevention

Attempts to reduce the incidence of or prevent NEC must consider the probable pathogenesis of the disease and some of the putative perinatal risk factors. Investigations into preventive measures for NEC including limiting the nosocomial spread of microorganisms, augmenting host defense, decreasing bacterial colonization and overgrowth in the GI tract, and providing factors that enhance intestinal maturation and attenuate the inflammatory cascade may be useful. Infection control measures, breast-feeding, cautious feeding of sick premature babies, immunoglobulin supplementation of feedings, corticosteroid therapy, administration of growth factors, and the use of inflammatory mediator antagonists are some of the preventive strategies that have been studied.

## INFECTION CONTROL MEASURES

Adoption of infection control measures in the nursery may limit the incidence and restrict the spread of infections, thereby potentially eliminating the epidemic waves of NEC.

It has been demonstrated that the initiation of infection control measures stops epidemics of NEC.[219,361] During clustered occurrences, identical microorganisms can be isolated from both the afflicted neonates and their caretakers.

## AUGMENTATION OF HOST DEFENSE

### Oral Immunoglobulin Preparations

The protective immunoglobulins, principally IgA, are deficient in the premature gut. In the absence of breast-feeding, there are only trace amounts of secretory IgA and gut-associated IgG and IgM. Secretory IgA acts by binding bacteria and preventing their attachment to the intestinal mucosa. Eibl[13] demonstrated that enteral administration of an IgG-IgA preparation decreases the incidence of NEC. Their randomized trial involved feeding 179 high-risk infants weighing 800 to 2000 g a human preparation of IgG and IgA with their formula, whereas controls received formula alone. Neither group received breast milk. No cases of NEC developed in the immunoglobulin group, but 6 cases developed in the 91 controls. In a recent study in rabbits, Dickinson[362] demonstrated that IgA supplementation in feedings prevented bacterial translocation by enhancing gut mucosal barrier functions. This effect was not seen with IgG or lactoferrin. In a randomized double-blind controlled trial, enteral IgG supplementation in infants failed to reduce the incidence of NEC.[363] A Cochrane review[364] of three eligible trials (total of 2095 infants) on oral administration of IgG or IgG/IgA combination for preventing NEC did not yield any statistically significant reduction in the incidence of definite NEC (RR 0.84, 95% CI, 0.57 to 1.25), suspected NEC (RR 0.84, 95% CI, 0.49 to 1.46), need for surgery (RR 0.21, 95% CI, 0.02 to 1.75), or death from NEC (RR 1.10, 95% CI, 0.47 to 2.59). Similarly, a meta-analysis of three trials using antistaphylococcal immunoglobulins (INH A-21 and Altastaph) indicated no significant differences in the risk of staphylococcal infection and NEC between either of the antistaphylococcal immunoglobulins with placebos.[365]

### Maternal Glucocorticoid Administration

Glucocorticoids have been shown to accelerate epithelial cell maturation and improve gut barrier function including reduced mucosal uptake of macromolecules, decreased colonization with aerobic bacteria, reduced bacterial translocation, and increased activity of enzymes such as lactase, maltase, sucrase, and Na/K-ATPase.[366,367] Glucocorticoids have also been shown to down-regulate the inflammatory response by stimulating the enzymatic degradation of PAF.[165] These observations have been made both experimentally and clinically.[13,14] Bauer[368] retrospectively noted a significant reduction in the incidence of NEC in babies born to mothers who received antenatal glucocorticoids for fetal pulmonary maturation as compared with controls (2% vs. 7%). This large, multicenter, placebo-controlled trial was well controlled for many potentially confounding variables. Halac[14] conducted a randomized controlled trial of prenatal glucocorticoid administration to mothers in preterm labor. The control mothers received placebos, but their infants received an immediate postnatal course of high-dose dexamethasone for 7 days. The rate of NEC within and between groups significantly decreased after prenatal and postnatal steroid treatment. Although postnatal therapy did not decrease the incidence as effectively as prenatal therapy did, it improved the clinical outcome of NEC; however, many potentially confounding factors were not assessed in this study. Confirmatory prospective data and assessment of potential postnatal toxicity are necessary. In a double-blind randomized controlled trial comparing perinatal morbidities between antenatal betamethasone and dexamethasone (299 women),[369] no significant differences were observed to exist in the incidence of NEC (0 of 181 for betamethasone, 2 of 178 for dexamethasone). Furthermore, another multicenter randomized controlled trial[370] of 502 pregnant women demonstrated no difference in the incidence of NEC between weekly administration and a single course of antenatal corticosteroids (RR 1.06, 95% CI, 0.44 to 2.56, *P* value = 0.90).

### Breast Milk

Breast milk decreases the risk for a number of neonatal infections including lower respiratory tract illness, otitis media, bacteremia, meningitis, and NEC.[187] Human milk provides an array of humoral and cellular antiinfectious factors, growth factors, and probiotics, as well as essential vitamins and nutrients. Milk factors include IgA, macrophages, lymphocytes, components of the complement system, lactoferrin, lysozyme, transferrin, interferon, EGF, alpha fetoprotein, erythropoietin, the probiotics *Bifidobacterium infantis* and *Lactobacillus acidophilus,* PAF acetylhydrolase,[174] and several inflammatory mediators.[188,371] Strong evidence exists for the protective role of secretory IgA, the main immune component of the enteromammary axis. Breast milk also inhibits the growth of *E. coli* by providing an acidic environment, promoting competitive growth of *Lactobacillus bifidus,* and iron binding (an element essential for the growth of *E. coli*).[372]

Because invasion by infectious agents seems to be a prime factor in the pathogenesis of NEC, breast milk appears to be ideally suited to protect the infant against the disease. Administration of breast milk prevents experimental NEC.[372,373] Formula-fed babies have four to six times the incidence of NEC as breast-fed infants do.[374] A meta-analysis done by Quigley of five trials demonstrated a statistically significantly higher incidence of NEC in the formula-fed group versus the donor breast milk group (RR 2.5, 95% CI, 1.2 to 5.1; risk difference 0.03, 95% CI, 0.01 to 0.06; number needed to harm 33, 95% CI, 17 to 100).[375] Subsequently, two more clinical trials were conducted. The analysis of 1272 infants in the National Institute of Child Health and Human Development Neonatal Network Glutamine Trial showed a reduction of the likelihood of NEC or death after 14 days of diagnosis by a factor of 0.83 for every 10% increase in the proportion of total intake of human milk. For every 100 mL/kg increase in human milk intake with the 14 days of diagnosis, there is a decreased risk of NEC or death (hazard ratio 0.87, 95% CI, 0.77 to 0.97).[376] Similarly, Sullivan[377] showed in a trial of 207 infants (500 to 1250 g) comparing an exclusively human milk–based diet with a diet of both human milk and bovine milk–based products that there was a reduction in NEC of 50% and in surgical NEC of almost 90% in infants fed an exclusive human milk diet. The numbers to treat with an exclusively human milk–based diet to prevent 1 case of NEC and 1 case of surgical NEC were 10 and 8, respectively. The last two trials imply a dose effect of human milk in the reduction of both medical and surgical NEC.

### Feeding Practices

There is little disagreement that NEC is more common in fed infants and that bacterial overgrowth is facilitated by the substrate provided by formula. Although the potential benefit of carefully regulated feeding practices to prevent NEC is widely accepted, randomized trials have failed to demonstrate any difference in the incidence of NEC related to fast versus slow, early versus delayed, or continuous versus intermittent bolus feeding.[35–39,378–381]

## METHODS TO DECREASE INTESTINAL BACTERIAL COLONIZATION AND OVERGROWTH

### Administration of Probiotics

Probiotic bacteria are defined as "live microbial supplements that colonize the intestine to provide benefit to the host."[382,383] The use of anaerobic bacterial supplementation in the treatment or prevention of GI disease has been well described. There has been increasing interest in using probiotics for the prevention of NEC. Probiotic microorganisms commonly used are strains of *Lactobacillus, Bifidobacterium, Streptococcus salivarius,* and *Saccharomyces boulardii.* Multiple randomized, controlled trials have attempted to address this issue, and several meta-analyses have been published. The most recent meta-analysis by Deshpande[384] analyzed 11 trials[385–395] ($n = 2176$) in which enteral probiotic supplementation was started within the first 10 days and continued for 7 or more days in VLBW neonates (<1500 g). Compared with the control group of no probiotics, significant reductions of risk were noted for developing definite NEC (RR 0.35, 95% CI, 0.23 to 0.55, $P < 0.00001$) and dying from all causes (RR 0.42, 95% CI, 0.29 to 0.62, $P < 0.00001$). Further sensitivity analysis, examination through the funnel plot, and trial series analysis supported a 30% reduction in the incidence of NEC (alpha = 0.05; power of 80%). However, risks for sepsis, death from NEC, and longer time to full feed (120 to 150 mL/kg per day enteral feeds or as per the prestated definitions by authors) did not differ significantly between both groups after adjustments were made for heterogeneity via a random-effects model.

Rachmilewitz[396] and Mackey[397] considered applying similar concepts used in probiotic feedings by treating infants with isolated microbe-associated molecular patterns (MAMPs) to induce protective responses that promote intestinal health. An MAMP is a molecular sequence or structure in any pathogen-derived molecule that directly interacts with TLRs on the intestinal epithelium. It has been shown to effectively improve symptoms of colitis in mice.[396] The idea of administering inactivated probiotics (heat-killed commensals) or bioavailable TLR ligands that can potentially induce beneficial TLR-mediated protective effects without the risk of infection from administering probiotics is being actively investigated.

### Administration of Prebiotics

Besides probiotics, other researchers have suggested administering prebiotics, which are nondigestible dietary supplements such as long chain carbohydrates or mucins that promote proliferation of beneficial commensal bacteria. A meta-analysis of four trials ($n = 126$) by Srinivasjois[398] examined the efficacy and safety of prebiotic oligosaccharide supplementation of formula in reducing the incidence of NEC and sepsis. The duration of the supplementation ranged from 14 to 33 days. The analysis indicated no NEC in one trial, but the rest did not report specifically on NEC or sepsis. Two of the four trials demonstrated a significant increase in bifidobacterial counts in the prebiotic supplemented group. The major advantage of prebiotic supplements is the lack of live microorganisms, which reduces the risk of infection that may exist for the use of probiotics.

### Administration of Postbiotics

Similar to prebiotics, postbiotics, which are bacterial metabolites, may also be a potential treatment for NEC by generating some beneficial effects on the intestinal flora. Butyric acid, a short-chain fatty acid produced by commensal bacteria in the colon through anaerobic catabolism of complex carbohydrates, is a major energy source for colonic enterocytes and has a widely recognized but poorly understood role in intestinal growth and differentiation,[399,400] inflammatory suppression,[401] and apoptosis.[402] It has been administered with limited success in human inflammatory bowel disease.[403]

### Enteral Antibiotics

Nonabsorbable broad-spectrum antibiotics that inhibit bacterial growth have been administered in an effort to prevent NEC. The use of an enteral aminoglycoside (e.g., kanamycin or gentamicin) has been proposed as a means to decrease the incidence of perforation during nonoperative treatment. However, randomized, controlled studies found no difference in the clinical course, complications, or mortality rate between infants who received the antibiotic and those who did not.[404,405] In addition, oral aminoglycosides may be absorbed across the damaged gut, which can lead to increased serum levels and thereby potentially contribute to drug toxicity. Resistant strains of bacteria emerged after treatment with enteral kanamycin,[404] and there is the omnipresent risk for promotion of the growth of fungal species. In a recent randomized placebo-controlled study of oral vancomycin in preventing NEC in preterm infants, Siu[16] reported a 50% reduction in the incidence of NEC in the vancomycin group in comparison with controls. A meta-analysis of five trials ($n = 456$) by Bury[406] suggested that prophylactic enteral antibiotics resulted in a statistically significant reduction in NEC (RR 0.47 [0.28, 0.78]; RD −0.10 [−0.16, −0.04]; NNT 10 [6, 25]) and in NEC-related deaths (RR 0.32 [0.10, 0.96]; RD −0.07 [−0.13, 0.01]; NNT 14 [8, 100]). However, the summary analysis of three trials gave an increase in the incidence of colonization with resistant bacteria that was just significant (RR 1.73 [1.00, 2.97]; RD 0.07 [0.00, 0.13]). Furthermore, a subsequent retrospective cohort analysis of 5693 neonates (<1000 g) from the NICHD database by Cotton[407] demonstrated that for every antibiotic treatment day, there was at least a 4% increase in the odds of an infant having NEC or dying, especially when antibiotics were initiated in the first 3 postnatal days for 5 or more days of treatment.

The available studies do not support the routine administration of enteral antibiotics to all high-risk premature infants, many of whom have poor intestinal motility. Effectiveness has not been proved, and resistant organisms may develop.

Administering specific antibiotics to infants may be indicated in nurseries in which an outbreak of NEC is associated with a specific organism.

## METHODS TO DETER THE INFLAMMATORY CASCADE

### Inflammatory Mediator Antagonists

The effects of PAF are mediated by receptors, and many compounds that function as receptor antagonists or enzymes that degrade these proteins have been described. Animal experiments using PAF antagonists or PAF-degrading enzyme (PAF acetylhydrolase) have demonstrated the capacity to prevent bowel injury produced by the administration of endotoxin or hypoxia in rats.[47,115] PAF acetylhydrolase is also known to be present in breast milk. Despite promising results in animal models, no human trials using PAF antagonists or degrading enzymes in the treatment of NEC have been reported.

### Arginine

While NO has been linked to the pathogenesis of NEC, it may be beneficial to neonate intestine by regulating mucosal blood flow, inflammatory signaling, barrier function, and wound healing.[408] Arginine, a substrate for the production of NO, has been shown to be in low level in neonates with NEC as well.[153,409] Thus researchers tested the effect of arginine supplementation on the incidence of NEC. In the 2007 Cochrane Review[155] one trial[154] on arginine supplementation was reported to reduce the incidence of all stages of NEC (RR 0.24, 95% CI, 0.10 to 0.61; RD -0.21, 95% CI, -0.32 to -0.09), but further studies are necessary to confirm and elucidate the mechanism of this benefit.

### Epidermal Growth Factor

As discussed in previous sections, EGF is a growth factor that exerts its effects by binding to the EGF receptor. It has multiple effects including healing of damaged mucosa by inducing mucosal enzyme and trefoil peptide expression and inhibiting effects on gastric acid secretion.[62,65–67] Clark demonstrated intestinal protection by accelerating goblet cell maturation and mucin production and normalizing expression of tight junction proteins in a neonatal rat model. One prospective randomized controlled study[410] of eight neonates with NEC showed measurable trophic effects on the gastrointestinal mucosa and no significant difference in clinical safety between a 6-day continuous intravenous infusion of EGF and placebo. The administration of EGF is still at the testing stage. Further studies are necessary before any clinical use.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 95

# Crohn's Disease

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Crohn's disease (CD) is a debilitating chronic inflammatory bowel disorder with no known cure. The disease affects the entire digestive tract. The original article by Crohn, Ginzberg, and Oppenheimer described *regional ileitis* as the formation "of ulcers and hyperplastic inflammation in which the terminal loops of the small intestine, just proximal to the ileocecal valve, are implicated."[1,2] CD and ulcerative colitis (UC) comprise the vast majority of patients exhibiting a wide spectrum of clinical pathology under the broad heading of *inflammatory bowel disease* (IBD). The estimated annual health care cost of IBD in the United States is about $1.7 billion.[3] Approximately 10% of Americans with IBD are children and adolescents.[3]

The etiology of CD is unknown. However, it is believed that its pathogenesis is multifactorial, encompassing environmental, genetic, and immunologic causes.[4] Diagnosis requires a thorough history and physical examination, along with diagnostic imaging, histologic, and laboratory evaluations. Despite various pathognomonic features such as transmural inflammation, aphthous ulcers, and granulomas, CD may be indistinguishable from UC. In children the reported percentage of cases of IBD diagnosed as indeterminate colitis ranges from 4% to 23%.[5]

The natural history of CD is characterized by quiescence with symptomatic flare-ups leading to severe physical and social impairment,[6] as well as the long-term risk of colorectal cancer. Both medical and surgical therapies are used to combat the wide range of symptoms in children and adolescents with CD. It is imperative, therefore, that this disease is diagnosed and treated in a multidisciplinary fashion.

## Epidemiology

The worldwide incidence of pediatric CD is 0.2 to 8.5 per 100,000.[7,8] A prospective study of a Wisconsin population reported an incidence of 4.56 per 100,000.[9] It is more common in countries in the northern hemisphere and in industrialized nations.[7] The highest rates of CD are found in Scandinavian countries and Scotland, followed by England and southern Europe.[8,10] There has been a noticeable rise in the incidence of CD after World War II[10]; Scotland had a threefold increase in childhood CD between 1968 and 1983,[10] and northern France had an increased incidence of pediatric CD cases, from 2.1 to 2.6 per 100,000 between 1988 and 1999.[11] There is a positive family history of CD in more than 10% of patients,[11] with a high rate of concordance for monozygotic twins.[7] Although there is a higher percentage of boys diagnosed with CD in childhood, the proportions even out in adulthood. Twenty-five to 30% of patients with CD are younger than age 20 at the time of diagnosis.[7]

## Etiology

The etiology of CD remains unknown; however, there seems to be a complex interaction of environmental, genetic, and immune factors that lead to its development.[7] Some experts have suggested that a triggering event such as a bacterial infection or other immunogenic stimulus in a genetically predisposed individual can result in the onset of CD.[12]

In one recent study, 22% of patients with CD had an affected family member,[10] suggesting a genetic predisposition. Concordance for CD has been reported to range from 36% to 48% in monozygotic twins, compared with 4% of dizygotic twins.[13] The gene for the nuclear oligomerization domain 2 (NOD2) and the caspase activation and recruit domain 15 (CARD15) are located on chromosome 16.[14] Mutations in NOD2/CARD15 overexpress NF-$\kappa\beta$, a critical mediator of the inflammatory responses that control the transcription of genes for proinflammatory cytokines.[6,10] Mutations in this gene have been associated with ileocecal and stricturing disease phenotypes,[6] earlier disease onset, and early need for operative intervention.[3,10,12,15–17] Mutations of this gene have been identified in 30% to 43% of Caucasian North American CD patients.[10] Another gene, *IBD5,* located within chromosome 5q31, has been associated with CD-linked perianal disease.[6,7,10]

A recently discovered gene variant of *ATG16L1,* an autophagy gene, may be associated with CD.[16,18,19] This mutation results in defective macroautophagy in the Paneth cells of the intestines (within the crypts of Lieberkühn), resulting in the ineffective elimination of invasive pathogens.[19,20] This mutation also results in higher levels of interleukin $1\beta$, making intestinal cells more susceptible to an abnormal inflammatory response.[21] This *ATG16L1* gene variant opens a possible new mechanism for treating CD patients, focusing efforts on gene therapy, cytokine neutralization, and Paneth cell rejuvenation.[19]

## Pathology and Clinical Features

Within the pediatric population, disease involving both the small bowel and proximal colon (ileocecal) occurs in more than two thirds of patients; disease isolated to the small bowel occurs in about 20% of patients and is restricted to the colon in 10% of patients.[11] Endoscopic evidence of inflammation in patients with ileocolic disease has been noted on upper endoscopy in up to 40% of patients.[12]

CD initially manifests itself as small mucosal ulcerations (aphthous ulcers).[22] These ulcers subsequently coalesce to form linear ulcerations that surround islands of edematous mucosa, producing the "cobblestone" appearance.[22] Mucosal ulcers sometimes achieve transmural penetration, creating sinuses, abscesses, and fistulas (Fig. 95-1).[22]

The inflammation progresses through all layers of the bowel wall. "Creeping fat" forms from thickening of the mesentery, with proliferation of the surrounding fat on the serosal surface. With acute inflammation, the bowel becomes edematous and hyperemic.[22] As the inflammation becomes chronic, fibrotic scarring leads to bowel thickening and eventual stricture formation (Fig. 95-2).

Histologic examination reveals neutrophilic and eosinophilic inflammatory cell infiltration of the edematous, fibrotic submucosa (Fig. 95-3). Noncaseating granulomas are pathognomonic for CD but are seen in only half of resected specimens (Fig. 95-4).[22]

Common presenting signs and symptoms of CD include crampy abdominal pain, diarrhea, decrease in appetite, weight loss, growth delay, and delayed sexual maturation.[12] Abdominal pain is usually located in the right lower quadrant, associated with tenderness and fullness.[12] Failure to thrive can be present in nearly half of children diagnosed with CD.[23]

In 1998 a CD Working Party was organized to classify the behavior of this disorder into three subtypes: (1) nonstricturing, nonpenetrating; (2) stricturing; and (3) penetrating.[24] However, the clinical course of CD is often erratic and disease phenotypes often change as the duration of disease lengthens.[6] Location of CD in the gastrointestinal (GI) tract has also been broadly classified into four areas: (1) terminal ileum; (2) colon; (3) ileocolic; and (4) upper GI.[24]

Perianal disease may be the primary presenting sign of CD.[12] Anal fissures, perianal fistulas, or abscesses precede or present simultaneously with diagnosis of CD in many

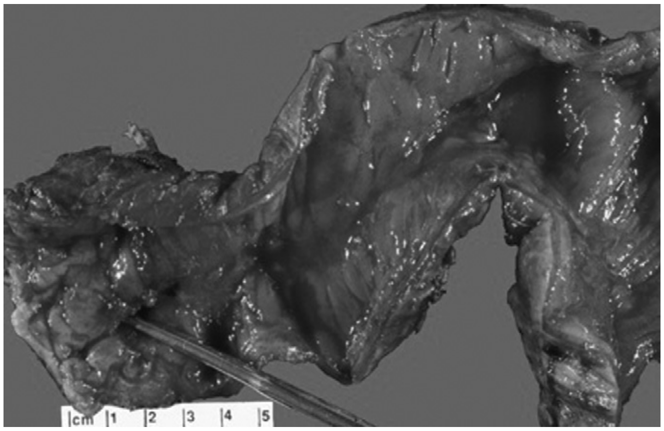


FIGURE 95-1 Ileocecal disease with fistula formation. (Courtesy Dr. David Kelly, Department of Pathology, The Children's Hospital of Alabama.)

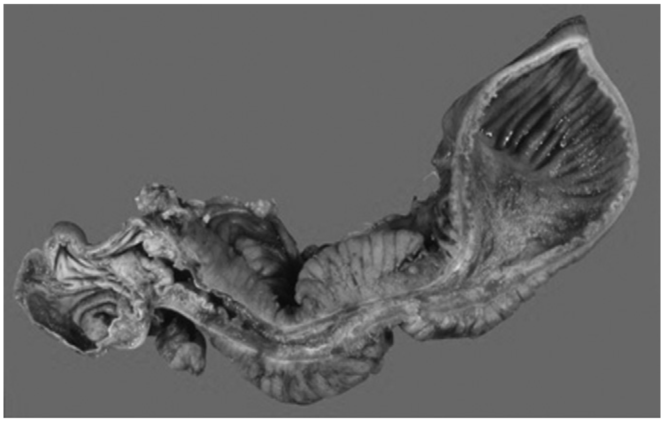

FIGURE 95-2 Disease with stricture. (Courtesy Dr. David Kelly, Department of Pathology, The Children's Hospital of Alabama.)

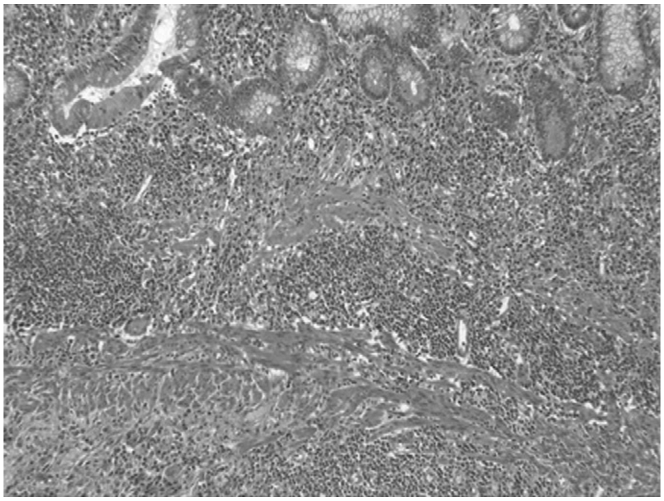

FIGURE 95-3 Neutrophilic inflammation with fibrosis within submucosa. (Courtesy Dr. David Kelly, Department of Pathology, The Children's Hospital of Alabama.)

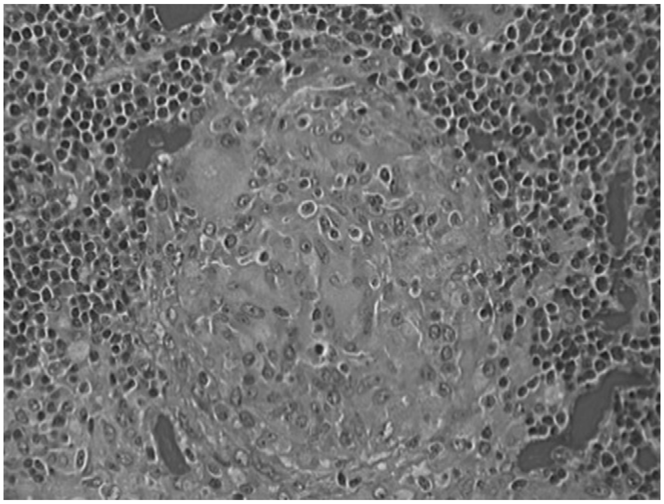

FIGURE 95-4 Noncaseating granuloma. (Courtesy Dr. David Kelly, Department of Pathology, The Children's Hospital of Alabama.)

patients.[8] The incidence of perianal fistulas in children with CD is approximately 10%.[25] Fistulas are classified as *simple* or *complex*. Treatment is discussed later in the chapter.

Musculoskeletal involvement is the most common extraintestinal manifestation seen in patients with CD. The incidence of peripheral arthropathy (arthritis or arthralgia) in CD is approximately 20%.[26] Erythema nodosum presents as tender, red nodules, usually on the extensor surfaces of the lower extremities, and is seen in about 10% of patients.[26] Pyoderma gangrenosum manifests itself as erythematous skin nodules that develop into ulcers, and it occurs in about 5% of patients with CD.[26] Episcleritis and uveitis also occur in about 5% of patients with CD.[26] Episcleritis is a painless hyperemia of the sclera and conjunctiva, whereas uveitis is a painful manifestation associated with blurring and photophobia. Nephrolithiasis, composed of uric acid and calcium oxalate stones, occurs in up to 5% of patients.[26] Hepatobiliary manifestations associated with CD include primary sclerosing cholangitis, gallstones, chronic hepatitis, and steatosis.

## Diagnosis

A thorough history often provides the clinician with important clues to the diagnosis of CD in children. Intermittent crampy abdominal pain, food intolerances, diarrhea, fever, family history of IBD, and perianal disease may be reported.[27] Physical examination should include an abdominal evaluation with special attention paid to the right lower quadrant for masses.

A rectal examination may reveal obvious perirectal disease. However, a thorough examination is sometimes difficult in an anxious pediatric patient. In these cases, an examination under anesthesia (EUA) is the gold standard,[28] providing a thorough assessment of the perirectal area. The accuracy of an EUA may be enhanced by the use of an anorectal endoscopic ultrasound (EUS) to help detect abscesses.[8]

Growth evaluations are an important aspect of the physical examination[7,12] because weight loss is present in most children with CD at diagnosis.[7,29] A Tanner assessment of pubertal status should be performed to identify delayed sexual development. The clinician should also look for signs of extraintestinal manifestations (skin rash, joint pain, eye pain).

A complete blood count (CBC) should be obtained, specifically looking for anemia, leukocytosis, and thrombocytosis.[12] The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) increase with acute disease activity.[27] Baseline nutritional laboratory tests (albumin, prealbumin, and transferrin) should be performed.[23] Detection of IgA and IgG anti-saccharomyces cerevisiae antibody (ASCA) is highly specific for CD in children.[6,7,12,30] Patients presenting with diarrhea should have stools checked for leukocytes, occult blood, and infectious etiologies *(Clostridium difficile, Giardia, Salmonella, Escherichia coli O157:H7, Campylobacter, Rotavirus, Shigella)*.[7,12,27]

An upper GI contrast study with small bowel follow-through assists in assessing existence, location, and extent of the disease.[12] Computed tomography (CT) and ultrasound (US) can evaluate for terminal ileal inflammation and intra-abdominal abscesses. In a recent study, gadolinium-enhanced magnetic resonance imaging (MRI) was shown to be highly specific and sensitive for the identification of proximal small bowel disease.[31]

Ileocolonoscopy and upper endoscopy are necessary for direct observation and biopsies of the terminal ileum, colon,

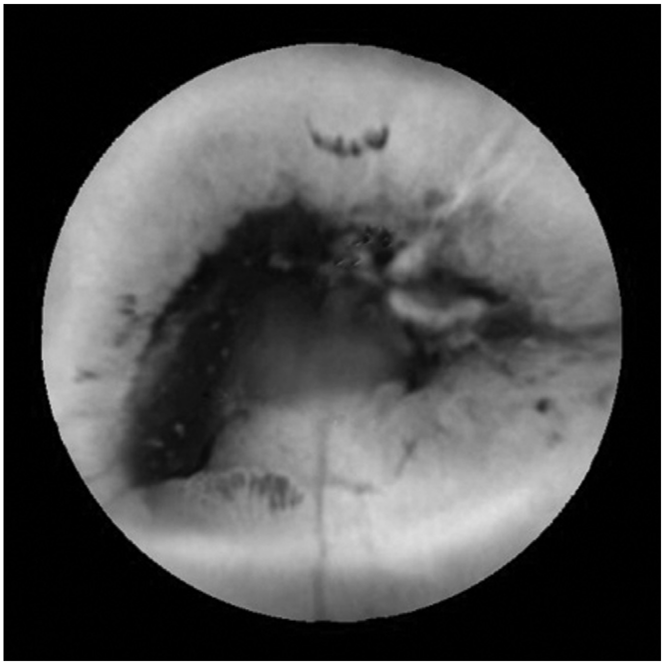

**FIGURE 95-5** Jejunal ulceration and bleeding via capsule endoscopy. (Courtesy Dr. Shehzad Saeed, Department of Gastroenterology, The Children's Hospital of Alabama.)

and stomach. Endoscopy may reveal skip lesions, rectal sparing, aphthous ulcers, and terminal ileal inflammation. Capsule endoscopy has gained popularity for identification of proximal small bowel disease (Fig. 95-5).[32] An upper GI contrast study with small bowel follow-through is recommended before capsule endoscopy to rule out strictures that may lead to capsule retention. In a retrospective study, capsule retention occurred in 3 of 207 pediatric patients (1.4%) without small bowel abnormalities, compared with 37.5% in patients with known strictures noted on prior small bowel series.[32]

## Medical Therapy

The goals of medical treatment are to (1) achieve remission of active disease, (2) promote growth through adequate nutrition and suppression of inflammation, and (3) decrease the need for surgical intervention.[6]

Systemic corticosteroid induces clinical remission and is standard of care for treatment of moderate to severe CD.[6,12] Corticosteroids decrease the transcription of proinflammatory cytokines (IL-1$\beta$, IL-6, tumor necrosis factor $\alpha$ [TNF-$\alpha$]).[33] Up to 90% of pediatric patients with moderate to severe CD show rapid improvement of symptoms when prednisone or a prednisone equivalent (i.e., prednisolone) of 1 to 2 mg/kg/day is given (maximum dose 40 to 60 mg/day).[33–35] Rectal steroid therapy as enemas and foam-based preparations may be administered for left-sided colitis.[12] About 50% of patients develop corticosteroid dependency, which is characterized by frequent relapses and a requirement for chronic corticosteroid use.[6] Long-term corticosteroid use is associated with osteopenia, weight gain, glucose intolerance, pubertal retardation, striae, acne, and many other well-described side effects.[6,33] It is therefore not recommended for maintenance therapy.[12,36] All patients on corticosteroids should be given

calcium and vitamin D supplements.[33] Budesonide, an alternative steroid therapy with a high affinity for intestinal glucocorticoid receptors, has been reported to have an enhanced first-pass therapeutic effect with a lesser systemic corticosteroid exposure causing fewer side effects.[33] As a timed-release oral medication, budesonide is indicated for ileal and right-sided colonic disease,[12,34] although it is not as effective as prednisone in achieving clinical remission in children.[6]

Mesalamine (an aminosalicylate) is the first-line therapy for mild to moderate active CD.[6] It is not effective in moderate to severe disease or in maintaining remission.[12] Asacol tablets provide mesalamine with an enteric coating that delays systemic release until it reaches the terminal ileum and colon.[33] Pentasa is mesalamine with an ethylcellulose carrier for time-release throughout the small and large intestine.[33] The mechanism of action of mesalamine is largely unknown. Adverse effects include rash, elevated liver enzymes, and renal impairment.

Azathioprine (AZA) and 6-mercaptopurine (6-MP) are thiopurine antimetabolite immunomodulators that inhibit the inflammatory response via immunosuppression. AZA is converted to 6-MP in plasma. The thiopurines are among the most effective treatments available for long-term maintenance of CD.[34] They are usually given as an “exit strategy” after induction of remission with corticosteroids to avoid dependency on the steroids.[6] Thiopurines can reduce the rate of corticosteroid dependence and resistance from 50% to less than 20%.[6] It has also been shown to decrease the rate of postoperative recurrence of CD following bowel resection.[37] Because of its slow onset of action (3 to 6 months), thiopurines should be administered early in the treatment of moderate to severe CD. Adverse effects include leucopenia, pancreatitis, and hepatotoxicity.[8]

Methotrexate is a second-line immunomodulator therapy for patients who do not tolerate 6-MP or AZA.[34] It is a dihydrofolate reductase inhibitor with corticosteroid-sparing effects.[33] Adverse effects include bone marrow, pulmonary, and liver toxicity.[33] As a known teratogen, women of childbearing age should not be administered this drug.

Infliximab is a chimeric (human/murine) monoclonal antibody against TNF-α.[7] In adults with moderate to severe disease, infliximab produces excellent symptom improvement and remission rates for refractory CD and chronic perianal or abdominal fistulas.[12,23,38–40] Infliximab is administered via infusion at 5 mg/kg given every 8 weeks after an initial loading period. A multicenter, randomized, open-label study of infliximab in pediatric patients with moderate to severely active CD demonstrated 88% of patients with a clinical response and 58.9% with clinical remission compared with placebo.[41] Concomitant use of an immunomodulator during therapy may help maintain clinical response to infliximab.[42] Infliximab has also been shown to decrease corticosteroid use[43] and improve height velocity.[44] The drug may also be used in the initial treatment of perianal disease in children and adolescents.[8] Crandall and colleagues[45] have shown that a majority of pediatric patients respond to infliximab for perianal disease. Adverse events from infliximab use include infusion reaction (flushing, rash, headaches); delayed hypersensitivity reaction; and an increase in the overall rate of infection (tuberculosis, histoplasmosis, PCP pneumonia, sepsis).[6,8] All patients should undergo testing for latent tuberculosis before infliximab therapy. Continued use of infliximab may lead to development of antibodies against itself, causing a diminished clinical response.[46,47] Infliximab is contraindicated in patients with intra-abdominal or perirectal abscesses.[48]

Adalimumab is a subcutaneously administered, recombinant, fully human, immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to human TNF-α.[49] In a randomized, phase III, double-blind, placebo-controlled trial, adalimumab was shown to be effective in induction and long-term maintenance of clinical remission in adults with CD.[49] A multicenter, retrospective study was performed to evaluate the safety and efficacy of adalimumab in children; it demonstrated a 70% clinical response rate that sustained at 6- and 12-month follow-ups.[47] A prospective study performed in a single tertiary institution consisting of 23 patients age 9 to 20 with moderate to severe CD treated with adalimumab showed a 65.2% clinical remission and a 91% clinical response for 48 weeks of treatment.[46] Adalimumab may be used to treat those who no longer respond or have experienced adverse effects to infliximab.[28,47] The recommended dosage for pediatric patients who weigh more than 15 kg is 20 to 40 kg every other week. The most common adverse event reported is pain at the injection site.[46] As with infliximab, patients may be required to undergo testing for latent tuberculosis before initiation of therapy.

Metronidazole and ciprofloxacin appear effective in children with mild to moderate active ileocolonic CD.[7,33] These antibiotics may also be used as first-line therapy for the induction of healing of perianal fistulae.[28,48] The addition of infliximab may promote a synergistic effect in healing the fistulae.[28] Metronidazole may delay anastomotic recurrence after surgery[50] with long-term use, but relapse often occurs soon after discontinuation.[33] Dosage of metronidazole should not exceed 40 mg/kg/day. Adverse effects of metronidazole include a metallic taste, glossitis, nausea, pancreatitis, neutropenia, and distal peripheral sensory neuropathy.[8,33] Ciprofloxacin should be administered cautiously to children due to the reported risk of Achilles' tendon rupture in animal studies.[33]

Enteral therapy (total liquid formula diet) has been used for both nutritional support and as a method of treatment for CD.[23] Exclusive enteral nutrition (EEN) can induce remission in up to 85% of newly diagnosed patients.[29] In 1995 two meta-analyses of randomized controlled trials comparing EEN with corticosteroids demonstrated that steroids were more effective than enteral nutrition for treatment and induction of remission in patients with CD.[51,52] However, a more recent meta-analysis focusing on pediatric studies suggests that enteral nutrition is as effective as corticosteroids in both the induction of remission and the treatment of CD.[53,54] This study also documented that pediatric patients with CD given enteral nutrition often experience improved growth.[34,53] Enteral formulas with transforming growth factor-β (TGF-β) and omega-3 fatty acids have been shown to increase mucosal healing[29,55] and may also have an immunomodulatory effect.[54] The improved growth and nutrition status that EEN provides, while avoiding the side effects of steroids, make it the preferred choice for first-line therapy in some centers.[29] However, because palatability necessitates use of a feeding tube,[4] compliance becomes a major issue. Most patients relapsed 12 months after discontinuation of EEN.[54]

Several studies suggest efficacy and safety of stem cell transplantation (SCT) in the treatment of CD.[56] In a retrospective review of 11 IBD patients (7 patients with CD, 4 patients with UC) who underwent allogeneic SCT for hematologic malignancies (age mean 41, range 27 to 55; median follow-up 34 months), 10 had relief of symptoms after transplantation.[57]

In another study, four of five patients with CD and leukemia who underwent allogeneic marrow transplantation remained free of CD after a follow-up of 4.5 to 15.3 years.[58] In an experiment observing the actions of hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) in colitis-induced rats, both HSCs and MSCs migrate to and repopulate damaged GI epithelium.[56] In a phase I clinical trial using autologous HSC transplantation in adult patients with CD, 11 of 12 subjects showed sustained remission after a median follow-up of 18.5 months.[59] Another phase I trial suggests that autologous MSCs harvested from adipose tissue can treat fistulizing CD.[60,61] More rigorous clinical trials, especially in the pediatric population, will need to be conducted before this form of therapy becomes mainstream.

## Surgical Therapy

Unlike UC, there is no surgical cure for CD. Operative interventions should be reserved for (1) failure of medical therapy, (2) complications of the disease, (3) severe dysphagia, (4) cancer, and (5) stagnated growth and development.[62] Medical failure can be secondary to noncompliance or long-term steroid dependency.[4,62] Many patients with CD will require surgery at some point in their therapy.[4,7]

Children often present with right lower quadrant pain and/or fullness, commonly associated with fever and vomiting. Imaging studies are indicated to look for a phlegmon, abscess, perforation, fistula, megacolon, or obstruction caused by strictures. Abscesses are best treated by image-guided drainage and a course of antibiotics, with a delayed resection if necessary. A few patients present with free perforation,[62] requiring an immediate operation. Fistulas entering the bladder, uterus, or other intestinal segments are treated with limited bowel resection and repair of the adjacent organ. Severe acute colitis and toxic megacolon affects about 5% of CD patients.[62] A trial of intravenous steroids may be cautiously initiated, but surgical resection is sometimes necessary.

Obstruction is the most common indication for surgery in children with CD, usually secondary to stricture formation. Many obstructions can be treated medically. Operative intervention is indicated when the risks of continued medical therapy outweigh its benefits. The type of operation depends on the length of the involved bowel and the number of strictures. The surgical goal is to alleviate the cause of the mechanical obstruction, while minimizing the loss of bowel length[7,63] to avoid the numerous complications of short-bowel syndrome.[64] Strictures up to 10 cm in length may be managed by resection or a Heineke-Mikulicz strictureplasty (Fig. 95-6) using a longitudinal incision through the stricture, with transverse closure of the defect. Longer strictures, up to 25 to 30 cm, may be treated by resection or a Finney strictureplasty (Fig. 95-7) using a

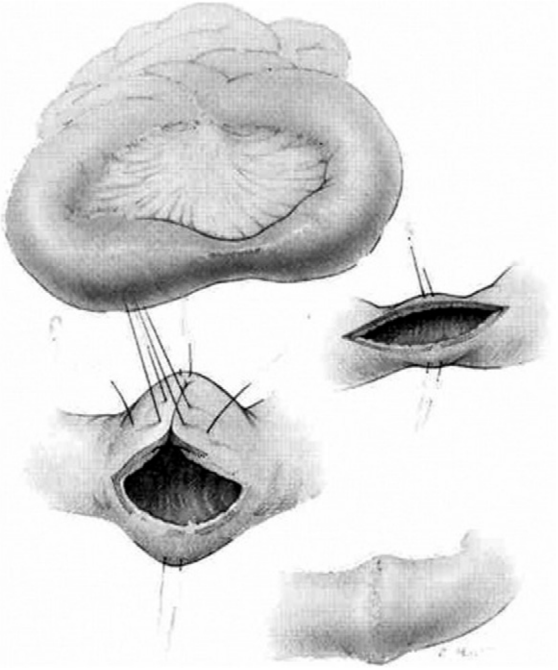

FIGURE 95-6 Heineke-Mikulicz strictureplasty. (From Cima RR, Pemberton JH: Strictureplasty in Crohn's disease. In Cameron JL [ed]: Current Surgical Therapy, 9th ed. Philadelphia, Mosby, 2008, p 129.)

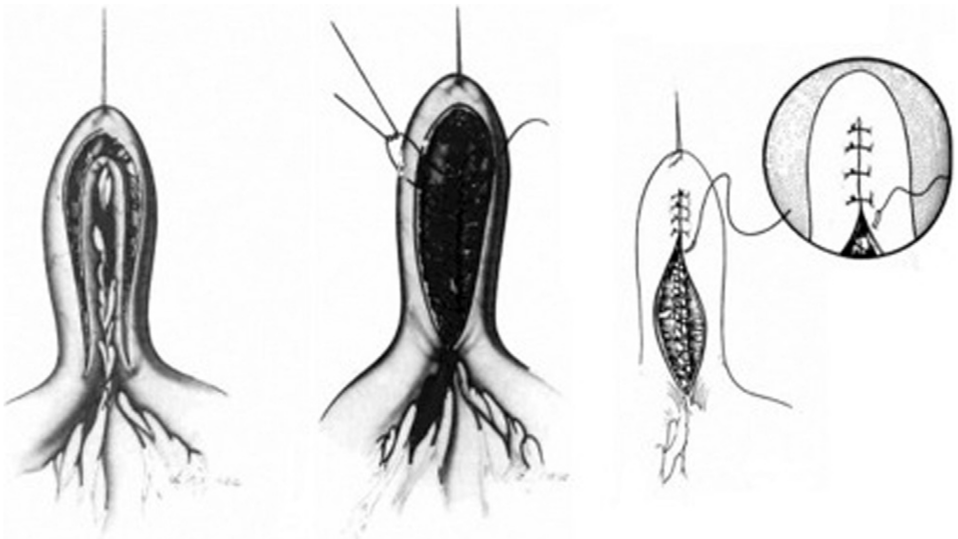

FIGURE 95-7 Finney strictureplasty. (From Cima RR, Pemberton JH: Strictureplasty in Crohn's disease. In Cameron JL [ed]: Current Surgical Therapy, 9th ed. Philadelphia, Mosby, 2008, p 130.)

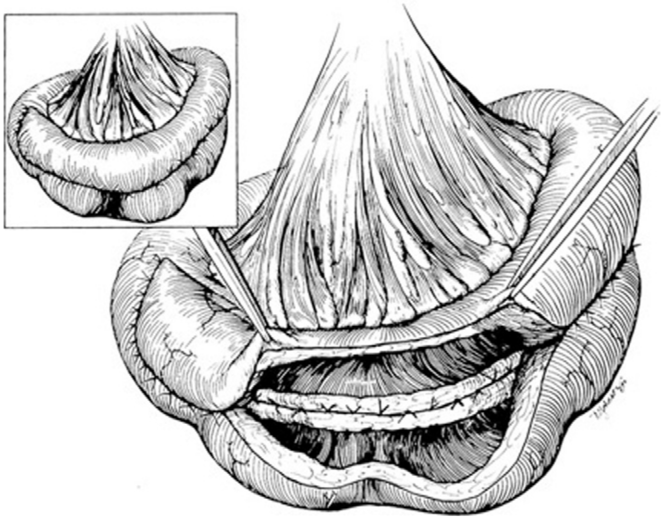

FIGURE 95-8 Side-to-side isoperistaltic strictureplasty. (From Michelassi F: Side-to-side isoperistaltic strictureplasty for multiple Crohn's strictures. Dis Colon Rec 1996;39:345-349.)

longitudinal incision through the strictured area, followed by a side-to-side anastomosis. Long segment bowel stenosis caused by CD may also be treated by the Michelassi technique, where the stenotic intestine is sectioned transversely at the midpoint of the stenosis, the mesentery is divided, a longitudinal incision is made on both loops, the proximal loop is advanced over the distal loop, and a side-to-side anastomosis is performed (Fig. 95-8).[65] Yamamoto and colleagues[66] performed a meta-analysis of studies on strictureplasty outcomes. They reported a 13% complication rate for patients who underwent jejunoileal strictureplasties. Complications included anastomotic leak, fistula, abscess, hemorrhage, wound infection, and bowel obstruction.[66] These complications are similar in type and incidence as seen after resection.[66] Risk factors for these complications included preoperative hypoalbuminemia, emergency operations, low hemoglobin level, and preoperative weight loss.[66] Steroid use was not a risk factor for complications.[66] There was no difference in recurrence rate after strictureplasty versus resection.[66] Resection is recommended for diseased bowel or multiple concurrent strictures greater than 30 cm.

Endoscopic balloon dilatation has been gaining popularity for treatment of ileal and colonic Crohn strictures. Dilations are carried out under fluoroscopic guidance using contrast-filled balloons. Intralesional injections of triamcinolone acetonide (Kenalog) have also been performed.[67] Tapering doses of prednisolone may be administered after dilatations.[68] After a mean follow-up of 81 months, Stienecker and colleagues reported a success rate of 80% and a perforation rate of 3% with balloon dilatation.[68] Others have reported similar results.[67]

Ileocecectomy is the treatment of choice for patients with isolated ileocecal disease. It often provides a disease-free interval of at least 2 to 3 years.[7] Traditionally, this operation has been undertaken via an open approach. However, laparoscopic resection has gained acceptance in the pediatric surgical arena. In a retrospective review comparing 12 laparoscopic and 16 open pediatric resections, the time to full feeds and hospital length of stay were shorter, while complication rates were similar.[69] In another study of 15 children and adolescents with ileocecal CD, the authors concluded that laparoscopic resection is safe and effective.[70] In an observational study from a prospectively collected database of 109 patients, Soop and colleagues[71] reported a complication rate of 11% after laparoscopic ileocecal resection. Prolonged ileus was the most common complication. No anastomotic leaks were reported, and the median hospital length of stay was 4 days.[71] Data collected from 2000-2004 via the Nationwide Inpatient Sample comparing laparoscopic and open ileocecal resections demonstrated an overall complication rate of 8% with the laparoscopic approach and 16% with the open approach.[72] Finally, a meta-analysis of 14 studies comparing laparoscopic and open ileocecal resection for CD demonstrated a shorter hospital length of stay, faster recovery of bowel function, and decreased morbidity with the laparoscopic approach.[73]

Resection is the definitive treatment for Crohn colitis refractory to medical therapy. Operative options depend on disease location; they include segmental resection, total abdominal colectomy with ileorectal anastomosis, and proctocolectomy with end ileostomy. In 2005 a prospective study involving 179 patients from the University of Chicago was reported comparing these three options; after 10 years, a segmental resection was associated with a 50% recurrence rate, while the recurrence rates for a total abdominal colectomy and total proctocolectomy were 30% and 20%, respectively.[74] Table 95-1 demonstrates the type of surgery, location of disease, and patients continuing medical therapy 1 year after their respective surgery.

Although we and others[74,75] do not recommend restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) in patients with CD, there is some evidence in favor for this option. In 2008 the Cleveland Clinic reported their long-term outcomes of 204 patients with CD who were offered a primary IPAA.[76] In their analysis of a prospectively maintained database, selected patients (highly motivated, preoperative diagnosis, isolated colon involvement, no ano-perineal fistulous disease) achieved an 85% pouch retention rate after a median follow-up of 7.4 years.

Perianal disease is seen in about one third of children with CD. It is more commonly associated with colonic CD than in patients with CD of the small bowel.[77] It may be the only presenting symptom in up to 5% of patients.[77] As

**TABLE 95-1**

**Type of Surgery in Relation to Extent of Disease, Location of Disease, and Long-term Medical Therapy After the First Year of Follow-up**

| *Procedure* | *>2 Segments* | *Distal Involvement* | *Taking Medication* |
|---|---|---|---|
| Segmental colectomy | 3/54 (5.6) | 29/54 (53.7) | 30/49 (61.2) |
| Total abdominal colectomy | 32/49 (65.3) | 43/49 (87.8) | 20/35 (57.1) |
| Total proctocolectomy | 47/76 (61.8) | 73/76 (96.1) | 9/43 (20.9) |
| *P* value | <0.0001 | <0.0001 | 0.0002 |

From Fichera A, McCormack R, Rubin MA, et al: Long-term outcome of surgically treated Crohn's colitis: A prospective study. Dis Colon Rectum 2005;48:963-969.

in intra-abdominal CD, perianal disease refractory to medical therapy requires operative intervention. Perianal CD usually presents as an abscess or a fistula. Superficial abscesses should be drained surgically. Simple incision and drainage with irrigation and debridement are recommended.[8] The cavity may be packed with gauze, which is then removed after 24 to 48 hours. Another option is to insert a small drain into the cavity, which is secured to the skin with a rapidly absorbing suture, allowing the drain to fall out with the passage of time. For deep abscesses, incision and drainage are also required, followed by insertion of a noncutting seton if a fistula is present or a self-retaining catheter if a fistula is not identified.[8] The catheter may stay in place for weeks. In most cases, incision and drainage should be attended by a course of antibiotic therapy.

Perianal fistulas may be classified as low/simple (superficial, low intersphincteric, low transsphincteric) or high/complex (high intersphincteric, high transsphincteric, suprasphincteric, extrasphincteric). The principles of fistula management are listed in Table 95-2. Evaluation of perianal fistulas in patients with CD requires an EUA to identify strictures, abscesses, and/or tracts.[63] The accuracy of EUA in detecting fistulas is about 90%, which can approach 100% with the use of an endoscopic ultrasound (EUS).[77,78] Sigmoidoscopy is also recommended to assess for any rectal disease. Low/simple fistulas are treated by fistulotomy,[8,63,77] with excellent healing rates but a recurrence rate of 20%.[8,77] For low/simple fistulas associated with rectosigmoid disease and for high/complex fistulas, placement of a noncutting seton is strongly recommended[8,62,63,77,79] because both fistulotomy and fistulectomy in these circumstances are associated with high rates of incontinence and nonhealing.[8,28] The seton can be left in place indefinitely. Better control of nonhealing high/complex perianal fistulas may be achieved via EUS-guided placement of the noncutting seton, in combination with an infliximab regimen.[28] Alternative treatments for high/complex fistulas include fibrin glue instillation,[80] fibrin glue with adipose-derived stem cell instillation,[81] and intralesional infliximab.[82] A diverting colostomy is recommended for patients who have failed medical management. An ostomy takedown may be considered after 1 year has elapsed with apparent healing of the fistula.

In a retrospective, multivariate analysis of 100 resective surgeries in 68 children with CD, there was a 17% symptomatic recurrence rate after 1 year, a 38% recurrence rate after 3 years, and 60% after 5 years.[83] Recurrence after partial colon resection was associated with a higher risk of recurrence than after an ileocecal resection (median, risk-free interval 1.16 years for colonic resection vs. 4.36 years for ileocecal resection).[83] After an ileal or ileocecal resection, second operations have been reported in 5% of patients after the first year, 11% to 32% of patients after 5 years, and 20% to 44% of patients after 10 years.[84,85] Strictureplasty has been shown to be both safe and effective in the treatment of CD, while reducing the risk of short-bowel syndrome. The complication rate and long-term recurrence rate after ileocecal strictureplasty are similar to the rates reported after resection.[63]

After a colectomy for CD, patients with an end ileostomy have lower recurrence rates than those with an ileorectal anastomosis.[85] Smoking in the postoperative period is a major risk factor for disease recurrence.[84,86] Genetic factors (NOD2/CARD15 carriers) may also increase the risk of recurrence.[84] Medications such as 6-MP, AZA, and metronidazole have been shown to decrease postoperative recurrence slightly.[84,85,87] Patients taking these medications before resection should continue them postoperatively.[83,84] Resection of diseased bowel often results in a rapid, postoperative increase in linear growth in children with CD.[7,29,83]

**TABLE 95-2**

**Principles of Fistula Management**

| |
|---|
| Define the anatomy of the fistula and, when indicated, assess the distribution and severity of disease |
| Drain any associated abscesses |
| Dilate associated strictures |
| Attempt to eradicate the fistula tract |
| Attempt to prevent recurrence |
| Preserve continence and sphincter integrity |

From Lichtenstein GR: Treatment of fistulizing Crohn's disease. Gastroenterology 2000;119:1132-1147.

## Cancer

The ongoing inflammatory process involved in CD predisposes patients to a relatively high risk of malignancy. A population-based study comparing IBD patients to a normal population showed an increased incidence rate (IR) of colon cancer (IR = 2.64, 95% confidence interval 1.61 to 4.12) and small bowel cancer (IR 17.4, 95% confidence interval 4.16 to 72.9) in patients with CD.[88] The risk of future colorectal and small bowel cancers may increase when IBD presents in the pediatric years.[89] One study demonstrates a 22-fold, lifelong increase in the incidence of colorectal cancer among men younger than age 32 at the time of diagnosis.[90] Screening guidelines for colorectal cancer in IBD include (1) a screening colonoscopy 10 years after onset of symptoms; (2) continued surveillance every 3 years in the second decade, then every 2 years in the third decade, then every year; and (3) patients with an IPAA should undergo yearly endoscopic surveillance of the pouch with biopsies.[89]

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 96

# Ulcerative Colitis

Jeremy Adler, Arnold G. Coran, and Daniel H. Teitelbaum

Early descriptions of ulcerative colitis (UC)-like illnesses date back to the late eighteenth century.[1] However, the first clear description of UC is believed to have been made by Wilkis and Moxon in 1859.[2]

By the end of the nineteenth century, fecal diversion became standard practice for severe cases, although improvement was rarely more than transient. In the early twentieth century, tube appendicostomy and frequent colonic lavage with bicarbonate solution was recommended.[3] Total fecal diversion by ileostomy, as advocated by Browne in 1913,[4] became widely practiced despite significant morbidity and mortality. Until the mid-1940s, ileostomy appliances were primitive and routinely associated with soiling and skin irritation. Surgery was usually delayed until the patients were critically ill; subsequent closure of the ileostomy commonly resulted in reactivation of disease.

It was not until 1944 that Strauss and Strauss introduced proctocolectomy with ileostomy for treatment of severe UC.[5] A three-stage operation with ileostomy followed by subtotal colectomy and sigmoid colostomy and then abdominoperineal rectal resection was recommended by Cattell in 1948.[6] Shortly thereafter, a two-stage operation evolved with initial ileostomy and simultaneous subtotal colectomy that, by 1951, was associated with a mortality of only 4.4%.[7] Ripstein in 1952[8] followed by Goligher in 1954[9] recommended ileostomy with one-stage proctocolectomy, which is now considered the standard elective operation for patients with UC.

Although total proctocolectomy with ileostomy provided a permanent cure for UC, delay in patient acceptance of a permanent ileostomy resulted in delaying surgery until most patients had advanced disease, were malnourished, and had complications from the extended medical therapy. Factors instrumental in improving the quality of life with an ileostomy include the eversion technique of ileostomy construction recommended by Brooke in 1952[10] and the development of successful adhesive ileostomy appliances. Subsequent improvements in peristomal skin care by Turnbull[11] and others, together with the development of nurses with special expertise in stomal care, has made it possible for most patients to leave the appliance attached to the skin for 4 to 6 days. For the goal of developing a continent ileostomy that required no stoma appliance and could be irrigated at a convenient place and time, Kock[12] developed the intra-abdominal reservoir with a nipple valve in the ileostomy stoma in 1969.

The search for a sphincter-saving operation for patients with UC began more than 50 years ago when Devine of Melbourne[13] recommended a staged ileosigmoidostomy. Aylett of London[14] became the leading proponent of colectomy with ileoproctostomy, and in 1966 he reported excellent results with 300 patients and a mortality rate of only 5.7%. Parc and colleagues[15] reviewed 17 studies comprising 1206 patients with colectomy and ileorectal anastomosis for UC and found that patients averaged 4.5 bowel movements per day and that 99% were continent. Proctectomy was eventually required in 15%. The risk for subsequent development of cancer in the retained rectum ranged from 2% to 20%. Ileoproctostomy is now used only in patients with minimal rectal disease.

In 1947 Ravitch and Sabiston[16] modified the previously unsuccessful procedure of ileoanal anastomosis and added the technique of rectal mucosectomy. Most patients who had this procedure had defecation frequency and urgency of unacceptable degree such that the operation was rarely used during the ensuing 3 decades.[17] In 1964 Soave[18] described a colonic pull-through procedure after distal rectal mucosectomy for Hirschsprung disease and reported good clinical results. Application of distal rectal mucosal stripping was combined with a total colectomy and a straight endorectal ileoanal anastomosis by Safaie-Shirafi and Soper[19] in 1973 in four young patients with familial polyposis coli. In 1977 Martin, Le Coultre, and Schubert[20] reported satisfactory results in young patients with UC.

The ileoanal pull-through procedure has undergone many modifications during subsequent years, the most important of which was the use of a pouch constructed from the distal ileum and placed immediately proximal to the anastomosis to reduce stool frequency and urgency. The development of the ileal reservoir was based on canine studies by Valente and Bacon in 1955[21] with a triple-limb ileal pouch, by Karlan, McPherson, and Watman[22] with a double-barrel isoperistaltic pouch, and by Ferrari and Fonkalsrud[23] with an S-shaped pouch and an ileoanal anastomosis. In 1978 Parks and Nicholls[24] combined an S-shaped ileal reservoir with rectal mucosectomy and a pouch-anal anastomosis and reported acceptable results in adult patients. Total colectomy with the ileoanal pouch procedure (restorative proctocolectomy) is now widely accepted as the most favorable option for the surgical treatment of UC in patients of all ages.[25–27]

# Etiology

UC is a chronic immune-mediated inflammatory condition of the colon. The precise etiology of UC remains elusive. Historically, theories of etiopathogenesis involved implicating specific pathogenic organisms as causative agents. Early theories of infectious etiologies were encouraged by the observation of the response of UC to sulfonamides and antibiotics.[28] No organism is consistently found in individuals with UC. And epidemiologic studies do not support an infectious etiology. After the discovery of UC's responsiveness to adrenocorticotropic hormone (ACTH), and later to glucocorticoid steroids, research focused on an immunologic etiology of UC.[28] The current understanding of pathogenesis involves an exaggerated immune response to commensal luminal flora.[29]

Early observations of familial patterns of disease have supported the expectation that there is a genetic basis for increased susceptibility to UC. Among individuals with UC, 13.8% have a first-degree relative with inflammatory bowel disease (IBD), predominantly UC.[1] In twin studies, the rate of UC in a twin sibling is 14% to 19% when one sibling is affected. The rate is decreased to 0% to 7% when nonidentical twins are considered (either dizygotic twins or nontwin siblings).[30]

Recent advances in genetic research have identified numerous genetic mutations that are associated with IBD. Early studies identified an increased risk associated with the presence of HLA-B27. More recently, genome-wide association studies have identified mutations in the nucleotide-binding oligomerization domain containing 2 (NOD2) and interleukin-23 receptor (IL23R) genes, which appear to be associated with an increased risk of developing UC, though the association is not strong.[31–33]

# Epidemiology

The incidence of UC in pediatric populations varies across the globe. Rates in industrialized countries are seen in the range of 2.2 to 4.5 per 100,000.[34,35] Though there is a clear increasing trend in the incidence of Crohn disease over time, the change in incidence of pediatric UC is less clear.[36,37] Males and females have an equal incidence of UC. Children are more likely to present with involvement of the entire colon (pancolitis) then their adult counterparts.[38] This is especially true in the youngest cohorts of patients.[39,40]

Environmental factors that modify the risk of UC include tobacco smoke and appendicitis. Tobacco exposure is associated with a lower incidence of UC in adults, and there is a higher rate of developing UC in former smokers.[41] The same protective association has been observed of secondhand smoke in children.[42] This is opposite the observed association of smoking and increased risk in Crohn disease.[41] Prior studies suggested a protective effect of appendectomy on the development of UC.[43] It appears, however, that it may be appendicitis itself, and not appendectomy, that is associated with a decreased incidence of the development of UC.[44]

# Pathology

UC is a chronic inflammatory disease of the rectal and colonic mucosa. The inflammation is limited to the superficial tissue layers including the epithelium and lamina propria. The muscularis mucosa may be involved, but the inflammation does not extend to the muscularis propria. The rectum is involved in more than 95% of cases, and the inflammation extends proximally in a contiguous manner without skipping regions.[45,46]

When the entire colon is present (pancolitis), the most severe changes usually occur in the rectum and sigmoid colon. However, cases of more severe involvement of the proximal colonic segments have been described and may be consistent with UC.[46,47] Children are more likely to present with pancolitis at diagnosis than are adults, who are more likely to present with more limited left-sided colitis or proctosigmoiditis.[38]

Limited inflammation of the ileum can be seen with UC. The ileal inflammation of UC is generally limited to the distal 10 cm of ileum and consists of villous atrophy and superficial inflammation with crypt abscesses and without granulomas.[47] Ileal inflammation with UC is present only in pancolitis and is not present in limited left-sided colitis.[48] More extensive ileal inflammation, or ileal involvement without pancolitis or ileal stenosis or the presence of granulomas, should raise the suspicion of Crohn disease.[48]

The characteristic microscopic appearance of UC consists of crypt architectural distortion with crypt abscesses that lead to mucosal ulceration with undermining of adjacent mucosa. Mucosal bridging with pseudopolyp formation often develops in a circumferential pattern, in contrast to granulomatous colitis in which ulceration is usually more linear and located on the mesenteric side of the colonic lumen (Fig. 96-1).

As the disease progresses in the acute phase, the colon distends, peristalsis decreases, and the muscularis becomes thin and diffusely hemorrhagic; severe disease may progress to acute dilatation, bacteremia, peritonitis, and rarely perforation (toxic megacolon). The incidence of toxic megacolon is increased with severe UC. The use of systemic corticosteroids and antimotility agents (including narcotics) increase the probability of developing toxic megacolon.[49]

With chronic UC, however, the muscularis becomes thickened with flattening of haustral folds and reduction of meaningful peristaltic contractions.[50–52] The mucosa becomes atrophic and may become dysplastic in long-standing disease. The colonic mesentery becomes shortened, and the

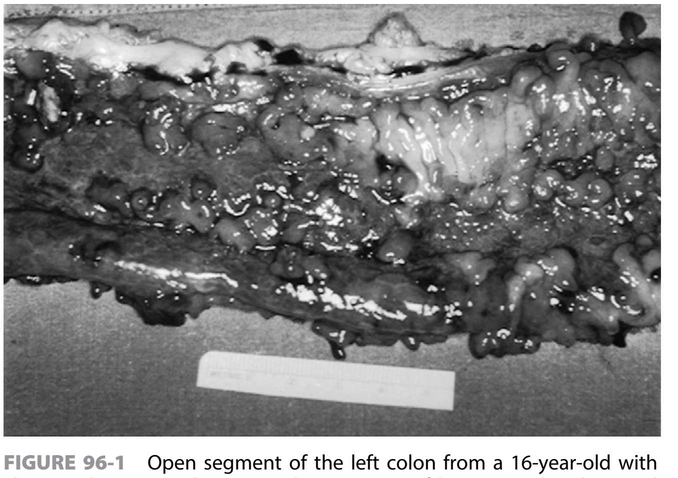

**FIGURE 96-1** Open segment of the left colon from a 16-year-old with chronic ulcerative colitis. Note the presence of large pseudopolyps and the absence of normal mucosal folds.

serosal surface often develops increased superficial vascularity and an overabundance of adipose tissue. In remission, the mucosa may return to a nearly normal appearance on microscopic examination. Mucosal biopsy is helpful in confirming the diagnosis of UC and in assessing disease activity.

## Clinical Manifestations

Approximately 25% of patients diagnosed with UC had the initial presentation of their disease during childhood. Of pediatric patients diagnosed with UC, by one retrospective estimate 38% were diagnosed before the age of 10 years.[38] In a later prospective multicenter study, of patients with childhood onset, 21.6% have onset before 6 years of age.[40] An additional 46.1% have the onset of disease between 6 and 12 years of age, and 32.3% have onset between 13 and 18 years of age.[40]

Symptoms typically present insidiously with persistent diarrhea followed by the appearance of blood, mucus, and pus in the stools. An intermittent, cramping lower abdominal pain, tenesmus, and anemia are common. Anorexia, weight loss, and growth retardation can occur in up to 38% of children with UC.[34] The etiology of anorexia is multifactorial and may be due to increased circulating cytokines or may be due to pain associated with peristalsis or tenesmus. Growth failure can also be associated with prolonged use of systemic corticosteroids.[53]

Children often feel tired as a result of anorexia and/or anemia. Additionally, there is evidence of disturbed sleep patterns in children with UC due to nighttime bowel movements and other factors such as an increased incidence of restless leg syndrome.[54] Children with UC may also limit their social interactions due to fecal urgency and fears of fecal incontinence.[55–58]

Without treatment, most children develop remitting colitis with periodic relapses.[59,60] Over time, many progress to chronic colitis with shorter and less frequent remissions. Approximately 10% of patients develop chronic symptomatic colitis.[38] Rarely, patients may experience a single attack of colitis with subsequent complete remission (11% to 16% in historical literature).[59,60] Relapses may be precipitated by intercurrent infections. Emotional stress does not trigger exacerbations of disease, though stress may worsen perceived symptoms.[61]

Approximately 10% to 15% of children with UC initially present as fulminating disease with profuse bloody diarrhea, severe abdominal cramps, fever, and occasionally sepsis, necessitating prompt treatment.[25] Most of these patients improve with medical therapy, although patients occasionally (5%) develop toxic megacolon that requires emergency surgery. Historically, the colectomy rates for pediatric UC were approximately 50% by 5 years after diagnosis.[60] More recent estimates of colectomy rates are around 25% after 5 years.[38] These rates do not take into account any potential change in colectomy rate since the advent of tumor necrosis factor (TNF)-α antagonist therapy. An accurate estimate of rates of colectomy after therapy with infliximab remains to be determined.

Carcinoma of the colon or rectum has been reported in 3% of patients during the first 10 years of disease and increases by approximately 10% to 15% in each subsequent decade.[62] Malignant conditions may develop even in patients with apparent remission of colitis. Cancer is more common in patients who have pancolitis, those whose symptoms began in childhood, and those who have frequent exacerbations of disease.[63,64] Evidence of dysplasia of the colonic mucosa on biopsy indicates a high risk for subsequent carcinoma.[65,66]

Extracolonic manifestations of UC include growth retardation, arthralgias, delay of sexual maturation, skin lesions, anemia, osteoporosis, primary sclerosing cholangitis, nephrolithiasis, uveitis, and stomatitis (Fig. 96-2). Growth retardation with delay in bone development frequently accompanies chronic UC in adolescence.[34] Delayed sexual maturation may be caused in part by abnormally low levels of urinary gonadotropins.[67,68] Growth hormone levels are usually in the normal range for the patient's age.

Arthralgias occur in approximately 15% of children with UC and commonly involve the knees, ankles, wrists, fingers, and hips.[69,70] Joint symptoms, which occasionally precede the onset of intestinal symptoms, may be confused with juvenile idiopathic arthritis.[71] Symptoms are more common with active UC. But patients may have symptomatic arthralgias or arthritis with quiescent colitis as well.[69]

The most common skin lesions are erythema nodosum of the lower extremities and occasionally the trunk. Pyoderma gangrenosum (i.e., chronic ulceration of the skin) most often occurs on the lower limbs and occurs in less than 5% of children with UC.[72] These lesions are often resistant to local or systemic therapy and frequently do not heal until the patient goes into remission or the disease is surgically corrected. Pyoderma gangrenosum may persist after remission of colitis. Pyoderma may be successfully treated with infliximab.[73] Primary sclerosing cholangitis (PSC) is uncommon in children, although it may occur in up to 15% of adult patients with chronic UC.[74] Approximately 50% to 80% of children with PSC will develop UC.[75,76] Development of PSC may precede the develop of colitic symptoms. PSC may also develop simultaneously with UC or may develop after colectomy. Anemia is common and usually results from overt or occult blood loss in the stools. Patients may also develop anemia of chronic disease as well.

Osteopenia may occur from decreased calcium absorption associated with diminished uptake of fat-soluble vitamins and by increased urinary losses of calcium resulting from steroid therapy.[77] However, the exact risk of fracture is difficult to estimate in childhood where fractures are not uncommon in active healthy children. It is unclear whether the risk of fracture is increased in association with UC.[78,79] Nephrolithiasis occurs in approximately 8% of patients with UC, largely because of inadequate fluid intake to compensate for fluid loss through diarrhea.[80] Uveitis (i.e., inflammation of the iris) occurs in less than 2% of patients but may be severe and can permanently compromise vision.[81,82] Uveitis may present with painless red eyes or may cause photophobia with pain. Aphthous stomatitis is common in patients with UC, particularly during disease exacerbations.

## Clinical Examination

Children with active UC may present with a range of complaints. In mild colitis, patients may present with diarrhea with small amounts of blood. Tenesmus may be present and occasionally may be the primary complaint. With more severe presentations, patients may have grossly bloody diarrhea.

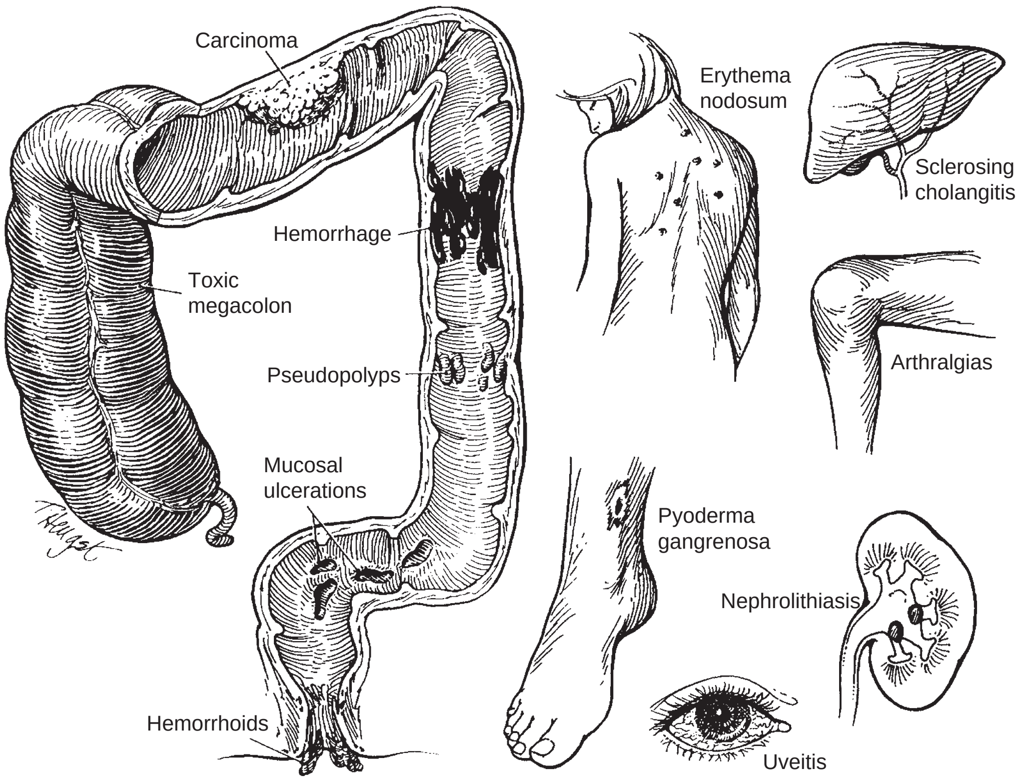


**FIGURE 96-2** Manifestations of ulcerative colitis in the colon and rectum. Extracolonic disorders occur in more than 60% of children with ulcerative colitis.

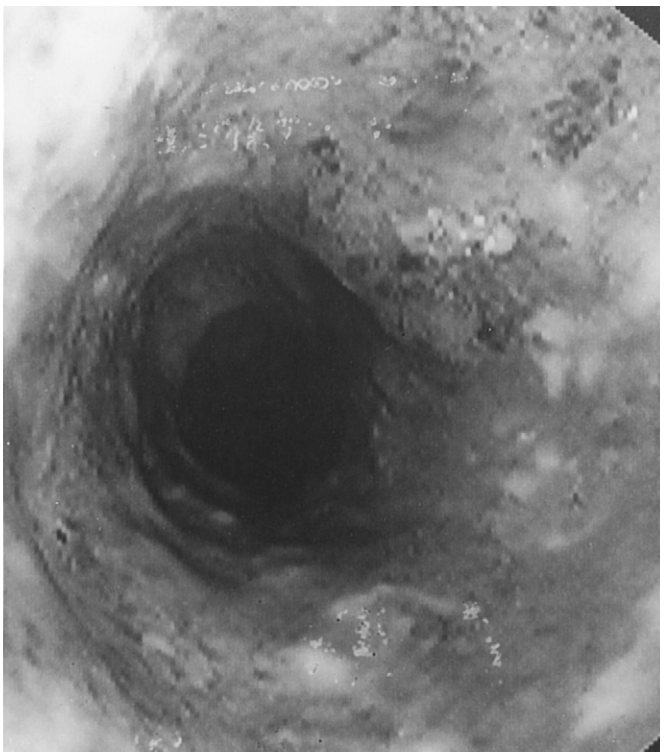

**FIGURE 96-3** Appearance of the transverse colon from an 18-year-old boy with severe ulcerative colitis as viewed through a colonoscope. Note the mucosal ulceration and loss of mucosal folds.

With severe or fulminant colitis, children may become profoundly anemic and may present with pallor, weakness, and weight loss. Constitutional symptoms such as fever, weakness, and listlessness may be present. Stools may vary from watery with scant blood in mild colitis to grossly bloody, liquid stools with mucus and little solid content.

Children with mild UC or who are in remission may manifest few positive findings for disease on physical examination, although endoscopy may demonstrate friable and edematous colonic mucosa with a thin, purulent exudate. Children with chronic UC often show delayed growth in height, delayed sexual maturation, anemia, and pallor. With long-term corticosteroid therapy, children may develop Cushingoid features. With acute disease, fever, dehydration, and systemic toxicity are common. Pain is often elicited by palpation over the sigmoid colon. External hemorrhoids frequently develop from frequency of defecation; however, anal fistulas, fissures, and abscesses are rare and, if present, suggest Crohn disease. Sigmoidoscopy or colonoscopy often shows an edematous and hemorrhagic mucosa that contains superficial ulcers and is covered with a purulent, bloody exudate (Fig. 96-3).

Anemia from blood loss occurs in approximately two thirds of patients. The erythrocyte sedimentation rate is typically elevated as is the C-reactive protein. Hypoalbuminemia frequently develops secondary to protein loss from weeping colonic mucosa. Hyponatremia and hypokalemia often occur with protracted diarrhea. Stool cultures are consistently negative for pathogenic bacteria and parasites. However *Clostridium difficile* infection may coincide with the onset of colitis, may complicate the clinical picture, and may delay diagnosis of UC.

Barium enema radiographs in a patient with chronic UC may show a shortened, narrow, and rigid colon with loss of haustral folds and extensive formation of pseudopolyps (Fig. 96-4). In acute colitis, the intestinal contour may have an irregular serrated border from mucosal ulcerations. The edematous mucosa between areas of ulceration appear as pseudopolyps. Because a contrast enema can stimulate acute manifestations of colitis and because more meaningful information can be obtained from colonoscopy, contrast enemas are now used much less frequently. Upper gastrointestinal barium contrast study with small bowel follow-through is more commonly used to image the small bowel. This is frequently performed to assess the small bowel to rule out small bowel involvement of Crohn disease and in support of the diagnosis of UC. CT enterography (CTE) can provide more detailed assessment of the small bowel; however, CTE typically exposes patients to larger doses of ionizing radiation than a small bowel follow-through (Table 96-1).[83]

The Pediatric Ulcerative Colitis Activity Index (PUCAI) was recently developed for assessing pediatric UC disease activity (see Table 96-1). This scoring method was prospectively validated and is useful both as a research tool, as well as a clinically useful means of assessing patients.[84,85] The total score ranges from 0 to 85. A score of less than 10 is consistent with remission of disease, 10 to 34 indicates mild disease, 35 to 64 moderate disease, and 65 to 85 severe disease. A clinically significant response is defined as a PUCAI decrease of greater than or equal to 20.[86] A PUCAI score of greater than 45 on the third day of illness is predictive of a high likelihood of failure of systemic corticosteroid therapy. And by day 5 of illness, a PUCAI score greater than 65 to 70 suggests the need to escalate medical therapy.[87]

**TABLE 96-1**
**Pediatric Ulcerative Colitis Activity Index (PUCAI) from the Hospital for Sick Children, Toronto**

| *Item* | *Points* |
|---|---|
| **Abdominal Pain** | |
| No pain | 0 |
| Pain can be ignored | 5 |
| Pain cannot be ignored | 10 |
| **Rectal Bleeding** | |
| None | 0 |
| Small amount only (<50% of stools) | 10 |
| Small amount with most stools | 20 |
| Large amount (>50% of the stool content) | 30 |
| **Stool Consistency of Most Stools** | |
| Formed | 0 |
| Partially formed | 5 |
| Completely unformed | 10 |
| **Number of Stools per 24 Hours** | |
| 0-2 | 0 |
| 3-5 | 5 |
| 6-8 | 10 |
| >8 | 15 |
| **Nocturnal Stools (Any Episode Causing Wakening)** | |
| No | 0 |
| Yes | 10 |
| **Activity Level** | |
| No limitation of activity | 0 |
| Occasional limitation of activity | 5 |
| Severe restricted activity | 10 |
| Sum of PUCAI (0-85) | |

**FIGURE 96-4** Barium enema radiograph from a 17-year-old girl with chronic ulcerative colitis. Note the shortening of the colon and loss of haustral markings, which give the colon a characteristic "lead-pipe" appearance.

## Medical Management

Therapy for UC is aimed at symptom relief and prevention of exacerbations of disease. Historically, medical treatment options were limited to sulfasalazine and corticosteroids. Systemic corticosteroids are effective at inducing remission in approximately 54% to 77% of patients.[88] However, toxicities prevent steroids from being useful for long-term management. 5-Aminosalicilates (5-ASAs) are as effective as sulfasalazine for UC.[89] 5-ASAs are generally effective for induction of remission in mild UC.[90] And 5-ASAs are better than placebo at maintaining remission for patients with mild to moderate disease.[49] In cases of limited rectosigmoid disease, rectal preparations of mesalamine may be effective, whereas the combination of oral and rectal preparations is often superior to either one alone.[91,92]

Azathioprine is not effective for use in acute disease. However, for patients with steroid dependent UC, azathioprine is more effective than mesalamine at inducing remission and allowing patients to maintain remission without systemic corticosteroids.[93]

Infliximab has been demonstrated to be effective at inducing remission in 27% to 39% of adults with moderate to severe UC. In the same study by Rutgeerts and colleagues,[94] 26% to 37% of adult patients with moderate to severe UC maintained remission for up to 30 weeks. In pediatric studies, infliximab has been demonstrated to spare corticosteroid use.[53] And

infliximab induces both short-term remission in 82% of patients and long-term remission in up to 67% of pediatric patients after 9 months of therapy.[95] A recent study by Hyams and colleagues[96] demonstrated maintenance of steroid-free remission in 21% of pediatric patients with UC at 2 years.

In the case of fulminant colitis, Järnerot and colleagues[97] demonstrated 17 of 24 (71%) remained in remission after 90 days of infliximab therapy compared with 7 of 21 (33%) in the placebo control group.

Adherence to medical therapy is critically important to maintaining long-term remission. Adherence to therapy in patients with UC who were in remission on mesalamine monotherapy has been extensively reviewed. Over 24 months, 89% of patients who took 80% of their medication remained in remission, although only 39% of those patients who took less than 80% of their medication remained in remission after 24 months.[98]

For patients who develop acute exacerbations of disease, a course of corticosteroids (prednisone) for 2 to 3 months may induce remission.[99] Steroid doses are typically tapered, and alternate-day therapy is initiated as soon as possible. Prolonged use of steroids in young patients is often associated with side effects including growth failure, osteopenia, and Cushingoid features. Rectal steroids (hydrocortisone) or mesalamine enemas may be helpful in treating colitis confined to the rectum and lower left colon with lower systemic absorption than systemic steroids. Steroids should be accompanied by gastric acid suppression with H2-blocking drugs (cimetidine, ranitidine) or proton pump inhibitors (lansoprazole, pantoprazole, omeprazole) to reduce the incidence of peptic ulcer or gastritis.

Antidiarrheal medications such as diphenoxylate hydrochloride with atropine sulfate (Lomotil) or loperamide hydrochloride (Imodium) may reduce the number of bowel movements and decrease rectal spasm but should be used cautiously because the drugs, as well as opiates, may occasionally induce toxic megacolon.[100] Antibiotics are occasionally used for treatment of mild symptoms, though there is little evidence for their efficacy.[101,102]

Though patients frequently identify dietary factors that they feel influence their disease activity, there is little evidence that diet affects the course of UC.[103,104] However, at least one study suggests an association between red meat consumption and exacerbations of UC.[105]

Psychotherapy may help patients with chronic UC adjust to the disease, its complications, and its side effects. Even more important is the ready availability of a sympathetic and interested physician and an understanding family on whom the patient can rely.

During acute exacerbations of UC, most patients require hospitalization with intravenous fluids and increased doses of steroids. These measures commonly correct metabolic deficits and reduce clinical symptoms but often do not alter the course of the colitis. Progression of the colitis or failure to respond to therapy is an indication for emergency surgery. If patients do not tolerate enteral nutrition or if malnutrition is present, parenteral nutrition may be beneficial. However, there is little evidence to support the routine recommendation of bowel rest or hyperalimentation for treatment of UC or for anticipation of surgery.[106–108]

Complications following surgical management of UC in children increase with the duration of the disease and the length and dosage of immune-suppressing medications.[26,109] Surgical treatment in children receiving high doses of corticosteroids and immunosuppressive drugs is associated with a relatively high complication rate that is further increased in children who have received longer courses of therapy.[25]

Although intravenous cyclosporine therapy may be rapidly effective for patients with severe corticosteroid-resistant UC, the need for colectomy in more than 60% of patients within 6 months after discontinuation of cyclosporine therapy suggests that the drug merely delays colectomy.[110] Furthermore, cyclosporine is associated with a high rate of nephrotoxicity and other systemic toxicities.

Steroids have been demonstrated to have an adverse effect on healing of colonic anastomosis.[111] Furthermore, aggressive medical therapy for UC has increased the incidence of emergency-staged colectomy with a resulting increase in morbidity, hospital stay, and cost and a less optimal functional result.[109] Restorative proctocolectomy, however, may be safely carried out in selected patients requiring emergency surgery for severe acute UC. In many cases, medical management should be abbreviated if prompt control of colitis cannot be achieved.[112]

## Surgical Management

Although medical therapy often induces remission for varying periods, UC can be cured by removing the diseased colon and rectum; up to 40% of patients will require surgical intervention. Because the operative resection has provided excellent long-term results, colectomy should be seriously considered for any patient with UC before severe disability and major complications develop. Elective resection is done for patients with persistent symptoms of UC despite medical therapy, growth retardation, severe limitation of activities, and an unacceptable quality of life. It is often distressing for both the patient and family when the child misses many days of school and must limit participation in physical and social activities because of severe symptoms. Emergency operation is indicated for patients (approximately 20%) with fulminant disease that is refractory to medical therapy, extensive rectal bleeding, or toxic megacolon. Children with UC are more likely to have an acute onset and more severe symptoms from UC than adults. Growth potential is the main differentiating consideration in adolescents compared with adults. Thus for children, consideration should be given for colectomy while the epiphyses are still open to allow for optimal growth and development. A recent study showed that the cumulative rates of colectomy were 8% at 1 year, 15% at 3 years, and 20% at 5 years. Predictors of increasing the risk of colectomy were the presence of extraintestinal manifestations (EIMS) at diagnosis and in the first 5 years after diagnosis of UC, resulting in 20% of these children undergoing a colectomy.[132]

Surgical options should be discussed in detail with the patient and parents. It may be helpful for the patient to speak to another child who has been operated on, in order to alleviate fears and concerns about an ileostomy and to support the decision. A preoperative discussion with an enterostomal therapist will help prepare the child and parents for an ileostomy. Although care of an ileostomy is usually easily mastered by a child, the presence of a stoma appliance often creates embarrassment during physical and social activities. Impotence and bladder dysfunction after proctocolectomy in

children are uncommon; however, these major concerns have caused many children, parents, and physicians to delay surgical resection until the colitis becomes debilitating or medical therapy results in systemic complications. Another important issue to discuss with families is what the immediate and long-term stooling frequency and patterns are postoperatively (see later).

Anemia, hypoalbuminemia, and electrolyte abnormalities should be corrected preoperatively. Corticosteroid therapy is maintained to avoid an acute flare-up; however, should the amount of steroids remain high, it may influence the surgical approach. Oral intake is restricted to clear liquids for 48 hours preoperatively. Cathartics should be avoided. However, a gentle administration of hyperosmolar polyethylene glycol solutions such as Golytely may be used. Cleansing enemas are avoided because they may stimulate an acute flare-up of colitis. Oral antibiotics (erythromycin and neomycin) are given the day before, and intravenous broad-spectrum, second-generation cephalosporin antibiotics should be given within 1 hour of skin incision.

Historically, total proctectomy with permanent ileostomy has been the standard surgical treatment of UC that is refractory to medical therapy for more than 50 years. This procedure cures the disease, is associated with a relatively low rate of complications, and has good long-term results. Nevertheless, patients of all ages often find the need to wear an ileostomy appliance for life disturbing, and this is particularly troublesome for pediatric patients. Furthermore, approximately 30% of patients with ileostomies experience appliance-related problems including skin discomfort, skin irritation, leakage, and odor. In the United States, it is estimated that ileostomy maintenance costs at least $1000 per year. Currently, few patients select proctocolectomy with permanent ileostomy when given a choice of available surgical alternatives. The Kock continent ileal reservoir with a nipple valve obviates the need for wearing an ileostomy drainage bag and has been reported to provide a good alternative to permanent ileostomy for several years.[113] Because of the need for multiple drainages each day, need for frequent reoperation, and pouch complications related to the nipple valve and stagnant loop syndrome,[114] unless an ileo-anal pull-through is contraindicated, a Kock pouch is generally now avoided. Subtotal colectomy with ileorectal anastomosis should not be considered because active colitis will typically persist in the rectum of most of these patients and often eventually requires total surgical removal. The remainder of this section concentrates on the ileo-anal pull-through—the standard approach for children and adults today.

## APPROACHES TO THE ILEO-ANAL PULL-THROUGH

The key principle for this procedure is the removal of the entire colon. To avoid an extensive dissection in the deep pelvis, with potential injury to the nervi erigentes, a mucosectomy is then carried down through the distal rectum to within a centimeter above the dentate line. Dissection in this fashion allows for avoidance of injury to the internal anal sphincter and preserves continence. Additionally, this approach leaves the patient the ability to discriminate between gaseous, liquid, and solid contents.[115] Two general approaches may be taken: a straight pull-through of the ileum or creation of an ileal pouch with anal anastomosis. Both are described later, along with their overall long-term results.

## STRAIGHT PULL-THROUGH

One of the initial operative approaches was the straight endorectal ileal pull-through technique. Although the initial passage of stool on closure of an ileostomy will be fairly high and associated with moderate degrees of urgency, patients' symptoms improve over the first 2 years after pull-through. Reported experience with the straight endorectal pull-through technique has produced results roughly similar to those seen with the various pouch procedures.[117,118] The straight endorectal ileal pull-through technique retains peristaltic contractions and generates spike waves down to the anal anastomosis. From a technical standpoint, the procedure is easier than the creation of a pouch as well. One particular advantage of a straight pull-through is that if a child has a foreshortened ileal mesentery, the surgeon may well be faced with a situation where a J pouch (which after folding the bowel back on itself becomes inherently shorter) will not afford an adequate length to bring the ileum down to the anus. In this case a straight pull-through may be an ideal option and should be considered. Another advantage of a straight pull-through is the markedly reduced incidence of pouchitis (see later).

## ILEOANAL POUCH PROCEDURE

The ileoanal pouch was developed to create a reservoir just above the anus. This reservoir allows for the retention of stool and fewer number of bowel movements per day compared with the straight pull-through.[27] Regardless of the type of reservoir used, as long as the lower 4 cm of the rectal muscle is not damaged and the internal anal sphincter is not excessively stretched, the resting and squeezing pressure of the anal sphincter will approach normal values within 3 months.[120] The number of bowel movements, however, will remain much higher than normal values (see Outcomes later).

Four pouch configurations have been used clinically: the lateral and S-, J-, and W-shaped pouches (Fig. 96-5). Both the S- and W-shaped pouches are hand sutured and require a longer operating time than the J-shaped and lateral pouches, which are usually constructed with a stapling instrument. Stasis is more common in these large pouches, and an irrigating

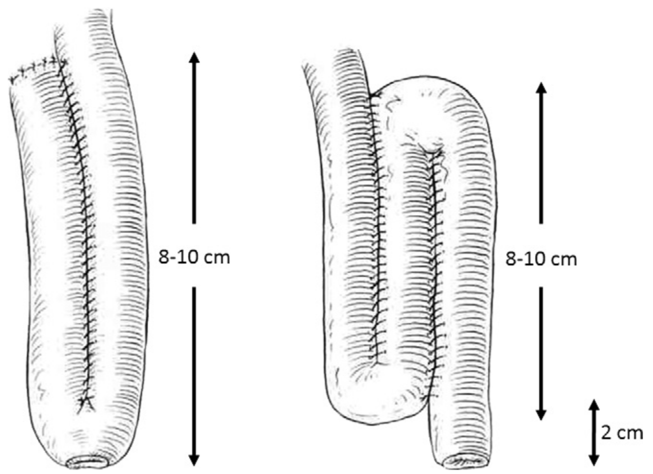


**FIGURE 96-5** Configuration of the two most common pouch procedures—J *(left)* and S *(right)*. Note the limitations on length, as well as a short spout at the base of the S pouch.

catheter is occasionally required for adequate emptying. After several months, all pouches commonly enlarge; however, if the ileal spout of the S-shaped or lateral pouches is created too long (>2 cm) or if it elongates, pouch enlargement and stasis may be pronounced.

The J-shaped pouch configuration, which was first described by Utsunomiya and colleagues,[123] has been used most widely, is the simplest to construct, and produces the fewest long-term complications in children and adults. The lateral ileal reservoir has been used extensively in the past for children and achieves good long-term results, provided that the ileal spout between the lower end of the pouch and the anus is short.[25] The lateral pouch has been used infrequently in recent years, but this approach, like the straight pull-through, may be used for patients with a short ileal mesentery in whom it is difficult to obtain sufficient length for a J-shaped pouch (i.e., it cannot reach the anus without tension). One key consideration of pouch configuration is to keep the total length of the pouch short, usually around 8 cm. This allows for efficient evacuation of stool and a presumably lower incidence of pouchitis.

# Ileoanal Pouch Construction

## OPEN OPERATIVE APPROACH

For most patients, the ileoanal pouch procedure is performed in two stages. During the first operation, the patient is given general anesthesia and then placed in the lithotomy position. A nasogastric tube and bladder catheter are placed. Positioning for this procedure requires great attention with careful padding of the lower extremities so as to avoid neurovascular injury. In general the area of the peroneal nerve is left completely free, and weight of the lower extremity is placed on the volar aspect of the feet. A long midline incision is made from the pubis to just above the umbilicus. The abdominal colectomy proceeds in routine fashion. The colon is then divided at the rectosigmoid junction. The peritoneal reflection of the rectum is incised, and the endorectal dissection is begun.

Endorectal dissection is generally begun with a low-energy cautery in a circumferential fashion. Gaining entry into the submucosal space may be quite difficult with UC, particularly when there has been an acute flare-up. Should one encounter an undissectable plane, one should restart the dissection several centimeters more distal. As the rectal muscular cuff is developed, countertraction on the mucosal/submucosal tube in an upward fashion and outward traction on the muscular cuff helps the dissection, which should be taken down to just above the dentate line (Fig. 96-6, *A*). Placement of a suction catheter into the rectum (from below) may also make more distal dissection easier. Once the endorectal dissection is completed, one of the surgeons moves to the foot of the table. Narrow retractors are placed at the anal mucocutaneous junction, and a clamp is inserted into the rectum. An assistant working in the abdominal field places the end of the mucosal-submucosal tube into this clamp. The segment is then everted outside the perineum. The end of the everted tube is placed in a clamp and held on traction by an assistant to assist the anastomosis. The submucosal-mucosal tube is incised on the anterior one half, 1 cm proximal to the dentate line. A Kelly clamp is inserted into this opening, and the ileum is brought down to this point by grasping two previously placed traction sutures (Fig. 96-6, *B*). Great care must be taken not to twist the bowel as it is brought through the muscular cuff. A standard anastomosis is performed to the ileum, as either a pouch or straight pull-through. Rectal examination at this point should show a well-formed anastomosis 1.5 to 2 cm above the anodermal junction. Gloves are then changed, and attention is directed to the abdominal field. The pulled-through ileum is attached with seromuscular sutures to the muscular cuff to prevent it

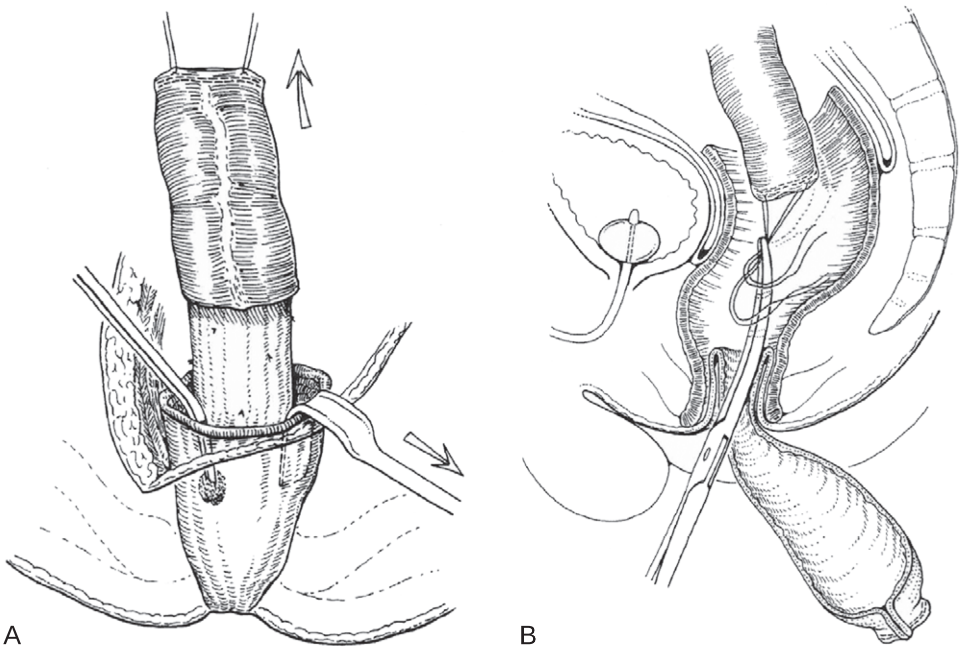


**FIGURE 96-6** **A,** Technique for the endorectal dissection. Note that dissection is assisted with appropriate traction on the cuff and the rectal stump *(arrows)*. **B,** The ileum is pulled through an incision in the submucosal tube. Note that care is taken to avoid twisting of the bowel (in this case shown as a straight pull-through).

from prolapsing in the early postoperative period. In general, a reperitonealization should be done. A temporizing loop ileostomy is typically created in a spot previously marked by an enterostomal nurse. It is important to carefully inspect this site to ensure there is no kinking or twisting of this stoma. Additionally, only peritoneal sutures are placed because this will greatly ease takedown of this stoma after healing has taken place. The loop may be suspended using a red-rubber-type catheter, and this can be removed in approximately 2 weeks. Once the abdomen and skin are closed, the stoma is opened.

# J Pouch Construction

The ileal mesentery is mobilized adjacent to the superior mesenteric vessels into the upper abdomen to provide sufficient length for the distal ileum to reach the anus without tension. A good measure is the ability to easily drag the small bowel (after pouch creation) over the most distal portion of the pubic symphysis. For the J pouch, the ileum is folded back on itself for a length of 8 to 10 cm. The bowel is opened at the apex of the J pouch, and an automatic stapling device is fired to create the anastomosis. In general 2.5-mm staples appear to yield a satisfactory anastomosis. Typically, a small section of ileum will remain separated at the proximal side of the J. An additional firing of the stapling device will allow the remaining portion of the pouch to be anastomosed. Leakage and bleeding along the staple lines is not uncommon. Eversion of the stapled line will allow for inspection and control of any bleeding. Following this, seromuscular sutures at the top of the suture line will take tension off of this critical area. Note that the length of the J pouch has become progressively shortened because longer-length pouches tend to lead to increased stool stasis and higher rates of pouchitis.[133]

# Modification of the Pull-Through

Over the past several years our group and others have made several modifications to this standard open pull-through procedure.[134] One of the major restrictions in performing a J pouch pull-through is the difficulty in bringing down the end of the pouch sufficiently out of the anal canal to perform a hand-sewn anastomosis. Strategies of placing the patient in reverse Trendelenburg and extensive dissection of the mesenteric vessels may help; however, in some cases this may not be sufficient. To address this, the mucosal/submucosal everted tube is stapled outside of the patient approximately 1 cm above the dentate line (Fig. 96-7, *A*). The residual anorectum is placed back into the anal canal, and the largest possible circular end-to-end anastomosing (EEA) stapler is inserted. The assisting surgeon from the abdominal field places the anvil of the EEA device into an opening in the end of the J pouch and secures a purse-string of absorbable, monofilament suture around this opening. Care is taken to ensure that this opening is away from mesenteric vessels, which may be injured during the subsequent anastomosis. The J pouch is guided down, and an anatomosis is created within the anal canal. This allows for a much more rapid anastomosis and much less traction to be placed on the anastomosis (Fig. 96-7, *B* and *C*). Both tissue donuts are inspected, and in some patients a sigmoidoscope with air insufflation is performed to assess the integrity of the completed anastomosis. EEA-type anastomoses commonly narrow down and must be digitally dilated two to three times during the interim 2 months while the child has a protective ileostomy. Once the child begins stooling, the anastomosis generally stays patent.

## LAPAROSCOPIC APPROACH

Minimally invasive surgical (MIS) approaches to a proctocolectomy and pull-through have been advanced over the past decade. Two general approaches have been taken. The first is to perform the entire proctocolectomy, mucosectomy, and pull-through via an MIS approach, with the colon being brought out either through the rectal canal or through a small lower incision.[135] This method has the advantage of excellent cosmetic results but may be time consuming. An MIS alternative approach is to perform the dissection of the colon including mobilization and ligation of mesenteric blood vessels via a laparoscopic approach, followed by a transverse lower incision for the mucosectomy and pull-through procedure.[136] In our experience, we have noted a significantly lower operative time and less blood loss with this modified approach.

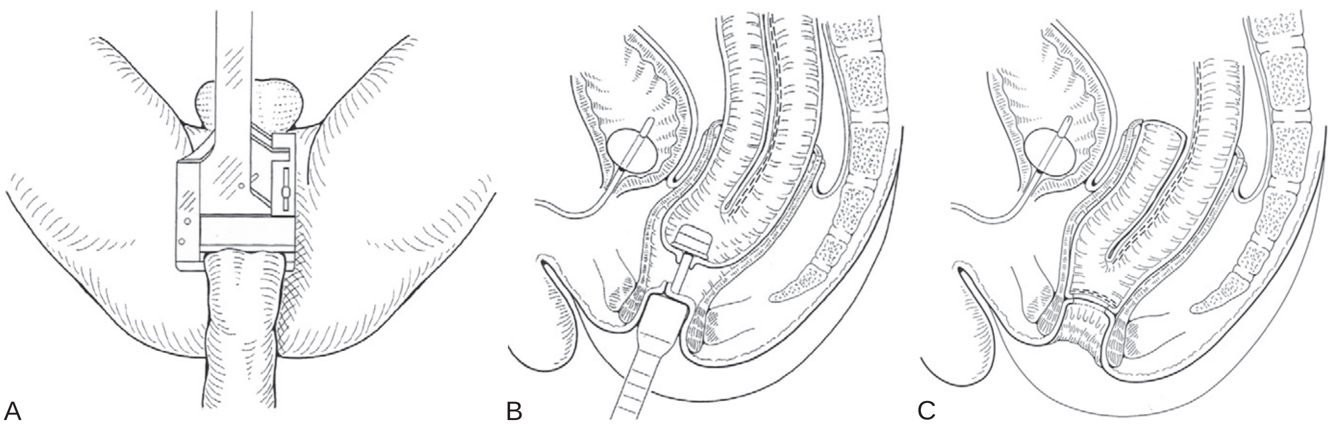


**FIGURE 96-7** Modification of the pull-through procedure with the use of stapling devices. **A,** Note the stapling of the submucosal tube just above the dentate line with a linear stapling device. **B,** Insertion of an end-to-end anastomosing (EEA) stapler transanally and connection with the J pouch via the abdomen. As with an open procedure, great care is taken to ensure the J pouch is appropriately oriented during this process. **C,** Appearance of the anastomosis after firing of the EEA stapler.

Two recent comparisons between open versus laparoscopic techniques demonstrated similar outcomes between these two groups,[137,138] suggesting that laparoscopy is a viable and safe approach. Conversion rates are fairly small and were reported at 7% in a recent pediatric series.[139]

An initial umbilical port, followed by three to four 5-mm ports, are placed as shown in Figure 96-8. The umbilical port initially contains the camera with a 30-degree telescope. This is followed by an epigastric port and then left and right lateral ports. The colon, from the terminal ileum to the midrectum, is mobilized and released from the peritoneal attachments and the splenic and hepatic flexures. Initial mobilization of the lateral attachments is assisted by "air-planing" the patient to the contralateral side, with traction on the colon using a blunt bowel grasper through either the epigastric or the contralateral trocar sites, and using a cautery scissors via the remaining trocar site. The ureters are identified early during this dissection. Depending on the site of mobilization, the camera and operating ports will vary.

The more time-consuming aspect of the dissection is the mobilization of the omentum off the transverse colon—a particular challenge in more obese or high-dose steroid-dependent children. A pair of 5-mm ultrasonic scissors or the use of an endoscopic stapling device will help at this point of the dissection. Care is taken to identify and ligate the middle colic vessels, which will greatly help bring the transverse colon down to the pelvis. Alternatively, the omentum may be spared by retracting it superiorly and using electrocautery dissection between the stomach and colon.

Once the colon is fully mobilized, a low transverse, suprapubic incision is made, predominantly on the left side of the midline (see Fig. 96-8). The operating surgeon pulls the entire colon out through this incision and sequentially ligates remaining mesenteric vessels. The ileum is divided, and an ileal pouch is then created. The endorectal dissection is then performed as described earlier.

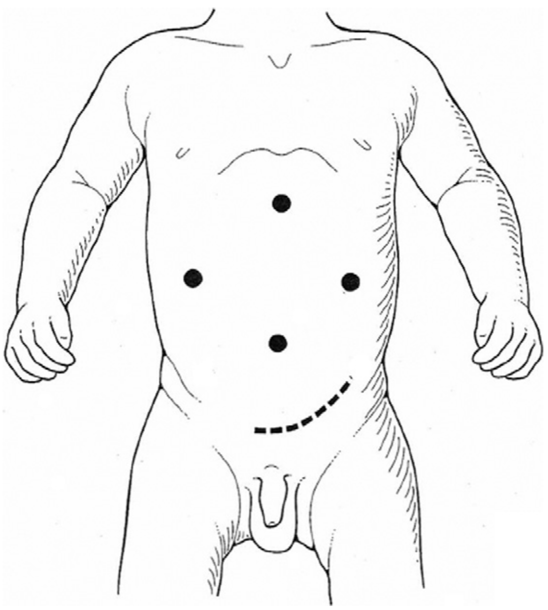

FIGURE 96-8 Suggested port sites for a laparoscopically assisted colectomy.

# Postoperative Care

Intravenous steroids are tapered after operation; oral prednisone can usually be discontinued within 3 to 4 weeks. Most children are discharged from the hospital by the sixth day after surgery. A water-soluble contrast enema is performed within 2 months to ensure that the ileal reservoir has no leaks or sinus tracts. Most children resume full physical activities within 3 weeks.

Approximately 2 to 3 months after the first operation, the patient is rehospitalized for ileostomy closure. The ileoanal anastomosis is dilated under anesthesia.

One to two digital dilations are performed in the clinic before ostomy closure to prevent narrowing of the anastomosis.

# Additional Surgical Considerations

## PROTECTIVE ILEOSTOMY

The early experience with pull-through operations demonstrated that a protecting ileostomy that completely diverts the fecal stream for approximately 2 to 3 months minimizes the risk of pouch leak and pelvic infection. Leaks from the ileal pouch when not used in conjunction with an ileostomy have been reported to be more than twice as frequent as when an ileostomy is used.[121] On the other hand, the one-stage pull-through operation has been performed successfully for many years on patients with polyposis coli. Patients with chronic UC who receive long-term steroids or other medications are often malnourished and frequently have a suppressed immune response. Such children would probably be at high risk from a primary procedure. However, patients with UC who may be considered for the one-stage pull-through procedure would include those in good general health and adequately nourished, those taking only low-dose steroids and minimal immunosuppressive drugs, those who have minimal rectal inflammation, and those who are not obese.[122] Considerable judgment must be given when deciding whether to perform a protective ileostomy. High-dose steroids, weight loss, urgent surgery, or recent (within 3 months) anti-TNF therapy should provide strong consideration for the performance of a protective ostomy.

### Stooling Patterns Post Pull-Through

In general stooling patterns become one of the key outcome measures in children after a pull-through. Stooling always takes considerable adjustment. First, nocturnal incontinence is strikingly common in the first few months, and patients and families need to be educated about this fact. This appears to be most common in younger, preadolescent patients and decreases with the age of the patient and time from surgery. Frequency of bowel movements may range widely from 6 to 15 motions per day immediately after ostomy closure. Stooling frequencies decrease over the first 2 to 3 years following ostomy closure. This is another important factor in the education of patients. Generally, after the first 3 years, further reduction in stooling frequency will not occur.

### Straight Versus J Pouch

The question as to whether children fare better or worse with a straight versus a J pouch reconstruction remains an important question. A meta-analysis comparing the two procedures in

pediatric patients showed a trend toward lower stool frequency in those children who underwent a pouch. Unfortunately, because of the nature of a meta-analysis review, there were limitations in being able to comparatively analyze patients between the selected papers in this meta-analysis.[140] A more recent multicenter series retrospectively examined stooling outcomes.[141] This study showed that rate of stooling was significantly higher in those undergoing a straight pull-through; however, rates in both groups progressively declined over time. In fact, by 24 months post-pull-through rates were fairly similar between the groups (nocturnal and during day time); however, children undergoing a J pouch had a fivefold higher rate of pouchitis compared with those with a straight pull-through (Fig. 96-9, *A* and *B*).

### Medical and Dietary Management of Stooling

Two strategies may be taken to modify the diet for reducing stool frequency. The first is an avoidance of highly spicy foods, chocolate, or acidic foods. Additionally, a bland diet with reduced simple carbohydrates may prove useful, as is a strategy of separating liquid intake from solids. One obstacle is that many children tend to lose weight after colectomy, and one needs to balance such dietary restrictions with the need to encourage good energy delivery to the child.[142]

Bulking agents (fiber) are occasionally helpful. Although they will not reduce the frequency of stooling, they will provide bulk, which may make stooling more manageable. Initiation of loperamide hydrochloride (Imodium) is often helpful in decreasing the frequency of stooling. In general this should not begin until approximately 2 weeks after ostomy closure but may need to be started earlier in some individuals. Starting doses should be 2 mg three times a day but may increase to 2 to 4 mg four times a day. Patients and their families need to be educated about the need to maintain good hydration and electrolyte intake.

## Complications and Outcomes

Although the mortality rate for children is strikingly low, morbidity is high. Complications following the ileoanal pouch procedure are reported to occur in 35% to 65% of patients.[119,126–128] The most common complications are discussed next.

### POUCHITIS

Pouchitis is the most frequent complication following a pull-through procedure, regardless of whether a straight or pouch reconstruction was performed, and may be observed in 10% to 50% of patients.[141,143] Pouchitis results in cramping lower abdominal pain and increased frequency of stooling, often with watery diarrhea. For cases that present in a nonspecific manner, the use of fecal calprotectin has been shown by several investigators to have a fairly high level of sensitivity in making the diagnosis.[144] With more systemic manifestations, one may observe fever, malaise, and occasional arthralgias.[129] Although pouchitis occurs more frequently within the first 2 years post pull-through, it may be persistent. The etiology of pouchitis has not been fully elucidated. What is particularly striking is that those children who undergo a pouch reconstruction for either multiple polyposis or Hirschsprung disease rarely develop pouchitis. This suggests that the ileum has an underlying abnormality that predisposes patients to pouchitis. One interesting observation is that those patients who received pre-pull-through calcineurin inhibitors had a low incidence of pouchitis[145]; however, this has not been

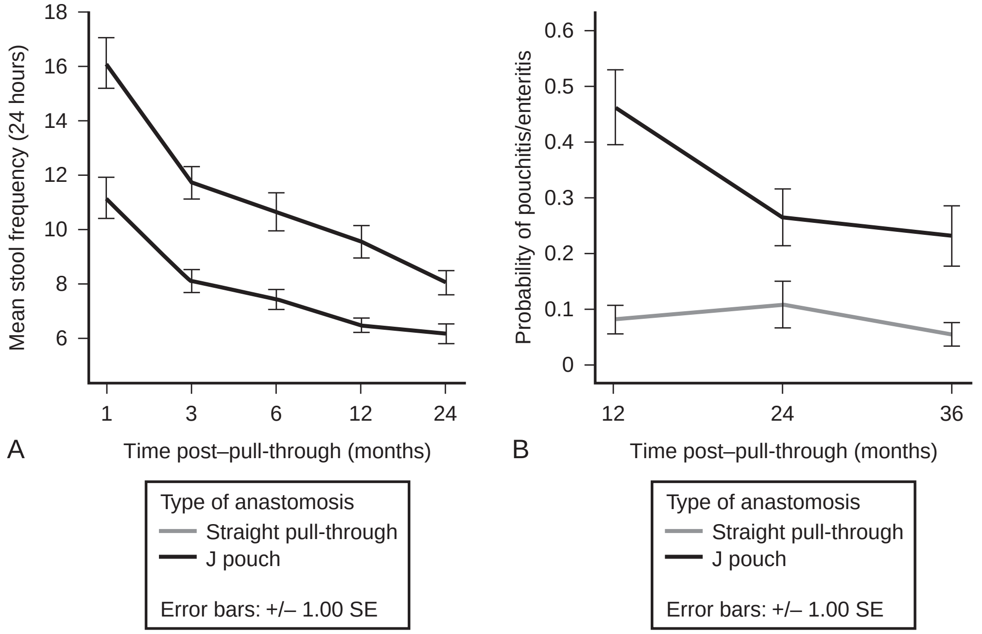


**FIGURE 96-9** **A,** Mean 24-hour stooling frequencies for children undergoing a straight and J pouch pull-through. Note the decrease in the frequencies over the first 2 years. **B,** Mean rates of pouchitis/enteritis for children undergoing a straight and J pouch pull-through. Note the rates are markedly higher in those undergoing a pouch reconstruction. (Modified from Seetharamaiah R, West B, Ignash S, et al: Outcomes in pediatric patients undergoing straight versus J-pouch ileoanal anastomosis: A multi-center analysis. J Pediatr Surg 2009;44:1410-1417.)

subsequently substantiated. Others have found an association of pouchitis with an abnormal intestinal microbiome, which is distinct from other patients without pouchitis, or those with familial adenomatous polyps. This suggests that alteration in the microbiome may be a causative factor and may allow future work to be directed at eliminating or treating this disorder.[146]

Treatment for pouchitis typically begins with a 2- to 4-week course of oral metronidazole and confirmation that the anastomosis is widely patent. More than 90% of children will respond to this approach. Should this fail, or recurrence occur, an alternative antimicrobial may be tried; in general ciprofloxacin is a good alternative. Should this fail, one should try the addition of daily pouch washouts with tap water or Rowasa (Solvay Pharmaceuticals, Inc., Marietta, Ga.) enemas. Once in remission, there is some evidence in adults that the implementation of probiotics may avoid or decrease the incidence of recurrence.[147]

For more persistent cases, oral mesalamine and hydrocortisone retention enemas may be added. When the disorder is recalcitrant, a diverting ileostomy may become necessary, particularly in children in whom chronic pouchitis may cause delayed growth and development. Several recent publications have shown that the use of probiotics can put patients into remission after antibiotics have resolved the acute pouchitis episode. Most of the recent data trends toward supporting the use of these probiotics[148] once the acute pouchitis has subsided.

## GASTROINTESTINAL OBSTRUCTION AND FISTULA FORMATION

Adhesive obstruction of the small intestine occurs in 10% to 30% of patients and remains one of the most common surgical complications.[25,30,117,149] Obstructions due to complications of the diverting ileostomy are also not uncommon and may be seen in up to 20% of cases. Not uncommonly these may be due to a tightening around the fascia or from a food bolus obstructing the lumen. One should always attempt to clear this obstruction using a large red rubber catheter through the proximal limb of the ostomy. Stricture formation at the ileo-anal anastomosis is common, particularly when an EEA type anastomosis is performed, or when a diverting ileostomy is placed. Stricture formations have been reported in 10% to 20% of cases.[25,141,143,149] Most of these strictures are readily dilatable, and once the ileostomy is closed, the passage of stool often keeps the passage open. However, if there is a devascularization of the ileum, dilations may not succeed. Fistula formation has been reported in most series.[149] In a recent multicenter study, 13% of those undergoing a straight and 5% of J pouch pull-throughs developed fistulas.[141] Fistula formation may occur to the vagina, skin, perineum, and other portions of the small bowel. In more than half of these patients, a temporary or permanent ileostomy will be necessary.[141] Miscellaneous complications include hemorrhage and hernia formation.

## CONTINENCE

One key aspect of continence is differentiation of daytime and nighttime continence. A large proportion of children will complain of nighttime accidents, with approximately 40% initially incontinent.[124] This is an important factor to educate patients and parents on ahead of the pull-through procedure. Nocturnal incontinence is most prevalent over the first 6 months after a pull-through but will often persist in preadolescent children because they typically sleep much more soundly than older patients. Daytime incontinence is far less common but has been reported in approximately 5% of all patients. However, depending on the stringency to which continence is graded, some degree of decreased continence may be found in up to 50% of children in some series.[150] In one large series of children, the occurrence of incontinence was reported at 6% and perioperative complications, particularly leakage at the anastomosis, were associated with the development of lower continence scores.[30]

## VENOUS THROMBOSIS

Postoperative mesenteric vein thrombosis with extension into the portal venous tree has been described in a number of adult series[151] and has also been reported in children.[152,153] The development of this complication may be due to excessive tension on the pull-through segment, as well as a proinflammatory state that predisposes IBD patients to the development of lower extremity deep vein thrombosis.[154] Strong consideration should be given to placing pneumatic compression stockings on children during the pull-through and prophylactic low-molecular-weight heparin.

### Pull-Through (Pouch) Failure

Approximately 15% to 45% of patients will require a repeat operation. Furthermore, anywhere from 6% to 25% will develop a pull-through failure, many of which will require removal of the pouch and construction of a permanent ileostomy.[25,124,141,155,] For approximately one third of patients who require pouch removal, the diagnosis will be found to be Crohn disease.[157] Other causes of failure include intractable stricture; leak; frequent stooling, which results in poor quality of life; and intractable pouchitis. In these cases a child should undergo an end ileostomy. Although consideration should be given to a completion proctectomy in cases of Crohn disease or intractable stricture, for those with frequent stooling or pouchitis, the pouch should be retained and an ileostomy performed, with closure 1 to 2 years after the patient has recovered from these symptoms. Interestingly, in a large meta-analysis of pediatric patients having a straight pull-through, there was a significantly higher rate of pull-through failure by almost twofold[140]; however, the cause of these failures was not identified. Another group that suffers from an increased risk of pouch failure is patients with a diagnosis of indeterminate colitis. This group of patients may make up between 5% and 25% of children.[158] In general they will present at a much younger age (some under 2 years), typically have a more severe diarrhea (often with blood), and have a more extensive pattern of ulcerations, usually with rectal sparing.[159] This group may well benefit from a total colectomy with ileostomy and retention of the distal rectum for future pull-through. Up to one third of patients with indeterminate colitis will go on to be subsequently diagnosed with either Crohn disease or UC.[158] Because of the future risk of Crohn disease, one may strongly consider waiting on the definitive pull-through until this can be determined. One way to help distinguish these patients is with the use of a gadolinium magnetic resonance imaging study. Another is with the use of serum antibodies. Those children who are

p-antineutrophil cytoplasmic antibodies (p-ANCA) positive and anti-*Saccharomyces cerevisiae* antibodies (ASCA) negative will reclassify to UC in 63.6%, whereas those who are pANCA negative and ASCA positive will reclassify to Crohn disease in 80%.[160] In contrast, another large study of children with pouch failures found a fairly high incidence of failures (15%) but was unable to attribute this to the diagnosis of indeterminate colitis.[157] In fact, these authors associated failure with female gender, perianal disease, Crohn disease, and early and late complications.

### Diagnosis of Crohn Disease After Pull-Through

As suggested in the previous paragraph, it is not uncommon to secondarily have the diagnosis of UC change to Crohn disease. In fact, between 5% and 10% of all children undergoing a proctocolectomy and pull-through will eventually be diagnosed with Crohn disease.[161] Many of these patients will initially have a diagnosis of indeterminate colitis; however, others would have little to no indication of Crohn disease at the time of pull-through. It is incumbent on the surgeon to make sure that outside pathology studies are read by their pediatric or gastrointestinal pathologist and a complete evaluation of the remainder of the gastrointestinal tract has been thoroughly evaluated before a pull-through procedure. Postoperative suspicion should arise if a child presents with any of the following: markedly increased stooling, bloody stools, frequent pouchitis, weight loss, or most importantly fistula formation (to perineum, bladder, or vagina). Although some patients with Crohn disease may remain stable with adequate medical therapy, up to one third of all pull-through failures are due to this diagnosis.[157]

### Risk of Postoperative Complications and Preoperative Medical Therapy

Complications are frequent, and a number of investigators have attributed some of these complications to the use of these therapies. Some authors have attributed the use of corticosteroids to increased infectious complications,[162] and others have demonstrated that the association of steroid use with poor preoperative nutrition is related to an increase in infectious complications.[163] Interestingly, others have failed to associate steroids, or other conventional therapies (azathioprine or 6-mercaptopurine) with the development of such complications.[164] Although conventional therapy has typically involved corticosteroids, recent therapies have included a number of additional immunosuppressive therapies including cyclosporine A and anti-TNF therapies. Tremendous controversy has arisen in the literature regarding the risk to secondary septic and leak complications postsurgery for both patients with Crohn disease and UC. Although a meta-analysis failed to show an increased risk,[165] more recent publications have identified an increased risk. Unfortunately, virtually all studies are retrospective and in part are lacking precise details regarding the length of time between last therapy and performance of surgery or are lacking details as to the disease severity of the IBD process.[166] For UC, two recent studies, one of which did stratify patients on the basis of their severity of disease, identified the use of infliximab as being associated with increased risk of postoperative complications.[167,168] Further, many who were on such therapy underwent a three-stage operation due to the surgeon's preference. Because virtually all levels of infliximab are out of a patient's circulation by 12 weeks, caution should be taken should a surgical procedure be undertaken before this time period; however, no data exist on whether there are longer-term immune-suppressive effects. Additionally, little to no data exist as to how the pediatric patient population might be affected by the use of these agents.

## QUALITY OF LIFE

Most patients have a remarkably poor quality of life (QOL) before their pull-through, so it is not surprising that most patients report a strikingly improved QOL after such a procedure.[169] Although large series have reported excellent results,[126] it is important to emphasize that QOL is not ideal after these procedures. Most patients have urgency, leakage, nocturnal incontinence, pouchitis, and occasionally sexual dysfunction. Each of these adverse events will significantly reduce QOL. Despite this, in two series on QOL in children, results showed that QOL was not significantly different from age-matched U.S. children, with little or no adverse effects from the surgery.[170,171] In fact, the surgical scar was noted to be a negative factor of significance in one series and chronic pouchitis was a factor associated with poorer QOL in the other.

## LONG-TERM FOLLOW-UP

Performance of a proctocolectomy and pull-through will require a child to be followed for the rest of his or her life. Although 99% of the colon and rectum are removed, a flexible or rigid sigmoidoscopy to monitor the small amount of remaining tissue above the dentate line must be done every 3 years to ensure that no secondary dysplastic or malignant changes develop. In addition, this close follow-up will allow the surgeon or gastroenterologist to screen for secondary complications, evaluate the patient's nutrition, and rule out extraintestinal manifestations.

# Conclusions

UC has a significant morbidity in pediatric patients. The disease process requires extensive expertise from the medical, nutritional, nursing, and surgical specialties. With comprehensive and aggressive care, excellent results may be obtained. Many patients in the pediatric age group will require surgical care. Although most children do well with a proctocolectomy and pull-through, realistic outcomes need to be emphasized to the family. More than half of all patients will encounter early or late complications after such surgery. With time, most patients will improve and their lives normalize; however, care following surgery requires patients to maintain continual follow-up with their medical providers throughout life.

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 97

# Primary Peritonitis

Robert Baird and Jean-Martin Laberge

Primary peritonitis (PP), also referred to as *idiopathic* or *spontaneous peritonitis*, has been defined as an infectious process involving the peritoneal cavity without an intra-abdominal source.[1–3] Such infection may seed the abdomen through hematogenous or lymphatic routes or by direct extension from the vagina. With the exception of the ends of the fallopian tubes, the peritoneal cavity is a completely closed space that can be penetrated by foreign bodies such as ventriculoperitoneal shunts and peritoneal dialysis catheters. In prepubertal and adolescent girls, retrograde spread of fluid out through the fallopian tubes may account for the presence of an ascending vulvovaginitis or "swimming pool peritonitis."[4–7]

By the early 1900s, up to 10% of abdominal operations in children fell into the category of PP and carried an associated mortality of up to 50%.[2] In 1964 Conn linked the presence of intra-abdominal ascites with the bacterial translocation of intestinal flora resulting in primary peritonitis.[8] Today, PP is a rare cause of peritonitis in children and represents less than 1% of all pediatric laparotomies because the diagnosis is often made and treatment frequently does not require an operation.[3] Most cases of PP in the pediatric age group are associated with nephrotic syndrome (NS) or chronic hepatic states in which ascites and/or cirrhosis is present. This group includes infants and children with biliary atresia, cystic fibrosis, hepatic fibrosis, and lupus erythematosus (Table 97-1).[9–11] Organisms isolated from the peritoneal cavity vary according to the associated conditions (Table 97-2). For instance, gram-positive organisms including *Streptococcus pneumoniae* and group A streptococci are most commonly found in patients with NS.[12–14] The same gram-positive groups are cultured in patients with underlying liver disease, but this patient population also demonstrates gram-negative isolates including *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas* species.

## Clinical History, Laboratory Data, and Diagnostic Studies

Children with PP have acute abdominal pain associated with a febrile illness, nausea, vomiting, diarrhea, or other viral-like prodromes. The time course may be more protracted than that for secondary peritonitis, and diffuse rebound tenderness is often present. The absence of localized pain may result from irritation of visceral surfaces.[15–16] Diagnostic paracentesis may be helpful in the presence of ascites, as is sampling of the dialysate in children with renal failure on ambulatory peritoneal dialysis programs. The diagnosis of PP is made when the peritoneal fluid leukocyte count is higher than $500/mm^3$ and granulocytes predominate (lymphocytes are usually present in higher numbers in normal peritoneal fluid). Typical peritoneal fluid in PP also has a pH of less than 7.35 and an elevated lactate level.[17] If more than one organism is present on Gram stain, a perforated viscus should be suspected. Sending a minimum of 10 mL of fluid for Gram stain and culture analysis will increase the number of positive isolates, yet cultures may be negative in up to 60% of reported cases.[18] The isolation and sensitivity pattern of specific bacteria decreases the spectrum of antibiotics required and potentially eliminates the use of nephrotoxic drugs in patients with compromised renal function.[13] Samples of blood and urine should be sent for culture, and radiographs of the chest and abdomen should be obtained. These studies will help eliminate a perforated viscus or a pneumonic process as the cause of the abdominal pathology. Routine electrolytes and total protein levels should be investigated because low serum protein levels and concomitant decreased opsonins may contribute to the development of PP.[19]

Ultrasound studies and computed tomography (CT) of the abdomen have been used to differentiate primary from secondary peritonitis (caused by such common pediatric processes as appendicitis) when the clinical picture is confusing. Double-contrasted CT scan findings in PP include the presence of a patent appendiceal lumen, diffusely distributed peritoneal fluid, and secondary enhancement of the bowel wall.[9]

## Primary Peritonitis in Healthy Children

Gross reported 58 cases of PP in a group of previously healthy infants and toddlers (mean age, 2 years) who had a preexisting upper respiratory infection.[20] The complex of initial symptoms included vomiting, fever, irritability, abdominal distention, and tenderness. *S. pneumoniae* was the predominant organism isolated. A later series from the same facility

**TABLE 97-1**

**Conditions Associated with Primary Peritonitis in Childhood**

| |
|---|
| Nephrotic syndrome |
| Hepatic dysfunction |
| Adrenogenital syndrome |
| Cystic fibrosis |
| Chronic renal failure with the need for chronic ambulatory peritoneal dialysis |
| Complications after splenectomy |
| Diseases requiring long-term steroid administration (systemic lupus erythematosus, dermatomyositis) |
| Familial Mediterranean fever |

**TABLE 97-2**

**Microorganisms Associated with Primary Peritonitis**

| |
|---|
| *Streptococcus* species (*S. pneumoniae;* group A streptococci) |
| *Escherichia coli* |
| Gonococcus |
| *Haemophilus influenzae* |
| *Klebsiella pneumoniae* |
| *Listeria monocytogenes* |
| *Parainfluenza* |
| *Salmonella typhi* |
| *Serratia marcescens* |
| *Yersinia enterocolitica* |

recorded 33 patients with a mean age of 5 years who were treated for PP over the next 30 years.[21,22] The decrease in number of affected children was considered the result of increased availability and use of oral antibiotics. Although multiple potential sources of infection have been implicated including hematogenous (dental procedures, bacteremia), lymphatic, gut translocation, and ascending gynecologic processes, the etiology remains unclear in most cases. In 1985 two previously healthy children with dehydration, abdominal distention, and group A streptococcal peritonitis were reported. At the time of laparotomy no source of infection was identified, although one of the children had a concomitant right-sided diaphragmatic hernia.[23] The literature has since identified a group of healthy children with idiopathic peritonitis and simultaneously positive cultures for group A streptococci from the trachea, pharynx, or tonsils.[24–26] *Haemophilus parainfluenzae* was recently isolated during an abdominal exploration when no intestinal pathology was identified.[27]

In prepubertal girls with gonococcal vaginitis, 6% may have evidence of peritonitis. Treatment with parenteral cephalosporins is indicated, and the presence of other associated simultaneous sexually transmitted diseases should be investigated.[6] In earlier reported series of PP, most of the patients were girls and the vagina was often implicated as the source of the infections. However, vaginitis was uncommon and the ultimate source of the infection remained obscure.[21] The prepubertal cervix lacks the endocervical glands that may harbor bacteria, so ascending infections in this age group would more likely be associated with some traumatic force that pushes the bacteria up through the vagina, as in sexual abuse cases or by jumping feet first into a swimming pool or lake water.[5] In more recent series the incidence of PP is equally distributed between boys and girls.[15,28,29] In some cases the same bacteria causing the peritoneal infection have also been cultured from the respiratory and urinary tracts, as well as from the oral cavity.[1]

In all instances of peritonitis without an overt source of infection, failure to improve with intravenous antibiotics is an indication for laparoscopy or laparotomy. An appendectomy can be done safely even in the presence of cloudy exudate, and the bowel surface can be inspected for secondary causes of the infection. After the surgical intervention, antibiotics should be continued until the leukocytosis normalizes and the ileus resolves.[2,16]

# Nephrotic Syndrome

PP has been reported in 3% to 17% of children with NS.[12,30–35] Before the availability of antibiotic therapy, PP was the leading cause of death in this group of patients. An increased susceptibility to infection in these patients may be influenced by impaired cellular immunity and chemotaxis, decreased opsonization, and reduced levels of circulating immunoglobulins. Complement proteins I and B are reduced in the serum but increased in the urine of patients with peritonitis and NS.[36] The episodes of peritonitis are recurrent in 15% to 26% of cases and have been associated with decreased levels of circulating IgG.[31,35]

Large reported series in children indicate that gram-negative organisms are isolated in 6% to 30% of patients with NS and peritonitis, whereas *S. pneumoniae* was cultured in 4% to 38%.[12,31,37] Even when the peritoneal fluid showed no bacterial isolates, children symptomatically responded to the systemic administration of intravenous penicillin.[10] Initial treatment of PP should include the administration of antibiotics to cover both gram-positive and gram-negative bacteria. In cases in which clinical improvement does not occur within 24 hours after the initiation of therapy, further diagnostic studies such as abdominal CT or diagnostic laparoscopy should be employed to eliminate other causes of peritonitis. Abdominal CT scans may not always successfully differentiate primary from secondary peritonitis. Laparoscopy and abdominal irrigation have been successfully used with medical management when the clinical course shows no improvement.

In almost 80% of children with NS in whom PP developed, either steroids were being used as treatment of the condition or a relapse of NS had occurred.[12,34,55] Pneumococcal vaccination (Pneumovax) has been recommended in this group of patients, yet peritonitis has occurred despite protective immunization.[37,38] In the context of the developing world, a recent report advocates immunization only for the small number of children who have steroid-dependent or steroid-resistant nephrotic syndrome.[39] Resistant organisms can develop in children treated with oral penicillin prophylaxis.[38]

# Peritonitis with Peritoneal Dialysis

In children maintained on chronic peritoneal dialysis (PD), peritonitis is the primary complication compromising survival. The problem has prompted formation of the International

Pediatric Peritonitis Registry, an Internet-based prospective registry of 47 pediatric centers across 14 countries.[35] Peritonitis (either bacterial or fungal) occurred at a rate of one episode per 11.1 to 13.2 patient-months in separate multi-institutional studies.[14,40–42] Gram-positive organisms were isolated in 44% to 49% of the cases (most commonly *S. aureus* and *S. epidermidis*). Gram-negative bacteria were in 21% to 25% of the cases, and fungi were in 1.8%. Of the symptomatic patients, 21% to 31% did not have positive cultures (Table 97-3).[35,40] Gonococcal peritonitis has been reported in a sexually active adolescent undergoing peritoneal dialysis.[7] Risk factors for the development of peritonitis in this group of children include contamination of the connectors during dialysate fluid exchange, exit site or tunnel infections, local trauma to the tunnel site, and nasal colonization with staphylococcal organisms.[40] Additional risk factors for the development of PD-related peritonitis include the duration of PD (longer than a year), chronologic age younger than 2 years, and decreased serum IgG levels.[43]

Clinical findings include abdominal pain, fever, and an elevated neutrophil count in the cloudy dialysate. Once suspected, the fluid should be cultured and both intravenous and intraperitoneal antibiotics should be instituted, with close monitoring of antibiotic levels. Because in vitro evaluation revealed 69% sensitivity of gram-positive organisms to a first-generation cephalosporin and 80% sensitivity of gram-negative organisms to a third-generation cephalosporin worldwide, current treatment guidelines for empiric therapy include either a first-generation cephalosporin and ceftazidime or a glycopeptide (vancomycin or teicoplanin) with ceftazidime.[44] Aminoglycosides may play a role in empiric therapy for high-risk patients, and antibiotic therapy should be tailored once culture and sensitivity results become available.

Symptoms should begin to improve within 24 to 36 hours after initiation of therapy.[45] Long-term multi-institutional longitudinal studies suggest that the PD catheter must be removed to eradicate the infection when *Pseudomonas, Candida,* or atypical mycobacterial species are involved.[14,40,43,46] There is also a risk of peritoneal membrane failure when these organisms are involved, thus precluding the continued use of PD. Peritonitis rates are decreased when a two-cuff system is used and when the exit site is directed downward.[29,40] Nonetheless, relapsing peritonitis remains a common clinical problem for these patients. Defined as recurrence of peritonitis with the same organism within 4 weeks after termination of antibiotic treatment, relapsing peritonitis was found to occur in 11% of PD patients experiencing an episode of peritonitis; it significantly decreased the rate of full functional recovery and increased the rate of necessitating permanent PD discontinuation.[47]

**TABLE 97-3**
**Organisms Involved in Peritonitis in Children Maintained on Chronic Ambulatory Peritoneal Dialysis***

| *Organism* | % |
|---|---|
| *Staphylococcus aureus* | 38.9 |
| *Staphylococcus epidermidis* | 13.2 |
| Group A streptococci | 9.7 |
| *Pseudomonas* species | 9.0 |
| Other bacteria or fungi | 13.9 |
| No organisms found on culture | 13.9 |

*Data from 144 episodes of peritonitis in 66 children at J.W. Riley Hospital for Children, Indianapolis.

## Hepatic Dysfunction

In a child with impaired hepatic function, cirrhosis, and ascites, the PP that develops is characteristically associated with both gram-negative and gram-positive organisms.[19,48] The liver with its rich reticuloendothelial tissue normally filters the bacteria found in the portal circulation. As cirrhosis develops, portal venous flow is partially shunted away from the liver, thereby decreasing the clearance of bacteria and fungi from both the blood and lymphatic systems. This decreased clearance likely allows for the persistence of bacteria in ascitic fluid.[11,18,49–51] Children will have fever and abdominal pain in 50% of PP cases. Paracentesis fluid that has greater than 500 leukocytes/mm$^3$, bacteria on Gram stain, and a pH of less than 7.35 had 100% sensitivity and 96% specificity for active PP.[13] Patients with cystic fibrosis and hepatic dysfunction as a result of cirrhosis or impaired synthetic function are also at risk for episodic PP.[52] The treatment of choice for PP in this context is a third-generation cephalosporin in most pediatric patients. Children at risk should be maintained on trimethoprim-sulfamethoxazole for prophylaxis.[53] Long-term fluoroquinolone use in infants and young children is discouraged due to safety concerns regarding possible quinolone-induced arthralgia or cartilage toxicity.

## Ventriculoperitoneal Shunts

Spontaneous bacterial peritonitis has been described in children with indwelling ventriculoperitoneal (VP) shunts without evidence of cerebrospinal fluid infection.[54] Cultures from these patients have resulted in a variety of gram-positive organisms, and improvement in peritoneal irritation occurs with exteriorization of the shunt tubing. On the other hand, VP shunt infection from a readily identifiable source remains a common complication (see Chapter 128); a complete diagnostic workup is required including a shunt series, tapping of the shunt reservoir for culture and sensitivity, head CT scan, and abdominal imaging depending on presenting complaints. When shunt fluid appears sterile, Gram stain and culture of peritoneal fluid may help to differentiate PP or shunt infection from an intra-abdominal source. Common intra-abdominal infectious processes like appendicitis must be treated promptly, and shunt exteriorization strongly considered. In patients with indwelling VP shunts and recurrent episodes of PP, consideration should be made for elective appendectomy.

## Sterile Peritonitis

Although PP is traditionally defined as an infectious process, certain disease entities are associated with peritoneal inflammation without the presence of an offending organism.

## SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a rheumatologic condition characterized by the formation of autoantibodies directed at self-antigens. The pathophysiology is multifactorial, and the presentation can vary greatly among patients. Serositis is a frequent manifestation of the disease, and PP has been described as the index presentation for SLE.[55] Peritoneal inflammation is not a consequence of bacterial contamination, but rather a reaction to antibody-antigen interaction. A recent review of pediatric-onset SLE demonstrated a 19% rate of abdominal involvement, most commonly due to pancreatitis or new-onset ascites. Three children in the series, one of whom was found to have acalculous cholecystitis, underwent laparotomies for peritonitis before the diagnosis of SLE.[56] For patients with known SLE, high-dose steroids usually prove effective as first-line therapy for acute abdominal pain once other surgical pathologies have been ruled out. This can sometimes prove difficult in immunodepressed children, in whom clinical signs of intra-abdominal perforation or ischemia may be masked. Clinical vigilance is required, and extensive investigations are frequently necessary.

## FAMILIAL MEDITERRANEAN FEVER

Familial Mediterranean fever (FMF, also known as *recurrent polyserositis*) is characterized by transient episodes of pleuritis, arthritis, and peritonitis and primarily affects Armenians, Turks, and Jews originating from the Mediterranean area. Its inheritance is generally recessive, although varying penetrance has been reported depending on the genetic mutation. Nonsense or missense mutations in the *MEFV* (Mediterranean fever) gene appear to cause the disease in many cases. *MEFV* causes the production of inflammatory proteins, pyrin (derived from the association with predominant fever) or marenostrin (derived from the phrase “our sea,” because of the Mediterranean heritage of most patients). Frequent episodes of inflammation of the peritoneum (85%), joints (50%), and pleura (33%) are associated with high fever and abdominal tenderness. A recent review has demonstrated that 31% of patients manifest symptoms by 2 years of age, although this young cohort is less likely to present with peritonitis.[57] In FMF, the abdominal symptoms begin to abate within 12 hours of onset, with resolution within 24 to 48 hours. If surgical intervention is undertaken, the bowel is characteristically coated with a sterile exudate containing fibrin. As in SLE, ascitic fluid is characteristically sterile in FMF; antibiotics do not play a role in the acute setting or as prophylaxis. The use of colchicine may decrease the severity of painful episodes and reduce the incidence of long-term adhesive small bowel disease.[58] Five to ten percent of patients have not responded to colchicine; anakinra (an interleukin-1 receptor antagonist) can control the acuity of febrile attacks in adolescents.[59] Once the diagnosis of FMF has been considered, a complete family history should be obtained and genetic testing promptly offered. Long-term complications include the development of adhesive small bowel obstruction in 3% of pediatric cases.[60]

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 98

# Stomas of the Small and Large Intestine

Michael W. L. Gauderer

## Historical Note

The word *stoma* originates from the Greek *stomoun* (to provide with an opening or mouth). Intestinal stomas, considered basic surgical procedures, have a long and colorful history.[1–4] As a method of treating intestinal obstruction, colostomies date back to the latter part of the eighteenth century and some of the first survivors of this procedure were children with an imperforate anus.[5–7] Despite sporadic early successes, the use of stomas in the large intestine and later the small intestine in children evolved slowly. Surgeons were understandably reluctant and even strongly opposed to performing these drastic procedures, which were associated with major complications. However, as the experience of surgeons increased toward the end of the nineteenth century and beginning of the twentieth century, colostomies and occasionally jejunostomies were used to manage a few pediatric conditions. With the advent and the development of pediatric surgical practice in the mid to late 1900s and survival of children with conditions that were formerly likely to be fatal, the need for stomas increased. Enterostomal construction techniques, originally developed for adults,[8–12] were modified and adapted for use in children, particularly newborns with congenital intestinal obstruction.[13–18] New techniques that combined proximal decompression and distal feeding for neonates with atresia of the duodenum or high jejunum were introduced next.[19,20] In the past 3 decades, endoscopic, laparoscopic, and various image-guided approaches have been added to established open techniques continuously fostering the creation of feeding, venting, decompressing, irrigating, and special-purpose stomas. Understanding of stomal physiology and of specialized enteral and parenteral nutrition, as well as the diagnosis and management of stoma-related complications, have paralleled the advances in technique significantly improving outcome.

Several other factors have contributed to the safety, effectiveness, and ease of care of stomas in adults and children. Paramount among these is the advent of enterostomal therapy, which has evolved into a specialty in its own right.[21,22] Enterostomal therapists are now an integral part of health care teams in most medical institutions. Major national and international ostomy associations[23] foster the dialogue among professionals and provide a wealth of information through traditional and web-based material including publications for parents, caregivers, and teenage patients.[24,25]

Regional and local chapters are involved in establishing nonmedical support systems and guidance to access resources.[26] Greater awareness and acceptance of ostomates, as well as the recognition of their needs and rights among the lay population, has also helped to improve their quality of life. The knowledge and experience derived from enterostomal care has led to the creation of appliances in a wide variety of types and sizes, manufactured of well-tolerated biomaterials and complemented by numerous stoma care products.[27] Not surprisingly, at times, parents, caregivers, or ostomates contribute innovative ideas to the established management techniques.[28]

In the contemporary clinical setting, primarily because of earlier diagnosis of certain gastrointestinal anomalies such as Hirschsprung disease, improved surgical approaches, and perioperative care, pediatric surgeons were able to safely perform more single-stage procedures, thereby decreasing the need for preliminary decompressing enterostomies (ileostomies and colostomies).[29–33] Conversely, due to an ever-increasing number of children with a variety of complex surgical and nonsurgical pathologies, there has been a greater demand for upper gastrointestinal access for long-term enteral feeding (gastrostomies and jejunostomies),[34–38] as well as lower intestinal access for antegrade enemas (appendicostomies, tube cecostomies, and tube sigmoidostomies).[39–43] Often requiring a team approach, the creation, care, and closure of enterostomas continue to occupy a substantial portion of pediatric surgical practice.

## Child with a Stoma

An enterostoma in a child is a major disruption of normality and frequently leads to substantial psychologic trauma for the child and parents. However, most decompressing intestinal stomas in the pediatric age group are temporary and correction of the underlying problem often leads to closure of the diverting opening. Although pediatric surgeons continuously search for alternatives to intestinal exteriorization, an appropriately indicated, properly constructed temporary stoma is frequently unavoidable and lifesaving. Moreover, in several instances of noncorrectable and crippling pathologic conditions of the lower intestinal tract, a permanent, well-functioning stoma contributes to an improved quality of life.[44,45]

Despite many advances related to enterostomas, their placement, care, and closure are still associated with a surprisingly high rate of both early and late complications.[46–70] These facts present the surgeon, the enterostomal therapist, the nurses, the parents, and the child with major challenges. Therefore when the need for a stoma arises, the best results are achieved by carefully evaluating the child's pathologic condition and health status, weighing the pros and cons of diversion, planning ahead (for eventual closure) whenever possible, and considering both construction and takedown as major interventions.

In addition to the well-defined guidelines for stomal placement established for adult patients, pediatric factors including anatomic and physiologic differences, delicate structures, growth, and physical and emotional maturity, as well as preoperative preparation, whenever possible, need to be considered.[24,25,71] The surgeon and members of the surgical team must always keep in mind that the quality of life of a patient with a stoma is largely related to the quality of that stoma.

# Types of Enterostomas

The four basic types of enterostomas, primary purposes, and technique options are listed in Table 98-1. Examples of these methods are illustrated in Figures 98-1 to 98-3. Options for bringing the proximal stoma through the abdominal wall and handling the distal stoma are listed in Table 98-2. Examples are found in Figures 98-3 to 98-5.

**TABLE 98-1**
**Applications and Considerations for Enterostomas**

| |
|---|
| **Administration of Feedings, Medication, or Both** |
| Without entering the jejunal wall: nasojejunal tube, gastrostomy-jejunostomy tube[34] |
| Direct access through the jejunal wall: tunneled catheter,[9] needle catheter, T-tube,[82] button,[100] other |
| Isolated jejunal loop brought directly to abdominal wall: Roux-en-Y[108–110] |
| **Proximal Decompression and Distal Feedings** |
| Gastrostomy and distal feeding tube, same stoma or separately[20,34] |
| Double-lumen tube in dilated proximal jejunum with feeding end across an anastomosis[19]; or two single-lumen tubes inserted separately into divided, closed loops of small intestines[81] |
| Divided intestinal segments brought directly to skin level, with pouch applied to proximal stoma and feeding catheter inserted into distal one |
| **Access for Antegrade Irrigation** |
| Appendix or other intestinal conduit brought to abdominal wall for intermittent catheterization[5,52,85] |
| Catheter, T-tube, skin level device placed in intestinal lumen[37,41,81,88] |
| **Decompression, Diversion, or Evacuation** |
| End stoma, single opening[11] |
| Double-barrel stoma[10,17] |
| End stoma with an anastomosis below the abdominal wall[13,15] |
| Loop over a small rod or skin bridge[8,14] |
| Closed loop with catheter[81] or open loop with occluding valve-type device allowing controlled egress |
| Special stomas such as a catheterizable pouch[36,47] |

# Indications for Enterostomas in Children

Temporary and occasionally permanent stomas of the small and large intestine are used in the management of a wide variety of surgical and nonsurgical pathologic conditions in neonates, infants, and children. With the exception of feeding and antegrade enema access, more than one half of all stomas are placed in the neonatal period and another one fourth in infants younger than 1 year of age.[51,52,54,59]

## JEJUNOSTOMIES

Indirect access to the jejunum via naso-jejunal or gastro-jejunal route is adequate for short- or intermediate-length nutritional support.[36] Direct access to the proximal small bowel is most commonly used for long-term enteral alimentation as an alternative to a gastrostomy, which is the preferred route.[34,72] The majority of patients requiring a feeding jejunostomy are neurologically impaired children, usually with complex medical problems associated with foregut dysmotility. Some of these may require both a gastrostomy and a jejunostomy in their management. Jejunal access can also be useful in the care of patients with acute surgical problems benefiting from early enteral nutrition (e.g., major trauma or burn victims, children needing long-term supplemental feedings). Various types of exteriorized jejunal segments were once used in the management of infants with biliary atresia, in an attempt to reduce ascending cholangitis. However, this approach is no longer used, in part because of secondary problems such as bleeding from stomal varices associated with portal hypertension[50] and because the stoma adds complexity to a future liver transplantation.

On the other hand, the use of a segment of intestine or drainage device interposed between the gallbladder and the abdominal wall for partial drainage of bile has been helpful in the management of children with some types of genetic cholestatic syndromes.[73–76] As with other segments of the intestine, exteriorization[55,77–80] or tube decompression[81] is indicated following bowel resection when a primary anastomosis is unsafe or impossible (e.g., necrotizing enterocolitis, midgut volvulus).

## ILEOSTOMIES

These stomas are essential in the management of neonates with certain types of distal intestinal obstruction (e.g., long-segment Hirschsprung disease, complex meconium ileus, gastroschisis with atresia).[13,52,54,82] Ileostomies are commonly placed to divert bowel contents when reestablishing bowel continuity is precluded by peritonitis, ischemia, or hemodynamic instability ( e.g., neonatal necrotizing enterocolitis) (Figs. 98-6 and 98-7).[77–79,82] Ileal diversion has traditionally been used in the surgical approach to colonic pathology (e.g., ulcerative colitis, familial polyposis) as temporary, protective, or, at times, permanent stomas.[3,4,11,83,84] Less common indications include other forms of inflammatory bowel disease, rare manifestations of colonic dysmotility, and monitoring of the intestinal graft in patients with small bowel transplantation.

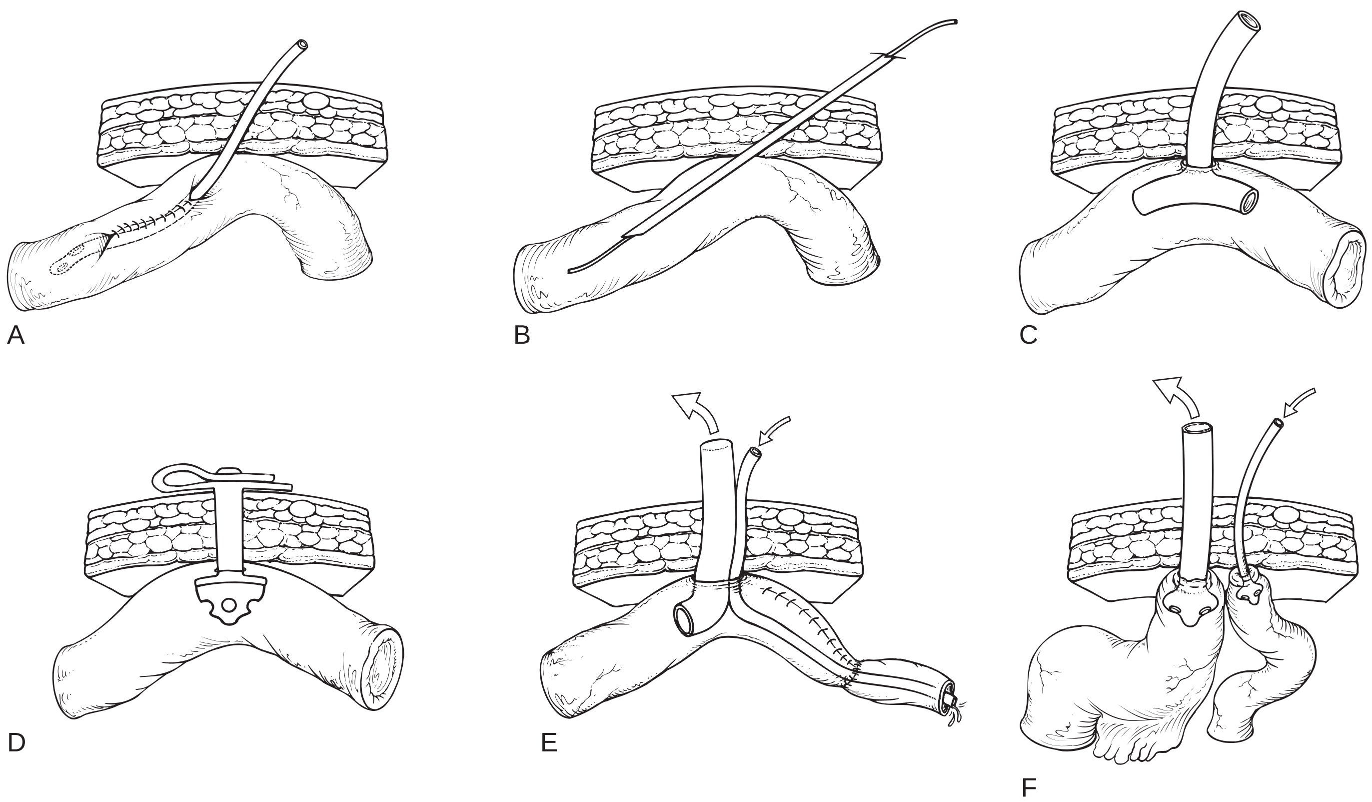


**FIGURE 98-1** Diagrams of select-feeding and decompressing-feeding jejunostomies. **A,** Tunneled catheter.[9] **B,** Needle catheter. **C,** T-tube.[82] **D,** Button.[100] **E,** Proximal decompression and distal feeding across an anastomosis.[19] **F,** Temporary decompression feeding using catheters when primary anastomosis is unsafe and intestinal exteriorization is undesirable or not possible.[81]

## APPENDICOSTOMIES, TUBE CECOSTOMIES, AND TUBE SIGMOIDOSTOMIES

The main indication for these interventions is to provide long-term access sites for antegrade intestinal irrigation in children with colonic motility, anal sphincter problems, and myelodysplasia.[39–42,85–91]

## COLOSTOMIES

Stomas of the large bowel have the longest history, and extensive experience with these enterostomies has accrued.[1–7] Diversion of fecal stream is essential in the treatment of several congenital hindgut pathologies (e.g., high forms of imperforate anus,[5,6,67] late diagnosis or complicated Hirschsprung disease,[68] complex pelvic malformations,[92] colonic atresia[93]). Colostomies are also used in patients with severe colonic, anorectal or perineal trauma,[32,94,95] perineal burns,[96] and complications of malignant conditions.[58,97] Unlike in the adult population, in which colorectal cancer is the most common indication, colostomies are rarely permanent in children.

## UROSTOMIES

Exteriorized segments of ileum or colon have been used as conduits in the management of urinary tract pathologies, although these diversions are seldom used today. However, the mobilized appendix, interposed between the bladder and the abdominal wall surface, is used in children with

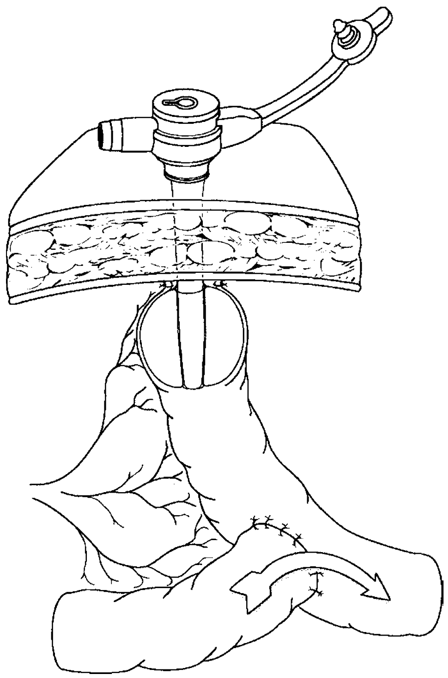

**FIGURE 98-2** Roux-en-Y feeding jejunostomy with a balloon-type skin-level access device.[108]

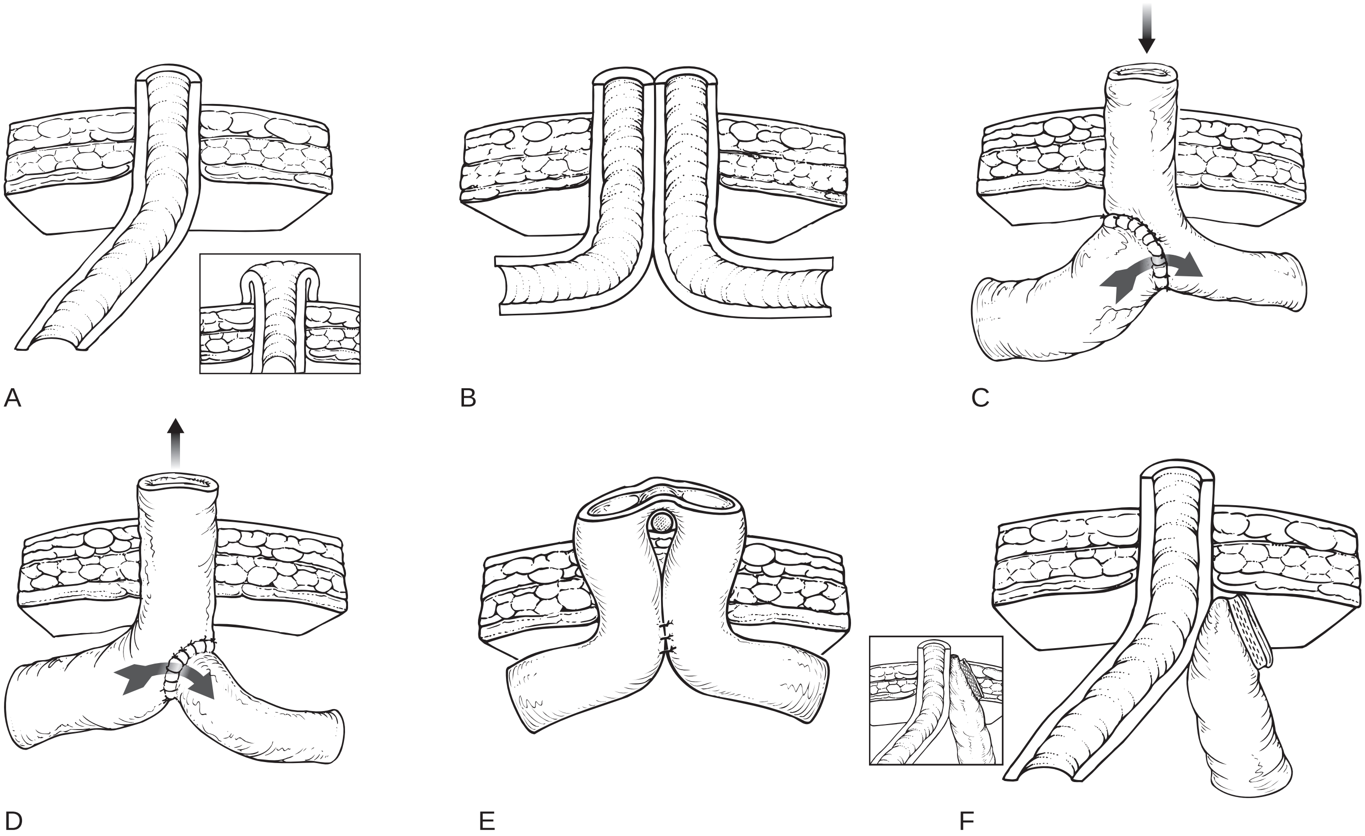


FIGURE 98-3 Examples of decompressing, diverting, or evacuating stomas. **A,** End stoma (*inset* shows typical maturation).[11] **B,** Double-barrel stoma.[10] **C,** End-to-side anastomosis with distal vent for irrigation.[13] **D,** Side-to-end anastomosis with proximal vent.[15] **E,** Loop stoma.[8] **F,** End stoma with closed subfascial distal of the end of the intestine (*inset* shows rodless end-loop stoma).

**TABLE 98-2**

| Enterostoma Exit |
|---|
| **Proximal Stoma** |
| Through celiotomy incision |
| Through separate opening |
| With proximal and distal limbs close to each other |
| With proximal and distal openings apart |
| Multiple stomas |
| Variations of the above |
| **Distal Stoma** |
| Exteriorization as mucus fistula adjacent to or separate from proximal intestine |
| Partial closure and placement next to the proximal stoma[92] |
| Closure and replacement into abdominal cavity |
| Closure after placement of a catheter for subsequent access for irrigation or contrast studies |

various urinary tract dysfunctions to provide a catheterizable conduit to the urinary bladder.[98,99]

# Choice of Enterostoma

## FEEDING JEJUNOSTOMY

Various approaches for establishing direct long-term access to the jejunum are now available. "Open" placement through a small, left upper quadrant incision permits excellent identification of the stoma site in the proximal jejunum, as well as secure attachment of the bowel to the abdominal wall.[36,37,100,101] Direct percutaneous endoscopic jejunostomy (PEJ) is applicable to older patients but difficult in small children due to limitations imposed by the endoscopic equipment.[102] A number of image-guided jejunostomies have been described but have been within the purview of radiologists in a few pediatric centers.[37,103,104] Laparoscopic or laparoscopically assisted techniques are now used with increasing frequency in all age groups.[105–107] Bringing the loop directly to the abdominal wall and placing a skin-level access device is simple and effective. Peristomal leakage is always a concern. An alternative intended to decrease this problem is the more complex Roux-en-Y approach.[108,109] However, this method has a greater potential for serious complications such as volvulus and internal hernias with intestinal obstruction.[110,111]

The choice of access device depends on the type of stoma and the age of the child.[27,112] Because straight catheters can be difficult to immobilize or replace in conventional tunneled jejunostomies, a good alternative is a T-tube for infants (because it does not obstruct the narrow lumen) (see Fig. 98-1, *C*), and an original type button (Fig. 98-1, *D*) or other nonballoon skin-level device for older pediatric patients. Balloon-type devices are suitable for the Roux-en-Y loop (see Fig. 98-2). As with a gastrostomy, these devices are both replaceable as an office procedure.

## ILEOSTOMY

In intra-abdominal interventions requiring intestinal resection, such as neonatal necrotizing enterocolitis, many surgeons prefer to exteriorize a single-end stoma through a counterincision

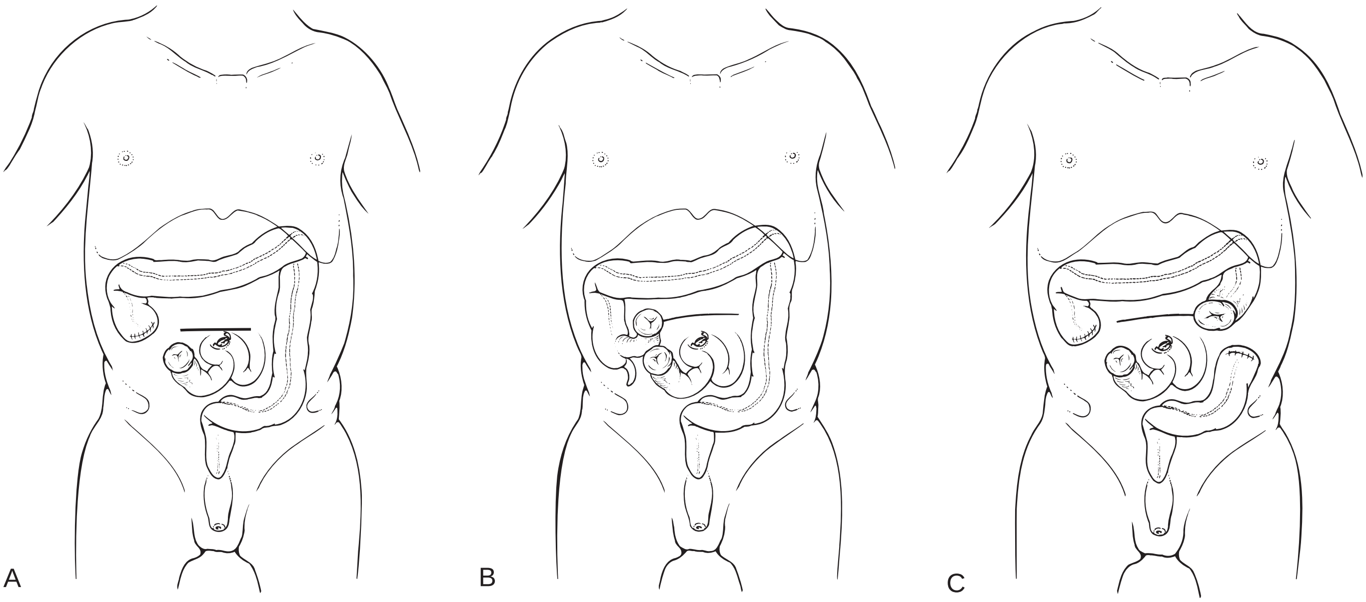


**FIGURE 98-4** Examples of options for the management of infants after intestinal resection. **A,** Exteriorization of proximal intestine through a counter-incision and closure of distal intestine beneath the abdominal wall. **B,** Same procedures as in **A** with exteriorization of proximal end of distal intestine through the wound edge. **C,** Arrangement after resection of two intestinal segments.

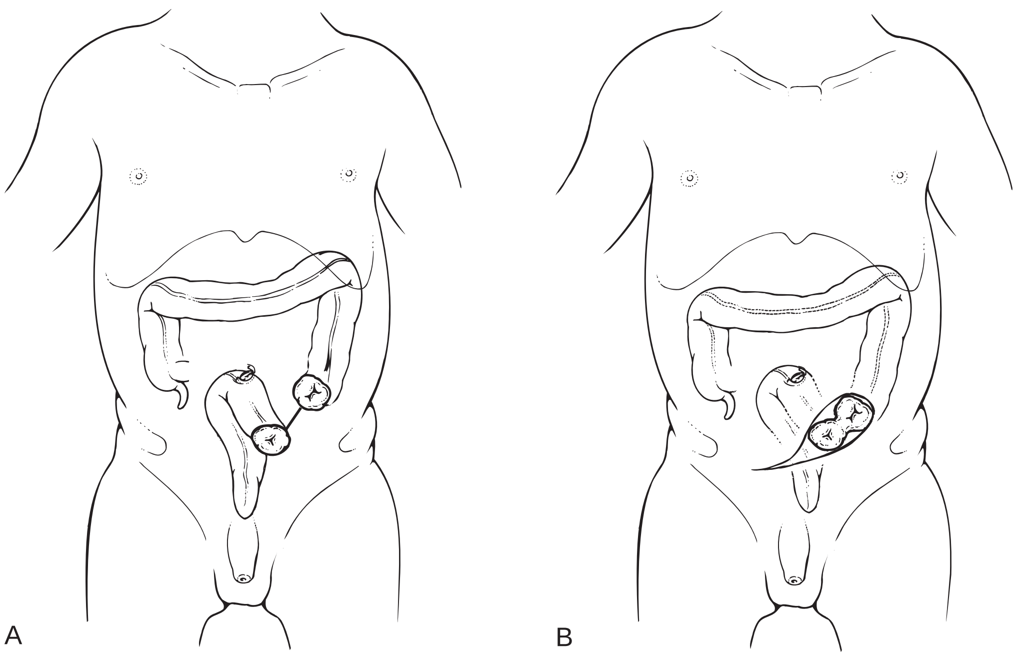


**FIGURE 98-5** Sigmoid colostomies. **A,** Separated stomas. The proximal intestine is at the upper end of the incision, and the mucus fistula is at the lower one. **B,** Loop colostomy. The intestine is exteriorized over a rod or skin bridge or with the help of sutures. The circumscribing comma-shaped incision is used for takedown and pull-through procedures.

(see Figs. 98-4, *A*, 98-6, and 98-7). A more expedient alternative is to bring the proximal intestine through the end of the incision (see Fig. 98-4, *B*). However, with this approach, wound complications are more common. In addition, if the stoma must remain for a prolonged period of time and the child gains weight, the fold created by the laparotomy incision may interfere with fitting of the stoma appliance (see Fig. 98-7).

With a healthy distal intestine and anticipated downstream patency, the distal limb may be closed and placed intra-abdominally adjacent to the proximal stoma. Otherwise, exteriorization as a mucus fistula is prudent (see Fig. 98-4, *B*). The use of an exteriorized loop stoma rather than an end stoma is an alternative in which the intact mesentery provides maximal perfusion.[79] A double-barreled stoma is a time-honored option.[77,78] To save as much intestine as possible, the placement of multiple stomas may be necessary (see Fig. 98-4, *C*). Although some ileostomy types were developed specifically for newborns with meconium ileus, they are no longer used. However, T-tube ileostomies have been useful for the instillation of liquefying solutions.[82]

In children with ulcerative colitis or familial polyposis, the enterostomal principles are similar to those established for adult patients. Choices for a temporary protective diverting

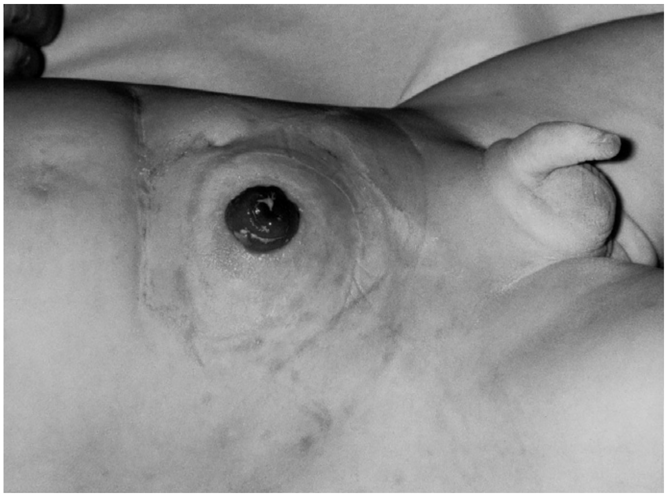

**FIGURE 98-6** One-year-old boy with severe necrotizing enterocolitis with loss of distal ileum and colon down to the peritoneal reflection before reanastomosis. Liquid stools precluded earlier reestablishment of intestinal continuity. Notice the appliance mark and the appropriate distance from the incision, the umbilicus, the inguinoabdominal fold, and the right anterior superior iliac spine.

**FIGURE 98-7** Same child as in Figure 98-6 in a sitting position. Notice the deep crease produced by the transverse supraumbilical incision. A stoma brought out through such an incision would have precluded proper use of the pouch, and a revision would have become necessary.

ileostomy include a simple loop, an end (distally closed) loop, and an end stoma, with the closed distal end under the fascia (see Fig. 98-3, *F*).

### APPENDICOSTOMY, TUBE CECOSTOMY, OR TUBE SIGMOIDOSTOMY

The choice of antegrade colonic enema (ACE) depends on the type of colonic pathology being managed. With normal peristalsis, either the right[41] or left[40,113] colon may be chosen for access. However, if dysmotility is a concern, access to the right colon is indicated. If the appendix is present, it is exteriorized with or without interposition of a "valve" by either an "open,"[88] or laparoscopic approach.[43,90] If the appendix is no longer available, the wall of the cecum may be fashioned into a conduit that is then brought to the skin level.[114] Exteriorizing the appendix at the umbilicus has cosmetic advantages. Either the appendix or the conduit so constructed is then catheterized to instill the enema fluid. A simpler technique, especially if there is no appendix, is the placement of skin-level device in the cecum by an open[115] or percutaneous approach.[87] For patients with normal colonic motility, access to the left colon by means of a sigmoid irrigation tube can be advantageous.[40]

### COLOSTOMY

Most colostomies fall into three categories: right transverse, left transverse, and sigmoid. The significant physiologic and anatomic differences among these three must be taken into consideration when choosing the site for the stoma. For infants with high imperforate anus, the high (proximal) sigmoid is the preferred site for exteriorization (see Fig. 98-5).[62,116] The main advantages are firmer stools with less tendency for skin excoriation, less tendency for prolapse, less surface for urine absorption, and less contamination of the urinary tract in male children with rectovesical fistula. Sigmoid stomas assist evacuation of meconium from the often dilated distal portion of the bowel during the initial procedure. The precise site is easily identified using the pelvic peritoneal reflection as a guide. A further advantage is that there are no scars in the epigastrium. However, if the low or mid sigmoid is inadvertently exteriorized, there may be interference with the blood supply, as well as insufficient bowel length for the future pull-through.[67,116] If the stoma is placed in the transverse colon, there is always adequate bowel length for pull-through, and the intestine is easy to mobilize and has a smaller diameter and no meconium. The disadvantages of transverse colon colostomy, however, are sizeable: The stools are looser, skin maceration and dehydration are more common, there is a greater prolapse rate, and there is an increased possibility of urinary tract problems. In addition, adequate evacuation of meconium is nearly impossible. Although high sigmoid loop colostomy is still used (Fig. 98-8), contemporary preference is for separation of the stomas, particularly in boys (Fig. 98-9).[67]

In children with Hirschsprung disease requiring a preliminary colostomy, the best site is the dilated segment that contains normal ganglion cells found proximal to the transition zone. A loop colostomy is usually chosen, although the tendency for prolapse is increased.[68] Because most transition zones are in the sigmoid colon, this lower left quadrant stoma is taken down at the time of the definitive corrective operation (see Fig. 98-5, *B*). If separation of the stomas is chosen, the distal intestine should not be oversewn in patients with Hirschsprung disease, particularly if the aganglionic segment is long, because mucus cannot be appropriately evacuated or washed out. Although similar data are not available in children, properly constructed loop colostomies are fully diverting in adults.[117]

## Select Technical Aspects

Feeding jejunostomies are generally placed in the left upper abdomen, slightly above the umbilicus, not so cephalic as to interfere with a possible gastrostomy and/or fundoplication.

FIGURE 98-8 Five-month-old child with high imperforate anus. The proximal sigmoid loop colostomy is equidistant from the umbilicus, the anterior superior iliac spine, and the inguinal fold. The original incision is only slightly longer than the stoma. Notice the raised "spur" between the two lumina, essential for proper diversion of stool.

FIGURE 98-9 Neonate with high imperforate anus. A divided proximal sigmoid colostomy was placed. The separation of the bowel ends minimizes the incidence of stoma-related problems.[67] The proximal bowel is slightly everted, and the mucus fistula is flush with the skin. (Courtesy Dr. Mark Levitt.)

In the "open" technique, the proximal jejunum is approached through a small, upper left quadrant incision. The ligament of Treitz is identified, and the catheter or skin-level device is inserted in the antimesenteric portion of the intestine, 10 to 20 cm distal to the duodeno-jejunal junction. A purse-string suture of fine multifilament synthetic absorbable material is placed around the enterotomy and tied. The catheter or skin-level device is then brought out through a counterincision. A second purse-string suture, made of monofilament synthetic absorbable suture is applied, with the sutures alternating between the intestine and the exit site of the catheter in the abdominal wall. When tied, this second suture approximates the intestinal serosa to the parietal peritoneum in a watertight manner.[100]

If a PEJ is chosen, the retaining intraluminal bumper must be size appropriate. Laparoscopic control can be used to increase the safety of PEJ, particularly in patients with abnormal epigastric anatomy. With laparoscopically assisted jejunostomies, particularly the Roux-en-Y type, proper loop orientation is essential. To minimize leakage (the most common problem with jejunostomies), appropriately sized skin-level devices must be selected. Devices that are too short or excessive tension on immobilizing crossbars must be avoided to minimize bowel wall or skin ischemia.

Decompressing ileostomies are usually placed in the right lower quadrant (see Figs. 98-4 and 98-6). The umbilicus is a possible site for a stoma[118] and is an excellent choice for the distended proximal intestine in newborns who have gastroschisis with atresia (Fig. 98-10).

Figure 98-11, *A* illustrates both appropriate and undesirable stoma exit sites in neonates, infants, and small children (e.g., those with necrotizing enterocolitis). Figure 98-12, *B* demonstrates ideal exit sites in older children or adolescents (e.g., those with ulcerative colitis or familial polyposis). Laparotomy incisions in the lower quadrants should be avoided in patients who may eventually have long-standing or permanent stomas because such incisions can create an uneven surface that interferes with pouch adherence.

When an enterostoma is anticipated, it is important that the site of the stoma and possible alternatives are marked on the abdominal wall before any incision is made. This planning is desirable in both elective and emergency settings. For elective, long-standing stomas, the best location is determined and marked the day before the operation (Fig. 98-12, *A* and *B*). The exit site should be located over the convex midportion of the rectus muscle, away from the incision, umbilicus, bony prominences, and skin folds. Special attention must be paid in overweight children because of the deep creases of the abdominal wall. In older children, if a vertical midline laparotomy is planned, it is advisable to create the opening for the ileostomy before making the incision. This is done in order to achieve a

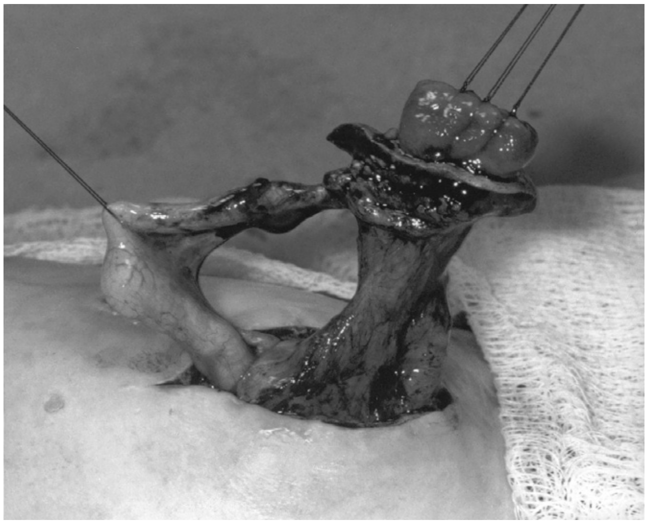

FIGURE 98-10 Four-month-old child with gastroschisis and small bowel atresia during reestablishment of bowel continuity. The dilated and edematous ileus was brought out as an end stoma through the umbilical site. The proximal closed end of the colon was attached to the side of the ileum underneath the abdominal wall. This maneuver allows prompt identification of the distal bowel, minimizing dissection and incision size.

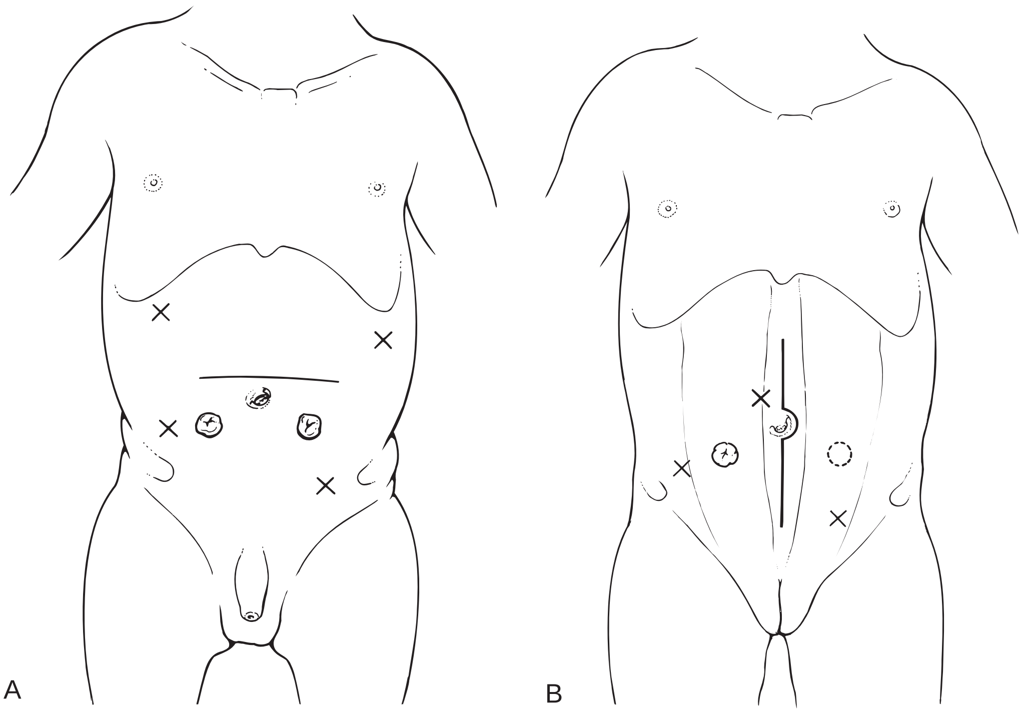


**FIGURE 98-11** Ideal sites for stomas. **A,** Infant. The end stoma can be brought out through a counterincision in the lower right or left quadrants. The sites marked with an "X" are unsuitable because they are too close to the rib cage, the anterior superior iliac spine, the flank, or the groin. **B,** Older child or adolescent. The best site for the stoma is in the mid rectus abdominis muscle in the right lower quadrant. The opposite side is an alternative. Areas marked with an "X" are unsuitable. The same sites are used with minimally invasive procedures.

straight course for the bowel and avoid distortion of the layers by traction on the edge of the incision. The entire opening should be just wide enough to allow for comfortable passage of the ileum without interfering with the blood supply. In laparoscopically placed stomas, adequate stoma exit size and bowel orientation are critical. With either approach, the bowel is secured intraperitoneally to avoid torsion and internal hernias and then secured with fine absorbable sutures to the rectus sheath. Depending on the size of the child, the matured ileostomy must protrude 2 cm or more to allow proper pouch fixation. This pouch is applied at the end of the procedure (Fig. 98-12, *C*). Stomas in neonates, particularly those established for necrotizing enterocolitis, should not be matured because this will interfere with the already tenuous blood supply. The exteriorized end of the stoma is simply anchored to the skin with four delicate sutures of a synthetic absorbable material. An antibacterial ointment is applied, and dressings are avoided. A pouch is applied with the onset of defecation. In infants, the mucosa grows rapidly over the exteriorized serosal surface. Deep, full-thickness sutures in the bowel should be avoided because they may cause a fistula from the lumen to the peristomal tissue, which will interfere with stoma pouch adherence.

The preferred colostomy site is the lower left quadrant. The guidelines for placement are similar to those for ileostomies. The most common site problem, particularly in newborns, is that the stoma is placed too caudally, close to the inguino-abdominal skin folds. When an infant flexes his or her hips, the resulting folds tend to lift the edges of the stoma appliance, leading to leakage. In children with imperforate anus, the meconium-filled sigmoid colon and the pelvic peritoneal reflection are identified once the abdominal cavity is opened. A suitable portion of the uppermost sigmoid colon is selected, and the bowel is exteriorized. When the dividing technique is used (see Fig. 98-5, *A*), the stomas are placed at each end of the incision and the intestine is secured with fine, synthetic, absorbable suture to all layers of the abdominal wall. There should be enough space between the two openings to permit a good fit for a pouch over the proximal stoma (or the distal stoma must be flush with the skin) (see Fig. 98-9). To avoid excessive narrowing of the stoma, an appropriately sized Hegar dilator or catheter is inserted into the intestinal lumen at the time of wound closure. End colostomies should only protrude slightly. With a loop stoma (see Figs. 98-5, *B* and 98-8), the incision is the length of that loop or only slightly longer. With the loop technique, a temporary catheter is placed through the mesentery of the selected segment, which is then lifted above the level of the skin. Triangulating sutures approximate the two limbs to each other and to the peritoneum on both sides to prevent internal hernias. The full circumference of the intestine is then attached to the peritoneum and fascia. Sutures lift the posterior bowel wall above the skin level. The intestine is opened longitudinally, and the edges everted. In all children with imperforate anus, the distal, meconium-filled segment of intestine is evacuated and flushed out at the time of colostomy placement. This is important to avoid formation of a fecaloma. In patients with Hirschsprung disease, the construction of the loop stoma must also be meticulous and may include tightening of the distended intestine to decrease the possibility of prolapse. This is particularly important in the distal segment. Rods or skin flaps placed under the loop are unnecessary if an appropriate "spur" between the two openings was created.

To facilitate subsequent takedown, when exteriorizing both ends of the small or large intestine, these should be kept as

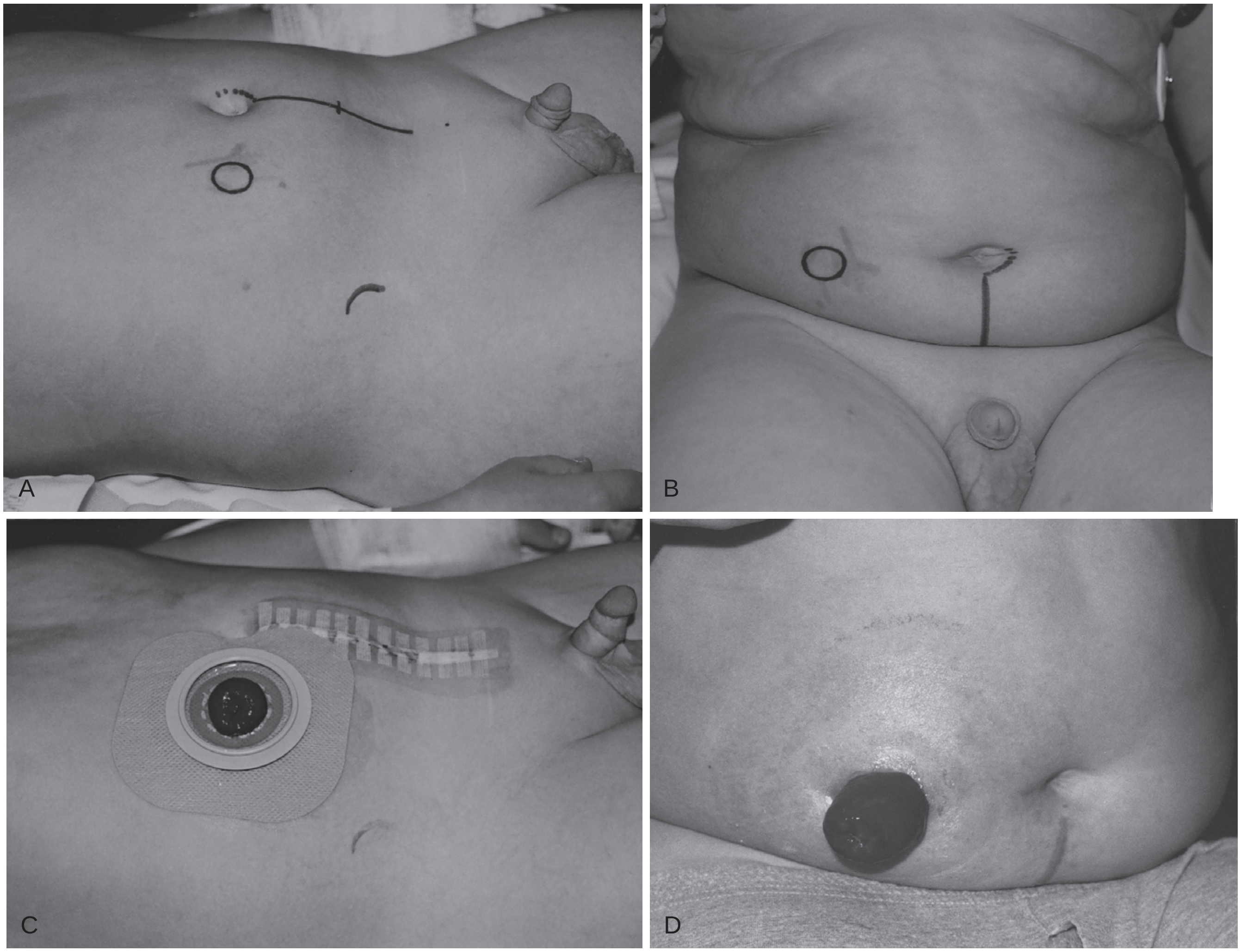

**FIGURE 98-12** Eight-year-old boy with intractable ulcerative colitis that failed to respond to aggressive medical management including corticosteroids, azathioprine, and infliximab. He underwent a total abdominal colectomy and ileostomy as a preliminary stage to an ileoanal anastomosis. **A,** The patient in a supine position. The stoma site had been determined several days before the procedure. The boy was asked to wear a two-piece pouch using the selected site as a guide. **B,** Bringing the already anesthetized patient into a sitting position confirmed the adequacy of the stoma site away from major abdominal folds. **C,** Skin barrier with flange (two-piece system) applied to the ileostoma at the completion of the colectomy. **D,** Six weeks later the stoma was well healed with mild residual edema. **E,** Same boy wearing a two-piece system with an opaque pouch. He emptied the pouch three to four times during the day and two to three times evening and nights. He enjoyed full physical activities including basketball. He did not use an ostomy belt and changed the skin barrier and pouch every 3 days. Bowel continuity has since been reestablished.

close as possible without interfering with the pouch. If the distal limb is placed underneath the abdominal wall, it is tagged with a nonabsorbable suture or a metallic clip (or both) and placed as close as possible to the exiting stoma to simplify identification at reanastomosis. Placing a metallic clip also helps with radiographic identification of the proximal end of the distal bowel and its patency when a barium enema is performed before reestablishment of bowel continuity in children with necrotizing enterocolitis.

Several of these techniques can be adapted for a minimally invasive approach.[43,107,119–123] In addition to smaller access sites, laparoscopy can be helpful in the precise identification of intestinal loops and targeted lysis of adhesions. However, the surgeon must exercise caution because the advantages of the laparoscopic approach can be negated by less than optimal handling of the bowel and exteriorization through openings of inadequate size.[119]

## Stoma Care

Proper care of an enterostoma begins with preoperative preparation whenever possible.[24,25,124] Parents, as well as older children, must be carefully taught and reassured before leaving the hospital and on subsequent follow-up visits. Ileostomies and proximal colon colostomies always require pouches. With the well-formed stools that result from sigmoid stomas, some parents of infants have used a skin barrier and diapers instead. A plant leaf has been recently suggested as an alternative.[125] A large selection of stoma appliances are commercially available including disposable and reusable pouches for all ages and sizes, even the smallest premature infants. Skin barriers, adhesives, powders, vented pouches, and odor control solutions are among the products that make the care of today's ostomate easier.[1,2,27,112,126]

Properly fitted appliances should remain in situ for several days; 3 days is a reasonable expectation. There are two basic types of pediatric appliances: the one-piece pouching system in which the adhesive skin barrier is already attached to the pouch and the two-piece system in which the adhesive skin barrier is separate from the pouch. In the latter, the pieces snap together with a flange (see Fig. 98-12, *C* and *E*). Because of the holding power of contemporary adhesive skin barriers, additional fixation with tape or belts is usually not necessary. The skin barrier is cut to the proper stoma size with the help of a template provided with the pouches. In addition to instructions provided by the surgeon, nurses, and the enterostomal therapist, parents are encouraged to contact one of the enterostomal societies such as the United Ostomy Association of America (an affiliate of the International Stoma Association) or the Wound Ostomy and Continence Nurses Society[23,127] and make use of the extensive printed and electronically available educational material. Although "continent stomas" using special intra-abdominal intestinal pouches,[83,128] magnetic caps,[129] valves,[130] inflatable plugs,[131] and other forms of luminal occlusion[132] have been attempted, there is limited experience with such operations or devices in children.

Candidiasis remains a common problem in the parastomal skin, and local antifungal medication should be used at the earliest sign of irritation. With skin excoriation, the area is exposed to air and a synthetic barrier is applied. A hair dryer can be useful. Mild stomal bleeding is usually self-limiting. Excision and/or application of silver nitrate may be necessary to control granulation tissue around the mucosa-skin interface in the early stages.

Remaining sutures are often the cause and should be removed. Routine dilatation of stomas is not recommended. Malfunctioning stomas often require early takedown or revision before more serious complications occur. Occasional irrigation of the distal intestine can be useful and help eliminate malodorous mucus plugs. Dietary and select pharmacologic manipulations are helpful in producing firmer stools. Children with high ileostomies must be carefully monitored to prevent electrolyte imbalance and insufficient nutrient absorption.[49,133,134]

## Reestablishing Intestinal Continuity

Timing of enterostoma closure varies widely depending on the underlying condition, health status of the child, and presence or absence of stoma-related complications.[78,135–139] Unnecessary delays in the reestablishment of bowel continuity tend to increase morbidity and should be avoided.[62,63,137] The more proximal the stoma, the earlier it should be closed to decrease metabolic complications.[62,133,134] Children who previously underwent resection because of ischemic intestine must have a preoperative contrast study of the distal segment to rule out strictures or complete luminal obstruction. Use of routine studies in other settings has been questioned.[140] Reestablishment of small bowel continuity generally does not require intestinal preparation. Takedown of a colostomy is preceded by antegrade intestinal irrigation, supplemented by conventional enemas. Although perioperative intravenous antibiotics are routinely administered, the use of intraluminal antibiotic solutions is controversial[141] and probably not indicated. When reestablishing continuity involves the left colon or sigmoid, the insertion of a soft catheter into the rectum assists the intraoperative identification of that loop, particularly if the anatomy has been altered by peritonitis or a previous operation. Good exposure with full mobilization of the intestinal ends is important. Laparoscopy can be helpful in select patients.[142] Although extraperitoneal closure has been used in children, it is not recommended for routine use.[143] For the intestinal anastomoses, a single-layer technique using fine interrupted sutures of synthetic absorbable suture material provides excellent results. Primary wound closure is generally safe and advantageous.[139,144,145] Early postoperative feeding after colostomy closure is encouraged.[146]

## Complications of Enterostomas

Problems related to construction, care, and closure of stomas in the small and large intestines are numerous and common. They can lead to significant morbidity and occasional mortality (Table 98-3). Analysis of pediatric series reveals complication rates that often reach and sometimes exceed 50%.[16–18,46–70,132–139]

In addition, stoma revision or early takedown is frequently necessary.[47,54,68,135] Complications of enterostomas used for feeding are often accentuated by the patient's underlying disease, particularly in malnourished, neurologically impaired children.[57,72,109] Stomas used for evacuation of the small intestine are associated with a higher morbidity than are

**TABLE 98-3**
**Common Complications of Enterostomas**

| |
|---|
| Prolapse |
| Stricture |
| Retraction |
| Wound separation, dehiscence |
| Wound infection, postoperative sepsis |
| Parastomal hernia |
| Intestinal wall separation or perforation with catheter change |
| Exteriorization of wrong intestinal segment or end |
| Intestinal obstruction (adhesion, internal hernia) |
| Intestinal torsion with ischemia |
| Fistula formation |
| Perforation by feeding or irrigating catheter |
| Poor appliance fitting and leakage |
| Psychological trauma |
| Skin excoriation, candidiasis, dermatitis |
| Mucosal excoriation and bleeding |
| Granulation tissue of mucosa-skin interface |
| Variceal bleeding with portal hypertension |
| Electrolyte imbalance |
| Acidosis (caused by urine absorption in the distal loop of intestine) |
| Fecal impaction (in the distal loop of intestine) |

colostomies because these stomas are compounded by fluid, electrolyte, and absorption losses.[39,133,134] Transverse colostomies are more prone to complications than are sigmoid stomas[47,53,62,67,147]; in several series, divided colostomies have been preferred over loop colostomies.[62,67]

Among the more common serious complications are prolapse (Fig. 98-13), stricture, and retraction.[51–57,63,66,67] The incidence of prolapse in children may exceed 20% and is more common if the distal loop is exteriorized.[51–57,62–69] Stomal prolapse may be categorized into minor and major forms. Minor prolapse is associated with a protuberant, edematous stoma that is still functional. It is usually amenable to nonsurgical techniques aimed at decreasing bowel edema, permitting manual reduction. The application of table sugar, ionized salt crystals, hyaluronidase, and hypertonic saline injections have been shown to effectively diminish bowel edema osmotically.[148–151] In major prolapse there is cyanotic, dusky, and edematous protruding bowel that may totally occlude the stomal orifice. This requires prompt attention, and general anesthesia is often necessary for intestinal reduction. Temporizing measures for control of prolapse include external devices,[152,153] modified purse-string suture techniques[154–156] or placement of U-shaped stitches from the lumen of the reduced intestine through the abdominal wall over an internal and external pledget or clothing button.[157,158] These pledgets hold the intestine against the abdominal wall and prevent the suture from cutting through. Stricture, if mild, may respond to dilatation. However, if evacuation is decreased and the proximal intestine begins to dilate, revision is advisable. This procedure is usually possible by incising all layers around the strictured stoma and bringing out healthy, at times dilated, bowel. The opening should not be excessive, however, because this might lead to prolapse. If the problem is more complex or a parastomal hernia is present, the pathologic process is addressed through a counterincision or laparoscopic repair.[159] Retraction of an end stoma results in poor fitting of the appliance and may lead to skin-level stricture and obstruction, whereas retraction of a loop stoma interferes with proper evacuation and leads to filling of the distal intestinal loop with stool. Stomal bleeding is a rare but serious complication in children on long-term parenteral nutrition with liver dysfunction leading to portal hypertension. The varices developing between the portal and systemic circulations at the level of the stoma are vulnerable and may result in significant drops in hemoglobin levels. Following the correction of a possible coagulopathy, most of these hemorrhages are amenable to direct pressure, suture ligation, or application of hemostatic substances.[160] Tranexamic acid, an antifibrinolytic amino acid, has been reported to stabilize formed clots and reduce rebleeding.[161] Nonparietal intestinal obstruction from adhesions or internal hernias can occur at any time,[111] even in the immediate postoperative period.[162]

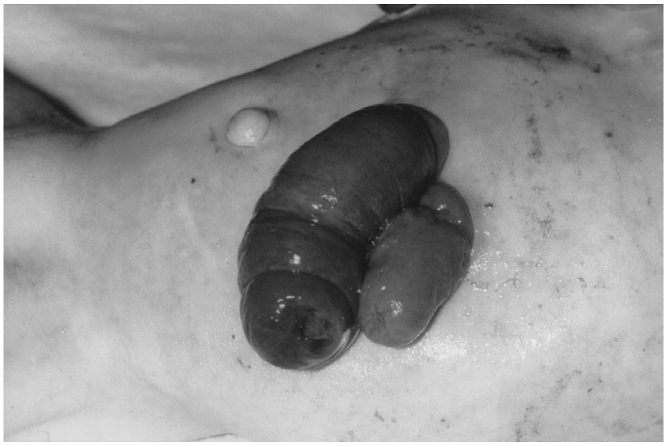

**FIGURE 98-13** Six-month-old child with Down syndrome, congenital heart, and Hirschsprung diseases. Proximal and distal colon prolapse have occurred through a left transverse colon loop colostomy. Notice the three openings at the end of the larger everted loop that correspond to the lumen of the cecum, the ileocecal valve opening, and the lumen of the appendix. The problem was managed by anchoring the cecum in the right lower quadrant and then securing the distal loop with a U-stitch and two rubber bolsters.[157] A definitive operation followed several months later.

Intestinal reanastomosis is also associated with a high rate of complications, most notably wound infection, dehiscence, fistula formation, and intestinal obstruction.[56,62,135,136] Among the various factors contributing to this morbidity are poor timing, inadequate bowel preparation, technical errors, and shortcuts such as improper choice of suture material and the excessive use of the electrocautery. Malnourished, debilitated, anemic patients and those on corticosteroids are at greatest risk for complications. These contributing factors should be corrected before reestablishment of intestinal continuity is contemplated.

Although the need, the indications, and various techniques for establishing stomas of the small and large intestine have shifted in the past couple of decades, the use of stomas remains a critical tool in the surgical care of children. Placement and takedown of any enterostoma should be carefully planned and considered a major procedure. Requirements include ideal operating conditions and, in a teaching setting, appropriate supervision. Pediatric stomas are quite different from adult stomas, and the importance of meticulous attention to detail cannot be overemphasized. Close follow-up is imperative to render these interventions as beneficial and complication free as possible.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 99

# Atresia, Stenosis, and Other Obstructions of the Colon

Marjorie J. Arca and Keith T. Oldham

## Atresia and Congenital Stenosis of the Colon

Although Binninger first described colonic atresia in 1673,[1] the first survivor was not reported until 1922, when Gaub[2] treated a child with atresia of the sigmoid colon with a proximal diverting colostomy. In 1947 Potts[3] performed a primary anastomosis of the transverse colon for atresia in a newborn who survived. Although colonic atresia is uncommon, colonic stenosis is exceedingly rare. Only 10 congenital colonic stenosis patients have been reported since 1966.[4–10] Most cases with congenital stenosis and atresia were managed with resection of the involved colonic segment and end-to-end anastomosis, but a staged approach using a decompressive colostomy in the proximal dilated segment was judged necessary in several patients. All the reported infants with congenital colonic stenosis have survived, while mortality in atresia patients is generally attributed to associated anomalies. It is clear that many such patients are no longer the subject of individual reports.

Colonic atresia is reported to occur from 1 in 1498 live births[1] to 1 in 40,000.[11] Episodic cases of isolated congenital colonic atresia are seen annually at most children's hospitals in the United States, corresponding to 1 in approximately 20,000 births.[5,12] Colon atresia is considered the rarest atresia of the gastrointestinal (GI) tract, comprising 1.8%[13] to 15% of intestinal atresias;[5,10,14] these estimates exclude related malformations of the rectum, which are traditionally considered within the spectrum of imperforate anus. There is no known gender or racial predilection of colonic atresia or stenosis. Although a similar abnormality is commonly inherited in an autosomal recessive pattern in Holstein cattle,[15] no familial association is known in humans. Hereditary multiple atresias of the intestines typically exclude the colon.

Colonic atresia is associated with several important anomalies of the musculoskeletal system (e.g., syndactyly, polydactyly, clubfoot, absent radius)[16]; eye[14]; heart[14]; GI tract[16]; and abdominal wall (e.g., gastroschisis, omphalocele, bladder or cloacal exstrophy).[17,18] Facial hemiaplasia, anophthalmia, and cloacal extrophy,[19] as well as facial asymmetry with agenesis of the corpus callosum, cerebellar hypoplasia, and enlargement of the fourth ventricle, are also reported.[20] Stickler syndrome, which is a chondrodystrophy with congenital alteration of type II collagen, has been reported in a patient with colon atresia.[21] In the largest relevant report, 22 of 36 infants with colonic atresia had no associated anomalies.[16] Of the remaining 14 infants in that report, 9 had midline abdominal wall defects and 5 had jejunal atresia. Davenport reported on 118 infants with colonic atresia. Twenty-eight percent of the lesions occurred in the ascending colon, 3% in the hepatic flexure, 23% in the transverse colon, 25% in the splenic flexure, and 20% in the descending and sigmoid colon.[22] A recent report from China reported on three babies with upper rectal atresia.[23]

Approximately 15% to 20% of infants with colonic atresia have proximal small intestinal atresia[14,16]; therefore neonates with intestinal atresia should routinely have distal patency including the colon evaluated in the operating room or with preoperative contrast enema. A combination of imperforate anus and colon atresia have been reported in six patients in the English literature.[24–29]

Hirschsprung disease is recognized in at least 2% of patients with colonic atresia.[30–34] Some authors have hypothesized that when a vascular insult occurs before retroperitoneal fixation of the colon at 11 weeks' gestation, caudal migration of the myenteric neurons is interrupted.[31] Therefore it is imperative to rule out Hirschsprung disease, typically with suction rectal biopsy, before reestablishing intestinal continuity in every patient with colonic atresia.

## Embryology

The classic etiology considered responsible for intestinal atresia is in utero vascular insufficiency after organogenesis.[35–37] Possible causes of vascular insult include volvulus, intussusception, embolic or thrombotic events, and incarceration or strangulation secondary to hernias or abdominal wall defects. Maternal use of cocaine, amphetamines, nicotine, and

decongestants has been implicated in intestinal atresia. Focal resorption of the compromised gut apparently occurs after ischemic necrosis. The spectrum of observed abnormalities is similar to that of small intestinal atresia, in which experimental work by Louw[38] and Barnard and Louw[39] confirmed the pathogenic role of in utero vascular occlusion. The classification system of Bland-Sutton[40] and Louw[38] for small intestinal atresia is also applied to the colon. Briefly, type I lesions are intraluminal obstructive webs; type II lesions are blind proximal and distal segments connected by a fibrous cord; and type III lesions are completely separated segments of intestine, with an intervening V-shaped mesenteric defect. Type III abnormalities are the most common.[14,17] Complex mesenteric defects and multiple atresias have been described. This classification system has limited clinical value because surgical principles and outcome are not dictated by the anatomic categorization of the lesion.

In the past decade, a possible genetic mechanism for intestinal atresia including duodenal, small bowel, cecal, and colonic has been elucidated. Fibroblast growth factor 10 (Fgf10), a protein expressed in the colon and mesenteric vasculature sites, has been widely implicated in cell survival and cell growth. Invalidation of the Fgf10 or its receptor, RFgfr2b, resulted in colon atresia in mice with intact mesenteric vasculature.[41] This finding suggests that intestinal atresia may be caused by more than simple vascular insufficiency.

Congenital colonic stenosis is much less common than colonic atresia. Seven of the eight reported cases of congenital colonic stenosis demonstrated a segmental stricture of the colon, with lengths ranging from 3 to 16.5 cm.[4–6,9,10] The cause of these stenoses has also been attributed to interruption of the blood supply of the developing colon. A partially obstructing intraluminal membrane has been described as the cause of colonic stenosis as well.[11,42]

## Clinical Presentation

Prenatal ultrasonography typically shows an enlarged loop of intestine or colon, leading to a presumptive diagnosis of distal intestinal atresia.[11,43] Polyhydramnios is usually not seen because the relatively distal point of obstruction allows amniotic fluid to be absorbed in the proximal small intestine.

Clinically, an infant with colonic atresia or stenosis usually develops a distended abdomen within 24 to 48 hours after birth. Because the obstruction is distal and usually complete, abdominal distention is predictably marked and progressive. Mechanical ventilatory support may be necessary due to massive intestinal dilatation and abdominal distention. Vomiting may be delayed in onset, with feculent vomiting as a late manifestation. Infants with colonic atresia typically pass little or no fecal matter. Rectal examination yields white mucus rather than bile-stained meconium. In neonates, coexisting cranial, musculoskeletal, or abdominal wall abnormalities may be apparent on inspection.

## Diagnosis

Abdominal radiographs of infants with colonic atresia show multiple distended intestinal loops with air-fluid levels. Although the small intestine and colon are not readily distinguishable in the neonatal period, the degree of distention immediately proximal to the obstruction is often more marked in the colon than in similarly obstructed small intestine (Fig. 99-1). In fact, the colonic obstruction may be so profound that it may be mistaken for a pneumoperitoneum. Pneumoperitoneum is a sign of proximal colon perforation, usually associated with abdominal tenderness. This is present in approximately 10% of

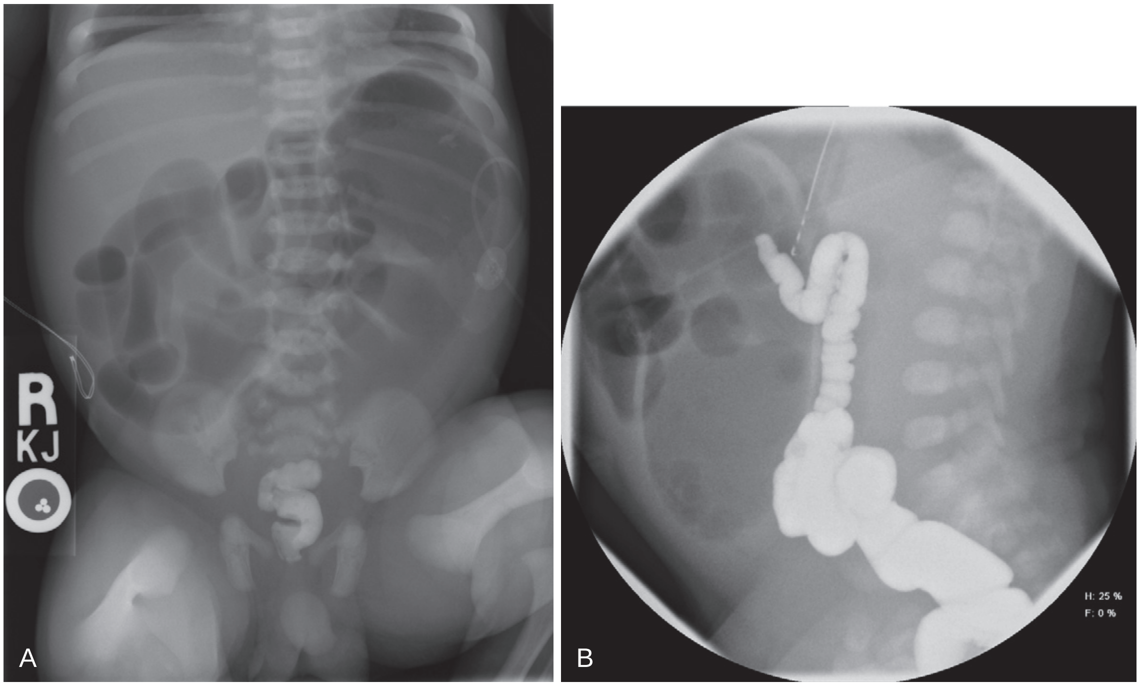


**FIGURE 99-1** Colonic atresia. **A,** Plain radiograph of a baby with significant intestinal dilation. Previously injected contrast that was injected per rectum remains in a diminutive rectal segment. **B,** Contrast enema in the same patient shows a microcolon. On exploration the atresia was at the level of hepatic flexure.

infants with this disorder at the time of diagnosis.[16] It appears that this scenario results when a competent ileocecal valve creates a segment of colon obstructed both proximally and distally, thereby increasing the risk for perforation.

Contrast enema using isotonic contrast agent establishes the diagnosis of colonic atresia or stenosis. Complete obstruction is characterized by a distal "microcolon," which is diminutive from disuse but is intrinsically normal in most circumstances. The contrast medium typically fills the lumen of the distal colon, terminating at the point of obstruction. Congenital stenosis is characterized by narrowing of the intestine and limited proximal filling with contrast medium; proximal intestinal dilatation is often seen.

A contrast enema is important in the evaluation of any neonate with suspected distal intestinal atresia because the surgeon must identify the likely cause of obstruction, as well as blockages that may be distal to the most proximal atresia before repair. Retrograde contrast may also differentiate between a fixed anatomic cause and other causes of distal obstruction such as meconium plug syndrome, Hirschsprung disease, or neonatal small left colon syndrome.[43] In patients with colonic atresia or stenosis, no other imaging is necessary to define the intestinal anatomy.

## TREATMENT

Any infant with suspected intestinal obstruction should have nasogastric tube decompression and resuscitation with intravenous fluids. Broad-spectrum antibiotics are generally administered before the procedure. Operative management should not be delayed because of the risks of perforation and segmental volvulus. The most common finding in colonic atresia is two blind ends of colon with no intervening mesentery (type III). In the past, emphasis was placed on the relevance of the site of atresia in surgical decision making.[14] In contemporary practice, primary anastomosis is preferred unless there is medical instability, vascular compromise, significant mismatch between the two ends, fecal soilage, or physiologically important comorbidities.

Laparotomy is usually undertaken through a transverse, supraumbilical position, taking into account the position of a possible stoma. The obstructing lesion is resected, along with compromised or excessively dilated proximal intestine in order to facilitate functional recovery. Preservation of intestinal length is, of course, an important principle for any intestinal atresia, but this can be reasonably moderated for colonic atresia, in an effort to minimize size mismatch for the anastomosis and facilitate onset of intestinal function. Patency of the distal segment should be demonstrated unequivocally either preoperatively or intraoperatively, as noted previously. Intestinal continuity is most commonly reestablished with a single-layer, end-oblique anastomosis.

Because of the association with Hirschsprung disease, a suction rectal biopsy to evaluate for ganglion cells should be performed in the operating room if primary anastomosis is planned. Similarly, if a colostomy is deemed appropriate, the myenteric plexus at the colostomy site should be examined at operation and a rectal suction biopsy done before reanastomosis.

Coloplasty is usually not recommended, given the excellent outcome of resection and anastomosis. Complex colonic atresias and those associated with abdominal wall defects may require other approaches such as proximal stoma formation and staged repair of the colon.

## RESULTS

Complications of colonic atresia and stenosis repair are generally the same as for other types of colonic surgery. These include anastomotic stricture, leak, proximal segment dysfunction, adhesive small intestinal obstruction, wound infection, and stoma-related problems.[14,16,44] In a report by Powell and Raffensperger,[14] 15 complications occurred in 19 patients treated between 1946 and 1978, with a mortality rate of 10.5% associated with colonic atresia. DellaVecchia and colleagues[45] reported 21 patients with colonic atresia and stenosis presenting from 1972 to 1997; 12 of these patients had complications including wound infection (1), stoma prolapse (1), prolonged ileus (2), and late adhesive bowel obstruction (8). In this more contemporary series, there was no operative mortality and the long-term survival rate was 100%.

# Acquired Colonic Stenosis

Various inflammatory, infectious, traumatic, and neoplastic processes may lead to acquired colonic stenosis in infants and children.[46] Of these, neonatal necrotizing enterocolitis (NEC) is the most common. About 11% to 35% of infants with this disorder develop intestinal strictures, with about 70% involving the colon.[47–49a] Submucosal fibrosis and varying maturation of intestinal scar are seen on resected stenotic specimens.[50] Butter and colleagues[51] performed a retrospective study of NEC patients with Bell's stage II or III disease and found an apparent increase in the overall stricture rate requiring operative intervention, from 46% in 1990-1994 to 69% between 1995 and 1999. Subgroup analysis showed the increase in stricture was seen in the medically treated infants, with stricture formation increasing from 15% to 48%. Interestingly, the surgically treated NEC patients had a stable stenosis rate between the two time points, from 36% to 33%. The sigmoid colon is the most common site of NEC-associated stenosis, but the entire intraperitoneal colon and small intestine are at risk. Several lesions may be present and are usually partially obstructing (Fig. 99-2). Failure to advance oral feeding, bilious vomiting, and abdominal distention are typical. The diagnosis is established by contrast enema radiography. Treatment generally consists of segmental resection and primary reconstruction. Resection with proximal diversion and staged reconstruction is an alternative in high-risk patients. Successful balloon catheter dilatation of focal colonic strictures has been reported, but the experience is quite limited and rarely used in contemporary practice.[52,53]

Other infectious and inflammatory disease states have been associated with colonic strictures. They have been reported as sequelae of hemolytic uremic syndrome[54] and methicillin-resistant *Staphylococcus aureus* enterocolitis.[55] In children with human immunodeficiency virus, angioinvasive *Candida* species have been reported to cause acute colonic obstruction and death.[56] A recent report of colon stenosis details a sealed perforation, apparently secondary to Mycobacterial infection, in a 10-year-old boy, managed with segmental colon resection and tuberculostatic medications.[87] Chronic nonsteroidal

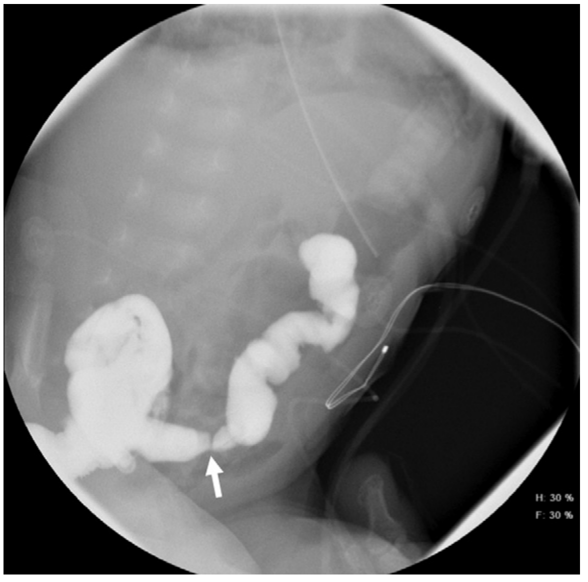


**FIGURE 99-2** Contrast enema radiograph in a 3-month-old infant with a history of necrotizing enterocolitis, treated without surgical intervention. He developed feeding intolerance, vomiting, and abdominal distention. A stricture is seen in the descending colon (*arrow*) and complete obstruction at the splenic flexure. Segmental resection and primary anastomosis were curative.

antiinflammatory drug use has been implicated in colonic stenosis in adults,[57] but thus far, there are no reports of this problem in the pediatric population.

Neoplasia may cause colonic obstruction by development of intraluminal lesions (polyps, neurofibromas,[58,59] adenocarcinoma[1,60,61,91–93]); extrinsic compression (lymphoma, retroperitoneal sarcomas or teratomas); or intramural infiltration (tuberous sclerosis, neurofibromatosis).[62] None of these is common. In all cases the underlying disease should be controlled, if possible. In general, focal benign lesions are resected, with primary reanastomosis of the colon. Congenital infantile fibrosarcoma of the colon has been reported in newborns, with perforation as the presenting sign.[64,90] Malignant and complex benign lesions may require fecal diversion, staged procedures, or more complex reconstruction of the colon.

Adenocarcinoma of the colon occurs rarely in young patients. A significant percentage of patients have predisposing factors such as ulcerative colitis and familial adenomatous polyposis.[65] Obstructive pain is the presenting complaint in 97% of patients younger than 21 years with adenocarcinoma.[66] Overall survival in children is approximately 25%; in adults, survival approaches 50%. Delay in diagnosis,[67,68] advanced disease stage at presentation,[69] and unfavorable histopathologic characteristics[66] all contribute to the observed lower survival rate in children. LaQuaglia and colleagues[35] reviewed 29 pediatric patients with adenocarcinoma and concluded that children are more likely to have poor-prognosis lesions such as "signet ring" or undifferentiated lesions (69%), compared with the moderately differentiated or carcinoma in situ (31%) found in adults. Histopathologic characteristics and lymph node involvement were the most important predictors of childhood mortality in patients who had resection. Patients with high-grade lesions or involved regional nodes should be considered for adjuvant therapy in addition to resection.[35]

# Functional Colonic Obstruction

Various disease processes are associated with functional colonic obstruction. These forms of colonic obstruction are discussed in detail in Chapters 101 and 102 but are noted here as part of the differential diagnosis of colonic obstruction in infants and children.

Intestinal neuronal dysplasia is a disorder of the myenteric nervous system that has a clinical presentation similar to that of Hirschsprung disease.[70] While controversy over nomenclature and treatment continues, type A intestinal neuronal dysplasia is characterized by decreased sympathetic innervation of the intestine, with moderately increased parasympathetic nerve fibers. Type B IND B has histopathologic involvement of the submucosal ganglia, where there is an increase of ganglionic (nerve) cells in the ganglion with more than eight nerve cells per ganglion. Nerve cells are smaller than normal and are grouped into spherical giant ganglia. A minimum 20% of giant ganglia in 30 serial sections must be found to make a diagnosis of type B IND.[71] Intestinal dysmotility is manifested by various degrees of abdominal distention or constipation.

Ogilvie syndrome is an acute distention of the colon, often occurring in nonambulatory and medically complex patients. There is absence of an identifiable mechanical cause. It is usually seen in adults but may also occur in children and adolescents. The cecum and the right colon are frequently involved. Risk factors for developing Ogilvie syndrome include electrolyte abnormalities and the use of certain medications, particularly narcotics, that impair intestinal motility. Distention of the cecum impedes the natural propulsive activity of the colon. Cecal distention may cause ischemic necrosis. Nasogastric suction, discontinuation of relevant medications, and colonoscopic decompression are the mainstays of therapy. Recently, the use of neostigmine (0.36 to 0.45 mg/kg), an acetylcholinesterase inhibitor, has been reported in the pediatric literature.[72,89] Oral erythromycin may also have efficacy.[73]

Chronic idiopathic intestinal pseudo-obstruction occurs in children and adults.[74,75] Abnormalities of the intestinal smooth muscle (myopathy), myenteric plexus (neuropathy), or a combination of both may occur.

In neonates, a visceral myopathy known as the *megacystis-microcolon-intestinal hypoperistalsis syndrome* is characterized by an anatomically patent intestinal tract with normal ganglion cells but clinical evidence of obstruction secondary to ineffective peristalsis. This syndrome is often fatal because definitive medical or surgical therapy is not available.[44,46,76,77,93]

The meconium plug syndrome and the small left colon syndrome appear to be specific but related entities in the spectrum of functional neonatal colonic obstruction. For clarity, they are considered separately as follows.

## MECONIUM PLUG SYNDROME

Meconium plug syndrome is a relatively common cause of functional colonic obstruction in neonates (see also Chapter 101).[78,88] Affected infants may be premature but are generally normal otherwise. It has been suggested that the syndrome results from an immature myenteric nervous system causing ineffective peristalsis[79] and excessive water absorption, thereby producing desiccated meconium plugs that obstruct the colon. The pathogenesis is unproved but is thought to be

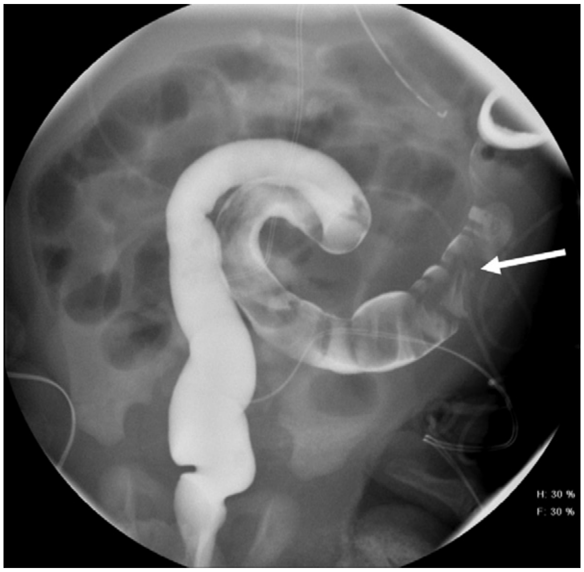

FIGURE 99-3 Radiograph of a term infant with the meconium plug syndrome. Contrast enema radiograph demonstrates many intraluminal filling defects (meconium plugs) throughout the colon (*arrow*).

related to temporary dysmotility. The clinical presentation is the same as that for distal intestinal obstruction. A water-soluble contrast enema is usually both diagnostic and therapeutic, but repeated enemas may be necessary for resolution (Fig. 99-3). Surgical management is rarely indicated, but rectal examination may be curative. Classically, two associated abnormalities need to be ruled out in a patient with meconium plugs—Hirschsprung disease and cystic fibrosis. In a retrospective survey encompassing 13 years, only 13% of patients with colonic meconium plugs were found to have Hirschsprung disease.[80] In the same analysis, no patient had cystic fibrosis, in contradistinction to other reports that showed up to 40% association between cystic fibrosis and meconium plug syndrome. The authors concluded that patients with isolated colonic plugs are less likely to have cystic fibrosis.[36] Suction rectal biopsy may be performed to identify Hirschsprung disease, although reserving this procedure for children who continue to have difficulties after evacuation of the plug is a reasonable approach. Sweat testing for cystic fibrosis may be reserved for infants with distal small bowel meconium plugging. Neonatal genotypic screening for the most common mutations for cystic fibrosis has become routine in most of the United States.

## SMALL LEFT COLON SYNDROME

Small left colon syndrome refers to a dysfunctional, diminutive left colon that causes transient obstructive symptoms.[69,81] Approximately 40% to 50% of infants with this disorder have diabetic mothers, almost all of whom are insulin dependent. In a retrospective study of infants born of mothers with either gestational or pregestational diabetes, Ellis noted a 4.7% incidence of small left colon syndrome.[82] Davis and Campbell[81] reported that 50% of asymptomatic infants of diabetic mothers also have radiographic evidence of a small left colon. The obstruction is typically partial and involves the descending colon distal to the splenic flexure (Fig. 99-4). The degree

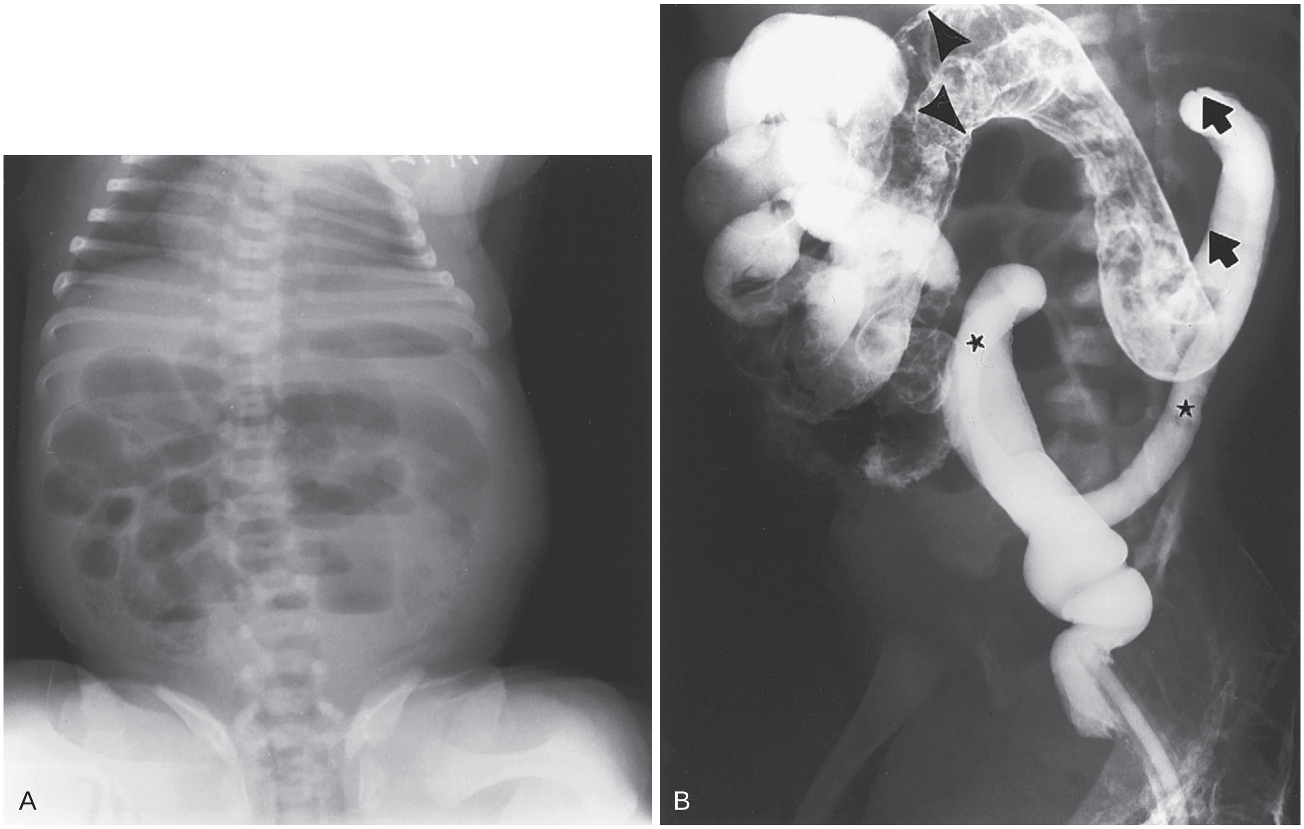


FIGURE 99-4 **A,** Plain radiograph of an infant born to a diabetic mother illustrating a distal intestinal obstruction. **B,** Barium enema radiograph shows typical findings of the small left colon syndrome. Note the distal microcolon (*asterisks*), the splenic flexure transition (*arrows*), and the dilated transverse colon proximal to the point of obstruction (*arrowheads*). (Courtesy D. Frush, MD)

FIGURE 99-5 Contrast enema radiograph illustrates inspissated stool in the transverse colon (*arrow*). The patient was an adolescent with cystic fibrosis who had recurrent obstructive episodes that were consistent with meconium ileus.

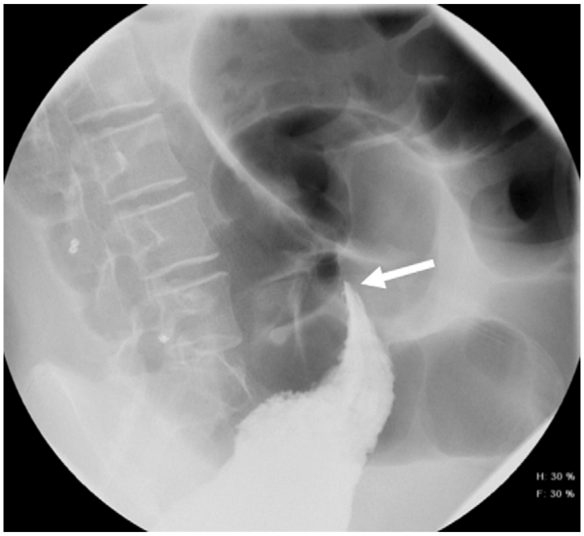


FIGURE 99-6 Contrast enema in a child with sigmoid volvulus. The *arrow* depicts the point of obstruction.

of obstruction varies. Proximal perforation, especially of the cecum, has been described.[83] The pathogenesis is thought to be related to hypoglycemia-induced release of glucagon in the infant. For reasons that are unclear, the neonatal left colon seems to be particularly sensitive to the smooth muscle constrictive effects of glucagon and other agents.[69] The problem is typically transient and resolves 24 to 48 hours after birth, corresponding to normalization of the infant's endogenous insulin output. A contrast enema is diagnostic and may be therapeutic by hastening resolution of the functional obstruction. The radiographic appearance of small left colon syndrome is quite similar to that of Hirschsprung disease because of the splenic flexure transition zone, so suction rectal biopsy is routinely performed to eliminate this possibility. It is prudent to also rule out cystic fibrosis.

## Meconium Ileus

Meconium ileus is the intestinal obstructive entity associated with cystic fibrosis and is discussed in detail in Chapter 83. Exocrine pancreatic insufficiency and water-deficient intestinal secretions are features of cystic fibrosis that combine to create thick, viscid stools that can impact and obstruct the small intestine or colon. This is classically seen in newborns but may also be a problem in adolescents with cystic fibrosis, whose compliance with exocrine enzyme replacement therapy may be erratic. The diagnosis is often revealed by the history and plain radiography but can be confirmed by contrast enema (Fig. 99-5). The preferred treatment is colonic irrigation in an antegrade or retrograde direction and the resumption of pancreatic enzyme replacement. Dilute (5% to 10%) N-acetylcysteine may be used occasionally. Chronic problems may require gastrostomy or cecal access for formal, periodic irrigation of the intestine.

## Miscellaneous Causes of Obstruction

Several rare causes of colonic obstruction merit brief mention. Among these are cecal or sigmoid volvulus, a wide variety of rare neoplastic lesions, anomalous congenital peritoneal bands,[63] hindgut duplication,[84] and congenital segmental dilatation (ectasia) of the colon.[27] Segmental dilatation of the colon is an idiopathic problem of infants and children and presents as partial colonic obstruction. It is a focal, functional defect in which the involved segment of colon lacks peristalsis and has no taeniae coli. Because both the proximal and distal colon are functionally and anatomically normal, surgical resection is curative.[85]

Segmental volvulus of the colon involves either the sigmoid colon or the cecum (Fig. 99-6). The typical patient is a child or adolescent with a long-standing history of constipation or pseudo-obstruction. The clinical presentation is abdominal distention, nausea, and vomiting. It may be difficult to distinguish from exacerbation of pseudo-obstruction in certain patients. Cecal volvulus has been reported in two children with Cornelia de Lange syndrome.[86]

The diagnosis is established with a contrast enema. Operative intervention, usually to resect the involved segment, is typically required. Endoscopic decompression can be useful to decompress the involved colon and convert this to a more elective operation, but this can be prohibitively difficult.

In the mid-1990s, long-segment colonic fibrosis was described in patients with cystic fibrosis. Colonic injury was determined to be caused by the ingestion of high doses of pancreatic enzymes (>19,000 units/kg/day).[85]

Resection of involved bowel was required in many of these patients. Alteration of the dosage of pancreatic enzymes has decreased the occurrence of this complication in recent years.

## Summary

The causes of colonic obstruction in infants and children are diverse. Generally, anatomic obstruction is easily addressed by surgical resection with primary anastomosis. Functional obstructions have a varied pathogenesis, and a nonsurgical approach is generally preferred. The clinical outcome of anatomic colonic obstruction is excellent in contemporary pediatric surgical practice; the exceptions are children with concurrent illness or peritonitis with sepsis at presentation.

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 100

# Appendicitis

James C. Y. Dunn

In 1886 Fitz[1] coined the term *appendicitis*. Morton is credited with performing the first deliberate appendectomy for a perforated appendix in the United States in 1887.[2,3] In 1889 McBurney[4] reported his treatment of appendicitis with appendectomy before rupture and described "the seat of greatest pain . . . has been very exactly between an inch and a half and two inches from the anterior spinous process of the ilium on a straight line drawn from the process to the umbilicus." From then on, this location was known as the McBurney point. Modern surgical care and antibiotic therapy have turned this once frequently fatal disease rarely so today. Appendicitis remains the most common acute surgical condition of the abdomen[5]; many aspects of the treatment of appendicitis remain controversial.

## Embryology and Anatomy

During embryogenesis, the appendix first becomes visible during the eighth week of gestation as a continuation of the inferior tip of the cecum.[6,7] The appendix rotates to its final position on the posteromedial aspect of the cecum, about 2 cm below the ileocecal valve, during late childhood. The variability in this rotation leads to multiple possible final positions of the appendix. The appendix is intraperitoneal in 95% of cases, but the exact location varies widely.[8] In 30% of cases the tip of the appendix is in the pelvis, in 65% it is behind the cecum, and in 5% it is truly extraperitoneal in the retrocolic or retrocecal position. In cases of malrotation or situs inversus, the malpositioned appendix may give rise to signs of inflammation in unusual locations.

The appendix averages 8 cm in length but can vary from 0.3 to 33 cm. The diameter of the appendix ranges from 5 to 10 mm. Its blood supply is the appendiceal branch of the ileocolic artery, which passes behind the terminal ileum. The base of the appendix arises at the junction of the three taeniae coli, a useful landmark in locating an elusive appendix. Its colonic epithelium and circular and longitudinal muscle layers are contiguous with the cecal layers. A few submucosal lymph follicles are present at birth. These increase to approximately 200 by age 12 and reduce abruptly after the age of 30.

Suppression of cecal development results in appendicular hypoplasia or agenesis. Appendiceal duplication has a reported incidence of 4 in 100,000.[9,10] The duplicated appendix may be partial (bifid appendix) or full, and it may have separate or common orifices in the cecum, which may also be duplicated.

The function of the appendix is unknown. Primates have an appendix, but most mammals do not. Curiously, rabbits do have an appendix and it is believed to be an important site for the immunologic development of B cells.[11]

## Spectrum of Disease

The geographic variation in the incidence of appendicitis is widespread. Appendicitis occurs less frequently in less industrialized countries.[12] Over the past few decades, the worldwide incidence has steadily decreased.[12–15] In the United States over 70,000 children are diagnosed with appendicitis annually, or approximately 1 per 1000 children per year. The lifetime risk for appendicitis is 9% for men and 7% for women.[16] About one third of patients with appendicitis are younger than 18 years of age. Appendicitis occurs more commonly in whites and during the summer months. The peak incidence occurs between ages 11 and 12. Although the disorder is uncommon in infants, perforated appendicitis can occur even in premature infants. Perforation may also be the end result of another disease process, as is seen in neonates with Hirschsprung disease.[17] Although the diagnosis and treatment have improved, appendicitis continues to cause significant morbidity and still remains, although rarely, a cause of death.[18,19]

Many terms have been used to describe the varying stages of appendicitis including acute appendicitis, suppurative appendicitis, gangrenous appendicitis, and perforated appendicitis. These distinctions are imprecise, with considerable variability among surgeons and among surgeons and pathologists. Clinically the only relevant distinction is between simple and complicated appendicitis. In general, acute and suppurative appendicitis tend to have a simple clinical course, whereas gangrenous and perforated appendicitis tend to have a complicated course.

Whether chronic and recurrent cases of appendicitis exist has been debated for decades. Literature contends that they do exist and should be considered in the differential diagnosis of recurrent lower abdominal pain.[20,21] Inflammation of the appendix does not inevitably lead to perforation because spontaneous resolution does occur.[22,23] Antibiotics may also assist the resolution of the inflammation. Recognition of this may contribute to the decreasing number of appendectomies.[14,15]

## Presentation

Traditional teaching is that appendicitis evolves as a continuum from simple inflammation to perforation, typically occurring after 24 to 36 hours of symptoms, and subsequent abscess formation occurring over a period of 2 to 3 days.[24,25] Nevertheless, the variability of the clinical presentation of appendicitis leads to laparotomies that do not reveal an inflamed appendix. Clinical experience and advances in imaging methods have improved the diagnostic accuracy but are not foolproof. The clinical presentation of appendicitis can be understood in terms of its pathophysiology.

Appendicitis results from luminal obstruction followed by infection. This process was first described by van Zwalenberg[26] in 1905 and experimentally confirmed by Wangensteen[27] in 1939. Wangensteen showed that the human appendix continues to secrete mucus even when intraluminal pressures exceed 93 mm Hg. Although it is clear that luminal obstruction causes appendicitis, the cause of the obstruction is not always clear. Inspissated and sometimes calcified fecal matter, known as a fecalith, often plays a role.[28] Fecaliths can be surgically found in approximately 20% of children with acute appendicitis and are reported in 30% to 40% of children with perforated appendicitis.[29,30] The presence of fecaliths can often be documented radiographically. Hyperplasia of appendiceal lymphoid follicles frequently causes luminal obstruction, and the incidence of appendicitis closely parallels the amount of lymphoid tissue present.[31] Causes of local or generalized reaction of lymphatic tissue such as *Yersinia, Salmonella,* and *Shigella*[32–35] can lead to luminal obstruction of the appendix, as can parasitic infestations by *Entamoeba, Strongyloides, Enterobius vermicularis, Schistosoma,* or *Ascaris* species.[36–38] Enteric and systemic viral infections such as measles, chicken pox, and cytomegalovirus may also cause appendicitis.[39,40] Patients with cystic fibrosis have an increased incidence of appendicitis, which presumably results from alterations in the mucous-secreting glands.[41,42] Carcinoid tumors can obstruct the appendix, especially when they are located in the proximal third. Foreign bodies such as pins, vegetable seeds, and cherry stones have been implicated as causes of appendicitis for more than 200 years. Trauma has also been reported as a cause,[43] as has psychologic stress[44] and heredity.[45]

Initially the patient may describe mild gastrointestinal symptoms before the onset of pain (e.g., decreased appetite, indigestion, or subtle changes in bowel habits). Anorexia is a helpful sign, particularly in children, because a hungry child rarely has appendicitis. Any severe gastrointestinal symptoms before the onset of pain, however, should suggest an alternative diagnosis. Distention of the appendix results in activation of its visceral pain fibers. Typical early visceral pain is nonspecific in the periumbilical region. This initial pain is poorly localized as a deep, dull pain in the T-10 dermatome. The continued distention of the appendiceal wall elicits nausea and vomiting, which typically follow the onset of pain within a few hours. Nausea is common, but vomiting is typically not severe. The appearance of these symptoms before the onset of pain casts doubt on the diagnosis.

The obstructed appendix is a perfect breeding ground for trapped bacteria. As intraluminal pressure increases, lymphatic drainage is inhibited, leading to further edema and swelling. Finally, the increase in pressure causes venous obstruction, which leads to tissue ischemia, infarction, and gangrene. Bacterial invasion of the wall of the appendix then occurs. Fever, tachycardia, and leukocytosis develop as a consequence of mediators released by ischemic tissues, white blood cells, and bacteria. When the inflammatory exudate from the appendiceal wall contacts the parietal peritoneum, somatic pain fibers are triggered and the pain localizes near the appendiceal site, most typically at the McBurney point. Pain occasionally occurs only in the right lower quadrant without the early visceral component. With a retrocecal or pelvic appendix, this somatic pain is often delayed in onset because the inflammatory exudate does not contact the parietal peritoneum until rupture occurs and infection spreads. Pain of a retrocecal appendix may be in the flank or back. A pelvic appendix resting near the ureter or testicular vessels can cause urinary frequency, testicular pain, or both. Inflammation of the ureter or bladder by an inflamed appendix can also lead to pain on micturition or the deceptive pain of a distended bladder secondary to urinary retention.

Further breakdown of the appendiceal wall leads to perforation with spillage of infected intraluminal contents with localized abscess formation or generalized peritonitis. This process depends on the rapidity of progression to perforation and on the patient's ability to mount a response and contain the spilled contents of the appendix. Signs of perforated appendicitis include a temperature higher than 38.6°C, leukocyte count greater than 14,000,[46] and the presence of more generalized peritoneal signs. Other reported risk factors include the male sex, extremes of age, and such anatomic factors as a retrocecal position of the appendix.[25,47] However, perforated and nonperforated appendicitis may be entirely separate entities.[13] Spontaneous resolution of appendicitis does occur. Patients may be asymptomatic before perforation, and symptoms may be present for longer than 48 hours without perforation. In general, however, the longer duration of symptoms is associated with a greater risk for perforation. Constipation is unusual, but the sensation of rectal fullness or tenesmus is common. Diarrhea occurs more frequently in children than in adults and can result in a misdiagnosis of gastroenteritis. Diarrhea is typically of short duration and often results from irritation of the terminal ileum or cecum; however, it may indicate a pelvic abscess.

Younger children typically present with complicated appendicitis due to their inability to give an accurate history and physicians' low index of suspicion that leads to misdiagnosis.[48–50] The most frequent presenting symptom in preschool children is vomiting, followed by fever and abdominal pain.[51] Perforation is almost always the finding at laparotomy, and these children may have associated small bowel obstruction secondary to extensive inflammation in the terminal ileum and cecum.

## Diagnosis

### PHYSICAL EXAMINATION

As with most disease processes, much can be learned before the patient is touched. Children with appendicitis usually lie in bed with minimal movement. A squirming, screaming child rarely has appendicitis. An exception to this is the child with retrocecal appendicitis and subsequent irritation of the

ureter presenting with pain similar to renal colic. Older children may limp or flex the trunk, whereas infants may flex the right leg over the abdomen. A recall of localized pain elicited by bumps in the road on the ride to the hospital is helpful.

Before starting palpation of the abdomen, it is useful to ask the child to point with one finger to the location of the abdominal pain. With the knees bent to relax the abdominal muscles, gentle palpation of the abdomen should begin at a point away from the location of perceived pain. Palpating the abdomen in an area remote from the site of pain may elicit tenderness in the right lower quadrant (Rovsing sign of referred pain), indicating peritoneal irritation. Younger children may be more cooperative if their hand or the stethoscope is used for palpation. The stethoscope can have several roles in the evaluation of a patient who potentially has appendicitis, the least important of which is auscultation. Although patients often have diminished or absent bowel sounds, this is not uniform and auscultation of the abdomen is of little benefit. However, auscultation of the chest to examine for lower respiratory infection is useful because right lower lobe pneumonia can mimic appendicitis. Cutaneous hyperesthesia, a sensation derived from the T10 to L1 nerve roots, is often an early although inconsistent sign of appendicitis. Lightly touching the patient with the stethoscope creates this uncomfortable sensation.

Localized tenderness is essential for diagnosis and is noted either on palpation or percussion. Tenderness can be mild and even masked by more generalized abdominal pain, especially during initial stages. The McBurney point is the most common location. Retrocecal appendicitis may be detected by tenderness midway between the twelfth rib and the posterior superior iliac spine. Pelvic appendicitis produces rectal tenderness. A child with malrotation will have localized tenderness that corresponds to the position of the exudative drainage from the inflamed appendix.

As the disease progresses to perforation, peritonitis ensues. The pattern of pain depends on the location of the appendix. Perforation may result in temporary relief of symptoms as the pain of the distended viscus is relieved. Initially, peritonitis is reflected as local muscular rigidity. This progresses from simple involuntary guarding to generalized rigidity of the abdomen. Other signs include rigidity of the psoas muscle (demonstrated by right hip extension or raising the straight leg against resistance) or of the obturator muscle (demonstrated by passive internal rotation of the right thigh), both of which indicate irritation of these muscles due to retrocecal appendicitis. Other tests of peritoneal inflammation such as rebound tenderness are seldom necessary for diagnosis and cause unnecessary discomfort.

The routine use of rectal examination in the diagnosis of appendicitis has recently been questioned.[52–54] Pain during this examination is nonspecific for appendicitis. If other signs point to appendicitis, the rectal examination is unnecessary. However, it may be a helpful diagnostic maneuver in questionable cases such as when a pelvic appendix or abscess is suspected or when uterine or adnexal pathologic conditions are being considered.

If appendicitis is allowed to progress, two results are possible: (1) diffuse peritonitis and shock will occur or (2) the infection will become isolated and an abscess will form. Diffuse peritonitis is more common in infants, probably because of the absence of omental fat. Older children and teenagers are more likely to have an organized abscess. The physical examination in cases of an organized abscess reveals a boggy, tender mass over the abscess.

A frequently unreported but critical aspect of the evaluation is serial examinations done by the same person. The safety and efficacy of serial observation was first reported by White in 1975[55] and has since been reinforced by other studies. Surana[56] reported a prospective study showing no increase in morbidity with appendectomy after active observation in a hospital compared with urgent appendectomy. When the diagnosis is unclear, serial abdominal examinations permit the physician to decrease the number of unnecessary laparotomies without increased risk to the patient.

## LABORATORY STUDIES

Much has been discussed concerning the laboratory findings of appendicitis. Total leukocyte and neutrophil counts have been extensively investigated.[57–59] The sensitivity of an elevated leukocyte count ranges from 52% to 96% and that of a left-shifted neutrophil count ranges from 39% to 96%. The latter is of better diagnostic value, but misinterpretation of the values is still common. Normal leukocyte count occurs in 5% of patients with appendicitis. Greater specificity and sensitivity have been reported using a neutrophil-lymphocyte ratio greater than 3.5.[60]

In the majority of children with suspected appendicitis, the combination of clinical history, physical findings, and laboratory studies should provide sufficient data for making the diagnosis. Nevertheless, misdiagnosis leading to negative appendectomy ranging from 10% to 30% has been reported.[61] An appendicitis score based on weighing eight clinical factors (localized right lower quadrant tenderness, leukocytosis, pain migration, left shift, fever, nausea-vomiting, anorexia, peritoneal irritation) was proposed to improve the diagnostic accuracy.[62,63] In prospective evaluations of children with acute abdominal pain, the sensitivity of the scoring system ranged from 76% to 100% and its specificity ranged from 79% to 87%.[64,61] In cases where the diagnosis is equivocal, serial observation is warranted and imaging studies may be useful.

## IMAGING STUDIES

Imaging studies have variable success in improving diagnostic accuracy. Plain radiography can be helpful. Fecaliths are present in 10% to 20% of patients and may be an indication for surgery when symptoms are present. An abnormal gas pattern in the right lower quadrant, lumbar scoliosis away from the right lower quadrant, and obliteration of the psoas shadow or fat stripe on the right are also helpful. A chest radiograph to rule out pneumonia may be indicated.

A barium enema contrast radiograph may show absent or incomplete filling of the appendix, irregularities of the appendiceal lumen, and an extrinsic mass effect on the cecum or terminal ileum. The sensitivity and specificity of this technique are low,[65] and it is best used in the diagnosis of nonspecific abdominal pain.

In skilled hands, ultrasonography has proven to be an effective diagnostic aid. A prospective study showed that ultrasonography was more accurate than the surgeon's initial clinical impression.[66] Most studies demonstrate a sensitivity greater than 85% and a specificity greater than 90%.[67]

Demonstration of a noncompressible appendix that is 7 mm or larger in anteroposterior diameter is the primary criterion for the diagnosis. The presence of an appendicolith is helpful. Such techniques as graded compression, self-localization,[68] and transvaginal or transrectal ultrasound approaches[69] have also improved results.

Computed tomography (CT) has become more widely used in the diagnosis of appendicitis.[70–73] The findings of an enlarged appendix (>6 mm), appendiceal wall thickening (>1 mm), periappendiceal fat stranding, and appendiceal wall enhancement are useful diagnostic criteria.[74,75] The sensitivity of CT scans is over 90%, and its specificity is over 80%.[76] Comparisons of ultrasonography and CT have shown that the latter is more sensitive, whereas the former is more specific.[67,70,77] These two imaging modalities, however, should be employed only if the diagnosis is uncertain. In a protocol that evaluated children with equivocal clinical findings for appendicitis, the combination of pelvic ultrasound followed by limited CT with rectal contrast, if necessary, yielded a sensitivity of 94% and a specificity of 94%.[78] The same protocol reduced the negative appendectomy rate from 12% to 6% at the same institution during the study period but performed imaging in almost 80% of children with suspected appendicitis. The perceived improved diagnostic accuracy led to a dramatic increase in the number of CT performed in the pediatric population,[79–81] even though there is no good evidence that supports the routine use of CT in the diagnosis of appendicitis.[82] In addition to the hospital resource utilization and the delay in surgical care, the potential cancer risk associated with ionizing radiation from CT should be considered.[79]

## DIFFERENTIAL DIAGNOSES

Acute appendicitis can mimic virtually any intra-abdominal process.[83] The differential diagnosis of appendicitis is listed in Table 100-1. Consideration of these other disease processes before surgery is as important as it is to examine for them carefully when the patient is under anesthesia and during surgery in the case of a normal appendix.

The clinical diagnosis of appendicitis is challenging because many symptoms of appendicitis are nonspecific and the presentations can be variable. Acute gastroenteritis is a common cause of abdominal pain in children. It is usually due to a viral illness and is self-limited. The symptoms include watery diarrhea, crampy abdominal pain, fever, nausea, and vomiting. Constipation is another common pediatric problem and may cause abdominal pain, nausea, and vomiting. Pain is usually persistent but not progressive. History and a plain radiograph will suggest the diagnosis. Urinary tract infection will also cause fever, nausea, and vomiting. A urinalysis should be obtained if urinary symptoms are present.

Despite advances in diagnostic imaging, operation done for appendicitis does not always reveal an inflamed appendix. Formerly accepted rates of laparotomy that did not reveal appendicitis range from 15% to 40%.[25] These rates are not supported by the recent literature that report negative appendectomy rates to be less than 10%.[84–87] When a normal appendix is encountered, most surgeons recommend that it be removed to allow for pathologic examination and to avoid potential confusion if the patient experiences right lower quadrant pain in the future. An exploration of the right lower quadrant should be performed to look for other causes of the symptoms. The terminal ileum may demonstrate mesenteric adenitis, enlarged lymph nodes in the ileal mesentery that may be secondary to an upper respiratory infection. These patients may have abdominal pain, fever, and nausea, but their

**TABLE 100-1**
**Differential Diagnosis of Acute Appendicitis**

| |
|---|
| **Appendix** |
| Appendiceal tumor, carcinoid tumor |
| Appendiceal mucocele |
| Crohn disease |
| **Cecum and Colon** |
| Cecal carcinoma |
| Diverticulitis |
| Crohn disease |
| Intestinal obstruction |
| Stercoral ulcer |
| Typhlitis (leukemic, amebic) |
| **Hepatobiliary** |
| Cholecystitis |
| Hepatitis |
| Cholangitis |
| **Small Intestine** |
| Adenitis |
| Duodenal ulcer |
| Gastroenteritis |
| Intestinal obstruction |
| Intussusception |
| Meckel diverticulitis |
| Tuberculosis |
| Typhoid (ulcer perforation) |
| **Urinary Tract** |
| Hydronephrosis |
| Pyelonephritis |
| Ureteral or renal calculus |
| Wilms' tumor |
| **Uterus, Ovary** |
| Ectopic pregnancy |
| Ovarian torsion |
| Ruptured ovarian cyst |
| Salpingitis |
| Tubo-ovarian abscess |
| **Other** |
| Cytomegalovirus infection |
| Diabetic ketoacidosis |
| Schönlein-Henoch purpura |
| Kawasaki disease |
| Burkitt lymphoma |
| Omental torsion |
| Rectus sheath hematoma |
| Pancreatitis |
| Parasitic infection |
| Pleuritis |
| Pneumonia |
| Porphyria |
| Psoas abscess |
| Sickle cell disease |
| Torsion of appendix epiploica |

tenderness is not as well localized as that in appendicitis. Lymphocytosis may be noted on the blood count differential. A search for a Meckel diverticulum should be done, but it rarely causes pain. Painless bleeding and obstruction are the more common presenting symptoms. If the patient has Crohn disease, the appendix should not be removed if it or the cecum is involved in the disease process because removal is associated with a high incidence of subsequent fistula formation.[88]

The diagnostic accuracy for appendicitis is lowest among young women because of the variety of gynecologic conditions that can cause low abdominal pain. Ectopic pregnancy should be considered in teenage girls with low abdominal pain. They may present with vaginal bleeding, amenorrhea, dizziness, nausea, and vomiting. Rupture of ovarian cysts and ovarian torsion may also present with low abdominal pain. Sexually active girls with pelvic inflammatory disease may present with low abdominal pain, vaginal discharge, and adnexal enlargement. Most will have cervical motion tenderness and will respond to antibiotics. Operative intervention may be indicated for those who do not respond or persistent abscess.

Carcinoid tumors are present in less than 1% of patients undergoing appendectomy.[89] Most appendiceal carcinoid tumors lack the serotonin-containing cells that are typical of midgut carcinoid tumors, so they are rarely symptomatic and typically present incidentally at appendectomy.[90] Most are benign, and simple appendectomy is curative.[91,92] Controversy surrounds the proper surgical management of potentially malignant carcinoid tumors. The consensus is that carcinoid tumors larger than 2 cm in diameter, those that have obviously metastasized, and those located at the base of the appendix require right hemicolectomy,[90,93] whereas those that are smaller than 1 cm in diameter and have not metastasized at the time of diagnosis are treated by appendectomy alone. Treatment of tumors that are 1 to 2 cm in diameter remains controversial. Moertel[91] believes that a conservative surgical procedure is all that is required regardless of tumor size or location as long as metastases are not present.

# Treatment

Although it is generally agreed that the treatment for appendicitis is appendectomy, the details of the management vary considerably.[94] For example, surgical techniques such as the laparoscopic approach, the use of drains, the necessity of peritoneal irrigation, the handling of the appendiceal stump, and the closure of the incision continue to be debated. The need for interval appendectomy after initial nonoperative management of an appendiceal phlegmon is unclear. The choice of antibiotics and the length of its use vary considerably from surgeon to surgeon.

## ANTIBIOTICS

The use of antibiotics for the treatment of appendicitis is clearly beneficial.[95] Intraoperative cultures have not been shown to alter the treatment outcome.[96,97] The best regimen and duration of antibiotics use is a subject of continued controversy. A 10-day course of intravenous ampicillin, gentamicin, and clindamycin or metronidazole is the gold standard for the treatment of complicated appendicitis,[98] and the effectiveness of other antibiotic combinations are usually measured against this empiric regimen. More recently, it has been shown that a single or double broad-spectrum antibiotic is equally effective for the treatment of complicated appendicitis.

There is a trend toward decreasing the duration of antibiotic therapy.[99] Only perioperative antibiotics are required for simple appendicitis. The recommended duration is from a single, preoperative dose to 24 hours of postoperative antibiotic therapy for simple appendicitis.[100,101] For complicated appendicitis, recent studies have suggested that as little as 48 hours of coverage is adequate.[69] Others suggest that treatment be continued as clinically indicated using the leukocyte count and presence of fever as guides.[102–104] There is also a trend to use oral antibiotics instead of intravenous antibiotics when gastrointestinal function returns. A prospective, randomized study demonstrates equivalency between a 10-day course of intravenous antibiotics and a 10-day course of combined intravenous and oral antibiotics for complicated appendicitis.[105]

## APPENDECTOMY

The most widely accepted treatment of appendicitis is appendectomy. Randomized trials that compared medical therapy with appendectomy in adults with appendicitis showed that medical therapy is associated with a 10% to 20% chance of recurrence but has lower rates of complications. There is a trend away from performing immediate operation.[106,107] There was no increased rate of complications noted between a group of patients diagnosed with acute appendicitis and operated upon within 6 hours of admission and those with delays between 6 and 18 hours of admission.[55,56] Nevertheless, the majority of pediatric surgeons will perform appendectomy within 8 hours.[94]

In the open technique, a transverse or oblique right lower quadrant incision is made through the McBurney point (Fig. 100-1). The muscles of the abdominal wall are usually split. After the abdomen is entered, the cecum and appendix are mobilized and the appendix is brought out through the incision. The mesoappendix is then divided, and the base of the appendix is ligated. A short base is left to avoid inflammation in the stump.[108] The stump is managed by simple ligation, ligation with inversion using a purse-string or Z-stitch suture, or inversion without ligature. Simple ligation can be done quickly and may reduce adhesions.[109] Inversion theoretically leads to better hemorrhage control, a doubly secure closure, and less chance of contamination; however, it can create artifacts on future contrast examinations and can cause intussusception.[110] For simple appendicitis, irrigating the wound is unnecessary. The wound is closed in layers, and no drains are placed. A normal diet can be given soon after appendectomy, and the patient can be discharged in 1 to 2 days. If a normal appendix is found, the peritoneal cavity should be inspected for inflammatory bowel disease, mesenteric adenitis, Meckel diverticulitis, or, in females, pathologic conditions of the ovary.

"Endoscopic" appendectomy was first described in 1983.[111] Laparoscopic appendectomy can be done by a laparoscopic-assisted technique in which the appendix is mobilized laparoscopically using one or two ports and is drawn through a small abdominal opening and removed by standard open technique.[112,113] Alternatively, the appendix can be removed entirely laparoscopically. Three trocars are usually

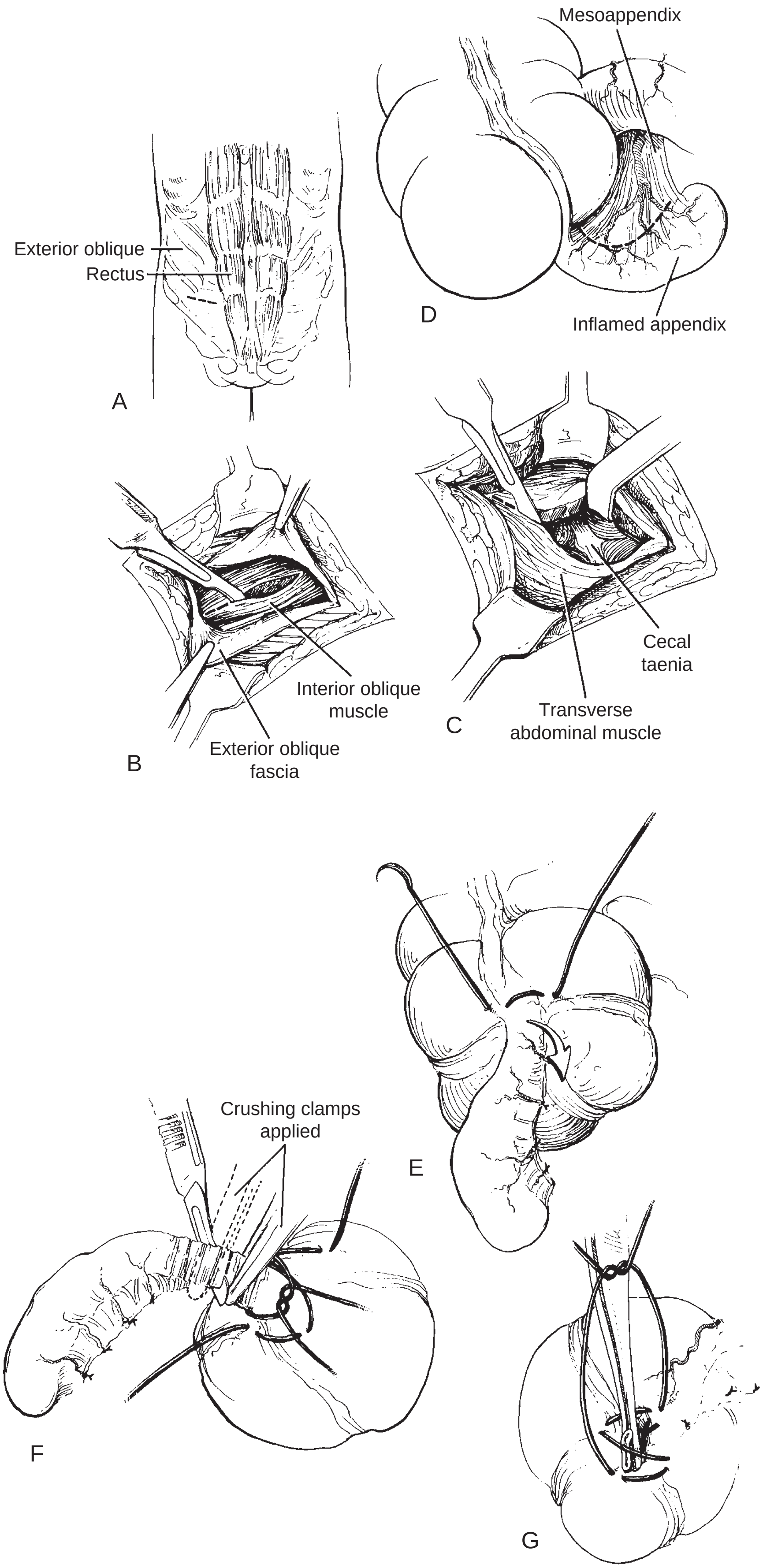


**FIGURE 100-1** **A,** A transverse incision is made in the right lower quadrant over the lateral musculature. **B,** The external oblique fascia is incised exposing the internal oblique fascia and muscle. **C,** The transverse abdominal muscle and peritoneum are opened, and the cecum is identified. **D,** An inflamed appendix is identified, and the mesoappendix is isolated, clamped, divided, and tied. **E,** A purse-string suture is placed in the cecal wall. **F,** The base of the appendix is crushed and tied, and the appendix is excised. **G,** The appendiceal stump is inverted into the cecal wall, and the purse-string suture is tied. (From Rowe M, O'Neill JS, Grosfeld JL: Essentials of Pediatric Surgery, Philadelphia, Mosby, 1995.)

employed: one at the umbilicus for the scope, one in the suprapubic area, and one in the left lower quadrant (Fig. 100-2), although a single-incision multiport approach may also be employed. The appendix is found by following the cecum, and the mesoappendix is grasped near the tip to lift the appendix toward the abdominal wall. A window is made in the mesoappendix near the base to allow its division by applying electrocautery, clips, staples, or the harmonic scalpel. Many variations of ligating and removing the appendix have been described.[85,114] The simplest technique applies an endoscopic stapler to the base of the appendix, and the appendix is delivered through the umbilical trocar site. There is now early experience with single port/incision techniques.

Despite prospective, randomized trials that compared open and laparoscopic appendectomy, the advantages and disadvantages of laparoscopic appendectomy continue to be debated.[115–124] Advantages claimed include shorter hospitalizations, decreased postoperative pain, decreased wound complications, increased ability to diagnose uncertain cases, surgical ease in an obese patient, and faster postoperative recovery.[84,85,125–129] Disadvantages are a higher cost because of equipment needs and longer time for surgery, increased training and experience required for surgeons and ancillary support staff, increased incidence of finding a normal appendix, and an increased incidence of intra-abdominal infection.[84,130–133] Although the conclusions regarding the

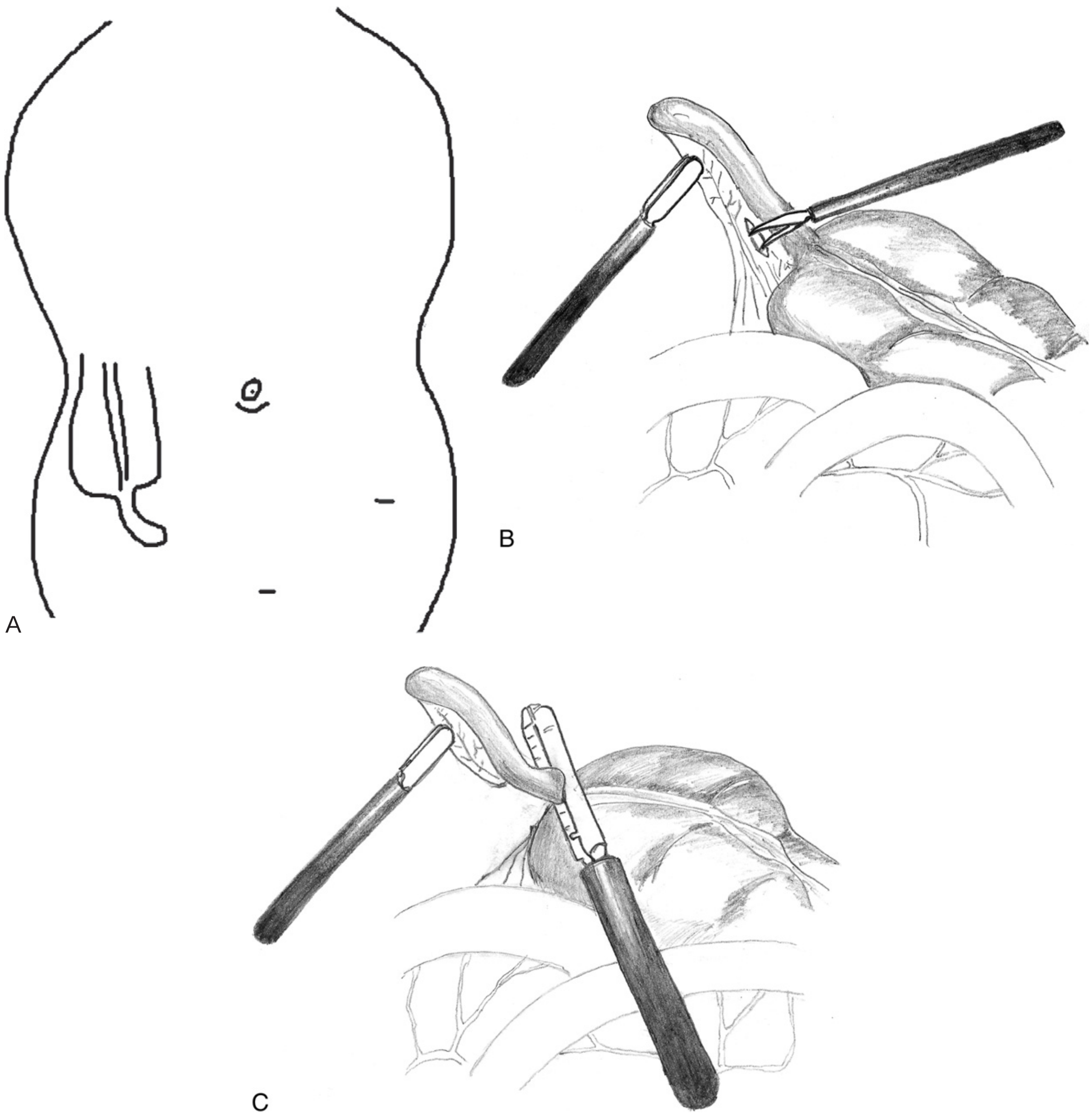


FIGURE 100-2 **A,** Three ports are placed for laparoscopic appendectomy. The umbilical port is 12 mm in size to accommodate the endoscopic stapler. The other two ports are 3 or 5 mm in size for dissecting instruments. **B,** The appendix is lifted upwards by a grasper placed on the mesoappendix, and a window is made at the base of the mesoappendix by a dissector. The mesoappendix is divided by electrocautery or harmonic scalpel. **C,** The scope is switched to the left lower quadrant port to allow the endoscopic stapler to come through the umbilical port to divide the appendix.

advantages of this technique over the open technique vary widely, laparoscopic appendectomy is a safe and effective means of performing an appendectomy and its utilization has increased dramatically over the past decade.

Treatment of patients with complicated appendicitis is more controversial. Due to social, cultural, economic, and medical influences on the diagnosis and treatment of this disease process, perforation rates vary from 16% to 57% in different institutions. There is no consensus on the optimal treatment of patients with complicated appendicitis. Opinions range from nonoperative treatment to aggressive surgical resection with antibiotic irrigation, drainage of the peritoneal cavity, and delayed wound closure.[134–138] Weiner[139] reported no significant differences in the number of hospital days, cost of treatment, or overall complication rates using initial nonoperative treatment of complicated appendicitis followed by interval appendectomy in 8 weeks. In another study that examined initial nonoperative therapy for complicated appendicitis confirmed by imaging, 22% of the patients were converted to appendectomy because of small bowel obstruction.[140] Operative treatment remains the standard approach because of the difficulty in determining whether perforation has occurred before exploration.

The operative procedure for complicated appendicitis is appendectomy. Controversy continues regarding the details of the procedure: whether to drain the peritoneal cavity, whether to close the wound or leave it open with delayed closure, whether to irrigate the peritoneal cavity and, if so, whether to use antibiotic solutions. Drains have been described as both increasing infectious complications and preventing them.[29,30,46,141–143] Most studies do not support the use of drains, with the possible exception of retrocecal abscesses that cannot be properly debrided. Delayed wound closure is not supported by the literature[46,85–87,98] and does not seem to be warranted because the wound infection rate associated with appendectomy is less than 3%. Irrigation remains controversial. Putnam, Gagliano, and Emmons[87] suggest that irrigation prolongs ileus and may cause small intestinal obstruction and report excellent results without irrigation. Other recent studies support saline irrigation of the peritoneal cavity with or without antibiotics.[29,46,85,86,98]

Management of patients with a palpable abdominal mass is another controversial topic. It occurs in a small but significant fraction of patients with complicated appendicitis, especially in young children after perforation. Some advocate immediate appendectomy,[144] whereas others perform the procedure only if a mass is confirmed with the patient under anesthesia. If an operation is done, care should be taken to avoid damage to adjacent structures subject to inflammatory processes such as the small intestine, the fallopian tubes and ovaries, and the ureter. Surana[145] and Nitecki[146] recommend treatment with intravenous antibiotics until the leukocyte count is normal and the patient remains afebrile for 24 hours. If the patient's condition worsens or the mass enlarges on serial ultrasonography, the mass is drained percutaneously, followed by interval appendectomy. Interval appendectomy prevents repeated episodes of appendicitis and affords the surgeon the opportunity to evaluate the patient for other conditions that can masquerade as an appendiceal mass. Whether an interval appendectomy is necessary is also debated.[146–152] Nitecki[116] has suggested that interval appendectomy is unnecessary because only 14% of patients have recurrent symptoms, and recurrence within 2 years after initial diagnosis is uncommon. The current standard of treatment is conservative management with interval appendectomy after 8 to 12 weeks.

# Complications

The incidence of complications increases with the degree of severity of the appendicitis. The complications include wound infection, intra-abdominal abscess formation, postoperative intestinal obstruction, prolonged ileus, and rarely enterocutaneous fistula. Wound infection is the most common complication, but the rate has fallen from 50% to less than 5%, even in complicated appendicitis.[29,30,47,85–87] Intra-abdominal abscess formation is also more common in complicated appendicitis but is still less than 2%. The abscess can be drained percutaneously under CT guidance or transrectally in the operating room, although others have advocated more conservative management.[153–155] Postoperative intestinal obstruction occurs in 1% of patients with complicated appendicitis, which often requires operative adhesiolysis.[156] Enterocutaneous fistula is a rare complication and will usually respond to nonoperative management. Suppurative pylephlebitis is a particularly serious, although rare, complication.[157] Sepsis and multisystem organ failure can occur in young children who had prolonged illness before diagnosis. Major complications including postoperative intestinal obstruction and intra-abdominal abscess formation have also fallen to an incidence of less than 5%.

An unresolved issue is the effect of complicated appendicitis on fertility in females; available studies contradict each other. Puri, McGuinness, and Guiney[158] report that complicated appendicitis before puberty plays little if any role in the cause of tubal infertility, whereas Mueller[159] reports that the condition is associated with a fourfold risk for tubal infertility. The consequences of complicated appendicitis may be mitigated through both public and medical education that ensures prompt, early treatment before perforation.

# Outcomes

The mortality rate for complicated appendicitis has dropped to nearly zero. Antibiotics have markedly decreased the incidence of infectious complications. Although the length of hospitalization and the morbidity of patients with complicated appendicitis still far exceed those with simple appendicitis, the overall morbidity in children with complicated appendicitis is less than 10%.

The widely varied postoperative management of appendicitis is beginning to be addressed by implementing evidence-based clinical pathways.[160,161] Prompted primarily by economic pressures, there is increasing scrutiny of patient treatment and outcome.[162–164] Early outcome research has shown that hospitals that perform fewer than one appendectomy per week are associated with higher likelihood of misdiagnosis.[165] There are also reports that suggest better outcome in younger children with appendicitis when they are cared for by pediatric surgeons.[166,167] The combination of surgical evaluation, prompt operation when the diagnosis is clear, a period of observation if the diagnosis is equivocal followed by imaging if necessary, and care provided by

experienced clinicians and institutions will lead to the best outcome for children with appendicitis.

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 101

# Hirschsprung Disease

Jacob C. Langer

Hirschsprung disease is a developmental disorder of the intrinsic component of the enteric nervous system that is characterized by the absence of ganglion cells in the myenteric and submucosal plexuses of the distal intestine. Because these cells are responsible for normal peristalsis, patients with Hirschsprung disease present with functional intestinal obstruction at the level of aganglionosis. In most cases the aganglionosis involves the rectum or rectosigmoid, but it can extend for varying lengths, and in 5% to 10% of cases can involve the entire colon or even a significant amount of the small intestine. The incidence of Hirschsprung disease is approximately 1 in 5000 live-born infants.

## History

The condition of "congenital megacolon" has been recognized for centuries. The first description of this condition was in the seventeenth century by Frederick Ruysch, who described a 5-year-old child dying from an intestinal obstruction, followed by another account of a child with congenital megacolon by Battini in 1800.[1] It was not until 1887 that Harald Hirschsprung, a pathologist at Queen Louise Children's Hospital in Copenhagen, described two cases of the condition that ultimately bore his name.[2] Until the beginning of the twentieth century, most children with congenital megacolon died, presumably from malnutrition and enterocolitis. Because the underlying pathologic abnormality was not recognized, surgeons who operated on these children usually resected the dilated proximal bowel with or without primary anastomosis, with mixed results.[3]

The absence of ganglion cells in the distal colon of a child with Hirschsprung disease was first noted by Tittel in 1901. Over the following decades numerous papers were published to document abnormalities of innervation within the colon and recognize the absence of ganglion cells that is now pathognomonic of Hirschsprung disease. The first surgical recognition of aganglionosis as the cause of congenital megacolon was by Ehrenpreis in 1946. In a landmark paper, Whitehouse and Kernohan summarized the literature and presented a series of cases of their own, which documented that the aganglionosis within the distal colon or rectum was the cause of the functional obstruction.[4]

In 1949 Swenson published a paper in the *New England Journal of Medicine* recommending rectosigmoidectomy with preservation of the sphincters as the optimal treatment of this disease.[5] This operation was originally performed without a decompressing colostomy.[6] However, technical difficulties in small infants and the debilitated and malnourished state in which most children presented caused most surgeons to adopt a multistaged approach with colostomy as the initial step,[6] an approach that became the standard of care for decades. In recent years, improvements in surgical technique and earlier suspicion and diagnosis of the disease have resulted in an evolution toward one-stage and minimal access procedures. These advances have resulted in significantly improved morbidity and mortality in infants with Hirschsprung disease.

## Etiology and Genetics

Ganglion cells are derived from the neural crest. By 13 weeks postconception, the neural crest cells have undergone a process of migration through the gastrointestinal tract from proximal to distal, after which they differentiate into mature ganglion cells.[7] In infants with Hirschsprung disease this process is disturbed, so the ganglion cells are absent in the distal bowel. There are two theories as to why this occurs. The most prevalent is that the neural crest cells never reach the distal intestine because they either mature or differentiate into ganglion cells earlier than they should. Data supporting this theory come from spontaneously occurring animal models of aganglionosis[8] and from studies of normal neural crest cell migration done in chick embryos and human fetuses.[9,10] The second theory is that the ganglion cells do reach their destination but fail to survive or proliferate. Data in support of this theory include animal studies suggesting that there are at least two sources of neural crest cells (vagal and sacral), with migration both proximally and distally. In addition, a number of studies have suggested that the smooth muscle and extracellular matrix in the aganglionic bowel provides an inhospitable microenvironment for neuronal growth.[11,12] It is likely that Hirschsprung disease is actually a heterogeneous condition with multiple genetic causes and etiologic mechanisms, so each of these theories may be true in individual cases.

The heterogeneous nature of Hirschsprung disease is supported by increasing evidence that mutations in a variety of genes may be responsible.[13–15] The most commonly identified gene is the *RET* proto-oncogene, which was first identified in studies of Mennonite populations. *RET* encodes a tyrosine kinase receptor, and many mutations of this gene and related genes such as neurturin and glial cell line–derived neurotrophic factor (GDNF) have been identified in association with Hirschsprung disease. It remains unclear how these mutations result in aganglionosis, but there is some evidence that early neuronal cell death may be a prominent mechanism.[16,17] RET abnormalities are more commonly found in familial and long-segment disease. Mutations in the endothelin family of genes, particularly endothelin-3 and the endothelin-B receptor, are also commonly associated with Hirschsprung disease, although many of these children also have other abnormalities of neural crest–derived tissues, the most common of which is Shah-Wardenberg syndrome. There is evidence from animal models that mutations in the endothelin and SOX-10 genes may produce early maturation or differentiation of neural crest cells, which decreases the number of available progenitor cells and prevents the neural crest cells from migrating any further.[18,19] Other genes that have been associated with Hirschsprung disease include *S1P1* (now known as *ZFHX1B*), and *Phox2B*.

Hirschsprung disease is also associated with a number of syndromes for which the precise genetic basis of the aganglionosis has not yet been elucidated. These include Trisomy-21, congenital central hypoventilation syndrome, Goldberg-Shprintzen syndrome, Smith-Lemli-Opitz syndrome, neurofibromatosis, neuroblastoma, and a variety of other congenital anomalies.

# Diagnosis

## CLINICAL PRESENTATION

### Neonatal Obstruction

Approximately 50% to 90% of children with Hirschsprung disease present during the neonatal period with abdominal distension, bilious vomiting, and feeding intolerance suggestive of distal intestinal obstruction. Delayed passage of meconium beyond the first 24 hours is characteristic but is only present in approximately 90% of children with Hirschsprung disease. In some patients cecal or appendiceal perforation may be the initial event.[20] Plain radiographs usually show dilated bowel loops throughout the abdomen. The differential diagnosis includes intestinal atresia, meconium ileus, meconium plug syndrome, or a number of other less common conditions.

### Chronic Constipation

Some patients present later in childhood, or even during adulthood, with chronic constipation. This is most common among breast-fed infants, who typically develop constipation around the time of weaning. Although most children who present after the neonatal period have short-segment disease, this history may also be found in those with longer segment or even total colonic involvement, particularly if the child has been exclusively breast-fed. Because constipation is frequently seen in childhood, it may be difficult to differentiate Hirschsprung disease from more common causes of constipation. Clinical features that point to this diagnosis include failure to pass meconium in the first 48 hours of life, failure to thrive, gross abdominal distention, and dependence on enemas without significant encopresis.[21]

### Enterocolitis

Approximately 10% of children with Hirschsprung disease present with fever, abdominal distention, and diarrhea due to Hirschsprung-associated enterocolitis (HAEC), which may be chronic, or may be severe and life-threatening. Because Hirschsprung disease is generally thought of as causing constipation, presentation with diarrhea may be confusing and the diagnosis may not be considered. A careful history including the failure to pass meconium and the presence of intermittent obstructive episodes should lead to investigation for Hirschsprung disease.

The etiology of HAEC is controversial. The most common theory is that stasis caused by functional obstruction due to the aganglionic bowel permits bacterial overgrowth with secondary infection. Infectious agents such as *Clostridium difficile* or *Rotavirus* have been postulated as being causative, but there are few data to support a specific pathogen.[22] There is some evidence implicating alterations in intestinal mucin production and alterations in the mucosal production of immunoglobulins in children with Hirschsprung-associated enterocolitis, which presumably results in loss of intestinal barrier function and allows bacterial invasion.[23,24]

### Associated Conditions

Hirschsprung disease is associated with a variety of other congenital abnormalities, the presence of which should increase the clinician's level of suspicion (Table 101-1). These include malrotation, genitourinary abnormalities, congenital heart disease, limb abnormalities, cleft lip and palate, hearing loss, mental retardation, and dysmorphic features. In addition, Hirschsprung disease may be part of a large number of recognized syndromes such as trisomy 21, a variety of neurocristopathies, and congenital central hypoventilation syndrome.

**TABLE 101-1**

**Congenital Anomalies and Conditions Commonly Associated with Hirschsprung Disease**

| |
|---|
| Down syndrome (trisomy 21) |
| Neurocristopathy syndromes |
| 1. Waardenberg-Shah syndrome |
| 2. Yemenite deaf-blind-hypopigmentation |
| 3. Piebaldism |
| 4. Other hypopigmentation syndromes |
| Goldberg-Shprintzen syndrome |
| Smith-Lemli-Opitz syndrome |
| Multiple endocrine neoplasia 2 |
| Congenital central hypoventilation syndrome (Ondine curse) |
| Isolated congenital anomalies |
| 1. Congenital heart disease |
| 2. Malrotation |
| 3. Urinary tract anomalies |
| 4. Central nervous system anomalies |
| 5. Other |

## RADIOLOGIC EVALUATION

For the neonate with a clinical picture and plain radiographs suggesting distal neonatal bowel obstruction, the first step in the diagnostic pathway is a water-soluble contrast enema. The pathognomonic finding of Hirschsprung disease on contrast enema is a transition zone between the normal and aganglionic bowel (Fig. 101-1, *A*), although approximately 10% of neonates with Hirschsprung disease may not have a demonstrable radiologic transition zone.[25] It is important to use a water-soluble material because the enema may potentially be a definitive treatment for other conditions in the differential diagnosis such as meconium ileus and meconium plug syndrome. In older children an unprepped barium enema should be done rather than a water-soluble contrast study. The absence of a transition zone is less common in this age group but may still be present due to a short aganglionic segment. In both neonates and older children, the most important view is the lateral projection, in which a rectal transition zone will be most evident (Fig. 101-1, *B*). Other findings on the contrast enema that are suggestive of Hirschsprung disease include a reversed recto-sigmoid index (Fig. 101-1, *B*) and retention of contrast in the colon on a 24-hour postevacuation film.

## ANORECTAL MANOMETRY

The recto-anal inhibitory reflex (RAIR) is defined as reflex relaxation of the internal anal sphincter in response to rectal distension and is present in normal children but absent in children with Hirschsprung disease. The RAIR can be documented using anorectal manometry by inflating a balloon in the rectum while simultaneously measuring the internal sphincter pressure. Anorectal manometry is not widely available for neonates and is often operator dependent. In older children the test is technically easier, but false-positive results may occur due to masking of the relaxation response by contraction of the external sphincter, as well as artifacts created by movement or crying. Anorectal manometry is most useful in the evaluation of an older child with chronic constipation, where documentation of a normal RAIR effectively rules out Hirschsprung disease and avoids the need for a rectal biopsy.

## RECTAL BIOPSY

Definitive diagnosis of Hirschsprung disease is based on histologic evaluation of a rectal biopsy, which remains the gold standard diagnostic technique. The definitive finding that defines Hirschsprung disease is absence of ganglion cells in the submucosal and myenteric plexuses (Fig. 101-2, *A*). Most patients will also have evidence of hypertrophied nerve trunks (Fig. 101-2, *B*), although this finding is not always present, particularly in children with total colonic disease or a short aganglionic segment. Because there is normally a paucity of ganglion cells in the area 0.5 to 1 cm above the dentate line, the biopsy should be taken at least 1 to 1.5 cm above it. However, a biopsy too proximal may miss a short aganglionic segment. Most surgeons use a suction biopsy technique, which is associated with a low risk of perforation or bleeding. For children in whom the suction biopsy yields an inadequate specimen and in older children in whom the mucosa is too thick for a suction biopsy, punch biopsies or full-thickness biopsies provide more tissue and deeper levels.

In many centers the routine hematoxylin and eosin staining is supplemented by staining for acetylcholinesterase, which has a characteristic pattern in the submucosa and mucosa in children with Hirschsprung disease (Fig. 101-2, *C*). Other pathologists choose not to use acetylcholinesterase staining, believing that it is too subjective and does not add any information to the hematoxylin and eosin. A number of newer stains have recently been shown to have additional value for the diagnosis of Hirschsprung disease. The most accurate appears to be immunochemical identification of calcitonin, which is almost always absent in patients with Hirschsprung disease (Fig. 101-2, *D*).[26]

Occasionally a premature infant will develop distal intestinal obstruction, and the possibility of Hirschsprung disease will be raised on the basis of clinical and radiologic parameters. Early rectal biopsy in these children is not recommended for two reasons: (1) The pathologist may have difficulty recognizing ganglion cells due to their immaturity, and (2) it may be difficult to obtain enough tissue without increasing the risk of complications in a small premature infant. It is best in this situation to decompress the rectum using stimulations and/or irrigations and wait until the child is closer to term before

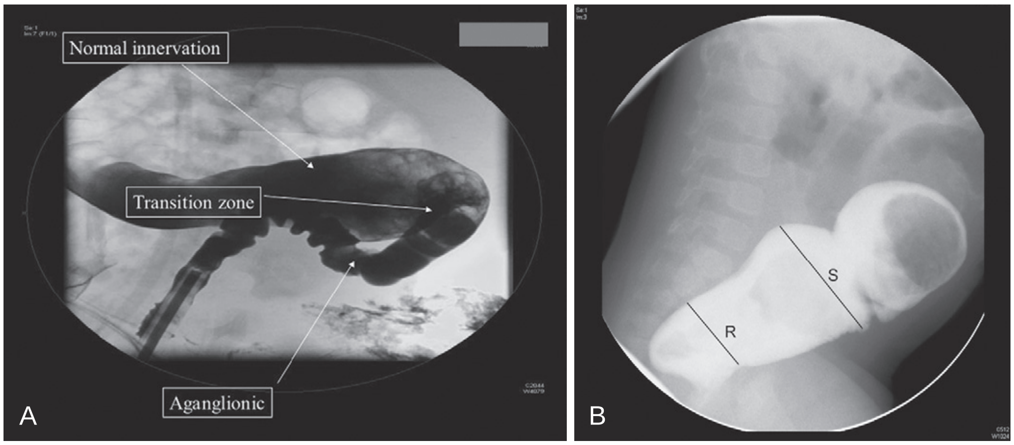


**FIGURE 101-1** **A,** Water-soluble contrast enema demonstrating a transition zone at the splenic flexure. **B,** The lateral view is the most important one to identify a low transition zone. In this case the recto-sigmoid index, consisting of the ratio of rectal diameter (*R*) to sigmoid diameter (*S*), is less than 1.0. D. Retention of contrast on a 24-hour postevacuation film.

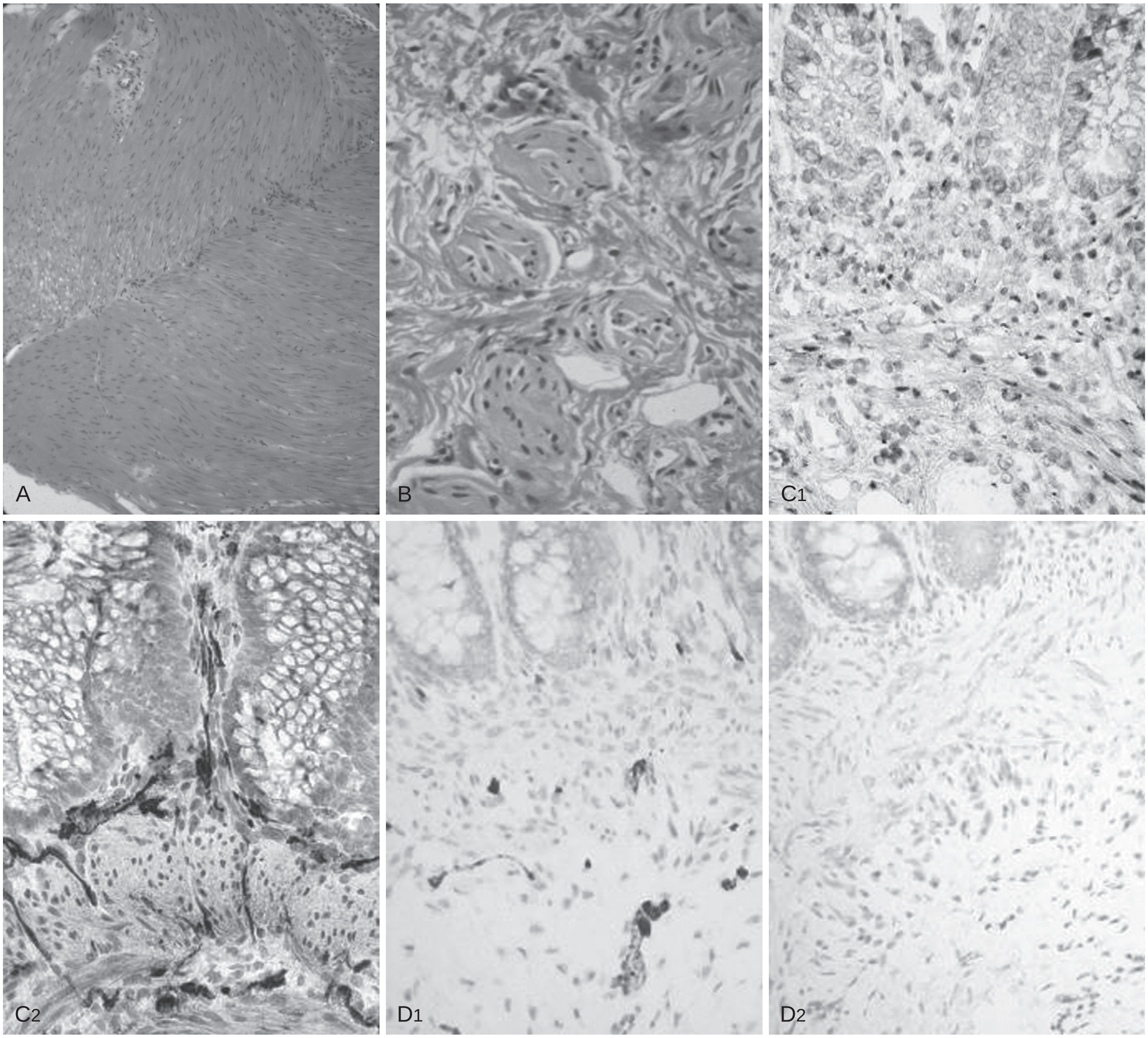


**FIGURE 101-2** Pathologic findings in children with Hirschsprung disease. **A,** Absence of ganglion cells in the myenteric plexus. **B,** Hypertrophied nerve trunks. **C,** Cholinesterase staining in normal colon and colon affected by Hirschsprung disease. **D,** Calretinin staining in normal colon and colon affected by Hirschsprung disease. (**D**, Courtesy Dr. Raj Kapur.)

doing the rectal biopsy. Although some surgeons believe that Hirschsprung disease is not seen in premature infants, this condition has been well-documented in a number of series.

## Preoperative Management

In most cases the treatment of Hirschsprung disease is surgical. However, there are a number of important preoperative interventions that must be considered before definitive surgical intervention. The first priority is resuscitation, particularly in neonates with intestinal obstruction or children presenting with enterocolitis. In both groups, intravenous fluids and broad-spectrum antibiotics against enteric organisms should be administered, and a nasogastric tube should be inserted. Children with associated abnormalities such as cardiac disease or congenital central hypoventilation syndrome must be investigated and managed before definitive surgical repair. Children with enterocolitis or those in whom immediate surgery cannot be done for other reasons should undergo decompression of the colon using digital rectal stimulation, irrigations, or occasionally an emergency stoma.

Once a child has been resuscitated and stabilized, operation can be done semielectively. While waiting, most children can be discharged home on breast milk or an elemental formula, in combination with rectal stimulations or irrigations. In the older child with an extremely dilated colon, operation should be delayed until the diameter of the colon has

decreased sufficiently to do a pull-through safely. This can sometimes be accomplished with weeks or months of irrigations, but some of these children may require a colostomy in order to adequately decompress the dilated colon (Fig. 101-3).

Some authors have advocated nonoperative long-term management of short-segment Hirschsprung disease using enemas and laxatives. Others have suggested that simple myectomy may be adequate.[27] However, these techniques do not provide a good quality of life for most children with Hirschsprung disease, and most pediatric surgeons recommend a pull-through procedure.

## Pull-through Procedure for Hirschsprung Disease

The goals of surgical management for Hirschsprung disease are to remove the aganglionic bowel and reconstruct the intestinal tract by bringing the normally innervated bowel down to the anus while preserving normal sphincter function. The most commonly performed operations are the Swenson, Duhamel, and Soave procedures (Fig. 101-4), although a number of other operations such as the Rebhein and State procedures have been described and are still done in some centers. Although many publications in the literature report results after each of these operations, few randomized or properly controlled prospective studies exist. Because of this lack of evidence, it is fair to say that all are acceptable alternatives and that the best operation for an individual patient is the one that the surgeon has been trained to do and does frequently.

### SWENSON PROCEDURE

Swenson provided the first description of a surgical approach to Hirschsprung disease in the late 1940s. Swenson's goal was removal of the entire aganglionic colon, with an end-to-end anastomosis above the anal sphincter. The operation was originally done through a laparotomy, with the anastomosis being performed from a perineal approach after eversion of the

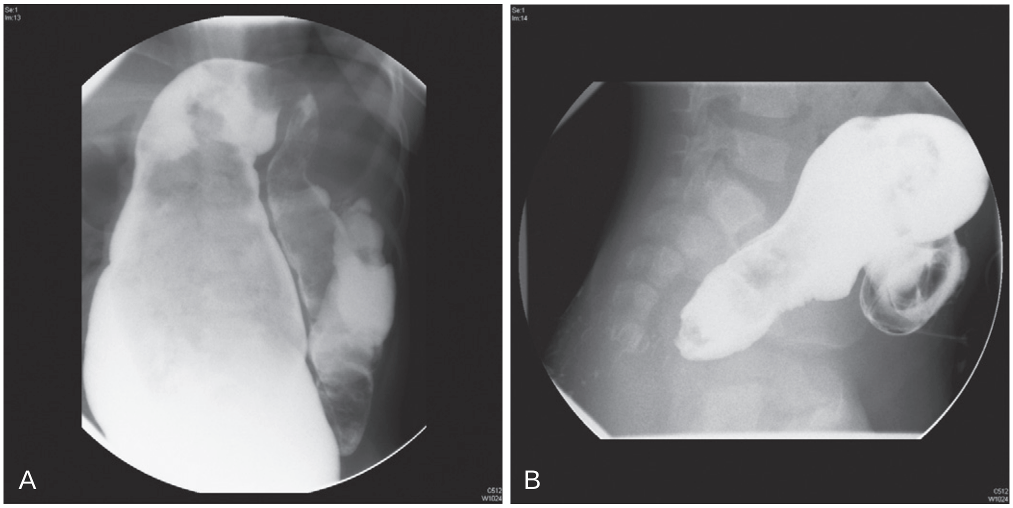


**FIGURE 101-3** Value of a decompressing colostomy to decrease the size of the dilated sigmoid colon before pull-through surgery. **A,** Before colostomy. **B,** Six months after colostomy.

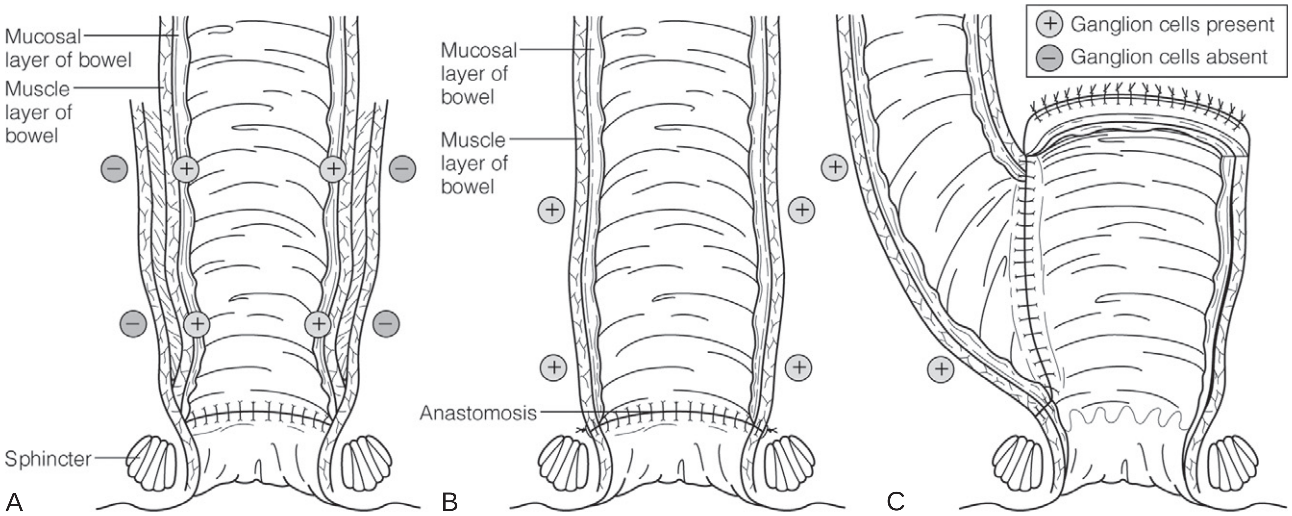


**FIGURE 101-4** The three most commonly performed operations for Hirschsprung disease. **A,** Soave. **B,** Swenson. **C,** Duhamel. + = ganglionic bowel, – = aganglionic bowel.

aganglionic rectum. Safe performance of the operation requires careful attention to dissection tightly on the rectal wall, in order to avoid injury to deep pelvic nerves, vessels, and other structures such as vagina, prostate, vas deferens, and seminal vesicles. Despite the theoretical risks inherent in the deep pelvic dissection, long-term outcome studies of the Swenson procedure report excellent functional results with respect to continence, urinary, and sexual function.[28]

### SOAVE PROCEDURE

The Soave procedure was designed to avoid the risks of injury to pelvic structures inherent in the Swenson procedure by doing a submucosal endorectal dissection and placing the pull-through bowel within a "cuff" consisting of aganglionic muscle. In the initial description of the operation, the pulled-through colon was left hanging out through the anus. This exteriorized bowel was excised, and the anastomosis done, at a second operation several weeks later. This was subsequently modified by Boley, who performed the procedure in a single stage.[29] Over the years there has been controversy regarding how long the cuff should be, as well as whether it should be split or a segment excised. Despite claims by some authors that the Soave procedure is more likely to result in long-term issues with constipation due to incomplete excision of the aganglionic rectum,[30] most late follow-up studies have reported similar outcomes to that seen with the Swenson procedure.[31]

### DUHAMEL PROCEDURE

The Duhamel procedure involves bringing the normal colon down through the bloodless plane between the rectum and the sacrum and joining the two walls to create a new lumen, which was aganglionic anteriorly and normally innervated posteriorly. In the initial description, two Kocher clamps were used to join the walls and were left in for a week. More recently, surgical staplers were used instead. The Duhamel procedure has several potential advantages over the Swenson or Soave procedures. It is believed to be easier and safer, with less pelvic dissection than the other two operations; it has a large anastomosis, which decreases the risk of anastomotic stricture; and the presence of a "reservoir" makes it appealing for children with longer aganglionic segments.

## Role of Colostomy

Swenson's initial operation was described as a one-stage procedure, but relatively high incidence of stricture, leak, and other adverse outcomes led him and others to recommend a routine preliminary colostomy, followed by a period of growth and a subsequent reconstructive operation.[32] This approach became surgical dogma, which was reinforced by the fact that many children with Hirschsprung disease presented late with malnutrition and dilated colon, so a colostomy was a lifesaving procedure. In the 1980s, however, a number of surgeons reported series of single-stage pull-through procedures even in small infants.[33,34] Over the next 10 to 15 years, one-stage operations became increasingly popular and many reports documented the safety of this approach, suggesting that a single-stage procedure avoids the known morbidity of stomas in infants and is also more cost-effective.[35–37] It is important to remember, however, that a stoma may still be indicated for children with severe enterocolitis, perforation, malnutrition, or massively dilated proximal bowel, as well as in situations where there is inadequate pathology support to reliably identify the transition zone on frozen section.

## Minimal Access Approaches

### LAPAROSCOPIC PULL-THROUGH

With the advent of laparoscopic surgery in the late 1980s, minimal access techniques became increasingly applied to pediatric surgical diseases. The first minimal approach to pull-through surgery for Hirschsprung disease was described by Georgeson in 1995,[38] who described a laparoscopic pull-through for Hirschsprung disease, involving laparoscopic biopsy to identify the transition zone, laparoscopic mobilization of the rectum below the peritoneal reflection, and a short mucosal dissection through a perineal approach (Fig. 101-5). The rectum is then prolapsed through the anus, and the anastomosis is done from below. This procedure has been associated with a shorter hospital time, and both early and mid-term results appear to be equivalent to those reported for the open procedures.[39] Laparoscopic approaches have been also described for the Duhamel and Swenson operations, with excellent short-term results reported.[40,41]

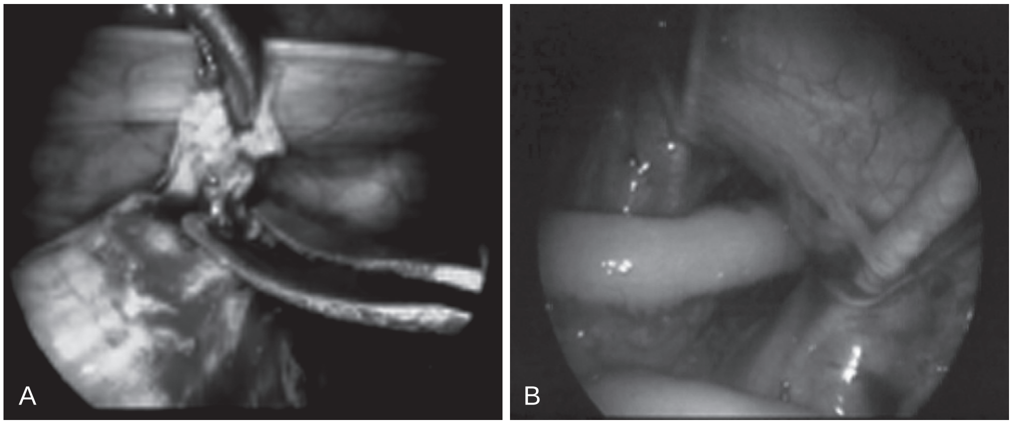


**FIGURE 101-5** Laparoscopic pull-through. **A,** Confirmation of the pathologic transition zone. **B,** Laparoscopic view of the completed pull-through from above. (Courtesy Dr. Steve Rothenberg.)

## TRANSANAL (PERINEAL) PULL-THROUGH

The transanal pull-through procedure uses the same mucosal dissection from below as the Georgeson operation, but without laparoscopic mobilization of the rectum. The mucosal incision is made 0.5 to 1 cm above the dentate line, depending on the size of the child, and the mucosa is stripped from the underlying muscle as in the Soave operation. The rectal muscle is then incised circumferentially, and the dissection is continued on the rectal wall, dividing the vessels as they enter the rectum. The entire rectum and part of the sigmoid colon can be delivered through the anus. When the transition zone is reached, the anastomosis is done from below (Fig. 101-6). In patients with a more proximal transition zone (usually above the proximal sigmoid colon), laparoscopy or a small umbilical incision can be used to mobilize the left colon and/or splenic flexure to achieve adequate length. A transanal approach can also be used if the patient has already had a colostomy, by using the stoma as the end of the pull-through bowel and performing the rectal excision using the transanal technique.

The transanal approach has a low complication rate, requires minimal analgesia, and is associated with early feeding and discharge.[42–45] Although there have not been any studies comparing the transanal and laparoscopic approaches, the transanal pull-through can be done by any pediatric surgeon, including those without laparoscopic skills, and by pediatric surgeons in parts of the world where access to appropriately miniaturized laparoscopic equipment is limited.

A number of ongoing controversies surround the transanal pull-through. The first is whether the pathologic transition zone should be defined before beginning the anal dissection. This was not done in the early descriptions of the operation and continues to be omitted by many surgeons. The main rationale for this practice is the known inaccuracy of the contrast enema in predicting the level of aganglionosis, with approximately 8% of children who have a rectosigmoid transition zone on contrast study having a more proximal transition zone on histology.[46] This step is particularly important for surgeons who do a different operation for long-segment disease than they do for rectosigmoid disease. The preliminary biopsy can be done using a laparoscopic approach, or through a small umbilical incision, both of which can also be used to mobilize the splenic flexure in children with higher transition zones.[47] The advantage of the umbilical approach is that it can be done by any surgeon, anywhere in the world, and does not require laparoscopic skills or equipment. Evidence would suggest that a preliminary biopsy to determine the pathologic transition zone does not have a deleterious effect on postoperative outcomes such as time to feeding, pain, or length of hospital stay.[45,48]

There is also controversy about whether the transanal pull-through is best done in the prone or supine position.[49] The prone position provides excellent visualization and is familiar to most pediatric surgeons because of their experience with it in the repair of anorectal malformations. The supine position has the advantage of access to the peritoneal cavity for initial colonic biopsy or for mobilization of the colon or a stoma if necessary. Finally, there is controversy about the length of the rectal cuff. The initial description of the transanal pull-through involved a long cuff, with a submucosal dissection extending into the peritoneal cavity. Many surgeons continue to do the operation this way, and most advocate division of the cuff to prevent narrowing. Other surgeons have modified the procedure by doing a short submucosal dissection for a few centimeters, and others have abandoned the submucosal dissection entirely and do what is essentially a transanal

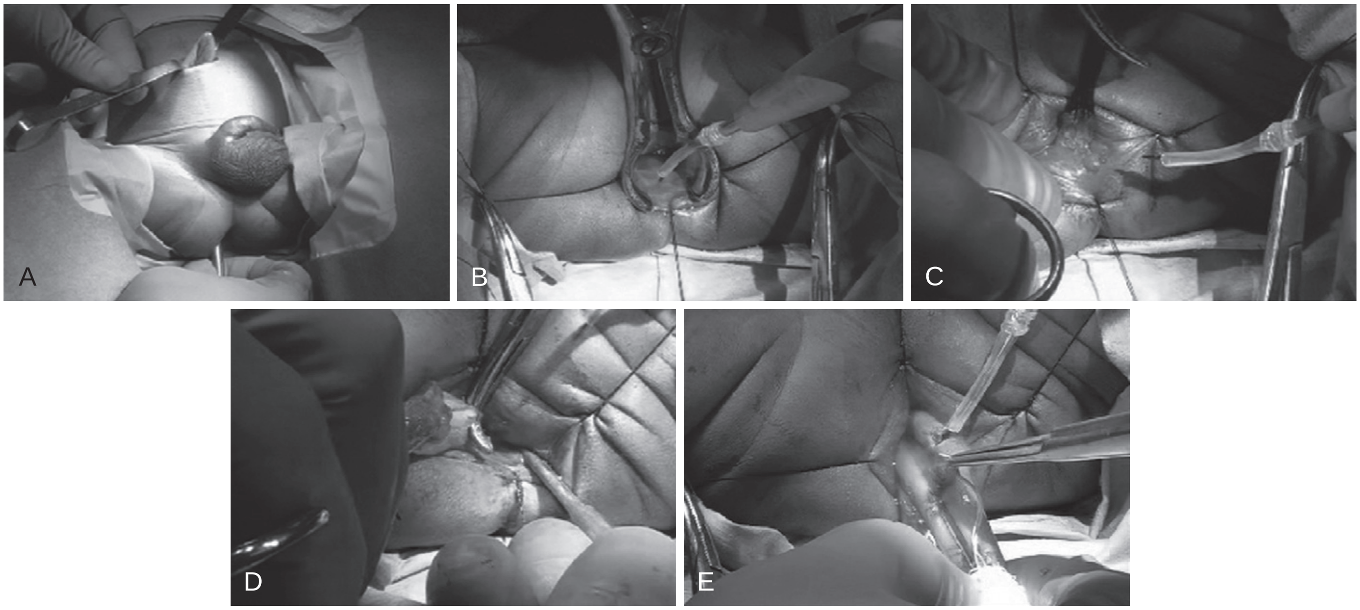


**FIGURE 101-6** The transanal Soave pull-through. **A,** An umbilical incision is used for a preliminary biopsy. A Heger dilator is used to push the sigmoid into the umbilical incision. **B,** Eversion sutures are placed, and a nasal speculum is used to provide exposure to the anal canal. A circumferential incision is made 5 mm from the dentate line. **C,** The submucosal dissection is carried 2 to 3 cm. **D,** Once the muscle cuff has been divided circumferentially, the dissection is carried proximally, staying right on the colonic wall. **E,** The bowel is divided at least 2 cm above the biopsy showing ganglion cells, and the anastomosis is performed. Care must be taken to do the anastomosis to the rectal mucosa, not to the transitional epithelium, or normal sensation will be lost and the risk of incontinence will be increased.

Swenson procedure.[50] The advantage of a shorter cuff is a lower rate of narrowing and potentially a lower risk of postoperative obstructive symptoms and enterocolitis.[48]

## Surgical Approach to Long-Segment Hirschsprung Disease

Long-segment Hirschsprung disease is usually defined as a transition zone that is proximal to the midtransverse colon. The most common is total colonic aganglionosis, which usually also includes some of the distal ileum. In rare cases most of or the entire small bowel is aganglionic. Long-segment disease is more likely to be associated with a positive family history[51] and is more likely to be diagnosed prenatally.[52] Contrast enema typically shows a shortened, relatively narrow colon ("question mark colon") (Fig. 101-7),[53] and there may also be a transition zone in the small bowel. The rectal biopsy shows absence of ganglion cells, but in many cases there are no hypertrophic nerves or abnormalities of acetylcholinesterase staining.

Early resuscitation and management is similar to that described for standard Hirschsprung disease. Sequential colonic biopsies are done looking for ganglion cells on frozen section. These can be done through a standard laparotomy, laparoscopically, or through an umbilical incision, which in a newborn can be used to access all parts of the colon. Traditionally, many surgeons started with an appendectomy, assuming that lack of ganglion cells in the appendix would be diagnostic of total colonic disease. However, this may result in a false-positive diagnosis of total colonic Hirschsprung disease because there may be a paucity of ganglion cells in the appendix in children with shorter segment disease.[54]


FIGURE 101-7 Contrast enema in a child with total colonic Hirschsprung disease. There is no transition zone in the colon, and the colon is foreshortened with a "question-mark" configuration.

Once the level of aganglionosis has been identified, most surgeons create a stoma, wait for permanent sections, and do a definitive reconstructive procedure at a later time. Although primary pull-through without ileostomy for total colonic disease has been reported, this approach requires a high degree of confidence in the pathologist because it requires doing a total colectomy on the basis of frozen sections alone. In addition, many surgeons believe that the results of pull-through surgery are better once the stool has thickened, which usually occurs in the first few months of life.

Three types of operations are available for reconstruction in children with long-segment Hirschsprung disease: straight pull-through, colon patch, and J-pouch construction. Straight pull-through procedures involve bringing the normally innervated ileum to just above the anal sphincter, using any one of the standard techniques (Swenson, Duhamel, or Soave). Colon patch procedures involve a side-to-side anastomosis between normally innervated small bowel and aganglionic colon, using the small bowel for motility and the colon as a reservoir for storage of stool and absorption of water. The Martin procedure consists of a Duhamel reconstruction that extends proximally to involve the entire left colon (Fig. 101-8, *A*). Kimura, using the rationale that the right colon is better at water absorption than the left colon, advocated a staged procedure, in which the right colon is anastomosed side-to-side to the ileum. The "ileo-colon" is then disconnected from the right colonic blood supply after several months and anastomosed above the anal sphincter (Fig. 101-8, *B*). The J-pouch procedure is done commonly for children and adults with ulcerative colitis and familial polyposis syndrome, and some pediatric surgeons have reported the use of this operation for children with long-segment Hirschsprung disease.[55]

There are no prospective or well-controlled series reporting long-term results of surgery for long-segment Hirschsprung disease. Although the colon patch procedures theoretically result in decreased stool output due to better water absorption, the aganglionic colon gradually tends to dilate and many of these patients develop severe enterocolitis, which requires removal of the patch or a permanent stoma. Children undergoing straight pull-through tend to experience gradually decreasing stool frequency over time, with an acceptable quality of life.[56–58]

### Near-Total Intestinal Aganglionosis

Rarely, almost the entire intestinal tract of a patient is aganglionic, usually leaving 10 to 40 cm of normally innervated jejunum. In most of these cases, there is not enough functional small bowel to support enteral nutrition and intestinal failure results. These children require total parenteral nutrition from birth, a situation that has been associated with a high risk of mortality from liver failure. The surgical approach at the time of the first laparotomy is to determine the extent of aganglionosis on the basis of frozen sections and to bring out a stoma at the most distal point that has normally innervated bowel. Some surgeons prefer to bring out a more distal stoma, but this approach may increase the risk of chronic intestinal obstruction and bacterial overgrowth. A central venous catheter should be inserted for parenteral nutrition, and a gastrostomy should be considered for continuous "trophic" feeding of breast milk or elemental formula.

The management of these children is similar to the management of any child with intestinal failure.[59] Strict attention to

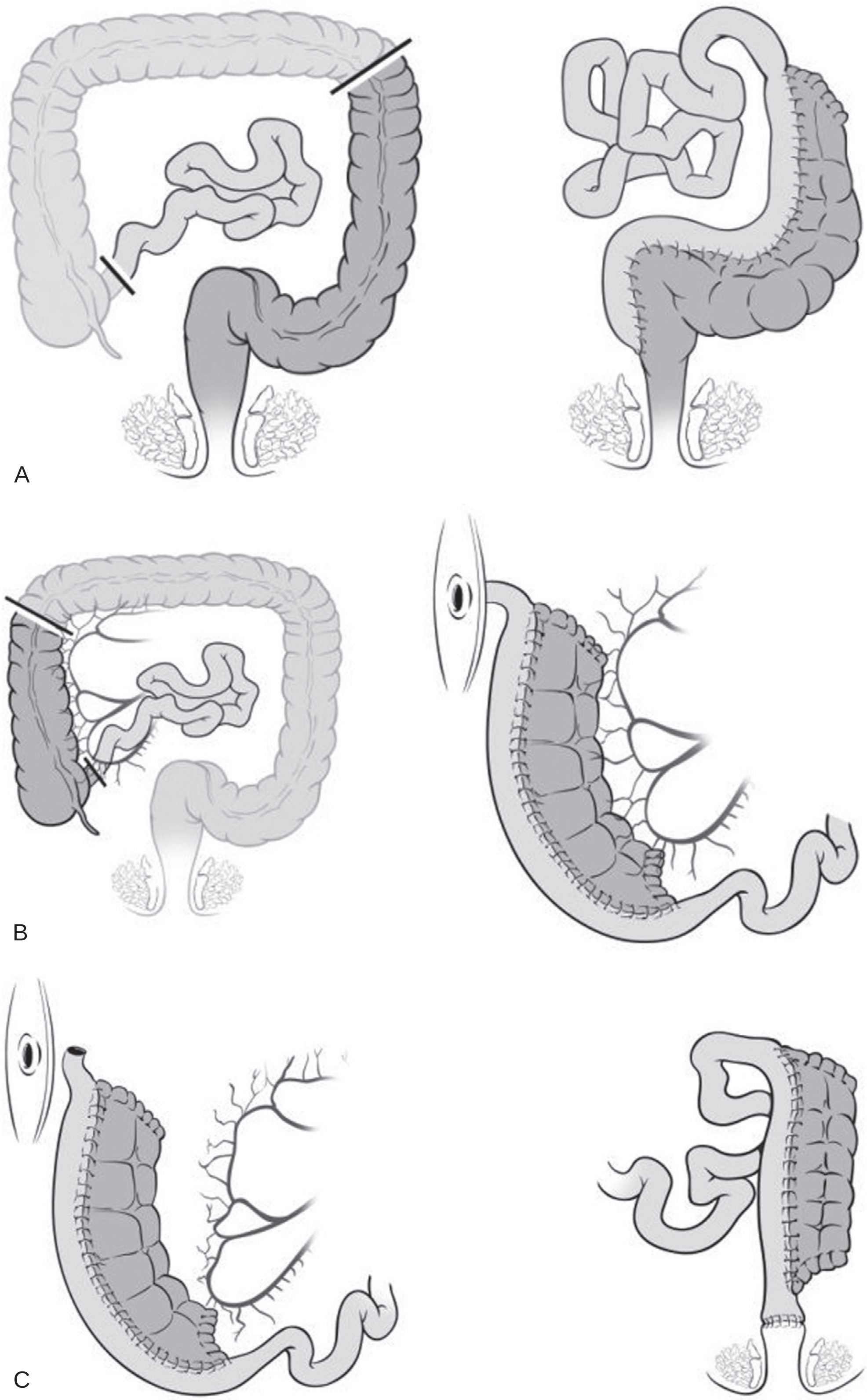


**FIGURE 101-8** Operations for long-segment Hirschsprung disease. **A,** Martin procedure. **B** and **C**, Kimura procedure.

prevention of sepsis, treatment of bacterial overgrowth, use of trophic feeds, and prevention of TPN-related cholestasis are all extremely important. Recent experience with omega-3 lipids has resulted in encouraging trends toward prevention and treatment of this problem.[60]

A number of surgical options are available for children with near-total aganglionosis.[61] For children who develop significant proximal dilatation of the normally innervated bowel, tapering, imbrication, or bowel-lengthening procedures such as the Bianchi or serial transverse enteroplasty (STEP)

procedure may be used.[62,63] Zeigler has popularized a technique known as “myectomy-myotomy,” in which a length of aganglionic small bowel distal to the transition zone undergoes myectomy.[64] Although a few successful cases using this technique have been reported, most surgeons have not found it to be successful and have noted high rates of postoperative complications. For children with ongoing liver failure, small bowel or combined small bowel-liver transplantation may offer the only chance for survival. A recent report from Paris documented extremely good results in 12 patients, many of whom underwent successful pull-through surgery following their intestinal transplant.[65]

# Postoperative Care

Most children undergoing a laparoscopic or transanal pull-through for standard Hirschsprung disease can be fed immediately, and most can be discharged within 24 to 48 hours. The anastomosis should be calibrated with an appropriately sized dilator or finger 1 to 2 weeks after the procedure. Although many surgeons instruct the parents to dilate the anastomosis on a daily basis, others have found it to be unnecessary in most cases and instead perform weekly calibration for a period of 4 to 6 weeks. It is important for the parents to protect the buttocks with a barrier cream because at least 50% of children will have frequent stools and perineal skin breakdown postoperatively. Fortunately, this problem tends to resolve over time.

As with any operation, children undergoing a pull-through may develop a wound infection or intra-abdominal bleeding. In addition, anastomotic complications such as leak or stricture may occur. Intestinal perforation can occur at a proximal biopsy site due to back pressure from anal sphincter spasm or due to unrecognized cautery injury. Bowel obstruction can result from intra-abdominal adhesions, a twist in the pull-through bowel, or a muscular cuff that has rolled down and constricted the pull-through bowel. In rare cases, rectovesical or rectovaginal fistulas have developed after pull-through surgery. Close monitoring for and early treatment of these complications is imperative. In addition, children with Hirschsprung disease can develop enterocolitis, even in the early postoperative period. The family and the primary care physician should be educated about the signs and symptoms of enterocolitis, and the family must be told to bring the child to the hospital if there are any signs suggestive of this problem because children can become very sick and even die from enterocolitis.[66]

# Long-Term Outcomes

Long-term problems in children with Hirschsprung disease include ongoing obstructive symptoms, soiling, and enterocolitis.[67] Quite often an individual child may have a combination of problems. Although early reports suggested that long-term issues were rare after surgical treatment of Hirschsprung disease,[68] it is now clear that these complications are more common than previously recognized.[31,69,70] It is important for the surgeon to follow these children closely, at least until they are through the toilet training process, in order to identify and provide early treatment for these problems.

## OBSTRUCTIVE SYMPTOMS

There are a range of obstructive symptoms that can be seen after a pull-through. Abdominal distension, bloating, vomiting, or ongoing severe constipation may be present immediately after surgery or may develop later after an initial period of normal bowel function. There are five major reasons for persistent obstructive symptoms following a pull-through: mechanical obstruction, recurrent or acquired aganglionosis, disordered motility in the proximal colon or small bowel, internal sphincter achalasia, or functional megacolon caused by stool-holding behavior (Table 101-2). The clinician will have much greater success in managing these difficult patients if an organized approach to this problem is taken. One proposed algorithm is shown in Figure 101-9.[71]

### Mechanical Obstruction

The most common cause of mechanical obstruction after a pull-through is a stricture, which usually occurs after a Swenson or Soave procedure (Fig. 101-10, *A*). Patients undergoing a Duhamel procedure may have a retained “spur” consisting of the anterior aganglionic bowel, which may fill with stool and obstruct the pulled-through bowel (Fig. 101-10, *B*). In other cases, there may be obstruction secondary to a twist in the pulled-through bowel (Fig. 101-10, *C*) or narrowing due to a long muscular cuff in children who have had a Soave procedure.

Obstruction can be identified using a combination of digital rectal examination and a barium enema. Initial management of anastomotic stricture consists of repeated dilatation using a finger, dilator, or radially dilating balloon. Some authors have advocated innovative techniques for recalcitrant strictures including antegrade dilatation over a string using Tucker dilators[72] and the use of intralesional steroid.[73] In some cases the stricture cannot be successfully dilated, and revision of the pull-through is necessary. This is best done using the Duhamel technique, although other operations have also been advocated.[74–76] Duhamel spurs can be resected from above or managed by extending the staple line from below, with or without laparoscopic visualization. Twisted pull-throughs and narrow muscular cuffs usually require surgical intervention, typically a repeat pull-through. In some cases, a muscular cuff can be divided laparoscopically without having to re-do the entire pull-through.

### Persistent or Acquired Aganglionosis

This rare problem may be due to pathologist error,[77] a transition zone pull-through,[78] or ganglion cell loss after a pull-through.[79] Repeat rectal biopsy, above the previous anastomosis (it must be posterior in the case of an initial Duhamel procedure), should be done to determine whether there are

**TABLE 101-2**
**Causes of Obstructive Symptoms Following Surgery for Hirschsprung Disease**

| |
|---|
| Mechanical obstruction |
| Recurrent or residual aganglionosis |
| Motility disorder involving the ganglionated bowel |
| Internal anal sphincter achalasia |
| Functional megacolon (stool-holding behavior) |

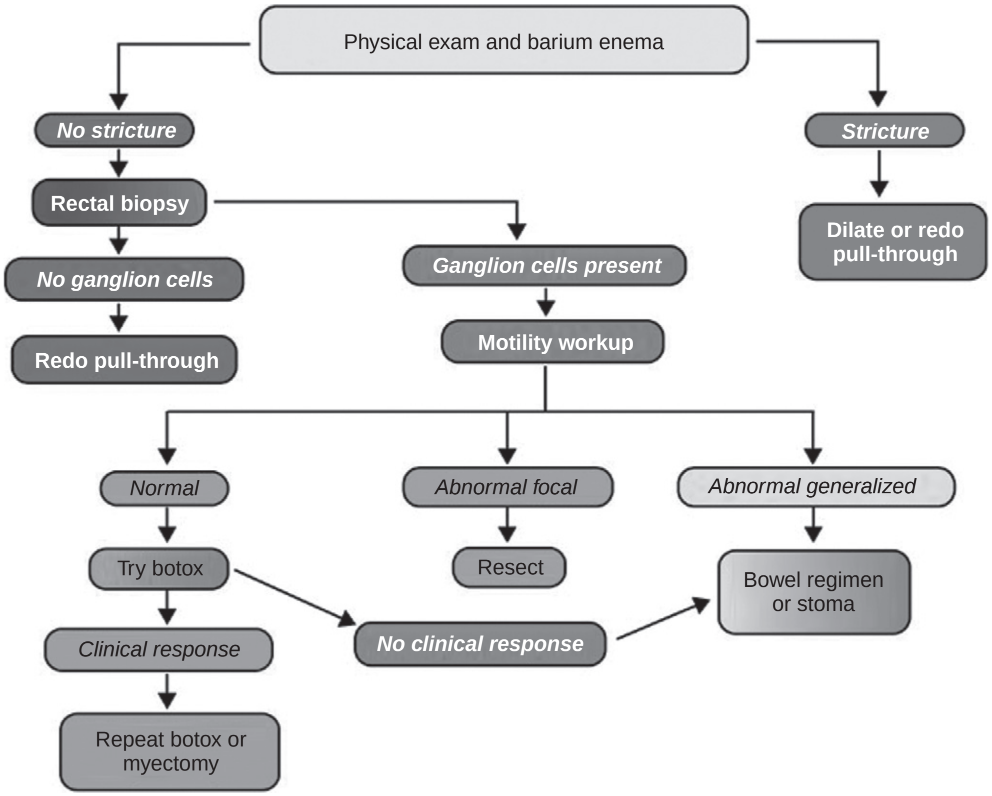


FIGURE 101-9 Algorithm for the investigation and management of the child with obstructive symptoms following a pull-through.

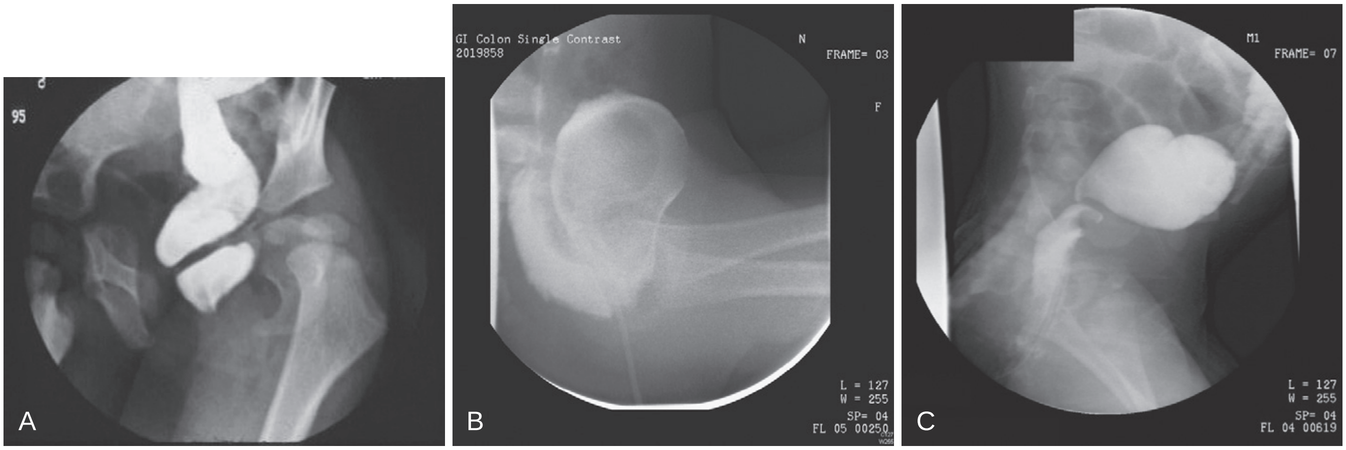


FIGURE 101-10 Causes of mechanical obstruction after a pull-through. **A,** Stricture following a Soave procedure. **B,** Anterior aganglionic "spur" following a Duhamel procedure. **C,** Twisted transanal pull-through.

normal ganglion cells present in all patients with persistent obstructive symptoms after surgery. The pathology from the original operation should be reviewed to ensure that there was normal innervation at the proximal margin, and in some cases further sections should be done circumferentially from the resection margin because the transition zone is often asymmetrical in children with Hirschsprung disease.[80] The best treatment for persistent or acquired aganglionosis in most cases is a repeat pull-through, which can be done using either a Soave or Duhamel approach.[75]

***Motility Disorder*** Children with Hirschsprung disease often have associated motility disorders including an increased incidence of gastroesophageal reflux and delayed gastric emptying,[81] small bowel dysmotility, and disordered colonic motility. Some cases are more focal, usually involving the left colon. In some cases the disordered motility may be associated with histological abnormalities such as intestinal neuronal dysplasia (discussed in greater detail later).

In children who have been shown not to have a mechanical obstruction and who have normal ganglion cells on rectal

biopsy, investigations for motility disorders should be undertaken. This can include a radiologic shape study, radionuclide colon transit study,[82] colonic manometry,[83] and laparoscopic biopsies looking for evidence of intestinal neuronal dysplasia.[84] If a focal abnormality is found, consideration should be given to resection and repeat pull-through using normal bowel. If the abnormality is diffuse, the appropriate treatment is bowel management and the use of prokinetic agents. Some children with particularly dysmotile colon will benefit from placement of a cecostomy for antegrade colonic enemas.[85]

***Internal Sphincter Achalasia*** This term refers to the lack of a normal RAIR that is present in all children with Hirschsprung disease (as described earlier in "Diagnosis"). It is unclear why only some children develop obstructive symptoms from this nonrelaxation, while others function normally in the postoperative period. It is also unclear why most children eventually "grow out" of this problem over time, usually by the age of 5 years. Internal sphincter achalasia is a diagnosis of exclusion, which is made after ruling out mechanical obstruction, aganglionosis, and dysmotility. The diagnosis can be confirmed by demonstrating a clinical response to intrasphincteric botulinum toxin.[86] However, the response to botulinum toxin is not related to the absolute value of the internal anal sphincter pressure (i.e., patients with a higher resting pressure are not necessarily more likely to benefit from botulinum toxin).

The standard treatment of internal sphincter achalasia has been internal sphincterotomy or myectomy,[87,88] but because this problem tends to resolve on its own in most children and there is concern about sphincter-cutting operations exacerbating future soiling issues, we prefer to use "chemical sphincterotomy" with intrasphincteric botulinum toxin.[86,89,90] In many cases repeated injection of botulinum toxin or applications of nitroglycerine paste or topical nifedipine are necessary while waiting for resolution of the problem.

***Functional Megacolon*** Functional megacolon is the result of stool-holding behavior, a common cause of constipation that some authors claim affects up to half of normal children at some time during their first few years of life.[91] This condition is probably even more common in children with Hirschsprung disease because of their predisposition to constipation, which leads to hard painful stools, withholding behavior, and a resulting vicious cycle.[92] The treatment for this problem is a bowel management regimen consisting of laxatives, enemas, and behavior modification including support for the child and family. In some severe cases of obstructive symptoms, the child may be best served by use of a cecostomy and administration of antegrade enemas, or even by the creation of a proximal stoma. In many cases the cecostomy or stoma can ultimately be reversed when the child reaches adolescence.

### Fecal Soiling

There are three broad causes of soiling after a pull-through: abnormal sphincter function, abnormal sensation, or "pseudo-incontinence" related to abnormal rectal function or obstipation (Table 101-3). Abnormal sphincter function may be due to sphincter injury during the pull-through or to a previous myectomy or sphincterotomy and can usually be identified using anorectal manometry. Two forms of abnormal sensation exist. The first is lack of sensation of a full rectum, which is also identifiable using anorectal manometry by expanding a balloon in the rectum and asking the child to state when he can feel it. The other type of sensation that may be abnormal is the ability to detect the difference between gas and stool, which is dependent on intact transitional epithelium in the anal canal. This sensation may be impaired if the anastomosis is done too low and the transitional epithelium is damaged. This problem is usually evident on simple physical examination. Neither sphincter weakness nor abnormal sensation is amenable to a surgical solution, and most of these children are best managed using a bowel routine that may include a constipating diet, rectal enemas, or antegrade enemas through a cecostomy. Biofeedback training has been advocated, especially for those children with sphincter weakness. In some cases the child is best served by a colostomy.

**TABLE 101-3**
**Causes of Soiling Following Surgery for Hirschsprung Disease**

| |
|---|
| Abnormal sensation |
| 1. Inability to feel rectal distension |
| 2. Loss of transitional epithelium |
| Abnormal sphincter function |
| "Pseudo-incontinence" |
| 1. Associated with severe constipation |
| 2. Associated with hyperperistalsis of the pulled-through bowel |

If both the sphincter and sensation are intact, the most common cause of soiling after a pull-through is "pseudo-incontinence."[93] Some patients have severe obstipation with a massively distended rectum and develop overflow of liquid stool around the fecal mass. Others simply leak small amounts of stool through the day, creating "skid marks" in the underwear on a constant basis. Other children suffer from hyperperistalsis of the pulled-through bowel, which results in inability of the anal sphincter to achieve control despite normal sphincter function.[83]

Successful management depends on a clear understanding of the underlying basis for the soiling, which requires a clear history and physical examination, as well as investigations such as abdominal radiograph, barium enema, anorectal manometry, and in some cases colonic manometry. Children with severe constipation will benefit from laxative therapy. However, if the sphincter or sensation, or both, are inadequate, passive laxatives such as lactulose or PEG 3300 will make the problem worse and the child should instead be treated with stimulant laxatives such as senna or enemas. On the other hand, children with stool-holding behavior who have a normal sphincter and sensation will often experience exacerbation of the behavioral problem by rectal enemas or any other kind of anal manipulation. Children without constipation who have hyperperistalsis of the pulled-through bowel or abnormal sphincter function or sensation will benefit from a constipating diet and medications such as loperamide. Children with slow transit constipation or stool-holding behavior, on the other hand, will benefit from a high-fiber diet and passive laxative therapy. The treatment of soiling must be based on a clear understanding of the child's underlying problem.

### Enterocolitis

Enterocolitis may be present both before and after surgical correction of the disease, and it can be severe or life threatening. HAEC is more common in children diagnosed at a younger age,[94] those with longer segment disease, and those with trisomy 21. The clinical features of HAEC are generally agreed on and include fever, abdominal distention, diarrhea, elevated white blood cell count, and evidence of intestinal edema on abdominal radiograph. Because there is overlap between HAEC and other conditions such as obstructive symptoms and gastroenteritis, there has been confusion in the literature as to the exact definition and the true incidence of the condition. A recently developed HAEC score may be useful in the future in both the clinical setting and in research into this area (Table 101-4).[95]

The treatment of postoperative HAEC involves nasogastric drainage, intravenous fluids, broad-spectrum antibiotics, and decompression of the rectum and colon using rectal stimulation or irrigations. The risk of HAEC can be minimized by using preventive measures such as routine irrigations[96] or chronic administration of metronidazole or probiotic agents, particularly in those who are thought to be at higher risk for this complication on the basis of clinical or histologic grounds. Because enterocolitis is the most common cause of death in children with Hirschsprung disease and can occur postoperatively even in children who did not have it preoperatively, it is extremely important that the surgeon educate the family about the risk of this complication and urge early return to the hospital if the child should develop any concerning symptoms.[66]

### Long-Term Outcomes

Despite the relatively common occurrence of postoperative problems, most children with Hirschsprung disease overcome these issues and do well. Obstructive symptoms, soiling, and enterocolitis, in the absence of an ongoing source of obstruction, usually resolve after the first 5 years of life. Studies of teenagers and adults with Hirschsprung disease suggest that sexual function, social satisfaction, and quality of life all appear to be normal in the vast majority of patients once they reach their late teens.[69,97]

Several populations of children have less optimistic outcomes. Children with long-segment disease appear to have a higher risk of enterocolitis, incontinence, and dehydration than children with shorter-segment disease. Children with Hirschsprung disease associated with Down syndrome have a greater risk of enterocolitis and incontinence.[98,99] Finally, prognosis may be poor in children with other types of comorbidity such as those with congenital central hypoventilation syndrome, congenital heart disease, and syndromes that are associated with mental retardation or other forms of disability.

**TABLE 101-4**
**Hirschsprung-Associated Enterocolitis (HAEC) Score***

| | |
|---|---|
| **History** | |
| Diarrhea with explosive stool | 2 |
| Diarrhea with foul-smelling stool | 2 |
| Diarrhea with bloody stool | 1 |
| Previous history of enterocolitis | 1 |
| **Physical examination** | |
| Explosive discharge of gas and stool on rectal examination | 2 |
| Distended abdomen | 2 |
| Decreased peripheral perfusion | 1 |
| Lethargy | 1 |
| Fever | 1 |
| **Radiology** | |
| Multiple air-fluid levels | 1 |
| Dilated loops of bowel | 1 |
| Sawtooth appearance with irregular mucosal lining | 1 |
| Cutoff sign in recto-sigmoid with absence of distal air | 1 |
| Pneumatosis | 1 |
| **Laboratory** | |
| Leukocytosis | 1 |
| Shift to left | 1 |

*A score of 10 or higher was associated with a positive diagnosis of HAEC by an international panel of experts.

## "Variant" Hirschsprung Disease

Some children present with signs and symptoms suggestive of Hirschsprung disease but have ganglion cells present on rectal biopsy.[100] There is a significant amount of controversy surrounding the definitions and features of many of these conditions,[101] and in some cases their existence has even been called into question.

### INTESTINAL NEURONAL DYSPLASIA

This condition was first described by Meier-Ruge in 1971. Two types are usually described.[102] Type A is less common and is characterized by diminished or absent sympathetic innervation of the myenteric and submucosal plexuses, as well as hyperplasia of the myenteric plexus. Type B consists of dysplasia of the submucous plexus with thickened nerve fibers and giant ganglia, increased acetylcholinesterase staining, and identification of ectopic ganglion cells in the lamina propria. Type B can occur on its own or can be present in the nonaganglionic bowel in children who also have Hirschsprung disease. In addition, intestinal neuronal dysplasia may be either diffuse or focal. The reported incidence of IND varies significantly from one center to another, largely due to differences in definition of the condition.

Despite multiple publications on the topic of IND, this topic still stimulates controversy among pediatric surgeons and pediatric pathologists.[103] The diagnostic criteria have changed over time, and there is disagreement among pathologists about the diagnosis both in general terms and with respect to individual patients.[104] Sophisticated histologic techniques including special stains and the use of thick sections are often believed to be necessary for an accurate diagnosis.[105] In addition, there is some evidence that the histologic finding of IND may in some cases be secondary to chronic obstruction rather than the cause of it, and in many cases there may not be good correlation between the histologic finding of IND and the motility function of the bowel.[106]

### Hypoganglionosis

This is a rare form of dysganglionosis, which is characterized by sparse and small ganglia, usually in the distal bowel, often associated with abnormalities in acetylcholinesterase distribution.

The appropriate treatment is to resect the abnormal colon and perform a pull-through procedure, much as one would do for a child with Hirschsprung disease.[107] It is important to differentiate this condition from immature ganglia, which is seen in preterm children who present with a picture of distal intestinal obstruction resulting from underdeveloped colonic motility. The colonic motility is self-limited and should not be treated surgically.[108]

## Internal Sphincter Achalasia

Some children have normal ganglion cells on rectal biopsy but lack the RAIR on anorectal manometry. These children will sometimes develop obstructive symptoms or severe constipation that mimics Hirschsprung disease. Similarly to the situation mentioned previously in which obstructive symptoms continue after surgery for Hirschsprung disease, this condition has been termed *internal sphincter achalasia*.[109] The diagnosis is made using anorectal manometry and rectal biopsy. The initial treatment is a bowel management regimen, consisting of diet, laxatives, and enemas or irrigations. If this is unsuccessful, many surgeons have advocated the use of anal sphincter myectomy.[110,111] Because the constipation associated with this condition usually improves over the first 5 years of life, the same rationale has been used to advocate temporary or reversible sphincter-relaxing measures such as botulinum toxin,[112] nitroglycerine paste,[113] or topical nifedipine.

## Ultrashort-Segment Hirschsprung Disease

There is much confusion in the literature regarding this condition and how it is defined. Some authors use this term to describe children with normal ganglion cells on rectal biopsy, but with absence of the RAIR (which is synonymous with the definition of internal sphincter achalasia). We prefer to reserve it for children who have a documented aganglionic segment of less than 1 to 2 cm. In children with this condition, the findings of hypertrophic nerves and abnormal cholinesterase staining may be absent.[114] The treatment of ultrashort-segment Hirschsprung disease is controversial. Some authors advocate simple anal sphincter myectomy,[115,116] and some prefer excision of the aganglionic segment and pull-through reconstruction.

## Desmosis Coli

This is a condition described by Meier-Ruge characterized by total or focal lack of the connective tissue net of the circular and longitudinal muscles and the connective tissue layer of the myenteric plexus, without any abnormality of the enteric nervous system.[117] Patients with this condition present with chronic constipation. In one family Hirschsprung disease and desmosis coli coexisted,[118] although in most cases they are completely separate entities.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 102

# Intestinal Dysganglionosis and Other Disorders of Intestinal Motility

Prem Puri

The typical patient with Hirschsprung disease (HD) is a newborn presenting with delayed passage of meconium and abdominal distension or a young child presenting with severe chronic constipation. The diagnosis is confirmed by the histologic and histochemical evaluation of suction rectal biopsies, which demonstrate absence of ganglion cells in the submucosa and increased acetylcholinesterase (AChE) activity in the lamina propria. However, there are a number of patients who clinically resemble HD despite the presence of ganglion cells in rectal biopsy. Various terms have been used to describe these conditions: "chronic idiopathic intestinal pseudo-obstruction," "pseudo-Hirschsprung disease," "neonatal intestinal pseudo-obstruction," and "intestinal hypoperistalsis syndrome." There is a growing interest to further investigate these relatively rare functional bowel disorders because the diagnosis and management of these patients continues to be a challenge for clinicians. Over the past 3 decades our group has focused its research interest into delineating variant HD on the basis of specific histochemical, immunohistochemical, and electron microscopic studies.

Between 1981 and 2009, full-thickness bowel biopsy or resected surgical specimens from 178 patients (75 boys and 103 girls) with clinical symptoms suggesting HD were examined in our research laboratory. Their ages ranged from 1 day to 9 years. One hundred and three patients had onset of symptoms in the neonatal period. Ninety-one patients were from Ireland, and in 87 patients biopsy material was sent to our laboratory from other countries. Table 102-1 shows various functional bowel disorders diagnosed using different histologic techniques. The vast majority of variant HD cases include intestinal neuronal dysplasia, isolated hypoganglionosis, internal sphincter achalasia, and megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS). Rarer motility disorders include immature ganglia, absence of argyrophil plexus, and smooth muscle disorders.

## Intestinal Neuronal Dysplasia

### HISTORY AND PATHOGENESIS

Intestinal neuronal dysplasia (IND) was first described by Meier-Ruge in 1971 as a malformation of enteric plexus.[1] The first association between IND and HD was reported by my colleagues and me in a 5-year-old Arab boy who had rectosigmoid aganglionosis and IND of descending and transverse colon.[2] In 1983 Fadda and colleagues[3] classified IND into two clinically and histologically distinguished subtypes. Type A, which occurs in less than 5% of cases, is characterized by congenital aplasia or hypoplasia of the sympathetic innervation and presents acutely in the neonatal period with episodes of intestinal obstruction, diarrhea, and bloody stools. Type B is clinically indistinguishable from HD, is characterized by a malformation of the parasympathetic submucous and myenteric plexuses, and accounts for more than 95% of cases of IND.[4,5] IND occurring in association with HD is of type B. Since its original description, little has been written about IND type A. IND has become synonymous with IND type B.

Many investigators have raised doubts about the existence of IND as a distinct histopathologic entity.[6,7] It has been suggested that the pathologic changes seen in IND may be part of normal development or may be a secondary phenomenon induced by congenital obstruction and inflammatory disease.[6,8] On the other hand, the literature contains several familial cases of IND suggesting that genetic factors may be involved in this condition. Martuccielo and colleagues[9] observed three families with multiple IND cases, and Moore and colleagues[10] and Kobayashi and colleagues[11] reported IND in monozygotic twins. The strongest evidence that IND is a real entity stems from the animal models. Hox11L1 is a homeobox gene involved in peripheral nervous system development and is reported to play a role in the proliferation or differentiation of neural crest cell lines. Two different Hox11L1 knockout mouse models have been generated. In both cases, homozygous mutant mice were viable but developed megacolon at the age of 3 to 5 weeks. Histologic and immunohistochemical analysis showed hyperplasia of myenteric ganglia, a phenotype similar to that observed in human IND type B.[12,13]

**TABLE 102-1**
**Variant Hirschsprung Disease (1981-2009)**

| | |
|---|---|
| Intestinal neuronal dysplasia | 76 |
| Isolated hypoganglionosis | 18 |
| Internal sphincter achalasia | 46 |
| Megacystis-microcolon-intestinal hypoperistalsis syndrome | 12 |
| Rarer intestinal motility disorders | 26 |
| **Total** | **178** |

However, the mutation screening of this gene in 48 patients with IND did not show any sequence variant, either causative missense mutation or neutral substitution.[14]

In 2002 Von Boyen and colleagues[15] reported abnormalities of the enteric nervous system in heterozygous *EDNRB*-deficient rats resembling IND in humans. They showed that a heterozygous 301-base-pair deletion of the *EDNRB* gene led to abnormalities of the enteric nervous system. Malformations of the enteric nervous system observed in +/sl rats included hyperganglionosis, giant ganglia, and hypertrophied nerve fibers in the submucous plexus resembling the histopathologic features of IND type B in humans. These findings support the concept that IND may be linked to a genetic defect. However, no mutations of the *EDNRB* gene were detected in a small series of IND patients.[16]

## INCIDENCE

Intestinal neuronal dysplasia is the most commonly encountered variant of HD.[5] The incidence of isolated IND has varied from 0.3% to 40% of all suction rectal biopsies in different centers.[5,17] The incidence varies considerably among different countries. IND immediately proximal to a segment of aganglionosis is not uncommon and often presents as persistent obstructive symptoms after a pull-through operation for HD.[18] Some investigators have reported that 25% to 35% of patients with HD have associated IND.[3] However, others have rarely encountered IND in association with HD. The uncertainty regarding the incidence of IND has resulted from the considerable confusion regarding the essential diagnostic criteria. The diagnostic difficulty is centered on a wide variability encountered in the literature, not only in terms of age of the patient, the type of specimen examined, and the stains performed but also in the diagnostic criteria used.

## CLINICAL PRESENTATION

The characteristic clinical pattern of IND can be found in infants younger than 1 year old with a history of constipation and abdominal distention, thus mimicking HD. Montedonico and colleagues[19] classified IND according to the severity of histochemical changes in rectal biopsies. The criteria used for the diagnosis of severe IND included hyperplasia of submucous plexus, giant ganglia, ectopic ganglia, and increased acetylcholinesterase (AChE) activity in the lamina propria or around submucosal blood vessels. Any biopsy that showed giant ganglia of the submucous plexus with only one of the other criteria was considered mild. Montedonico and colleagues reported that the patients with severe IND begin their symptoms at an earlier age than those with mild IND (5.2 ± 112 months vs. 17.5 ± 23 months).

The incidence of associated anomalies in IND has been reported to be between 25% and 30%.[9,19] The common associated anomalies include anorectal malformations, intestinal malrotation, MMIHS, congenital short bowel, hypertrophic pyloric stenosis, necrotizing enterocolitis, and Down syndrome.

## DIAGNOSTIC CRITERIA

Since the first description in 1971, most controversy surrounding IND has been regarding which histologic diagnostic criteria are required for definitive diagnosis. The presently recognized diagnostic criteria, previously reported by our group and supported by others, are hyperganglionosis and giant ganglia, in addition to the presence of at least one of the following on suction rectal biopsy: ectopic ganglia in the lamina propria and increased AChE-positive nerve fibers around submucosal blood vessels and in the lamina propria.[4,5,17,20] However, Lumb and Moore[21] believe that giant ganglia can be a normal feature in normal bowel, having identified them in segments of adult bowel removed during surgery for colorectal carcinoma. To overcome the confusion in diagnostic criteria, Borchard and colleagues[4] produced guidelines for identifying IND in mucosal rectal biopsies. These comprised two obligatory criteria (hyperplasia of the submucous plexus and an increase in AChE-positive nerve fibers around submucosal blood vessels) and two additional criteria (neuronal heterotopia and increased AChE activity in the lamina propria). In our experience, hyperganglionosis and giant ganglia are the most important features for the diagnosis of IND in suction rectal biopsies, except in the newborn, when hyperganglionosis is a normal finding.[22]

## DIAGNOSIS

Suction rectal biopsy is the principal method for the diagnosis of disorders of intestinal innervation. It is necessary to include a sufficient amount of submucosa in the suction biopsy specimens. Traditionally, hematoxylin and eosin and AChE histochemical staining (Figs. 102-1 and 102-2) in suction rectal biopsy specimens have provided the basis for the diagnostic evaluation of IND. However, there has been discussion about whether AChE histochemistry is sufficient for the accurate diagnosis of IND and other additional staining techniques have been proposed. Meier-Ruge and colleagues suggest lactate dehydrogenase histochemistry.[5,23] In my laboratory, neuronal markers currently being used are reduced nicotinamide-adenine dinucleotide phosphate (NADPH) diaphorase histochemistry and immunohistochemistry using antibodies raised against neural cell adhesion molecule, protein gene product 9.5 (PGP9.5), S-100, peripherin, and synaptophysin.[5,17] Ganglion-cell counting can be difficult. Standard immunohistochemical techniques, using antibodies raised against neuron-specific enolase or PGP9.5, which are commonly used to display the enteric nervous system, are less suitable for cell counting because they stain not only the cell bodies but also the axonal processes. Cuprolinic blue staining has been proposed as the method that stains the largest number of ganglion cells.[5] Furthermore, this method stains only the cell bodies and not the axons, which makes it relatively easy to distinguish the individual cells.

Barium enema in IND does not show any specific radiologic features other than rectosigmoid distention. Similarly,

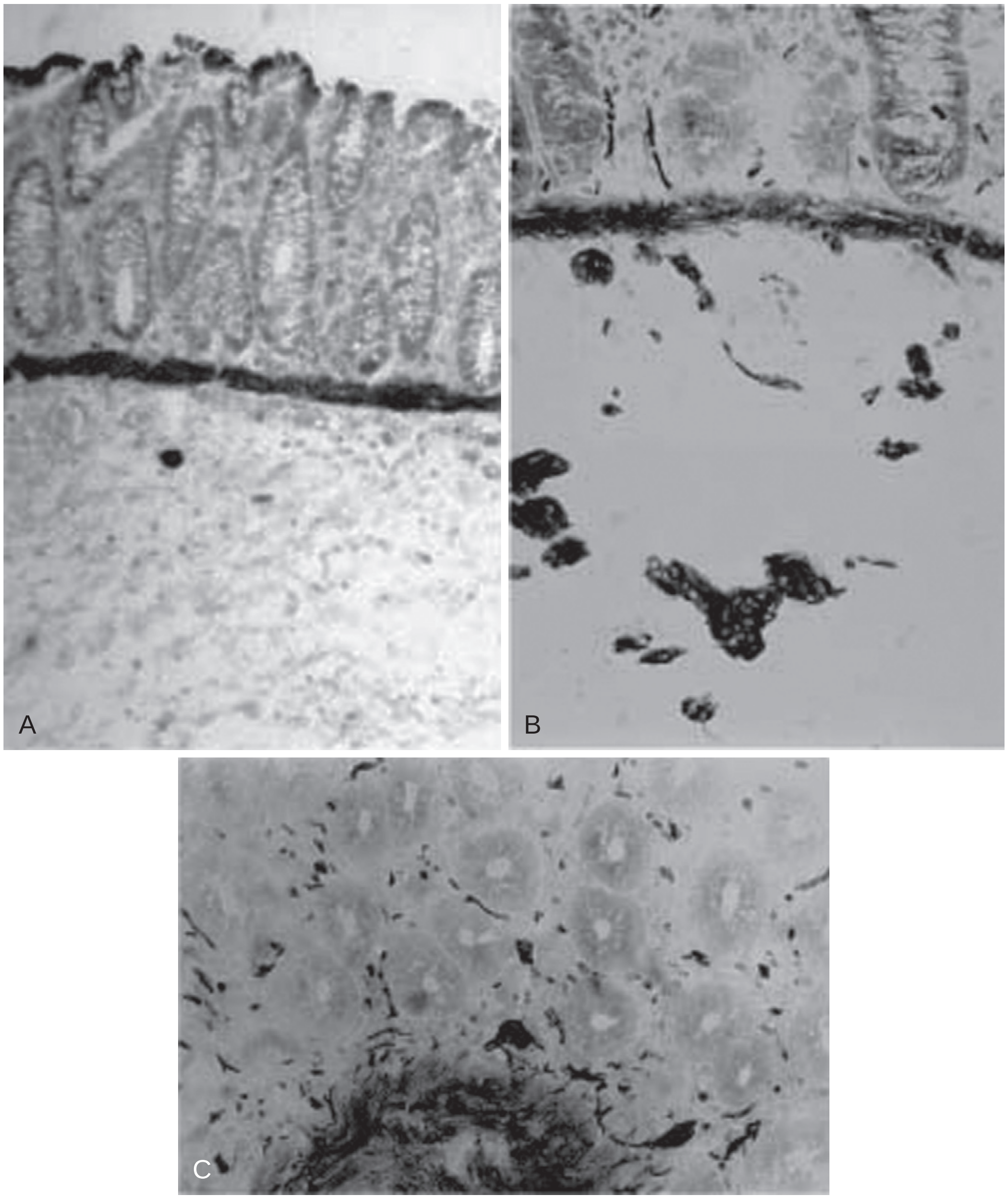

**FIGURE 102-1** Acetylcholinesterase staining of suction rectal biopsy. **A,** Normal biopsy showing a submucosal ganglion. **B,** Biopsy from a patient with intestinal neuronal dysplasia showing hyperganglionosis and giant ganglia. **C,** Ectopic ganglia in the lamina propria and increased AChE activity in the lamina propria in a biopsy specimen from a patient with intestinal neuronal dysplasia.

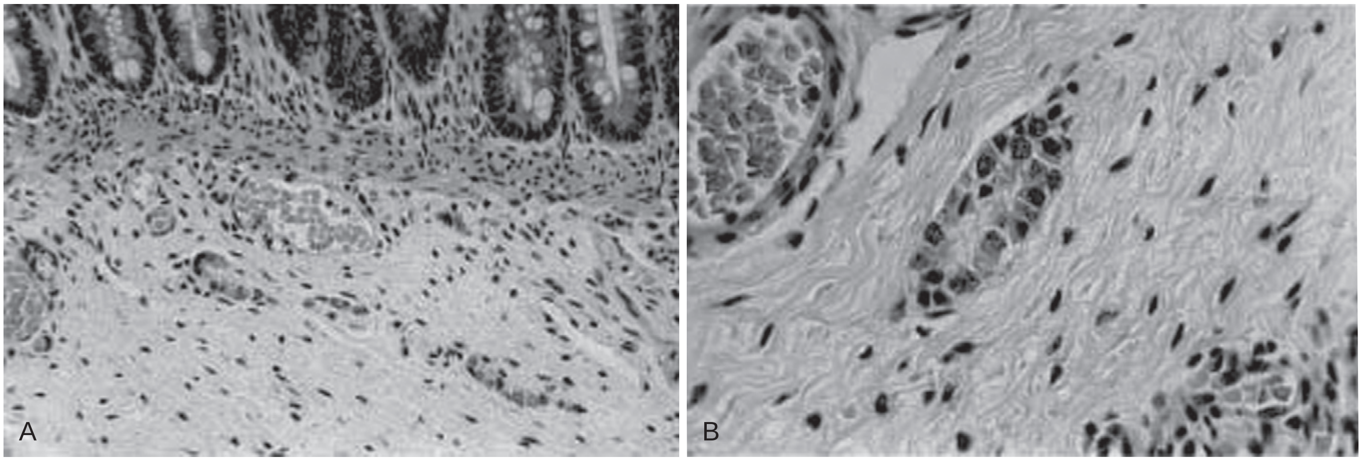

**FIGURE 102-2** Hematoxylin and eosin staining of suction rectal biopsy from a patient with intestinal neuronal dysplasia. **A,** Hyperganglionosis. **B,** Giant ganglia.

anorectal manometry may show the rectosphincteric reflex to be present, absent, or atypical.

### CORRELATION BETWEEN HISTOLOGIC FINDINGS AND CLINICAL SYMPTOMS

Several investigators have raised doubts about the existence of IND as a distinct histopathologic entity.[6,7] One reason for this has been the weak correlation found between the severity of clinical symptoms and the histologic findings. It has been suggested that the histologic findings of IND can be a part of normal development or secondary to prolonged constipation. Recently, Montedonico and colleagues[19] correlated specific clinical, radiologic, and manometric findings with the severity of histopathologic findings in 44 patients with IND treated at their institution over 20 years. They classified IND according to the severity of histochemical alteration into two groups: mild IND and severe IND. The criteria used for the diagnosis of severe IND included hyperplasia of the submucous plexus, giant ganglia with more than seven ganglion cells, increased AChE activity in the lamina propria or surrounding submucosal blood vessels, and heterotopic neuronal cells in the lamina propria. Any biopsy specimen that showed giant ganglia of the submucous plexus with only one of the other elements was considered mild IND. According to their results, the characteristic clinical pattern of severe IND can be found in infants younger than 1 year old with a history of constipation and abdominal distention, thus mimicking HD, with absence of internal sphincter relaxation in anorectal manometry but who have a normal barium enema. The median age at presentation of severe IND was 5 months, and similar results have been reported in other series.[3] These authors found a correlation between the histologic severity of IND and the clinical symptoms, suggesting that IND is a distinct entity. Although many cases of IND are clinically indistinguishable from HD, barium enema findings in IND are often equivocal or show slight to moderate rectosigmoid distention but lack the typical narrow segment of aganglionosis.

### MANAGEMENT

Current treatment of IND type B is in the first instance conservative, consisting of laxatives and enemas. In the majority of patients the clinical problem resolves or is manageable in this way because maturation of nerve cells is often observed in IND. If bowel symptoms persist after at least 6 months of treatment, internal sphincter myectomy should be considered. Resection and a pull-through operation are rarely indicated in IND. The indication for pull-through should not be determined on the basis of histopathologic findings alone; rather, the decision must be based on the individual patient's clinical symptoms.

### OUTCOME

Gillick and colleagues[24] reported results of treatment in 33 patients with IND observed for periods ranging from 1 to 8 years (mean 2.4 years). Twenty-one (64%) patients had a good response to conservative management and currently have normal bowel habits. Twelve patients (36%) underwent internal sphincter myectomy after failed conservative management. Seven of these patients now have normal bowel habits. Two patients were able to stay clean with regular enemas. Three patients who continued to have persistent constipation after myectomy and underwent resection of redundant and dilated sigmoid colon now had normal bowel habits.

## Isolated Hypoganglionosis

Isolated hypoganglionosis (IH) has been classified as a "hypogenetic type" of intestinal innervation disorders.[4] Clinically, IH resembles classical HD: Patients present with severe constipation or pseudo-obstruction. Due to the fact that IH is one of the rarest subtypes of intestinal innervation disorders, accounting for only 5% of all cases,[4] the number of reported cases in the literature is limited. Dingemann and Puri recently reviewed 92 patients with IH reported in the English literature between 1978 and 2008 and critically analyzed the current state of the epidemiologic, diagnostic, and therapeutic features of this rare neuronal intestinal disorder.[25]

### EPIDEMIOLOGY

In the reported review the overall male-to-female ratio of IH was 3:1. This is similar to the overall male-to-female ratio of HD, which is commonly considered to be 4:1. Although 29 (32%) patients were diagnosed in the newborn period, the median age at diagnosis of the reported patients with IH was 4.85 years. This is due to the fact that, in some patients, diagnosis was made as late as the age of 17 years. This differs significantly from HD. Although late diagnosis is also possible in HD, more than 90.6% of patients are diagnosed in the newborn period. This late diagnosis of IH might reflect the difficulties in diagnosing IH in rectal suction biopsies but also the rareness of the disease.

### CLINICAL PRESENTATION

Even though the median age at diagnosis is significantly higher in patients with IH than in those with HD, the symptoms of IH resemble classical aganglionosis. The symptoms reported in all IH included intractable constipation, ileus, and enterocolitis. As in HD, enterocolitis of the newborn remains the most serious complication of IH, as 6 of the 7 reported IH related deaths were neonates with enterocolitis.

### HISTOPATHOLOGIC APPROACH

The diagnosis of IH by means of rectal suction biopsy is difficult.[26] As recommended by the interdisciplinary consensus conference,[27] a full-thickness bowel is essential for the diagnosis of IH. Besides standard hematoxylin and eosin staining, histochemical evaluation of AChE was performed by 91% of the authors in the review by Dingemann and Puri to visualize the characteristic changes for IH such as low mucosal activity of AChE, deficiency of nerve cells in the myenteric plexuses, and hypertrophy of muscularis mucosae and circular muscle layers. Morphometric measurements in IH using AChE staining, as suggested by Meier-Ruge and colleagues,[23] represent one of the cornerstones of diagnostic criteria for the disease. It has been shown that plexus area and nerve cell number are dramatically decreased, and the distance between ganglia is almost doubled.

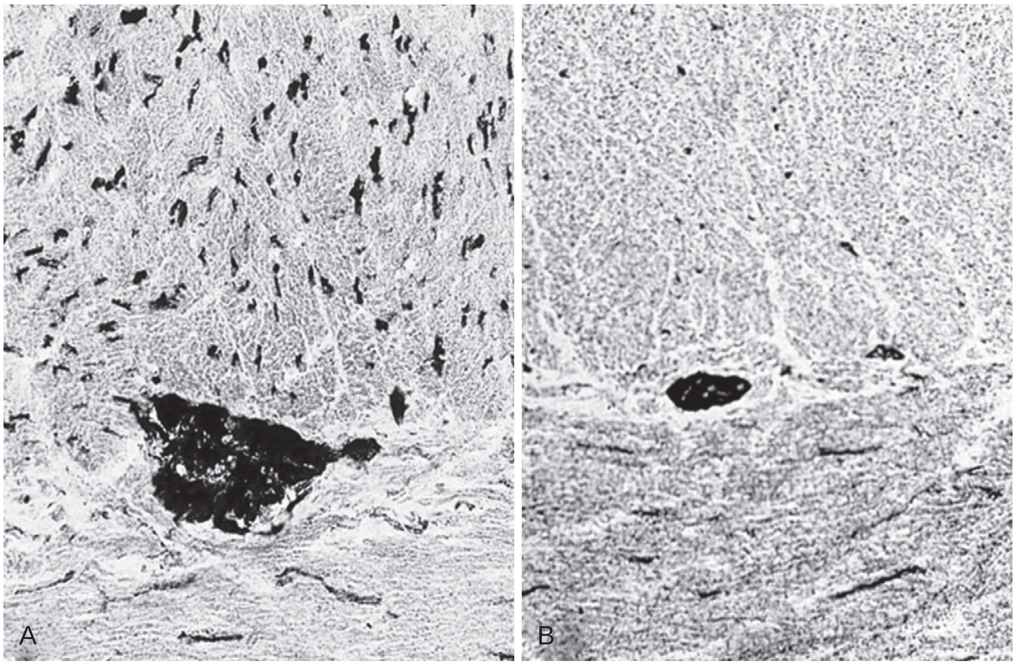


**FIGURE 102-3** Nicotinamide-adenine dinucleotide phosphate—diaphorase staining of the myenteric plexus. **A,** Normal colon showing normal myenteric ganglia and a large number of nitrergic nerve fibers in the circular and longitudinal muscle. **B,** Rectal biopsy in isolated hypoganglionosis patient showing small myenteric ganglia and reduced nitrergic innervation.

Several additional neuronal markers have been used to diagnose IH. Rolle and colleagues used NADPH diaphorase staining, which not only allows one to characterize the nitrergic innervation of the muscle but also differentiates mature fully developed ganglia from the immature ganglia in IH (Fig. 102-3).

## SURGICAL MANAGEMENT

According to literature, the treatment of hypoganglionosis is similar to HD involving resection of the affected segment and pull-through operation. In the review of 92 patients with IH reported by Dingemann and Puri, 54 patients received resection of affected bowel and pull-through procedures of different types; 11 underwent ileostomy, colostomy, or jejunostomy alone; and 2 underwent sphincter myectomy. In 25 patients, the operative treatment was not clearly stated. The treatment of choice remains resection of the affected segment. The exact method used must always be tailored to the extent of affected bowel, the localization of the disease, and presumably it will also depend on the surgeon's preference in this rare disease.

## OUTCOME AND COMPLICATIONS

The overall mortality of the patients included in this review was 8%. Six of the seven patients who died were newborns suffering from severe enterocolitis. The other patient died due to total parenteral nutrition–associated complications during follow-up. During a postoperative follow-up of 7 months to 12 years, typical complications reported were similar to those in HD. Enterocolitis, chronic constipation, overflow encopresis, and the need for redo pull-through for residual disease were reported.

# Internal Anal Sphincter Achalasia

The internal anal sphincter (IAS), a specialized smooth muscle continuation of the circular muscle layer of rectum, plays a significant role in the maintenance of anorectal continence and in the pathophysiology of incontinence and constipation.[28] The IAS relaxes in response to rectal distension, a phenomenon called the *rectosphincteric inhibitory reflex,* which is mediated by intramural nerves descending from the rectum to the IAS. The IAS receives adrenergic, cholinergic, and nonadrenergic noncholinergic (NANC) innervations.[29] Several investigators have reported that IAS relaxation is brought about by the activation of intramural NANC nerves. Nitric oxide (NO) is now recognized as a potent mediator of nonadrenergic noncholinergic inhibitory nerves, which regulate smooth muscle relaxation in the mammalian gastrointestinal tract including IAS.

Internal anal sphincter achalasia (IASA) is a clinical condition with presentation similar to HD but with the presence of ganglion cells on suction rectal biopsy. The diagnosis of IASA is made on anorectal manometry, which shows the absence of rectosphincteric reflex on rectal balloon inflation. Previously, IASA has been referred to as ultrashort segment HD. The ultrashort segment HD, which is a rare condition, is characterized by an aganglionic segment of 1 to 3 cm long and normal acetylcholinesterase (AChE) activity in the lamina propria and increased AChE activity in the muscularis mucosae.[30] Many patients who are considered to have ultrashort HD on abnormal anorectal manometric findings show presence of ganglion cells and normal acetylcholinesterase (AChE) activity in suction rectal biopsies. Many investigators have therefore suggested that the term IASA is more suitable

because it reflects more accurately failure of relaxation of the internal sphincter, which is the causative factor in this condition.[31]

## INCIDENCE

The exact incidence of isolated internal anal sphincter achalasia is not known. De Caluwe and colleagues[30] reported an incidence of 4.5% among 332 children who were investigated for severe chronic constipation.

## PATHOGENESIS

The exact pathogenesis and pathophysiology of IASA is not fully understood. Altered intramuscular innervation has been reported in IASA, and this is believed to be responsible for the motility dysfunction seen in these patients. Hirakawa and colleagues[32] reported absence of nitrergic innervation within the IAS muscle in patients with IASA and suggested that nitrergic nerve depletion may play an important role in the development of IASA (Fig. 102-4). Because nitrergic nerves regulate smooth muscle relaxation, their deficiency or absence in IASA may be responsible for the spasm or increased tone in the IAS in these patients.[33] Oue and Puri reported defective innervation of the neuromuscular junction (NMJ) of the IAS in patients with IASA. If the NMJ is abnormal, the neurotransmitter chemicals synthesizing neurons cannot be transmitted to muscle cells, thereby causing motility dysfunction.[29]

Altered distribution of c-kit positive interstitial cells of Cajal (ICCs) has been reported in the internal sphincter of patients with internal sphincter achalasia, which may further contribute to motility dysfunction in these patients. Piotrowska and colleagues reported deficiency or absence of ICCs in the IAS myectomy specimens obtained from patients with IASA at the time of internal sphincter myectomy.[34] The functions of ICCs include the generation of electrical pacemaker activity, generation of slow waves, and neurotransmission between the enteric nervous system and smooth muscle cells. It has been proposed that ICCs in certain regions of the gut may not act as pacemakers, but as stretch receptors.[32,35] The lack or deficient expression of NO and ICCs in the IASA may lead to defective generation of nitric oxide–mediated pacemaker activity causing motility dysfunction.

## DIAGNOSIS

Patients with IASA have clinical presentation similar to HD. The vast majority of patients present with severe constipation with or without soiling. About one third of the patients give history of abdominal distension. Laxatives usually fail to improve constipation in patients with IASA. Definite diagnosis of IASA is based on anorectal manometry, which shows absence of rectosphincteric reflex on rectal balloon inflation and the presence of marked rhythmic activity of the internal anal sphincter presence of ganglion cells and normal acetylcholinesterase activity in the suction rectal biopsy.

## TREATMENT

Posterior internal sphincter myectomy has been recommended as the treatment of choice for patients with internal sphincter achalasia. The myectomy is performed posteriorly starting at the level of the pectinate line, and a 5- to 10-mm wide strip of smooth muscle is resected extending proximally for varying lengths ranging from 15 to 50 mm.[30] De Caluwe and colleagues reported bowel function in 15 consecutive patients with IASA 2 to 6 years after posterior internal sphincter myectomy. At the time of follow-up, seven patients had regular bowel motions and were not on any laxatives. Six patients had normal bowel habits but were on small doses of laxatives. One patient was able to stay clean with a regular enema regimen. One patient required resection of dilated and redundant sigmoid colon and now has normal bowel habits with laxatives.

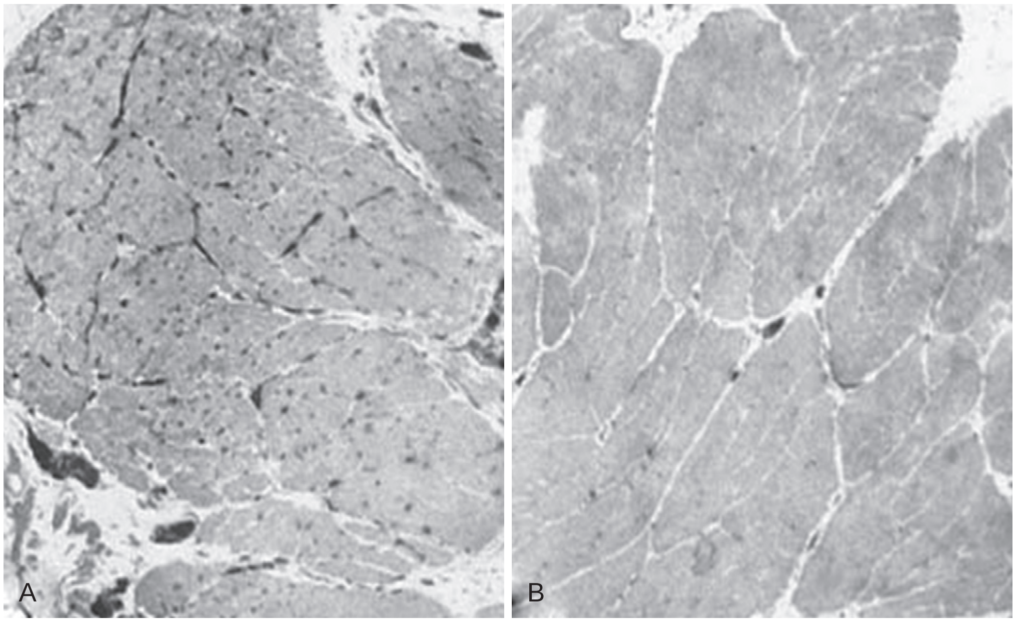


FIGURE 102-4 Nicotinamide-adenine dinucleotide phosphate–diaphorase staining of the internal sphincter. **A,** Normal specimen showing a large number of nitrergic nerve fibers. **B,** Internal sphincter achalasia patient showing nitrergic nerve depletion in the sphincter muscle.

Recently Heikkinen and colleagues[36] reported long-term follow-up in 10 IASA patients, 7 to 16 years after internal sphincter myectomy. Three of the ten patients in their study needed laxatives at the time of follow-up, and one patient had required resection of the dilated and redundant rectosigmoid 2½ years after myectomy. The remaining six patients had one to two bowel motions daily without the help of laxatives. Four of their patients suffered from soiling-related social problems.

Recently intrasphincteric injection of botulinum toxin has been used to treat patients with IASA. This is thought to work by interfering with the Ach release at the neuromuscular junction (NMJ) and thus inhibiting sympathetic stimulation to the IAS. Intrasphincteric injection is thought to produce a local and transient chemical denervation of the sphincter. This treatment modality has been found to be safe, but the effects are transient.[37] The IAS is injected in four quadrants, 25 i.u. per quadrant at the level of the dentate line. Irani and colleagues injected Botox in 24 patients with IASA and found that the duration of response following Botox injection was variable, ranging from 1 month to longer than 1 year. Foroutan and colleagues[38] compared efficacy of intrasphincteric Botox injection and internal sphincter myectomy in patients with IASA and found that Botox injection was as effective as myectomy. Further studies with longer follow-up are necessary to determine the effectiveness of this treatment modality in the management of internal sphincter achalasia.

## MEGACYSTIS-MICROCOLON-INTESTINAL HYPOPERISTALSIS SYNDROME

MMIHS is a rare congenital and generally fatal cause of functional intestinal obstruction in the newborn. This syndrome is characterized by abdominal distension caused by a distended nonobstructed urinary bladder, microcolon, and decreased or absent intestinal peristalsis.[27] Usually incomplete intestinal rotation and shortened small bowel are associated.

## PATHOGENESIS

MMIHS was first described in 1976 by Berdon and colleagues[27] and, to date, 182 cases have been reported in the literature.[39] The etiology of this syndrome remains unclear. Several hypotheses have been proposed to explain the pathogenesis of MMIHS: genetic, neurogenic, myogenic, and hormonal origin.

Histologic studies of the myenteric and submucosal plexuses of the bowel of MMIHS patients have found normal ganglion cells in the majority of the patients, decreased in some, hyperganglionosis, and giant ganglia in others.[39] Recently, Piotrowska and colleagues[34] reported absence of interstitial cells of Cajal (ICCs) in the bowel and urinary bladder of patients with MMIHS. ICCs are pacemaker cells that assist active propagation of electrical events and neurotransmission, and their absence may result in hypoperistalsis and voiding dysfunction in MMIHS. Puri and colleagues[40] showed, in 1983, vacuolar degenerative changes in the smooth muscle cells (SMCs) with abundant connective tissue between muscle cells in the bowel and bladder of patients with MMIHS and suggested that a degenerative disease of smooth muscle cells could be the cause of this syndrome. Several subsequent reports have confirmed evidence of intestinal myopathy in MMIHS. Other investigators have reported absence or marked reduction in α-smooth muscle actin and other contractile and cytoskeletal proteins in the smooth muscle layers of MMIHS bowel.[41] Contractile and cytoskeletal proteins are important structural and functional components of SMCs and play a vital role in the interaction of the filaments in smooth muscle contraction.

## PRENATAL DIAGNOSIS

Puri and Shinkai reviewed 182 cases of MMIHS reported in the literature.[39] In 54 cases ultrasound findings associated with MMIHS were described. The most frequent finding was enlarged bladder (88%), with hydronephrosis seen in 31 patients (57%). Normal amniotic fluid volume was revealed in 32 cases (59%), increased volume occurred in 18 (33%), and volume decreased in 4 (7%). In three cases (5%) abdominal distention caused by dilated stomach was detected. Three cases of oligohydramnios during the second and early third trimesters were reported, probably related to the functional bladder obstruction.

Serial obstetrical ultrasonography showed that the earliest finding in MMIHS is enlarged bladder, detectable from 16 weeks of gestational age. A later finding is hydronephrosis, caused by the functional obstruction of the bladder. Usually polyhydramnios develops late, appearing during the third trimester.

## CLINICAL PRESENTATION

Of the 182 cases reported in the literature, sex of the patient was mentioned in 149 patients. Ninety-eight were females and 43 were males. In four cases, pregnancy was terminated after ultrasonography detected MMIHS, which was confirmed at autopsy in all cases. The duration of pregnancy was reported in 98 cases. Fifty-eight patients (59%) were born at term, 25 (25.5%) at 36 to 39 weeks of gestation, 12 (12%) at 32 to 35 weeks, and 3 (3%) at 31 weeks and less. Dystocia delivery caused by abdominal distention was reported in eight cases. In four cases Caesarean section was required, and in four cases the bladder was so distended that the baby could only be delivered vaginally after removal of 250, 500, 650, 500 mL of urine, respectively, from fetal bladder by paracentesis. The mean birth weight was normal (3 kg) for gestational age.

The clinical symptoms of MMIHS are similar to other neonatal intestinal obstructions. Characterized by abdominal distention, bile-stained vomiting, and absent or decreased bowel sounds, abdominal distention was a constant and early finding. A consequence of the distended, nonobstructed urinary bladder was relieved by catheterization. Of 182 cases 61 had bilious vomiting, and failure to pass meconium was clearly reported in only 23 cases. The majority of patients were not able to void spontaneously.

In the review by Puri and Shinkai,[39] 19 sets of siblings affected with MMIHS were reported. Eighteen families had two affected siblings and one had three. Four sets of affected siblings occurred to consanguineous parents. In another case an affected child was born to a member of the family reported by Penman, and consanguinity was also present in these parents. In three further cases an elder sibling of the affected child died just after birth because of intestinal obstruction[30] or

multiple abnormalities; in another case a sibling of the patient was affected by prune-belly syndrome. The occurrence of MMIHS in 19 sets of affected siblings and consanguinity in four sets of parents suggest an autosomal recessive pattern of inheritance.

## RADIOLOGIC FINDINGS

In the vast majorities of the 182 cases, radiologic evaluation usually suggested the diagnosis of MMIHS. Plain abdominal films showed either dilated small bowel loops or a gasless abdomen with evident gastric bubble. An enlarged urinary bladder was present in all patients who had cystography or ultrasonography (Fig. 102-5). Intravenous urography or ultrasonography detected unilateral or bilateral hydronephrosis in 84 patients. Forty-four patients had an upper gastrointestinal series both before and after laparotomy: hypoperistalsis or aperistalsis in stomach, duodenum, and small bowel was a constantly detected symptom. In three cases reverse peristalsis from small bowel into the stomach was also observed. In two cases hypoperistalsis was associated with gastroesophageal reflux, and in one case the esophagus was aperistaltic. Barium enema showed microcolon in all 71 patients in whom this study was performed; in 39 cases malrotation was associated (see Fig. 102-5).

## SURGICAL OR AUTOPSY FINDINGS

Megacystis and microcolon were the two most frequent findings at surgery or autopsy and were present in all patients. In the review by Puri and Shinkai,[39] short-bowel syndrome was found in 37 cases, dilated proximal small bowel in 19, segmental stenosis of the small bowel in 3, duodenal web in 1, and Meckel diverticulum in 1. Malrotation was found in a total of 81 cases. Although surgical management was not mentioned in several reports, 93 patients (70%) underwent one or more surgical procedures. A variety of interventions were performed: gastrostomy, jejunostomy, ileostomy, cecostomy, segmental resection of jejunum and ileum, lysis of adhesions, and internal sphincter myectomy. Surgical manipulation of the gastrointestinal tract has generally been unsuccessful, and in most patients total parenteral nutrition was required. In 37 patients vesicostomy was performed to decompress the urinary tract and to preserve renal function.

## HISTOLOGIC FINDINGS

Histologic studies of the myenteric and submucous plexuses were reported in 93 out of 182 cases. In 72 the ganglion cells were normal in appearance and number, and in the remaining 21 cases the various neuronal abnormalities reported included hypoganglionosis, hyperganglionosis, and immature ganglia.

The majority of reports do not mention the histologic findings in the muscle layers of bowel and bladder wall. Nevertheless, some authors found significant abnormalities in SMCs. In nine cases thinning of the longitudinal muscle was found on light microscopy. Electron microscopy showed vacuolar degeneration in the center of the smooth muscle of the bowel in 11 cases and of the bladder in 8 cases. Connective tissue proliferation was found in the bowel in nine cases and in the bladder in eight cases. In three more cases the bladder showed elastosis. In two patients electron microscopy revealed vacuolar degeneration of smooth cells in the muscle layers of the bowel and the bladder in addition to neuronal abnormalities. Other investigators have reported absence or marked reduction in α-smooth muscle actin and other contractile and cytoskeletal proteins in the smooth muscle layers of MMIHS bowel.[41]

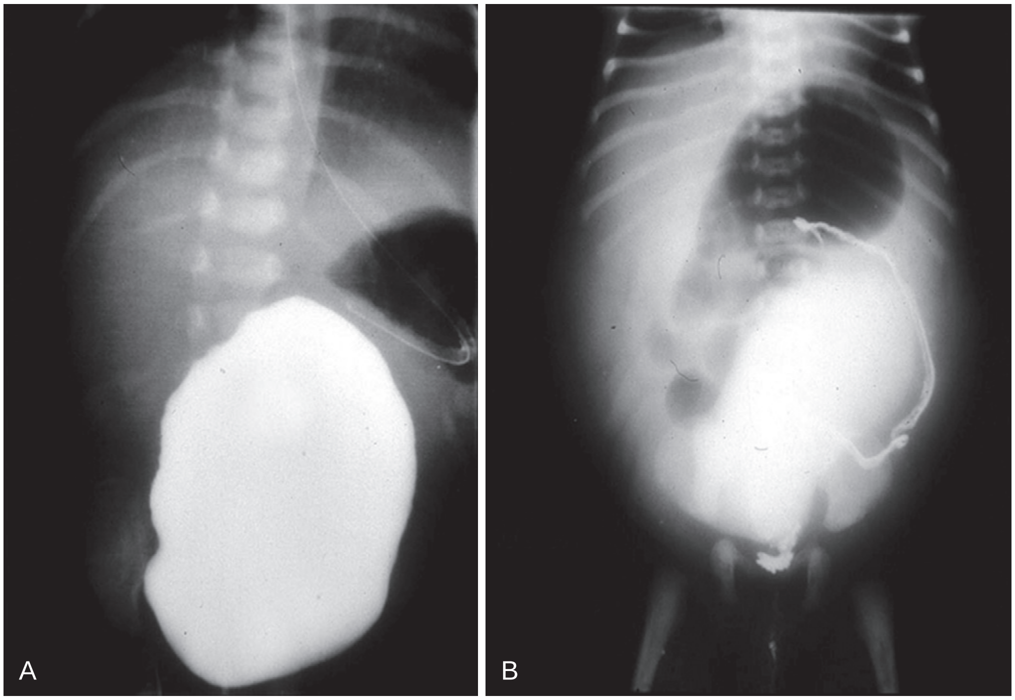


**FIGURE 102-5** Megacystis-microcolon-intestinal hypoperistalsis syndrome patient. **A,** Voiding cystourethrogram showing enlarged urinary bladder. **B,** Contrast enema showing microcolon.

## OUTCOME

The management of patients with MMIHS is frustrating. A number of prokinetic drugs and gastrointestinal hormones have been tried without success. Surgical manipulation of the gastrointestinal tract has generally been unsuccessful. The outcome of this condition is generally fatal: Only 23 of the 182 reported patients were alive, the oldest being 18 years old. Twenty-one of the 23 patients were being maintained by total or partial parenteral nutrition. The need for surgical intervention should be made carefully and individualized, in that most explorations have not been helpful and are probably not necessary.

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 103

# Anorectal Malformations

Marc A. Levitt and Alberto Peña

## History

Throughout history, surgeons have attempted to treat infants and children with anorectal malformations. The written accounts describe few patients, so it is likely that most patients died without treatment.[1–2] Successful maneuvers involved rupturing an obstructing membrane with a finger or the point of a knife[3] and evolved to making an incision to find the bowel in the perineum[4] or in the hollow of the sacrum. The first inguinal colostomy was performed in 1783,[5–6] but most infants died, and colostomy was thought of as a method of last resort. In 1835 Amussat mobilized the bowel through a perineal incision and sutured it to the skin, thus performing the first anoplasty[7] and avoiding the strictures that were common with earlier procedures. In the 1700s and 1800s, several authors suggested that the peritoneum be opened if the bowel was not encountered from below.[8–11] In the mid-1900s, single-stage abdominoperineal procedures became popular[12–13] and usually involved resection of the rectosigmoid. Shortly after these reports, Stephens described a procedure that emphasized passage of the rectum within the puborectalis sling.[14] Until the early 1980s, this approach with its modifications was used, but it involved blind dissection near the posterior urethra. A progressive increase in the length of the perineal incision to gain exposure eventually led to the posterior sagittal anorectoplasty,[15,16] which was rapidly adopted because it allowed full visualization of the sphincteric complex and more clearly showed the relationship of the rectum to the urologic system and the surrounding structures.

## Incidence

No specific cause of anorectal malformation has been described. The average incidence worldwide is 1 in 5000 live births,[17] although the condition is more common in certain geographic areas. Some families have a genetic predisposition, with anorectal malformations being diagnosed in succeeding generations.[18] In addition, imperforate anus occurs in association with several syndromes.[19–20] A slight male preponderance exists.

The most common defect in females is rectovestibular fistula, whereas the most common defect in males is rectourethral fistula. Cloacal malformations are more common than formerly thought, most likely because they were previously misdiagnosed as rectovaginal fistulas.[21] Imperforate anus without fistula occurs in 5% of patients, but interestingly, half of them also have Down syndrome. Patients with Down syndrome and anorectal malformations have this type of defect 95% of the time.[20]

## Classification

The classification system shown in Table 103-1 is anatomically descriptive with therapeutic and prognostic implications.

## Embryology

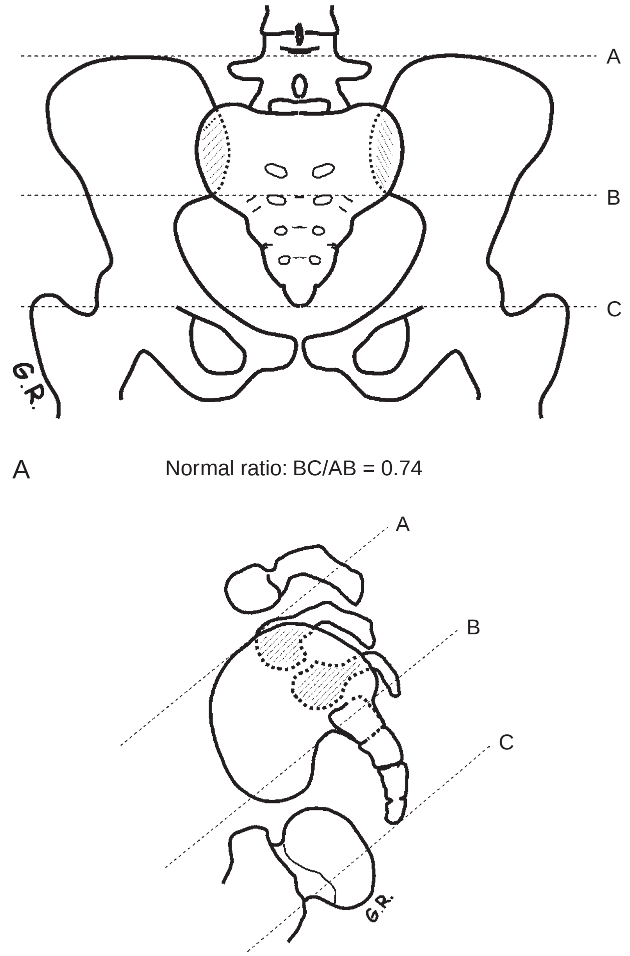
The cloaca in the embryo is a cavity into which opens the hindgut, tailgut, allantois, and later, the mesonephric ducts. The cloaca is first formed at around 21 days' gestation; it is U shaped, with the allantois lying anteriorly and the hindgut posteriorly. The septum in the middle grows downward and fuses with lateral folds (Rathke plicae) until it joins the cloacal membrane. In this 6-week process, a urogenital cavity anteriorly and an anorectal cavity posteriorly are created. Rapid growth of the genital tubercle changes the shape of the cloaca and the orientation of the cloacal membrane, which is displaced posteriorly. The cloacal membrane breaks down at 7 weeks' gestation, thereby creating two openings: the urogenital and anal openings.[22–24] The muscles that surround the rectum develop at the same time and are seen in the sixth and seventh weeks of gestation,[25] and by the ninth week, all relevant structures are in place. At this stage, differentiation into male or female external genitalia has not yet occurred.

## Associated Malformations

Most babies (50% to 60%) with anorectal malformations have one or more abnormalities that affect other systems.[26] Higher abnormalities are associated with more malformations. Many are incidental findings, but others, such as cardiovascular defects, may be life threatening.

**TABLE 103-1**
**Classification of Anorectal Malformations**

| *Males* | *Females* |
|---|---|
| Perineal fistula | Perineal fistula |
| Rectourethral fistula | Vestibular fistula |
| Bulbar | Persistent cloaca |
| Prostatic | ≤3 cm common channel |
| Rectobladder neck fistula | >3 cm common channel |
| Imperforate anus without fistula | Imperforate anus without fistula |
| Rectal atresia | Rectal atresia |
| Complex defects | Complex defects |




A Normal ratio: BC/AB = 0.74

B Normal ratio: BC/AB = 0.77

**FIGURE 103-1** Anterior-posterior **(A)** and lateral **(B)** sacral ratios.

## CARDIOVASCULAR ANOMALIES

Cardiovascular anomalies are present in approximately one third of patients,[27–29] but only 10% of these require treatment. The most common lesions are atrial septal defect and patent ductus arteriosus, followed by tetralogy of Fallot and ventricular septal defect. Transposition of the great vessels and hypoplastic left heart syndrome are rare.

## GASTROINTESTINAL ANOMALIES

A wide spectrum of associated gastrointestinal anomalies has been described. Tracheoesophageal abnormalities occur in about 10% of cases.[26–27] Duodenal obstruction caused by atresia or malrotation has been reported to have an incidence of 1% to 2%.[27,30] Hirschsprung disease has been found in only 3 patients in our series of 2100. Overdiagnosis of this association is probably due to the high incidence of constipation seen in patients with anorectal malformations.[31]

## SPINAL, SACRAL, AND VERTEBRAL ANOMALIES

Lumbosacral anomalies such as hemivertebrae, scoliosis, butterfly vertebrae, and hemisacrum are common. The most frequent spinal problem is tethered cord,[32–35] but spinal lipomas, syringomyelia, and myelomeningocele are also commonly seen. The more complex the anorectal anomaly is, the more likely is the presence of an associated spinal and vertebral anomaly. These problems are found by ultrasound or magnetic resonance imaging in one third to half of patients with anorectal malformations.[4,36–38] It is still unclear how many of these lesions are clinically significant and which lesions require prophylactic surgery.[35,39] A sacral defect, particularly hemisacrum, in association with imperforate anus and a presacral mass is known as the Currarino triad[40] and has a strong familial tendency.[41–43] The sacral ratio is a valuable prognostic tool (Fig. 103-1) because it quantifies the degree of sacral hypodevelopment. Patients with ratios less than 0.4 are universally incontinent. Ratios that approach 1.0 usually predict a good prognosis.

## GENITOURINARY ANOMALIES

Urologic abnormalities predominate.[44–45] Improved imaging has shown an increasing range of upper and lower urinary tract anomalies. The incidence ranges from one third to half of patients in several series and increases with increasing complexity of anorectal defect.[30,46] Vesicoureteric reflux is the most common anomaly found, and renal agenesis and dysplasia are the next most frequent findings.[46–47] Cryptorchidism is reported in up to 20% of males with imperforate anus,[47–48] and hypospadias occurs in approximately 5%.[48]

## GYNECOLOGIC ANOMALIES

Associated gynecologic anomalies have emerged as a significant concern in patients with anorectal malformations.[33,49–50] In the newborn period, hydrocolpos can lead to urinary obstruction or can cause pyocolpos. Müllerian anomalies may become manifest later when teenagers have obstruction of menstrual flow. Large intra-abdominal collections and peritonitis can develop, or patients may have amenorrhea because of absence of the müllerian structures. Asymmetric obstruction to menstrual flow can occur as a result of an anatomic abnormality at any level such as an obstruction of the tube, atresia of the cervix, or a blind hemivagina.[33,51] Uterine malformations (predominantly bicornuate uterus and uterus didelphys), vaginal abnormalities (particularly a vaginal septum), and associated vaginal atresia[33,49] occur in approximately one third of patients. A search for hydrocolpos needs to be performed in the newborn period. During definitive repair or at the time of colostomy closure, inspection of the intra-abdominal gynecologic structure is vital to prevent immediate and long-term sequelae. The full obstetric impact of these anomalies is not yet known.

# Anorectal Anatomy and Pathophysiology

Bowel control implies the ability to detect and retain flatus and stool until the appropriate time for evacuation. It is the result of a complex interplay among sphincter function, anorectal sensation, and colonic motility. All these factors are affected in children with anorectal malformations.[52]

## SPHINCTER MECHANISM

The muscle groups of the sphincter mechanism form a funnel-like structure in the pelvis. These muscles are innervated by the pudendal nerve, both motor to the voluntary muscles and sensory to the skin around the anus and anal canal. They are derived from the sacral plexus roots S2 to S4, as well as the autonomic nervous system via the nervi erigentes, from the same segments of the spinal cord. The exposure afforded by the posterior sagittal approach shows that the junction of the levator musculature with the fibers about the anal dimple is defined by a vertical group of striated muscle fibers called the *muscle complex.* Electrical stimulation of the upper end of the levator group pulls the rectum forward. Stimulation of the muscle complex (vertical fibers) elevates the anus, and stimulation of the parasagittal fibers closes the anus. Children with anorectal malformations have varying degrees of striated muscle development from almost normal-appearing muscle to virtually complete absence.

## SENSATION AND PROPRIOCEPTION

Under normal circumstances, the anal canal is an exquisitely sensitive area. It allows the individual to discriminate solids, liquids, and gas. The overwhelming majority of children with anorectal malformations is born without an anal canal and therefore lacks this anal canal sensation. There is, however, proprioception, which is described as a vague feeling that is perceived when the rectum is distended, simultaneous with stretching of the voluntary muscle that surrounds the rectum. Proprioception seems to be present to a variable degree in most patients. Thus these patients lose control when they suffer an episode of diarrhea but have the ability to be toilet-trained when they form solid stool and learn to perceive it.

## COLONIC AND RECTOSIGMOID MOTILITY

Normally it takes between 3 and 6 hours for the gastric contents to reach the small bowel. The intestinal contents reach the cecum in a liquid state. It then takes about 20 to 24 hours for that fecal material to reach the rectum and become formed stool with the absorption of water that occurs in the colon. The rectosigmoid acts as a reservoir and holds the fecal material for a variable period of time. The anal canal (below the pectinate line) is usually empty because of the action of the surrounding sphincteric mechanism. Occasionally, however, there are peristaltic waves in the colon that push the fecal material toward the anus. The rectal contents move distally and touch the exquisitely sensitive tissue of the anal canal, thereby providing valuable information related to the nature of the rectal contents (solid, liquid, or gas).

Depending on the surrounding social circumstances, the individual may contract the sphincteric mechanism to push stool or gas back into the rectum and then voluntarily relax at the appropriate time. Distention of the rectum produces a vague sensation of fullness or even colicky pain (proprioception) but does not provide specific information concerning the physical characteristic of the contents. Little is known about the mechanism that triggers peristalsis of the rectosigmoid to defecate, but it is clear that the degree of rectal fullness has an important role. Thus when the time comes, the rectosigmoid generates waves of peristalsis aimed at emptying the lumen. Individuals can restrain this process temporarily by using their voluntary sphincter. With a conscious decision made to allow the stool to come out, the sphincter is relaxed and the individual waits for the next peristaltic wave. Normal defecation allows massive emptying of the rectosigmoid, followed by another resting period of about 24 hours, during which the rectosigmoid again acts as a reservoir.

Children with anorectal malformations have a spectrum of rectosigmoid motility disorders. Those patients subjected to surgical techniques that preserve the rectosigmoid usually suffer from constipation. Constipation, one of the most important functional sequelae, is probably the result of hypomotility of the rectosigmoid, which is self-perpetuating and self-aggravating to the point that if left untreated, megasigmoid develops.[31] In extreme cases, fecal impaction and encopresis, or overflow pseudoincontinence, may develop. It seems that constipation is worse with lower defects. Knowing this and the fact that hypomotility can begin a vicious cycle leading to megasigmoid, it is vital that the clinician avoid the cycle of hypomotility, constipation, and megasigmoid, with aggressive patient follow-up plus dietary, mechanical, and pharmacologic treatment.

Children with anorectal malformations who have lost their rectosigmoid suffer from the opposite problem (i.e., tendency to have diarrhea). These children have no reservoir capacity, are highly sensitive to certain foods, and frequently suffer from incontinence.

# Clinical Findings and Initial Management

Figure 103-2 shows the decision-making algorithm for the initial management of male patients.

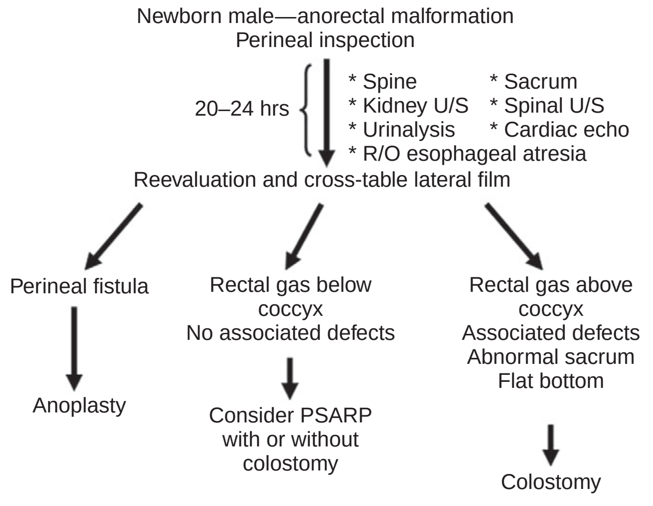



**FIGURE 103-2** Algorithm for the treatment of a male newborn with an anorectal malformation.

A clinician is called to see a newborn male with an anorectal malformation. First the clinician must perform a thorough perineal inspection, which usually provides the most important clues about the type of malformation that the patient has (Fig. 103-3). It is important to not make a decision about a colostomy or a primary operation before 20 to 24 hours of age. The reason for waiting is that significant intraluminal pressure is required for meconium to be forced through a fistula, which is the most valuable sign of the location of distal rectum in these babies. If meconium is visualized on the perineum, it is evidence of a rectoperineal fistula. If there is meconium in the urine, the diagnosis of a rectourinary fistula is obvious.

Radiologic evaluations do not show the real anatomy before 24 hours because the rectum is collapsed by the muscle tone of the sphincters that surround its lower part. Therefore radiologic evaluations done too early (before 24 hours) will likely reveal a "very high rectum" and therefore yield a false diagnosis.

During the first 24 hours, the newborn should receive intravenous fluids, antibiotics, and nasogastric decompression to prevent aspiration. The clinician should use these hours to evaluate for the presence of associated defects such as cardiac malformations, esophageal atresia, and urologic problems. An echocardiogram can be performed, and the baby should be checked for the presence of esophageal atresia. A plain radiograph of the lumbar spine and sacrum should be taken to evaluate for hemivertebrae and sacral anomalies. A spinal ultrasound helps screen for tethered cord and other spinal problems. Ultrasonography of the abdomen evaluates for the presence of hydronephrosis.

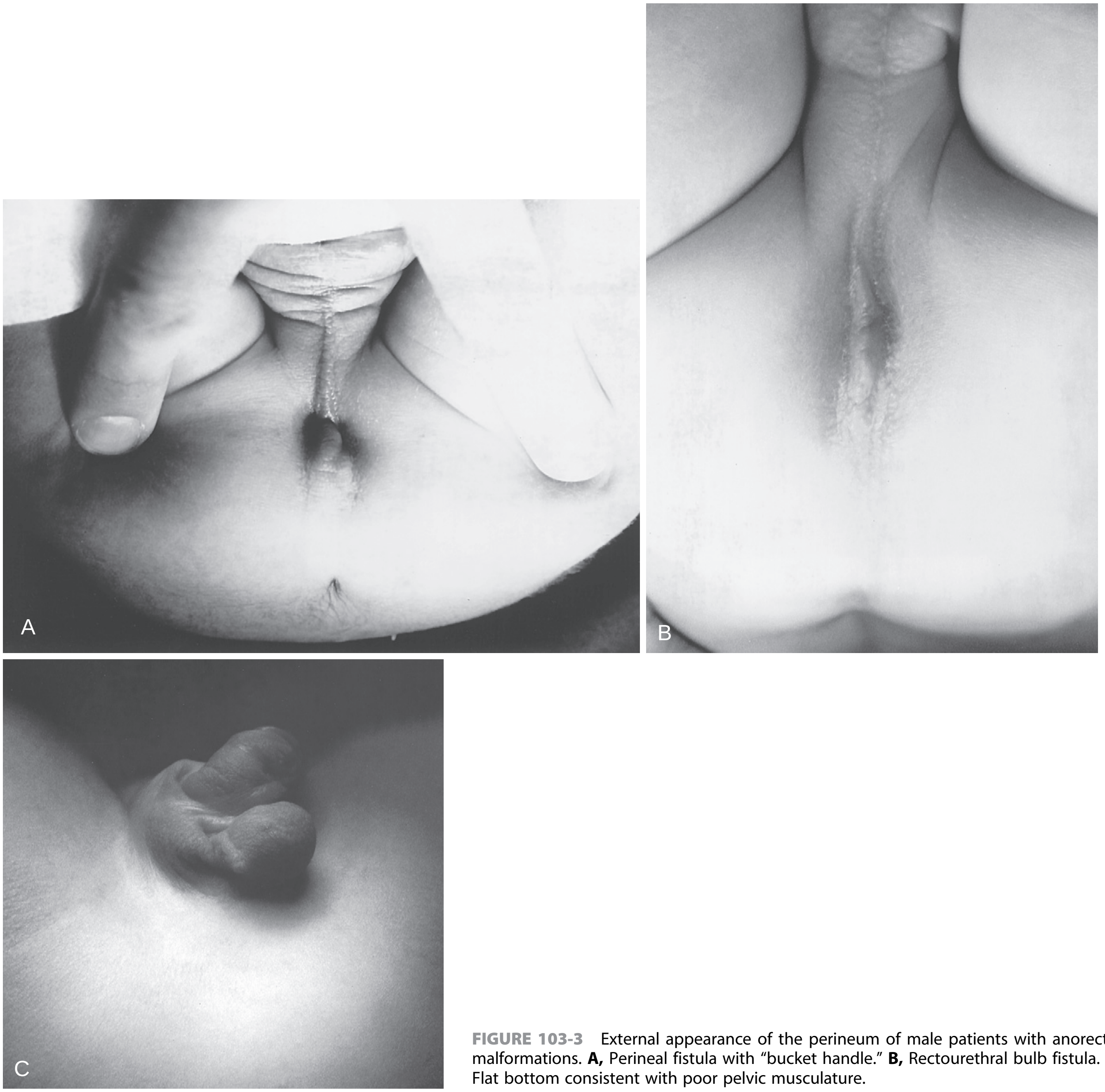



**FIGURE 103-3** External appearance of the perineum of male patients with anorectal malformations. **A,** Perineal fistula with "bucket handle." **B,** Rectourethral bulb fistula. **C,** Flat bottom consistent with poor pelvic musculature.

If the baby has signs of a perineal fistula, an anoplasty can be performed without a protective colostomy in the newborn period. If the baby is ill from associated problems, is very premature, or if the clinician chooses to wait until the baby is a little older, the fistula can be gently dilated. The repair in such cases should not be delayed more than several months. After 24 hours, if no meconium is seen on the perineum or in the urine, a cross-table lateral x-ray film with the baby in prone position should be obtained. If the gas in the rectum is located below the coccyx (Fig. 103-4) and the baby is in good condition with no significant associated defects, depending on the surgeon's experience, a posterior sagittal operation without a protective colostomy can be considered. A more conservative alternative would be to perform a colostomy, with the definitive repair planned for a second stage.

If rectal gas is seen above the coccyx (Fig. 103-5) or the patient has meconium in the urine, significant associated defects, and/or an abnormal sacrum or a flat bottom, a colostomy is recommended with postponement of the main repair for a subsequent operation. This can be performed 2 to 3 months later after a distal colostogram delineating the anatomy is performed, provided that the baby is gaining weight normally.

Performing the definitive repair at 2 to 3 months of age has important advantages for the patient including less time with an abdominal stoma, less size discrepancy between the proximal and distal bowel at the time of colostomy closure, easier anal dilation, and no recognizable psychologic sequelae from painful perineal maneuvers. In addition, at least theoretically, placing the rectum in the right location early in life may provide an advantage in terms of the potential for acquired local sensation.

The potential advantages of an early operation must be weighed against the possible disadvantages of an inexperienced surgeon unfamiliar with the minute anatomic structures of an infant's pelvis.

A trend to repair these defects without a protective colostomy[53–55] must be balanced against the concern that such a repair without a colostomy is done without precise anatomic information about the patient's specific type of anorectal defect. The most catastrophic complications seen in patients operated on without a colostomy occur in patients in whom the surgeon did not have a properly done preoperative distal colostogram. While looking for the rectum, the surgeon might inadvertently find and injure the urethra, an ectopic ureter, the bladder neck, the vas deferens, or the seminal vesicles.[56]

**FIGURE 103-4** Cross-table lateral radiograph, reachable rectum.

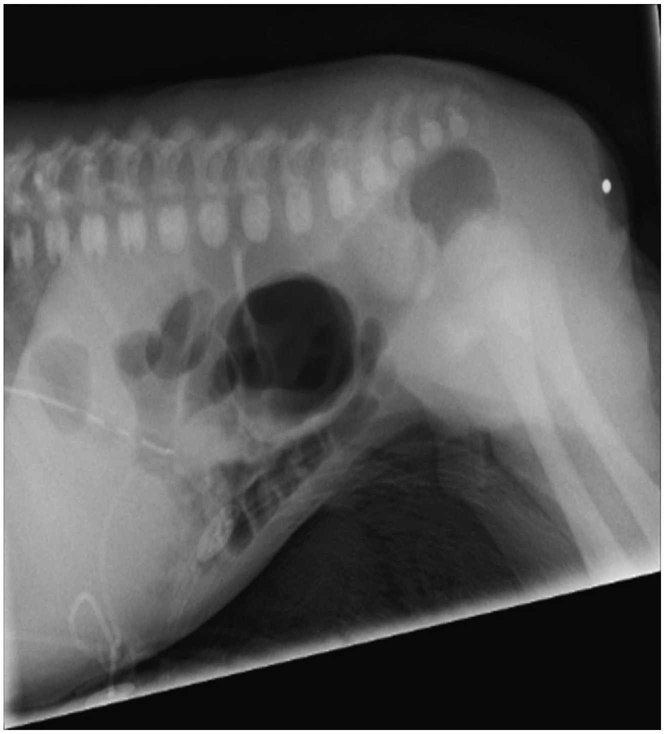


**FIGURE 103-5** Cross-table lateral radiograph, high rectum.

Figure 103-6 shows a decision-making algorithm for the initial management of female patients. As in males, the most important step in diagnosis and decision making is the perineal inspection (Fig. 103-7). The first 24 hours should also be used to rule out serious associated defects. Perineal inspection may disclose the presence of a solitary perineal orifice. This finding establishes the diagnosis of a cloaca. The clinician should know that such a patient has a high likelihood of a urologic defect. The presence of hydrocolpos should be ruled out by ultrasound.

Such a baby requires a colostomy. It is important to perform the colostomy proximally enough in the sigmoid to allow repair of the malformation without interference from the colostomy. In other words, the surgeon must leave enough redundant, distal rectosigmoid to allow for the pull-through and even a vaginal replacement if that is necessary. During opening of the colostomy, it is mandatory that the hydrocolpos be drained when present. If the hydrocolpos is not large enough to reach the abdominal wall above the bladder, to be sutured to the skin, it can be drained with a curled rubber tube. Because a significant number of these patients have two hemivaginas, the surgeon must be certain that the tube inserted into the hydrocolpos is draining both hemivaginas. Occasionally, one has to open a window in the vaginal septum to drain both with a single tube. At times the hydrocolpos is so large that it may even produce respiratory distress. Rarely, some patients with cloaca are unable to empty their bladder because the common channel is almost atretic. In such rare circumstances, the baby may require a vesicostomy. Endoscopy is best done outside of the

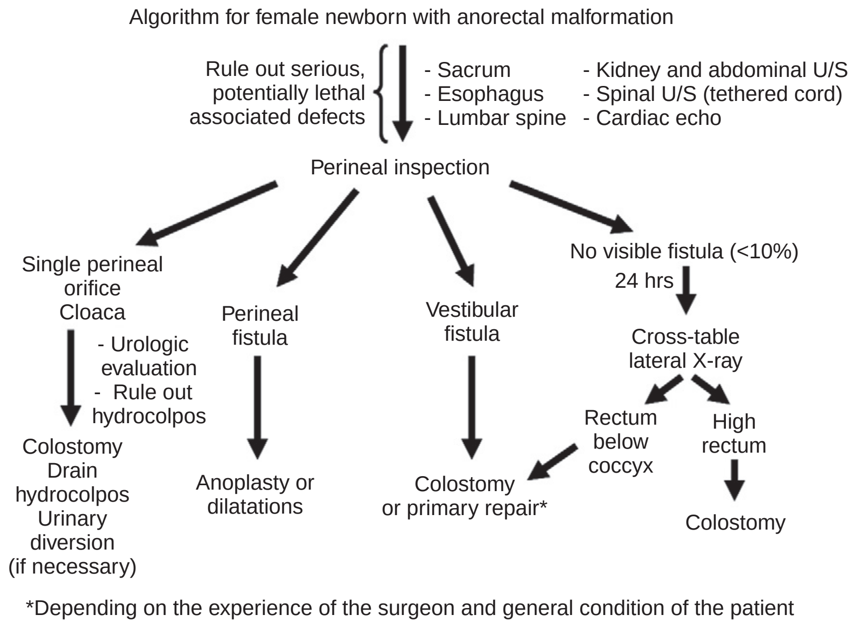



**FIGURE 103-6** Algorithm for the treatment of a female newborn with an anorectal malformation.

newborn period when the baby is larger and the perineum is less swollen, to determine the anatomy, particularly the length of the common channel, which helps with surgical planning.

Perineal inspection may show the presence of a perineal fistula, and an anoplasty can be performed without a colostomy.

The presence of a vestibular fistula is the most common finding in female patients. This malformation may be repaired during the neonatal period without a protective colostomy; however, these operations represent the most common source of complications in such patients. The decision to repair this malformation primarily or to open a colostomy should be based on the experience of the surgeon. Colostomy is still the most effective way to protect these patients from a perineal infection of dehiscence.

Occasionally (<10% of cases), no fistula is visible and there is no meconium apparent even after 24 hours of observation. This small group of patients requires a cross-table lateral radiograph. If the radiograph shows gas in the rectum located near the skin, the patient probably has imperforate anus with no fistula. If the patient is in good condition, one can perform a primary operation without a colostomy. Many of these patients with no fistula also have Down syndrome.[20]

When patients are subjected to primary repair of a vestibular fistula or perineal fistula later in life, strict preoperative bowel irrigation 24 hours in advance should be performed. Our routine is to keep such patients with nothing by mouth, on parenteral nutrition, for 7 days to decrease the passage of stool.

With emerging advancements in perinatology and prenatal ultrasound techniques, anorectal malformations are more commonly being suspected.[57] Sonographic findings such as a dilated rectum or hydrocolpos or demonstration of an associated anomaly such as an absent kidney, a vertebral anomaly such as a hemisacrum, or an orthopedic problem such as a missing radius can make the perinatologist suspicious that the fetus may in fact have an anorectal malformation. With improving technology, it is likely that this area of diagnosis and even fetal intervention for, perhaps, a massive hydrocolpos will continue to advance.[58–59]

Abdominal ultrasonography to evaluate for associated urologic problems and echocardiography should be performed during the initial newborn evaluation. It is also convenient at this time to perform a spinal ultrasound to evaluate for associated spinal anomalies such as myelomeningocele or a tethered cord. Such an ultrasound is an excellent screening examination for these anomalies, but it must be performed before sacral ossification, which occurs at 3 months of age. If screening is done later, magnetic resonance imaging is required. From a plain anteroposterior and lateral radiograph of the sacrum, a sacral ratio can be calculated (see Fig. 103-1), which can be helpful in predicting the prognosis for fecal continence with low ratios predictive of poor potential for bowel control and high ratios (>.7) predictive of good potential. If a hemisacrum is identified, a presacral mass may be present and must be looked for by magnetic resonance imaging. During the assessment conducted before performance of either anoplasty or colostomy, the baby is maintained on intravenous fluids, with a nasogastric tube in place to decompress the stomach. No oral feeding is allowed. Antibiotics are given at the time of surgery.

## LIMITED POSTERIOR SAGITTAL ANORECTOPLASTY

When a low anomaly (perineal fistula) is diagnosed, the fistulous track to the perineum is always located anterior to the sphincter mechanism. A limited posterior sagittal anorectoplasty can be performed in the newborn period. In newborns who cannot undergo such a procedure because they are ill, have significant associated anomalies, or the surgeon prefers to wait, dilatation of the fistulous tract is appropriate with a plan for repair in the future preferably within 2 to 3 months. Occasionally, such babies escape detection in the newborn period and delayed primary repair is then appropriate. It is advantageous to perform this operation in the first 48 hours of life because the meconium is sterile. When such an operation is delayed and performed at several months of life,

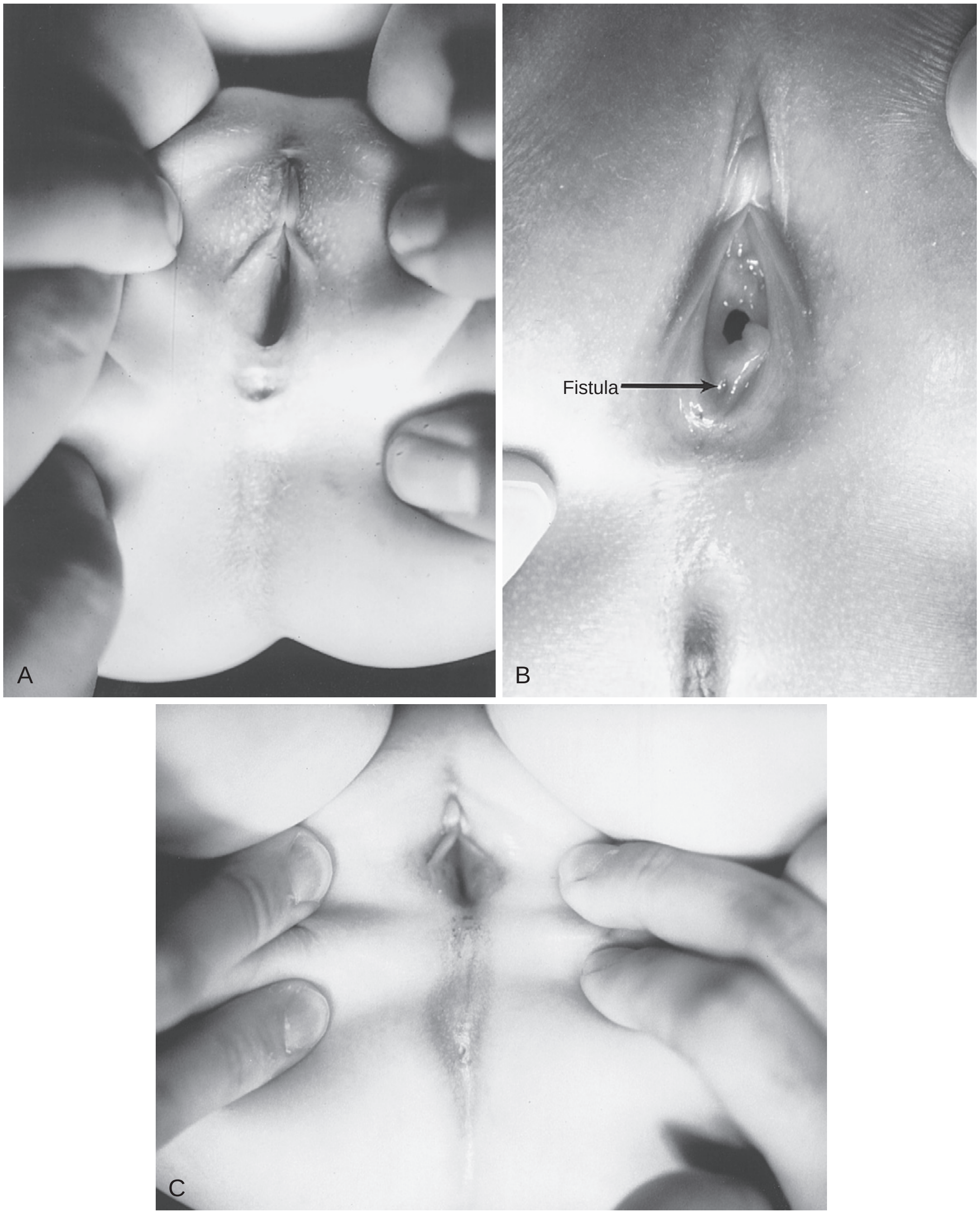



FIGURE 103-7 External appearance of the perineum of female patients with anorectal malformations. **A,** Perineal fistula. **B,** Vestibular fistula. **C,** Cloaca.

a complete bowel preparation including a postoperative period of parenteral nutrition without oral intake is recommended to reduce the risk of perineal infection.

For a limited posterior sagittal anorectoplasty, the baby is placed prone. In males, a urinary catheter is inserted. The distal end of the rectum is intimately attached to the posterior urethra, and urethral injury must be avoided. Multiple 6-0 silk sutures are placed at the mucocutaneous junction around the fistula orifice. An incision divides the posterior sphincter in half and is continued circumferentially around the fistula. While traction is maintained on the bowel, a circumferential dissection is performed to mobilize the bowel and reposition it within the limits of the sphincter. Mucosa is sutured to skin with fine, absorbable sutures under slight tension. The perineal body is reconstructed.

## COLOSTOMY

Colostomy is usually performed as a first stage in a newborn with a high anomaly. A descending colostomy is a relatively trouble-free stoma (Fig. 103-8). It also leaves the sigmoid colon entirely free for reconstruction. It is fashioned by making an oblique left lower quadrant incision. The stoma is divided, with the bowel openings placed at opposite ends of the

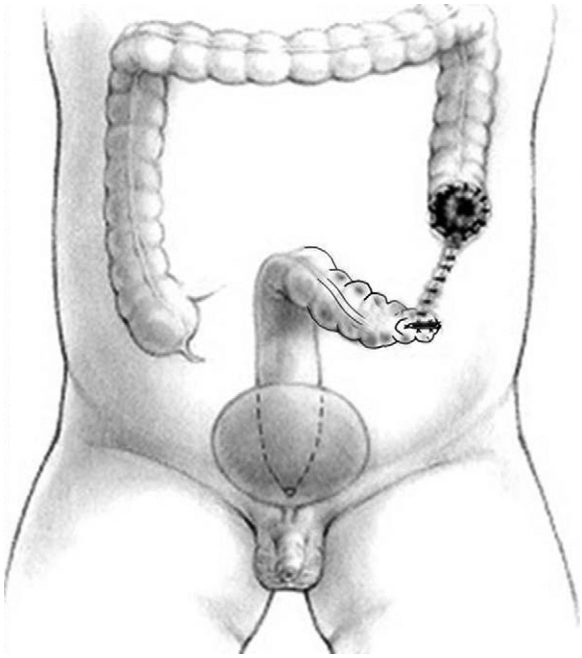


FIGURE 103-8 Descending colostomy.

FIGURE 103-9 Distal colostogram showing a rectourethral bulbar fistula.

FIGURE 103-10 Distal colostogram showing a rectobladder neck fistula.

wound. The proximal part of the stoma is at the start of the sigmoid colon, just after the colon comes off its left retroperitoneal attachment. The distal part of the stoma, in the upper sigmoid, is made intentionally small in an attempt to prevent prolapse. The distal segment should be copiously irrigated to remove all meconium. It should be placed far enough away from the functional stoma so that the stoma bag does not cover it. This way no spillage downstream can occur, and the stoma bag stays on more easily.

A colostomy can result in significant morbidity, so it is vital to construct it meticulously.[60] Transverse colostomies often lead to prolapse, make cleaning the distal segment difficult, and make delineation of the downstream rectourinary anatomy during the distal colostogram challenging.[61] Such colostomies also lead to megarectosigmoid and a left microcolon in the defunctionalized segment, particularly when the colostomy is left in place for many months. A colostomy that is placed too low in the sigmoid can limit the pull-through. A loop colostomy leads to distal contamination of the urinary stream if there is a fistula and to a dilated megarectosigmoid from stool spillage.

### MANAGEMENT AFTER COLOSTOMY

Before proceeding with definitive reconstruction, the anatomy of the anorectal malformation is delineated by high-pressure distal colostography (Figs. 103-9 and 103-10).[61] Patience is required when performing this study as the rectum is slowly distended with contrast. The muscles of the pelvis are normally contracted, and thus the distal rectum is compressed and can at first appear flat at the pubococcygeal line. With gentle pressure, this flat line begins to bulge, and it is at this point that the examiner can visualize the true extent of the rectum and the presence of a rectourinary fistula.

## Anorectal Reconstruction

### BASIC PRINCIPLES

All defects can be repaired using a posterior sagittal approach. Approximately 10% of male patients (those with a rectum-bladder neck fistula) and about 40% of female patients with a cloaca may, in addition, require an abdominal approach for mobilization of a high rectum or vagina. The patient is placed in a prone position with the pelvis elevated. A Foley catheter is inserted into the bladder before the patient is

positioned. A coudé catheter is ideal. The catheter sometimes goes into the rectum through the fistula rather than into the bladder. To avoid misplacement, the surgeon can direct the catheter with a lacrimal probe inserted in the tip of the Foley catheter to function as a guide. Occasionally, the catheter must be positioned intraoperatively once the fistula is exposed. Special care must be taken to cushion all the pressure areas of the baby's body (Fig. 103-11). Two small bolsters are used in front of each deltopectoral groove to avoid hyperextension of the neck and shoulders. Electrical stimulation of the perineum allows evaluation of the strength of the sphincter contraction. A midline incision is made, and the sphincteric mechanism is divided exactly in the midline, with equal amounts of muscle on each side. The rationale for this approach is based on the fact that important nerves or vessels do not cross the midline. Sharp Weitlaner retractors are used to achieve good exposure. The retractors should be placed superficially to avoid pressure damage to the muscles.

## POSTERIOR SAGITTAL ANORECTOPLASTY FOR ANOMALIES IN MALES

### Rectourethral Fistula (Bulbar and Prostatic)

The size of the incision must be adapted to the specific anatomy of the patient (Fig. 103-12). No deleterious effects are caused by extending the incision, provided that it remains in the midline. The incision usually extends from the lower portion of the sacrum through the center of the anal dimple and sometimes extends to the perineal body. Below the skin and running parallel to the midline are the parasagittal muscle fibers. Medial to these muscle structures and located within the limits of the anal dimple are other muscle structures that run perpendicular. These structures extend from the skin to the levator muscle and are called the *muscle complex*. Deeper to the parasagittal fibers, the ischiorectal fat becomes evident. Below this is the levator, which is also divided in the midline. The crossing of the muscle complex fibers with the parasagittal muscle structures defines the anterior and posterior limits of the new anus. These limits can be determined most clearly with use of an electrical stimulator.

**FIGURE 103-11** Patient in prone position with proper padding.

In boys with a rectourethral bulbar fistula, on opening the incision the bowel is evident. In boys with a rectoprostatic fistula, the rectum is much smaller and located much higher in the incision just under the coccyx. The distal colostogram provides information that is valuable at this point for determining where the rectum can be found (see Fig. 103-9). In the case of a rectobladder neck fistula, the rectum is not visible through a posterior sagittal approach and should not be searched for (see Fig. 103-10).

Temporary silk sutures are placed in the posterior rectal wall for traction, and the rectum is opened exactly in the midline. The incision in the rectal wall is extended distally. As the rectum is being opened, more sutures are placed to hold the edges of the rectal wall and improve exposure of the rectal lumen. The incision must be extended distally until the fistula site is found (Fig. 103-13).

Because there is no distinct plane of separation between the rectum and urethra, the surgeon must be extremely careful while separating the rectum from the urinary tract. Multiple 6-0 silk sutures are placed above the fistula site in a semicircular fashion (Fig. 103-14). These sutures allow the surgeon to exert uniform traction on the rectum while dissecting and separating it from the urethra. Dissection of the lateral aspects of the rectum first helps to delineate the anterior plane. The dissection then proceeds in the submucosal plane, anteriorly, for approximately 5 to 7 mm until the rectum and urethra gradually separate and become independent. The surgeon must be careful in this anterior plane because this is where the vas deferens and seminal vesicles can be injured if the dissection is too deep. A single suture is placed at the fistula site so that it can easily be identified and closed later. Once the rectum is fully separated from the urinary tract, circumferential perirectal dissection is performed to gain enough rectal length to reach the perineum. To achieve this, the fascia that surrounds the rectum must be divided including blood vessels and nerves attached to the rectum. This is a key plane to identity. While the surgeon is applying traction to the rectum, the dissection continues in a circumferential manner. The vessels that hold the rectum are coagulated and divided until enough rectal length has been achieved. The rectum has an excellent intramural blood supply; even with a high prostatic fistula, sufficient length can be obtained without making the rectum ischemic. When the rectal wall is injured, however, this blood supply is damaged and ischemia may occur. Therefore every effort must be made to perform this dissection as close as possible to the rectal wall but without interfering with the intramural blood supply. Once enough length has been achieved to perform a tension-free bowel-to-skin anastomosis, the size of the rectum must be evaluated and compared with the available space. If necessary, the rectum can be tapered by removing part of its posterior wall and reconstructed by closing the posterior incision with two layers of long-term absorbable interrupted sutures. The anterior rectal wall that used to be attached to the posterior urethra may require a few stitches to reinforce the wall by bringing the seromuscular layer together. The urethral fistula is closed with interrupted absorbable suture.

The perineal body is reconstructed by bringing together the anterior limits of the external sphincter, which was previously marked with temporary silk sutures. The levator muscle is sutured behind the rectum (see Figs. 103-12 and 103-15), and the posterior edge of the muscle complex is sutured together

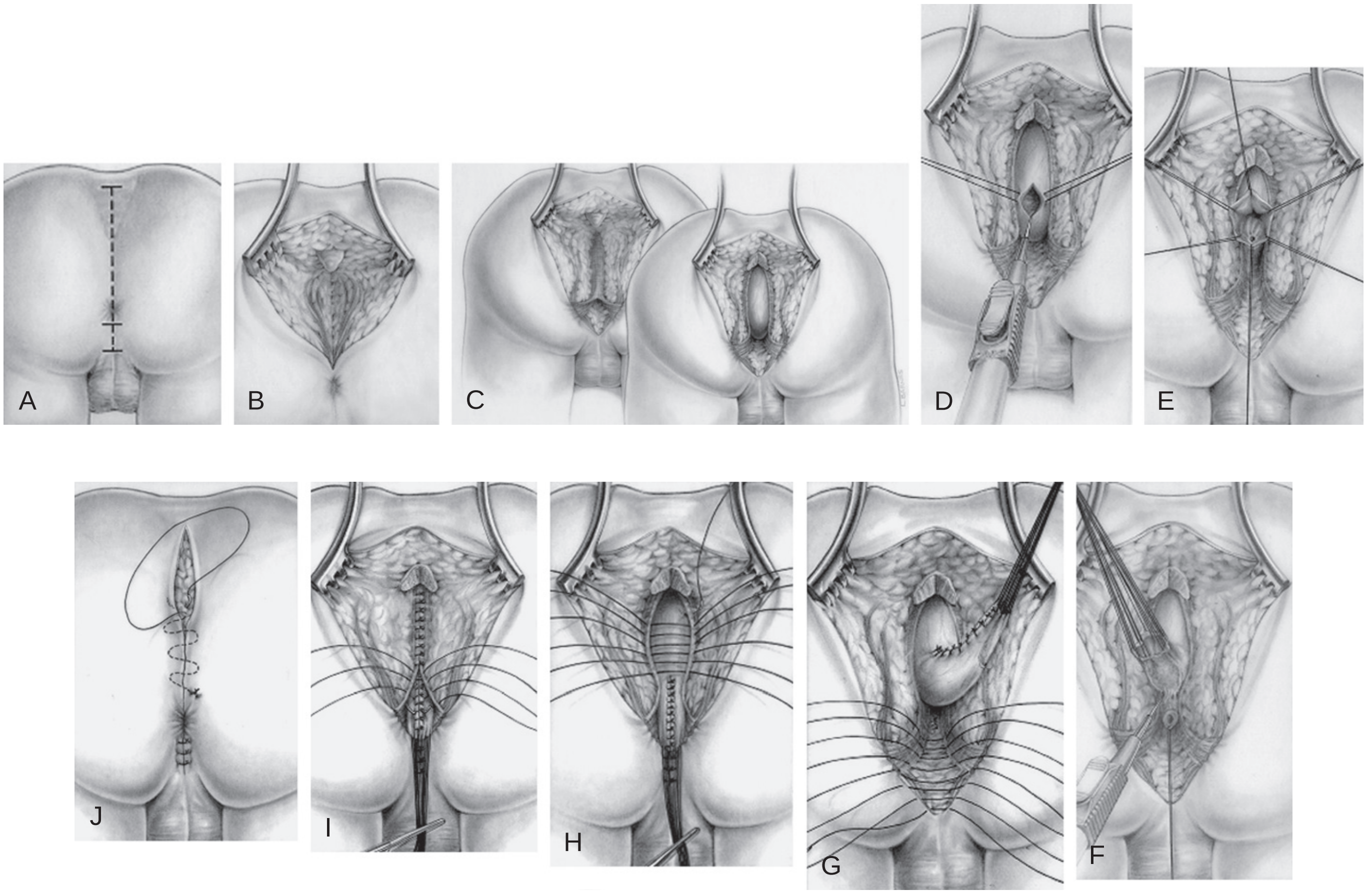



**FIGURE 103-12** Essential steps for posterior sagittal anorectoplasty in male patients. **A,** Planned posterior sagittal incision. **B,** Posterior sagittal approach with the parasagittal fibers and ischiorectal fat split in the midline. **C,** Posterior rectal wall exposed. **D,** Posterior rectal wall opened in the midline. **E,** Posterior rectal wall opened going anteriorly until the rectourethral fistula is identified. **F,** Separation of the rectum from the posterior urethra with dissection above the fistula. **G,** The rectum fully mobilized and in this case tapered. Sutures are placed anteriorly to close the perineal body. **H,** The rectum pulled through and placed within the limits of the sphincter mechanism. **I,** Closure of the levator and tacking of the posterior edge of muscle complex to the posterior rectal wall. **J,** Closure of the posterior sagittal incision and completed anoplasty.

in the midline while taking, with the same stitches, part of the posterior rectal wall to anchor the rectum. This helps to prevent prolapse (Fig. 103-16). The ischiorectal fossa and the subcutaneous tissue are then reapproximated, and the skin is closed. The anoplasty is performed by placing the rectum within the limits of the sphincter with the use of interrupted long-term absorbable sutures (Fig. 103-17).

### Rectobladder Neck Fistula

In patients with a rectobladder neck fistula, an abdominal approach via either laparoscopy or laparotomy, in addition to the posterior sagittal approach, is necessary to mobilize the rectum. The fistula is separated from the back of the bladder neck. Laparoscopy is well suited for this stage. The challenge thereafter is often mobilization of adequate rectal length to reach the perineum. Such mobilization, plus the bulbous distension of the rectum, makes the laparoscopic stage technically demanding. In general, for higher lesions such as a rectoprostatic urethral fistula, a laparoscopic approach has utility[62,63] because sufficient mobilization is often a challenge through the posterior sagittal incision. Lower lesions, however, such as a rectourethral bulbar fistula or the no-fistula defect, can be more safely repaired with a posterior sagittal approach without laparoscopic assistance because the rectum lies below the peritoneal reflection.

Before beginning operation on higher lesions, the entire body surface from chest to toes is prepared so that the surgeon can work simultaneously in the abdomen and the perineum. The abdomen is entered via either laparoscopy or laparotomy (Fig. 103-18). The sigmoid is identified and dissected down to the bladder neck. The distal rectum is usually located approximately 2 cm below the peritoneal floor and therefore requires minimal pelvic dissection. It is important to remember that the vas deferens and ureters run close to the rectum; thus the dissection must be carried out as close as possible to the rectal wall. The rectum narrows rapidly and opens into the bladder neck in a T-shaped manner. It is relatively easy to separate the rectum from the urinary tract because the fistula forms less of a common wall the higher the malformation. The rectum is divided at its most distal part, and the fistula is closed with absorbable suture.

In this type of high defect, mobilization of the rectum is sometimes limited by branches of the inferior mesenteric vessels. To gain length surgeons have traditionally been advised to divide the inferior mesenteric vessels at their origin from the aorta. This technique is contraindicated here because this is often the only blood supply of the rectosigmoid—the

FIGURE 103-13 Operative view, posterior sagittal approach. The rectourethral fistula is seen with a metallic probe in it.

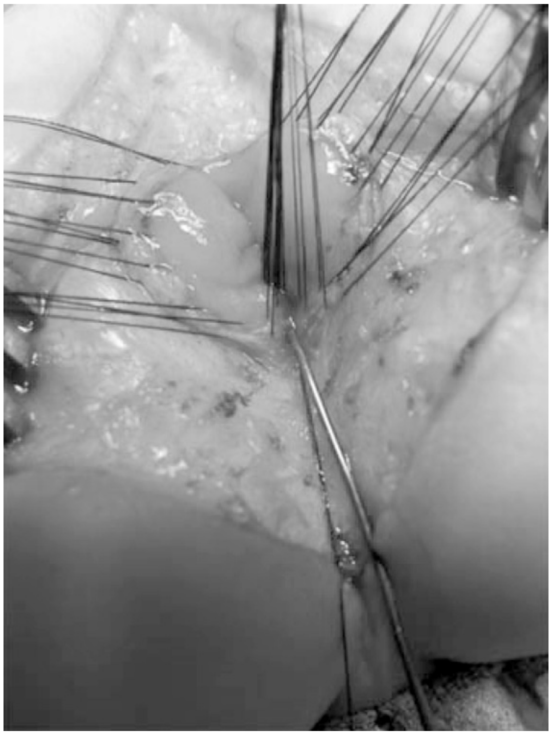


FIGURE 103-14 Operative view. Fine silk sutures are placed through the mucosa of the cephalad hemicircumference of the fistula.

FIGURE 103-15 Levator muscle sutured behind the rectum.

FIGURE 103-16 Sutures on the posterior edge of the muscle complex anchor the rectum.

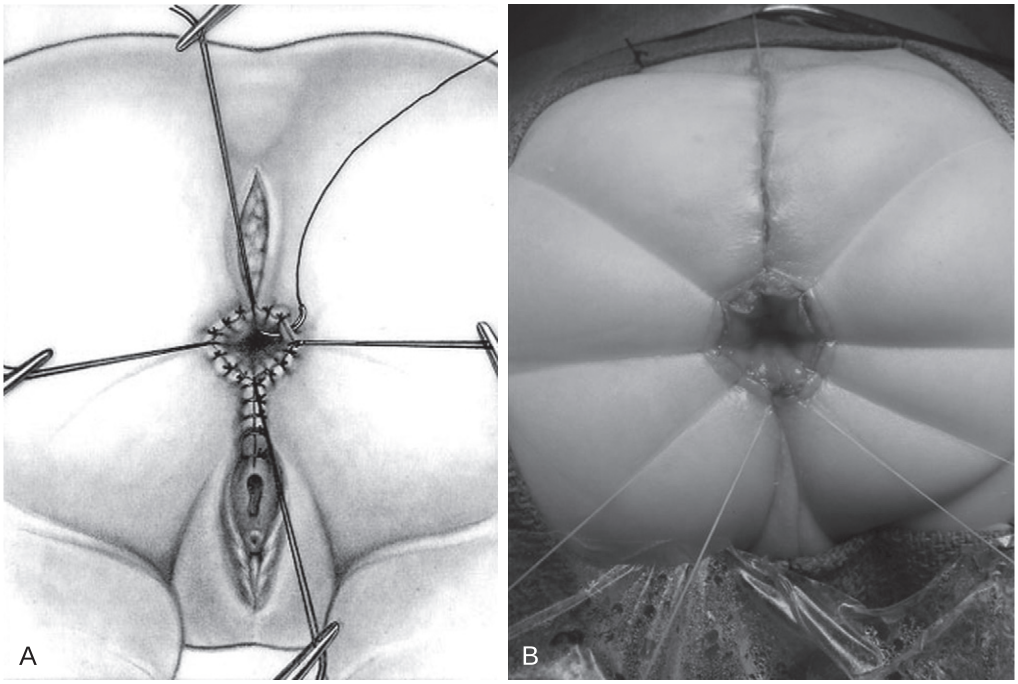



FIGURE 103-17 A, Repair of perineal body and anoplasty. B, Anoplasty performed with 16 long-term absorbable sutures.

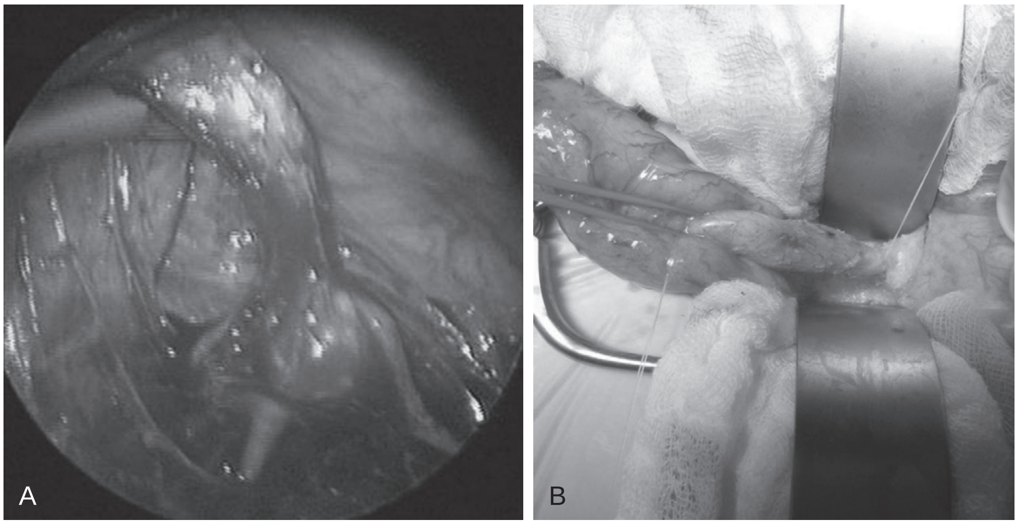



FIGURE 103-18 Operative view of a rectobladderneck fistula showing the rectosigmoid ending at the bladder neck. **A,** Laparoscopic view. **B,** View via laparotomy.

opening of the colostomy may have interfered with the continuity of the arcade that connects the middle colic vessels with the inferior mesenteric vessels. Therefore the blood supply of the distal part of the rectum may depend solely on the inferior mesenteric vessels, and therefore preservation of the main trunks is crucial to preserve the intramural blood supply of the rectum. Meticulous dissection along the rectum is required to gain length (Fig. 103-19). In extremely high defects, the rectum can be elongated by rectoplasty. Sometimes the distal rectum is wide and must be tapered. With the legs lifted up, a midsagittal incision is made and the presacral space dissected. Then the rectum is pulled through. An anoplasty should be performed as previously described. Tacking of the rectum to the muscle complex is important because these patients have poor pelvic musculature and are particularly prone to prolapse.

### Imperforate Anus Without a Fistula

In patients with an imperforate anus and no fistula, the blind end of the rectum is located at the same level as in a patient with a bulbar urethral fistula. Because the rectum is still intimately attached to the posterior urethra, separation from the urethra requires careful dissection. The rest of the repair is performed as described for rectourethral fistulas.

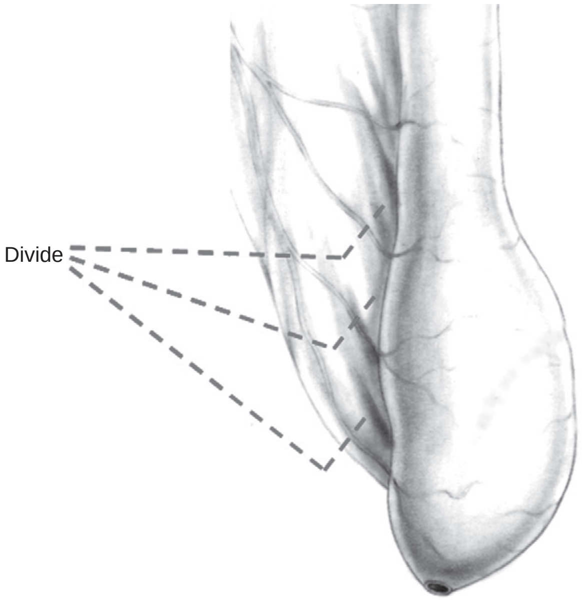



**FIGURE 103-19** Ligation of the peripheral branches of the inferior mesenteric vessels with preservation of the main trunks, in order to gain length on a high rectum.

### Rectal Atresia and Stenosis

Repair of rectal atresia and stenosis involves connecting the blind dilated end of the rectum proximally with the anal canal distally. Both structures are usually separated by a few millimeters of fibrous tissue. The rectum must be sufficiently mobilized to allow the performance of an end-to-end anastomosis to the anal canal. The wound is then closed by reconstructing all the muscle structures, as previously described. Because the anal canal is normal, these patients have excellent potential for bowel control. This defect in particular is associated with a presacral mass, often a teratoma; full evaluation is essential.

## POSTERIOR SAGITTAL ANORECTOPLASTY FOR ANOMALIES IN FEMALES

### Vestibular Fistula

The complexity of this defect is frequently underestimated. Patients with a vestibular fistula are born with excellent potential for bowel control. Thus every effort should be directed at successful reconstruction with a single operation; wound dehiscence and infection may compromise the final functional result. A protective colostomy minimizes these complications, but if the surgeon has adequate experience with this malformation, a primary repair can be performed in the newborn period. Occasionally, such patients escape detection in the newborn period and undergo reconstruction several months or even years later. A primary repair without colostomy under these circumstances can also be performed. However, to avoid a perineal infection, meticulous technique, excellent bowel preparation, 1 week without oral intake, and parenteral nutrition postoperatively are vital.

With the patient in prone position, a midline incision is performed, but it is not usually necessary to extend the incision as high as the middle portion of the sacrum. The midline incision continues around the fistula into the vestibule and multiple 5-0 sutures are placed circumferentially at the fistula site. While traction is placed on these sutures, the rectum is dissected in a circumferential manner. The posterior rectal wall can easily be identified, and the dissection must start from the posterior aspect and be extended laterally. The last step, separation of the rectum from the vagina, is the most delicate part of the dissection. The common wall between the rectum and vagina in this kind of defect is long and extremely thin. Once fully separated, the surgeon finds an areolar plane between the two structures. At this point branches of the hemorrhoidal vessels found on the lateral aspects of the rectum can be ligated with cautery, thereby mobilizing the rectum as previously described, to gain enough length to perform a tension-free bowel-to-skin anastomosis. The limits of the sphincteric mechanism are electrically determined and marked with temporary silk sutures. The perineal body is then reconstructed by bringing together the anterior limit of the sphincter complex. The anterior edge of the muscle complex is reapproximated taking bites of rectal wall, as described previously for males. The levator muscle is not usually exposed and thus does not need to be reconstructed. The anoplasty and wound closure are performed as described for males. For the extremely unusual case of a rectovaginal fistula, the technique is the same except that the rectum requires more mobilization to reach the perineum.

### Cloaca

This female malformation is managed by a variation of the posterior sagittal anorectoplasty. It is considered separately because of its complexity. The reconstruction requires a delicate, meticulous technique, as well as creativity, imagination, and a resourceful, experienced surgeon. Repair of this defect has three main goals: achievement of urinary control, bowel control, and sexual function. Because a spectrum of defects exists, these goals are achieved in some cases; in others, however, the defect is repaired anatomically, but the patients are left with functional sequelae that require extensive medical assistance to provide a good quality of life. During surgical exploration, the surgeon must be prepared to find bizarre anatomic arrangements of the rectum, vagina, and urinary tract (Fig. 103-20). A long midsagittal incision is made, extending from the middle portion of the sacrum through the sphincter mechanism and down into the single perineal opening.

Before undertaking repair of a cloaca, the surgeon should perform an endoscopy with the specific purpose of determining the length of the common channel. A contrast study of each of the three systems is valuable and can be done in three dimensions (Fig. 103-21). There are two well-characterized groups of patients with a cloaca.[64] These two groups represent different technical challenges and must be recognized preoperatively. The first group consists of patients with a common channel shorter than 3 cm; fortunately, this represents the majority. These patients can usually be repaired via a posterior sagittal approach alone, without laparotomy.

The second group consists of patients with longer common channels. These patients usually need laparotomy, followed by a decision-making process that usually requires intricate vaginal maneuvers or vaginal replacement, tricks to mobilize a high rectum, knowledge of bladderneck anatomy, and decision making related to ectopic ureters if found. This group should be cared for at centers with special dedication to the repair of these defects.

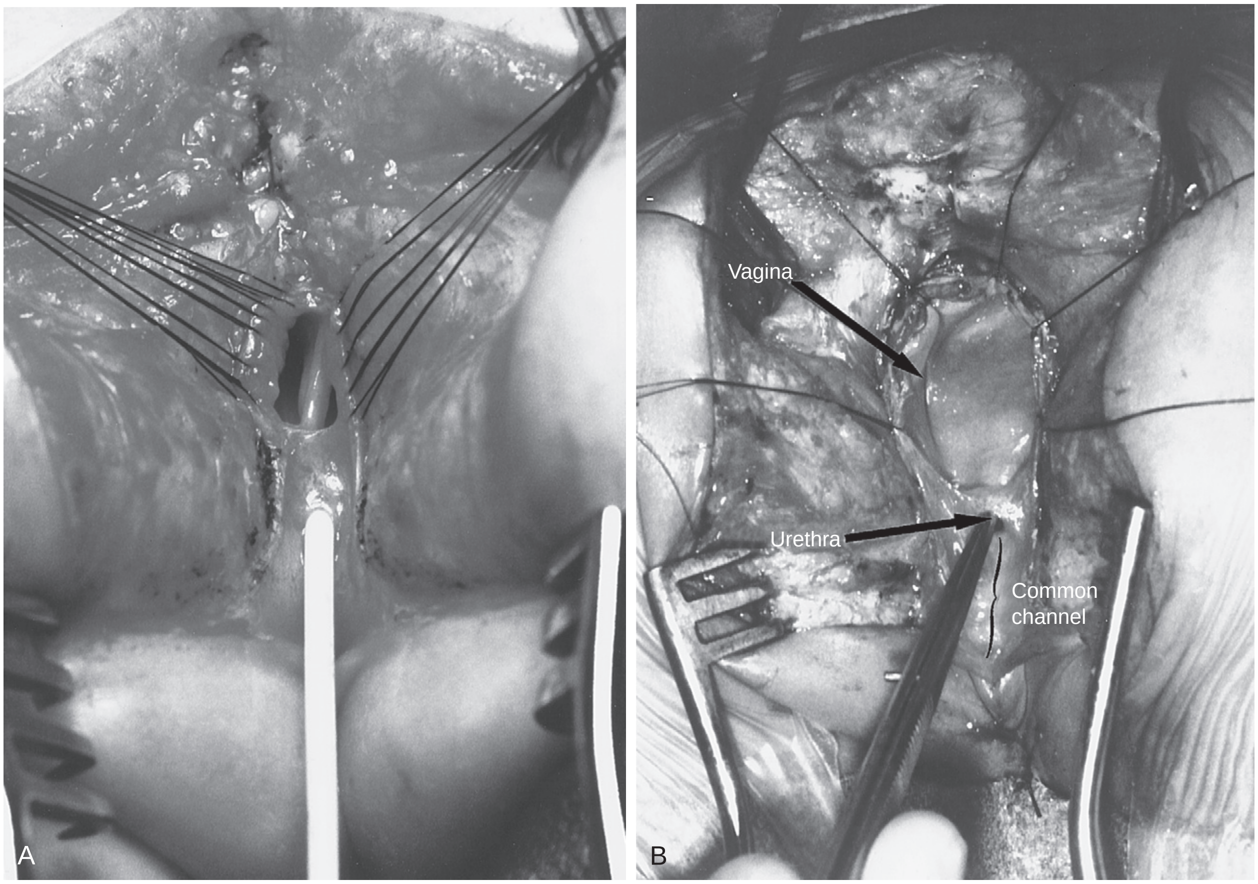



**FIGURE 103-20** **A,** Posterior sagittal view of a typical cloaca with a common channel of 2 cm with a visible vaginal septum. **B,** A cloaca with a very large vagina (hydrocolpos). The rectum opens higher in the vagina and is not seen here.

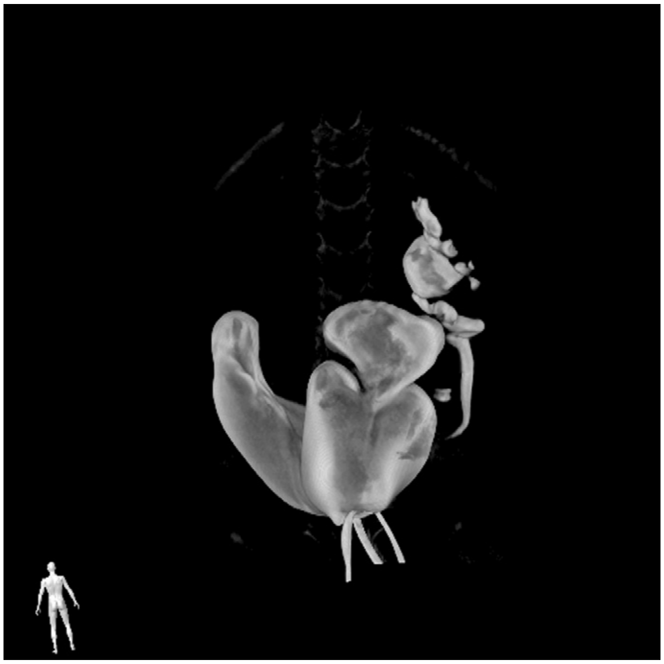


**FIGURE 103-21** Three-dimensional cloacagram.

***Cloacas with a Common Channel Shorter than 3 cm*** The incision extends from the middle portion of the sacrum down to the single perineal orifice. The sphincter mechanism is divided in the midline. The first structure that the surgeon will find after division of the sphincter mechanism is the rectum. The rectum is opened in the midline, and silk stitches are placed along the edges of the posterior rectal wall. The incision is extended distally through the posterior wall of the common channel. The entire common channel is exposed to allow confirmation of its length under direct vision (Fig. 103-22). The rectum is then separated from the vagina (see Fig. 103-22). This is performed in the same way as for repair of a rectovestibular fistula because the rectum and vagina share the same common wall already described. In patients with a vaginal septum, the rectum must be searched for at the posterior aspect of this septum.

Once the rectum has been completely separated from the vagina, a maneuver called *total urogenital mobilization* is used.[65] Before this advance, the vagina was separated from the urinary tract, which was a technically challenging maneuver associated with significant morbidity.

Total urogenital mobilization consists of mobilization of both the vagina and urethra as a unit without separating them. After the rectum has been separated, multiple silk stitches are placed through the edges of the vagina and the common channel to apply uniform traction on the urogenital sinus (see Fig. 103-22). Another series of fine stitches are placed

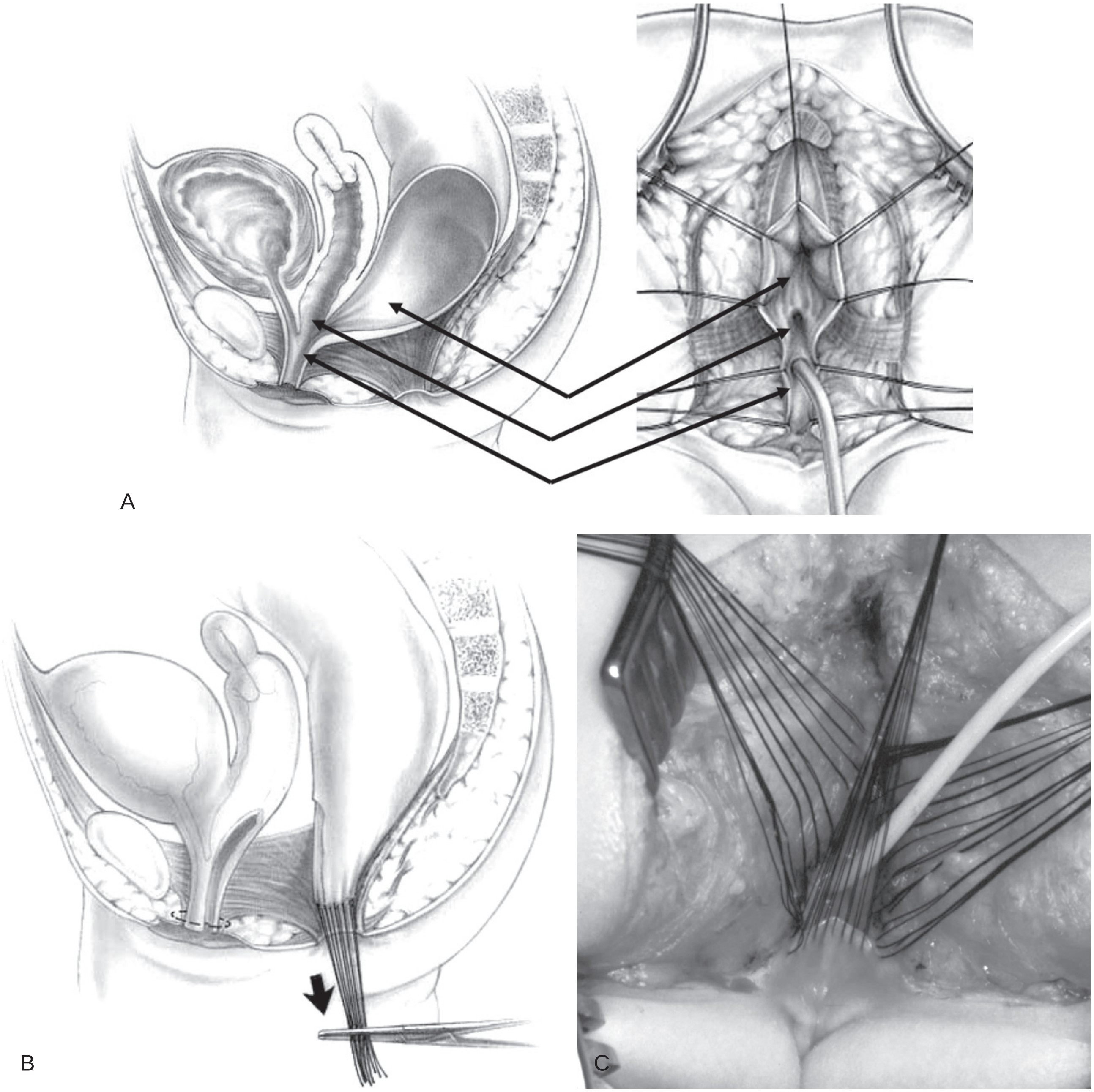


**FIGURE 103-22** **A,** Total urogenital mobilization (cloaca with a short common channel, <3 cm). **B,** The rectum is separated from the urogenital sinus. **C,** Sutures are placed around the urogenital complex for uniform traction to facilitate mobilization of the urogenital sinus.

across the urogenital sinus approximately 5 mm proximal to the clitoris. The urogenital sinus is transected between the last row of silk stitches and the clitoris. The dissection takes advantage of the fact that there is a natural plane of separation from the pubis. Rapidly and in a bloodless field, one can reach the upper edge of the pubis. There, a fibrous, avascular structure that gives support to the vagina and bladder is identified.

This structure is called the *suspensory ligament* of the urethra and bladder. This ligament is divided, which immediately provides significant mobilization (between 2 and 3 cm) of the urogenital complex. One can then dissect the lateral and dorsal walls of the vagina to gain an extra 5 to 10 mm. This dissection is enough to repair about 60% of all cloacas and is a reproducible maneuver. It has the additional advantage of preserving an excellent blood supply to both the urethra and vagina. It places the urethral opening in a visible location and provides a smooth urethra that can easily be catheterized. What used to be the common channel is divided in the midline to form two lateral flaps that are sutured to the skin to create the new labia. If a vaginal septum is present, it is removed. The vaginal edges are then mobilized to reach the skin to create the introitus. The limits of the sphincter are electrically determined. The perineal body is reconstructed by bringing together the anterior limit of the sphincter. The rectum is placed within the limits of the sphincter in the manner previously described. Patients can eat the same day, and the pain is usually easily controlled. Patients are discharged 48 hours postoperatively.

***Cloacas with a Common Channel Longer than 3 cm*** When endoscopy and a cloacagram show that the patient has a long common channel, the surgeon must be prepared to face several significant technical challenges.

Patients with a long common channel should receive a total-body preparation because it is likely that laparotomy will be required. The rectum is separated from the vagina and urethra via a posterior sagittal incision or via laparotomy when it is located very high. The presence of a long common channel (>5 cm) indicates there is no way that total urogenital mobilization will be sufficient to repair the malformation, and therefore it is advisable to leave the common channel in place, which can be used as urethra for intermittent catheterization. In this situation the vagina should be separated from the urinary tract by placing multiple 6-0 silk sutures through the vaginal wall to try to create a plane of dissection between the vagina and the urinary tract. This is best done through the abdomen when the vagina(s) are high. In such a high common channel case, when the vaginas are low and closer to the perineum, the surgeon may need to do a total urogenital mobilization and then deliver that mobilized urogenital complex into the abdomen. Sometimes dissection in the abdomen then allows this complex to reach the perineum. Often, though, at this point, the urinary tract and vaginas must be separated and the neourethra tubularized. These are delicate maneuvers. Often, the bladder must be opened in the midline, and feeding tubes placed into the ureters to protect them. In these types of malformations there is an extensive common wall between vagina and bladder. Both ureters run through that common wall, and therefore during separation of the vagina from the urinary tract, the ureters must sometimes be skeletonized and thus need to be protected. Once the separation has been completed, if the vagina does not reach, the surgeon has to make decisions about the vaginal reconstruction on the basis of specific anatomic findings.

Within the abdomen, the patency of the müllerian structures are investigated by passing a No. 3 feeding tube through the fimbriae of the fallopian tubes and injecting saline. If one of the systems is not patent, the atretic müllerian structure should be excised, with great care taken to avoid damage to the blood supply of the ipsilateral ovary. When both müllerian structures are atretic, they should be left in place. The patient must be monitored closely and further investigated with ultrasound when she enters puberty.

***Vaginal Switch Maneuver*** A specific group of patients are born with hydrocolpos and two hemivaginas. The hemivaginas are large and the two hemiuteri are separated, the distance between them being longer than the vertical length of both hemivaginas. In these cases it is ideal to perform a maneuver called a "vaginal switch" (Fig. 103-23).

One of the hemiuteri and the ipsilateral fallopian tube is resected with particular care taken to preserve the blood supply of the ovary. The blood supply of the hemivagina of that particular side is sacrificed. The blood supply of the contralateral hemivagina is preserved and provides for both hemivaginas. The vaginal septum is resected, and both hemivaginas are tubularized into a single vagina by taking advantage of the long lateral dimension of both hemivaginas. Then, what used to be the dome of the hemivagina where the hemiuterus was resected is turned down to the perineum. This is a useful maneuver that can be performed only when these specific anatomic characteristics are encountered.

***Vaginal Replacement*** In a patient with a small vagina(s) or in the rare case of an absent vagina, a vaginal replacement is required. In such cases the choices are rectum, colon, or small bowel. When the patient has internal genitalia or an upper blind vagina, the upper part of the bowel used for replacement should be sutured to the vaginal cuff. When the patient has no internal genitalia (no vagina and no uterus), a vagina is created and left with its upper portion blind and used only for sexual purposes.

*Rectum:* This form of vaginal replacement is feasible only in patients who have a good size rectum that is large enough to be able to divide it transversely or longitudinally into a portion with its own blood supply that will form a new vagina and another portion with enough circumference to reconstruct an adequately sized rectum (Fig. 103-24). The blood supply of the rectum will be provided transmurally from branches of the inferior mesenteric vessels. This can also work for patients with a rectosigmoid long enough to allow the distal portion to be used as a new vagina with its own blood supply and the upper portion to be pulled down as the new rectum.

*Colon:* The colon is an ideal substitute to replace the vagina (Fig. 103-25). However, sometimes the location of the colostomy interferes with this type of reconstruction. The left colon or sigmoid work well because their arcades reach the perineum nicely. Sometimes taking the colostomy down and using its distal segment for the vaginal graft is a helpful maneuver.

*Small Bowel:* When the colon is not available, the most mobile portion of the small bowel is used for vaginal reconstruction. The mesentery of the small bowel is longest in an area located approximately 15 cm proximal to the ileocecal valve, which is the best portion of the small bowel for vaginal replacement. A portion of the ileum is isolated and pulled down while preserving its blood supply (Fig. 103-26).

In the highest type of cloaca one may find two little hemivaginas attached to the bladder neck or even to the trigone of the bladder. In these cases the rectum also opens in the trigone (Fig. 103-27). Separation of these structures is done abdominally. Unfortunately, when the separation is completed, the patient is frequently left with either no bladder neck or a severely damaged one. At that point the surgeon must have enough experience to make a decision whether to reconstruct the bladder neck or close it permanently. In the first situation, most patients will require intermittent catheterization to empty the bladder. A vesicostomy is created in such cases, and the patient will require a continent diversion type of procedure and possibly a bladder neck procedure and/or bladder augmentation, done at the age of urinary continence (3 to 4 years old). In this particular type of malformation, the patient usually also needs a vaginal replacement, which should be performed in one of the ways previously described.

At the time of colostomy closure, endoscopy should be performed to be sure that the repair is intact and that there is no prolapse, stricture, or urethrovaginal fistula. If the cloaca repair did not require laparotomy, the time of colostomy closure is the opportunity to investigate the patency of the müllerian structures.

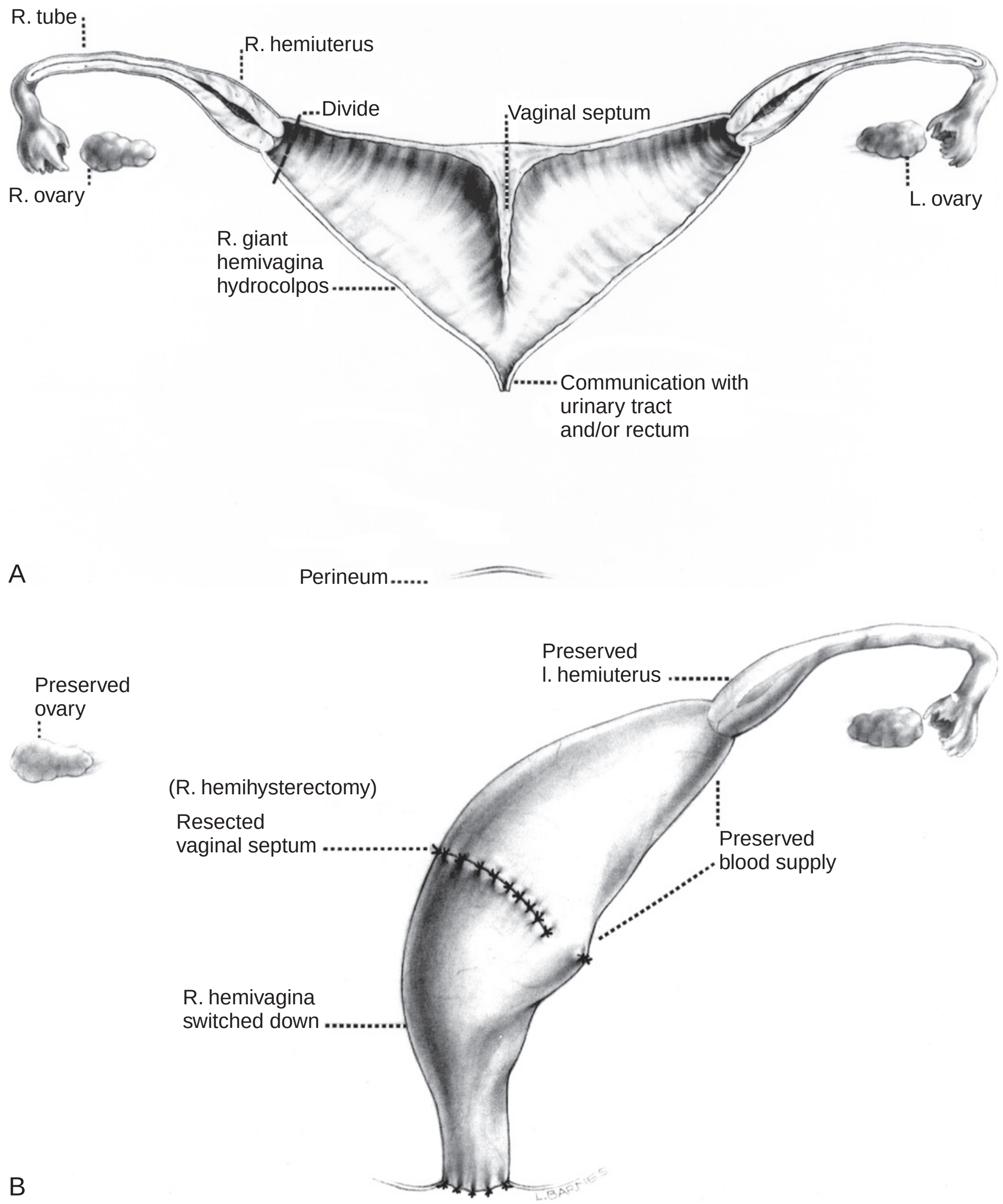



**FIGURE 103-23** **A,** Very large hemivaginas with a vaginal septum and long common channel. **B,** Vaginal switch maneuver.

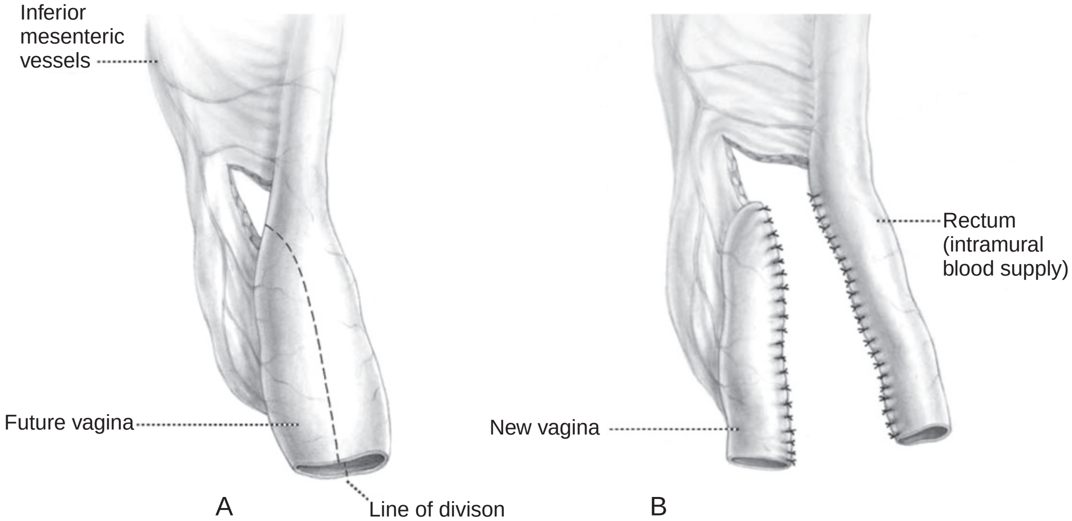



**FIGURE 103-24** **A** and **B,** Vaginal replacement with the rectum.

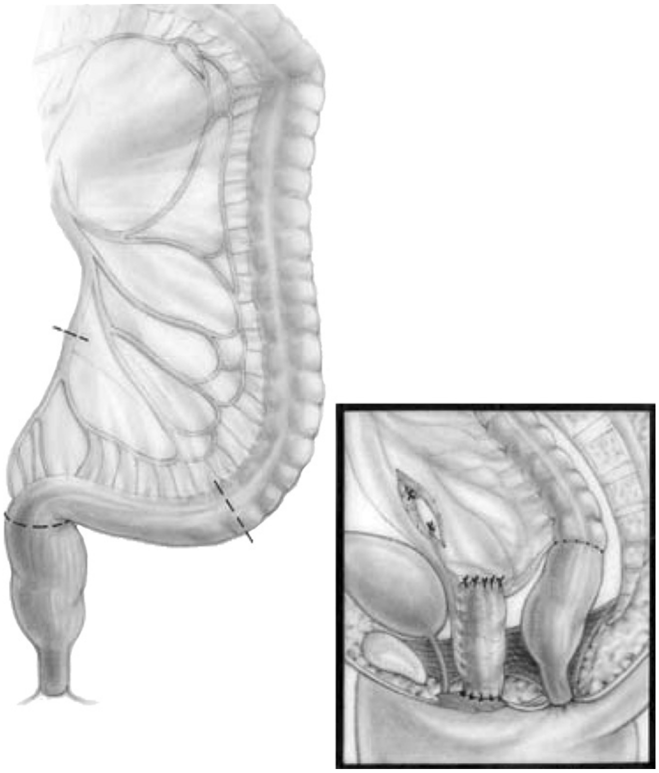


**FIGURE 103-25** Vaginal replacement with the sigmoid colon.

## GENERAL PRINCIPLES OF POSTOPERATIVE CARE

In the absence of a laparotomy, oral feedings may begin when the child is awake. Antibiotics are given for 48 hours. In males who had a rectourethral fistula, the urinary catheter should be left in place for 7 days. In patients who have undergone cloaca repair, the urethral catheter is left in place for 2 to 3 weeks until the urethral orifice is visible.

A dilatation program is begun 2 weeks after surgery. The anus is calibrated, and a dilator that fits snugly is initially used to dilate the anus twice a day. Every week, the size of the dilator is increased by one unit until the desired size is reached. The optimal size of dilator is shown in Table 103-2. Once the correct size is reached, the colostomy can be closed, which is usually 8 to 12 weeks after the reconstruction.

Dilatations must continue after closure. Once the dilator can be inserted easily, the schedule is reduced to once a day for 1 month, twice a week for 1 month, once a week for 1 month, and then once a week for 3 months.

After the colostomy is closed, the patient may have multiple bowel movements and perineal excoriation may develop. A constipating diet may be helpful in the treatment of this problem. After several weeks the number of bowel movements decreases, and most patients will essentially become constipated. This constipation must be anticipated and proactively treated.[31] After 3 to 6 months, a more regular bowel movement pattern develops. A patient who has one to three bowel movements per day remains clean between bowel movements

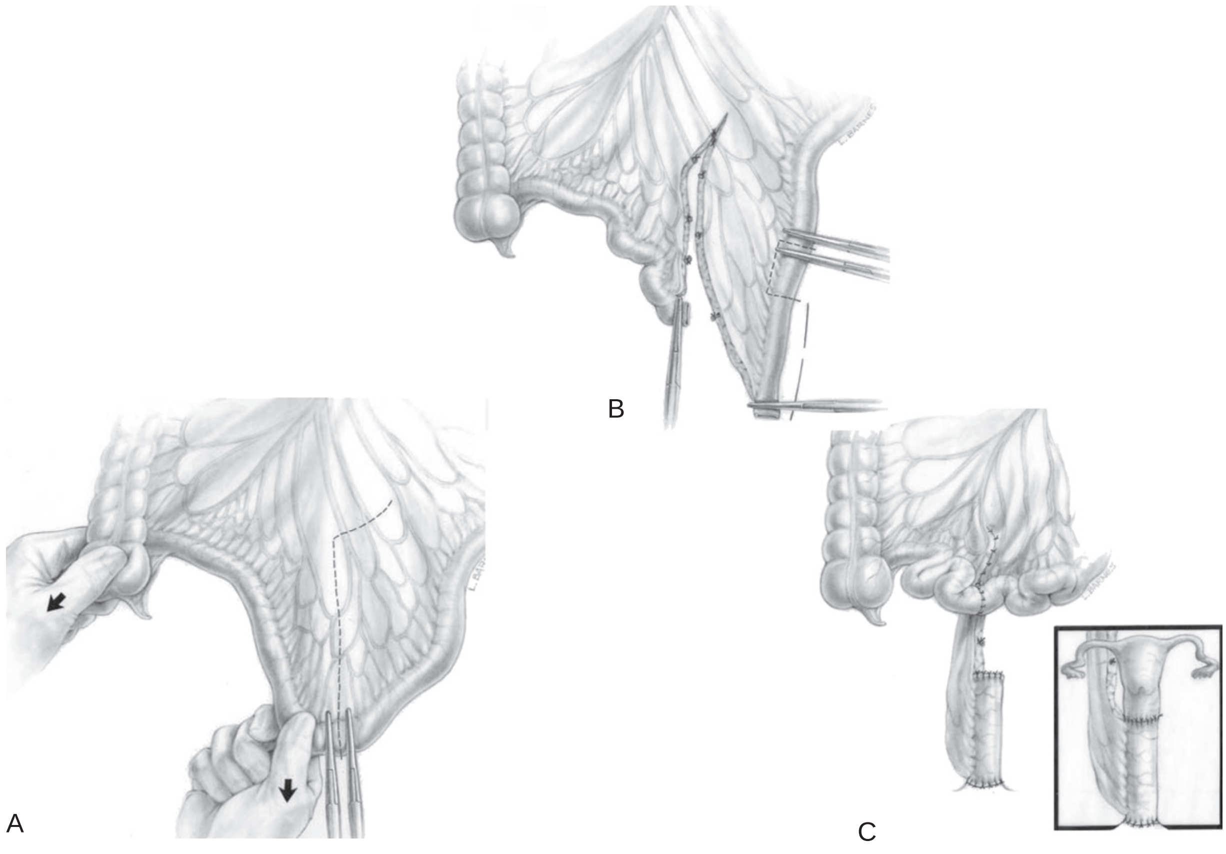



**FIGURE 103-26** Vaginal replacement with small bowel. **A** and **B,** Using the portion of ileum with the longest mesentery. **C,** Pulling the small bowel down as a neovagina (the *insert* shows an anastomosis to the upper part of the vagina).

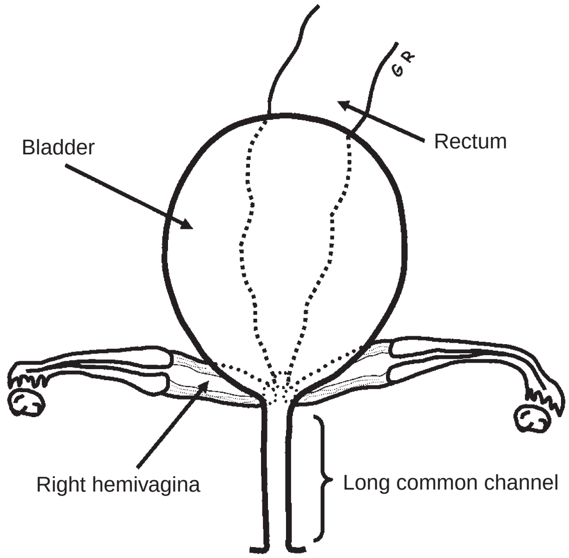



**FIGURE 103-27** Extremely long common channel–hemivaginas and rectum connected to the bladder neck.

and shows evidence of a feeling of pushing during bowel movements. This type of patient has a good bowel movement pattern, generally has a good prognosis, and is trainable. A patient with multiple bowel movements or one who passes stool constantly without showing any signs of sensation or pushing typically has a poor functional prognosis for bowel control. The original malformation type, as well as the quality of the sacrum and spine, predict the potential for voluntary bowel movements.

In cloacas the baby is watched to see whether she is capable of emptying her bladder. If she cannot pass urine and efficiently empty the bladder, she needs intermittent catheterizations.

# Outcomes

## COMPLICATIONS

All the usual postoperative complications may occur after surgery of this nature. In addition, some specific problems develop both early in the postoperative course and later.[66]

Wound infection and retraction are known to occur. When the infection affects only the superficial layers of the wound, is not accompanied by dehiscence of the structures pulled through, and is promptly treated, it is likely that no functional sequelae will result. On the other hand, infection accompanied by dehiscence may reach catastrophic proportions

**TABLE 103-2**
**Anal Dilatation Program**

| *Patient Age* | *Hegar Dilator* |
|---|---|
| 1-4 mo | Size No. 12 |
| 4-8 mo | Size No. 13 |
| 8-12 mo | Size No. 14 |
| 1-3 yr | Size No. 15 |
| 3-12 yr | Size No. 16 |
| >12 yr | Size No. 17 |

and leave sequelae that include incontinence, strictures, acquired atresias, recurrent fistulas, and severe pelvic fibrosis. We have reoperated on many such patients who suffered these kinds of complications at another institution and were referred to us for a secondary procedure.[67–68]

Infections and dehiscence have occurred mainly in patients operated on primarily, without a colostomy. Therefore although there is the benefit to operate earlier, primarily, and without a colostomy, it must be remembered that a colostomy is a valuable adjunct in the management of these defects. Surgeons must make decisions regarding this issue on the basis of their personal experience.

Determining the precise causes of these complications is difficult; however, it seems the main contributing factors are fecal contamination, ischemia, and suture line tension (often from the incomplete mobilization of structures).

Rectal or vaginal strictures (or both) are usually due to the previously mentioned complications, although they may occur independently. An anal dilatation program is recommended to avoid strictures; however, these maneuvers prevent only minor, ringlike strictures. Difficult anal dilatations usually reflect a major problem related to ischemia or tension that will result in a long narrow stricture or even acquired atresia.

Rectal mucosal prolapse is not uncommon after reconstruction. The rate of prolapse after posterior sagittal anorectoplasty in the authors' series was less than 5%.[69] Mucosal prolapse is uncommon after posterior sagittal anorectoplasty, probably because of several key technical steps: (1) tacking of the posterior rectal wall to the posterior edge of the muscle complex, (2) tapering a dilated rectum if necessary, and (3) performing the anoplasty under slight tension so that after the sutures of the anoplasty are cut, the rectum retracts slightly with no mucosa being visible. Mucosal prolapse is managed by full-thickness trimming and is performed when prolapse causes excess mucus production or ulceration or interferes with anal sensation.

A review of patients operated on at other institutions has revealed significant urologic injuries in male patients who underwent repair of anorectal malformations.[56] The posterior sagittal approach, when performed without a good preoperative distal colostogram, was the most important source of these complications. Urethral, ureteral, vas deferens, and seminal vesicle injuries can occur. The laparoscopic approach when done for malformations in which the rectum ends below the peritoneal reflection risks leaving behind a posterior urethral diverticulum (the original distal rectum). Postoperative neurogenic bladder in male patients who undergo a technically correct operation for the treatment of anorectal malformations must be extremely unusual because in our series it happens only in patients with an abnormal sacrum or spine.[70] Otherwise, we believe that it may reflect a poor surgical technique with denervation of the bladder and bladder neck during the repair.

Constipation is the most common sequela after surgical repair of anorectal malformations.[31] The lower the malformation, the more likely the development of constipation. A vicious cycle ensues with megarectosigmoid leading to more constipation. Constipation that is not properly managed will lead to more megarectosigmoid, resulting in overflow pseudoincontinence. Patients appear to be incontinent, but if their constipation is managed appropriately, they become

continent. Such patients sometimes benefit from sigmoid resection to reduce their laxative requirement.[71–74]

Every effort must be made to avoid this cycle and maintain a collapsed and clean bowel from the moment the baby is born. Transverse colostomies left for a long period of time lead to severe megarectosigmoid. Loop colostomies may also contribute to distal fecal impaction, dilation, and subsequent constipation. Adequate treatment of constipation starting after colostomy closure is vital.

## CONTINENCE

Long-term follow-up of our series suggests that good bowel control is achieved in about 75% of patients.

Our results according to the type of abnormality are shown in Tables 103-3 through 103-6. Patients with low anomalies have done extremely well; those with high lesions and those with associated spinal or sacral problems have done less well.

All patients with anorectal malformations, regardless of the complexity of the defect, can be kept completely dry of urine and clean of stool after the age of 3, either because they achieve bowel and urinary control or because we implement a program to keep them artificially dry and clean. The majority can have voluntary bowel movements, sometimes with the help of laxatives. For the others, we implement a bowel management program that uses enemas to ensure adequate emptying for a 24-hour period of cleanliness. With the rational administration of bowel irrigation, diet, and drugs, most patients, including those with inherent fecal incontinence, are able to remain clean for 24 hours.[75–76] Only patients with loose stool secondary to an absent or a short colon need a permanent colostomy.

Patients suffering from fecal incontinence are evaluated and classified into those with constipation or those with increased motility (tendency to have diarrhea). In the first group the saline enema must be of large volume, with additives (e.g., glycerin, soap, phosphate) to help empty the colon. This program takes advantage of the decreased bowel motility in constipated patients; they remain clean for the next 24 hours. No laxatives or diets are given as part of this protocol. The second group (patients who suffer from increased bowel motility because of loss of the rectal reservoir) require a constipating diet,

**TABLE 103-3**
**Constipation and Type of Defect**

| *Defects* | *# of Patients with Defect* | **Patients with Constipation** *n* | *%* |
|---|---|---|---|
| Atresia or stenosis | 10 | 7 | 70% |
| Bulbar fistula | 110 | 65 | 59% |
| Perineal fistula | 72 | 42 | 58% |
| Vestibular fistula | 141 | 77 | 55% |
| Imperforate anus without fistula | 41 | 20 | 49% |
| Prostatic fistula | 112 | 47 | 42% |
| Cloaca common channel ≤ 3 cm | 97 | 38 | 39% |
| Cloaca common channel > 3 cm | 60 | 17 | 28% |
| Vaginal fistula | 5 | 1 | 20% |
| Bladderneck fistula | 50 | 7 | 14% |
| Total | 698 | 321 | 46% |

**TABLE 103-4**
**Voluntary Bowel Movement and Type of Defect**

| | | **Patients with VBMs** | |
|---|---|---|---|
| *Defect* | *Cases* | *n* | *%* |
| Atresia or stenosis | 11 | 11 | 100% |
| Perineal fistula | 58 | 56 | 97% |
| Vestibular fistula | 146 | 131 | 90% |
| Imperforate anus without fistula | 40 | 31 | 78% |
| Bulbar fistula | 112 | 89 | 79% |
| Cloaca common channel ≤ 3 cm | 99 | 65 | 66% |
| Prostatic fistula | 109 | 71 | 65% |
| Vaginal fistula | 5 | 3 | 60% |
| Cloaca common channel > 3 cm | 69 | 24 | 35% |
| Bladderneck fistula | 49 | 10 | 20% |
| Total | 698 | 491 | 70% |

**TABLE 103-5**
**Soiling and Type of Defect**

| | | **Patients with Soiling** | |
|---|---|---|---|
| *Defect* | *Cases* | *n* | *%* |
| Perineal fistula | 57 | 9 | 16% |
| Vestibular fistula | 135 | 49 | 36% |
| Atresia or stenosis | 10 | 4 | 40% |
| Bulbar fistula | 105 | 51 | 49% |
| Imperforate anus without fistula | 39 | 20 | 51% |
| Cloaca common channel ≤ 3 cm | 91 | 57 | 63% |
| Prostatic fistula | 110 | 86 | 78% |
| Vaginal fistula | 5 | 4 | 80% |
| Cloaca common channel > 3 cm | 55 | 46 | 84% |
| Bladderneck fistula | 48 | 43 | 90% |
| Total | 655 | 369 | 56% |

**TABLE 103-6**
**Totally Continent* Patients and Type of Defect**

| | | **Totally Continent** | |
|---|---|---|---|
| *Defect* | *Cases* | *n* | *%* |
| Perineal fistula | 52 | 43 | 83% |
| Atresia or stenosis | 9 | 5 | 56% |
| Vestibular fistula | 135 | 86 | 64% |
| Imperforate anus without fistula | 36 | 18 | 50% |
| Bulbar fistula | 101 | 46 | 46% |
| Cloaca common channel ≤ 3 cm | 91 | 32 | 35% |
| Vaginal fistula | 5 | 1 | 20% |
| Prostatic fistula | 105 | 19 | 18% |
| Cloaca common channel > 3 cm | 52 | 6 | 12% |
| Bladderneck fistula | 46 | 3 | 7% |
| Total | 632 | 259 | 41% |

*Voluntary bowel movements and no soiling.

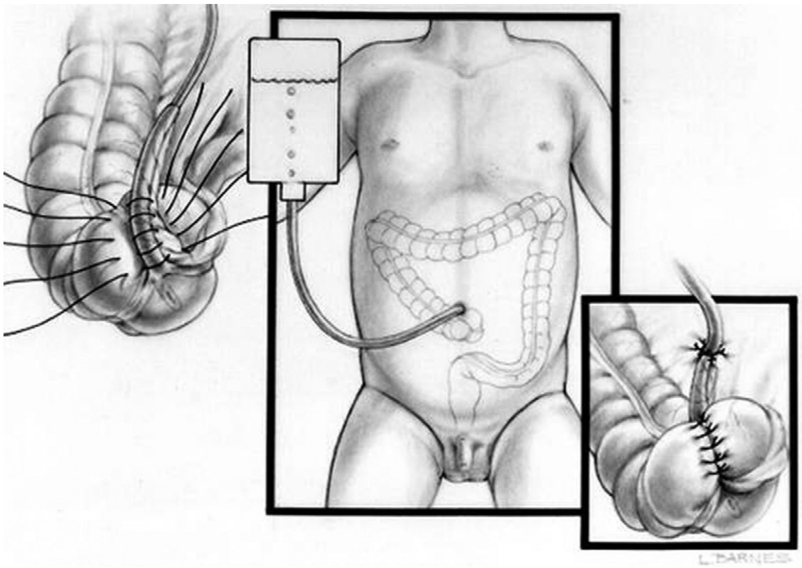


FIGURE 103-28 Diagram showing appendicostomy.

medication to decrease bowel motility, and a smaller daily saline enema.

The treatment is adjusted by trial and error over a period of 1 week, with 95% of patients remaining clean.[75] Bowel management is started just before the patient has to go to school and join his or her classmates, who are already wearing regular underwear. Most patients and parents are happy with the implementation of this program, but when the patient reaches the age of 7 to 12 years or sometimes younger, more independence is usually desirable.

At that point, creation of a continent appendicostomy (Malone procedure) is beneficial.[77–79] This operation creates a communication between the abdominal wall and the cecum through the patient's appendix. A valve mechanism is created by plicating the cecum around the appendix, which allows catheterization of the cecum but prevents leakage of stool. Patients can administer their own enema while sitting on the toilet. The operation consists of the plication and then the connection of the appendix to the umbilicus to make it inconspicuous. This is accomplished with a V-to-V anastomosis between the appendix and the umbilical skin (Fig. 103-28). A significant number of patients do not have an appendix. In such cases we make an appendix with a tubularized flap of the cecum and then plicate the cecum around it (Fig. 103-29). The stoma is also exteriorized through the umbilicus. Most patients who have undergone this operation express a great deal of satisfaction.

Some patients benefit from an enema program early on, but if they have potential for bowel control, when they are a little older, a laxative trial can be used to help their colon empty, with careful radiologic monitoring. This may allow them to demonstrate the capacity for voluntary bowel movement and thus eliminate the need for enemas.

FIGURE 103-29 Neoappendix made from a tabularized flap of colon.

Certain patients in whom the rectum was mislocated during the original operation may be candidates for a reoperation. This is recommended only in patients who were born with a good sacrum, good sphincters, and a malformation with a good prognosis. The results of this procedure vary, with worthwhile continence achieved in more than half of patients.[68,80–81]

Urologic problems in male patients and in female patients without cloacas are rare.[82] In patients with a cloaca, those with a common channel shorter than 3 cm require intermittent catheterization one third of the time. Patients with common channels longer than 3 cm require intermittent catheterization or a continent diversion 70% to 80% of the time.[64]

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 104

# Other Disorders of the Anus and Rectum, Anorectal Function

Risto J. Rintala and Mikko P. Pakarinen

## Anatomy

The anal canal measures 2.5 to 4 cm in length (Fig. 104-1).[1] It is the area between the anal verge and the junction of the stratified cuboidal and columnar epithelium (dentate line).[2] It is lined by squamous epithelium in the lower anal canal below which sebaceous glands and hair follicles arise but changes to stratified cuboidal and, finally, columnar epithelium of the rectum. Sensitive sensory receptors in this epithelium and in the more proximal anal mucosa respond to a variety of stimuli, permitting discrimination of solid, liquid, and gas. The mucosa of the rectum meets the epithelial lining of the anal canal at the dentate or pectinate line, marking the oral extension of the anal columns and valves. High in the anal canal, the mucosa forms four to six longitudinal folds.

The smooth muscle of the internal anal sphincter (IAS) is continuous with the inner circular muscle of the rectum. It becomes more prominent low in the anal canal. It is approximately 3 cm long and 5 mm thick.[3] IAS is bound to voluntary external sphincter and perianal skin by muscular strands. It is involuntarily in a tonic state of contraction, providing at least 85% of the resting anal canal pressure that keeps the anal canal closed.[4] The IAS can increase contraction only slightly, but it relaxes completely by reflex in response to rectal distention.[5] This reflex, mediated by the myenteric plexus, is intrinsic and thus remains independent from extrinsic innervation.

Both sympathetic and parasympathetic nerves innervate the internal sphincter.[6] Sympathetic innervation is primarily excitatory, contracting the IAS, and is supplied by the lumbar splanchnic nerves from L2 to L4 ganglia and by the hypogastric nerves from the inferior mesenteric ganglion. $\alpha$-Adrenergic stimulation is excitatory, but $\beta$-adrenergic stimulation is inhibitory. The continuous tonic state of IAS appears to be mediated by excitatory fibers of both adrenergic and cholinergic innervation. Parasympathetic innervation comes from the S2 to S4 ganglia through the pelvic nerves and is generally inhibitory, causing the IAS to relax.[7,8]

The IAS also has an important intrinsic innervation, which is responsible for reflex relaxation in response to rectal distention. These intrinsic nerves lie in intramural plexuses and in the myenteric (Auerbach), deep submucosal (Henke), and submucosal (Meissner) plexuses and are nonadrenergic and noncholinergic in origin.[6,7]

The external anal sphincter is a striated muscle that is partially under voluntary control. The muscle surrounds the anus below the dentate line and is attached anteriorly to the perineal body and posteriorly to the anococcygeal raphe. The external anal sphincter has traditionally been divided in three anatomic components: subcutaneous, superficial, and deep. It is innervated by rami of the pudendal and perineal nerves, which originate from sacral roots 2 to 4.[9]

Although capable of phasic contraction, the external anal sphincter may also have tonic contraction.[10] Unlike the IAS, the tonic contraction of the external sphincter depends on extrinsic efferent innervation. The phasic contractions are born voluntary and involuntary; thus the external anal sphincter provides part (10% to 15%) of the resting anal sphincter tone.[11]

The pelvic floor muscles consist of the levator ani muscle group, one part of which, the puborectal muscle, forms a sling around the anorectal junction. Although a striated muscle, the puborectalis remains in tonic contraction.[12] This creates an angle between the anus and the rectum, the anorectal angle, which is 80 to 90 degrees at rest and during defecation more obtuse, at 100 to 105 degrees.[13] With coughing, straining, or other sudden increases in intra-abdominal pressure, the puborectalis automatically increases its tonic contraction, hereby maintaining the sharp anorectal angle that plays a significant role in fecal continence.[12] The levator ani muscle complex that contracts in a vertical plane is shaped like a funnel that surrounds the rectum and tapers down to the anal canal, where its fibers merge with the voluntary anal sphincter.

## Physiology of Anal Continence

The adaptive compliance of the colon with the retentive mechanism of the anorectum is required for fecal continence. The simple anatomic impedence to the descending fecal mass occurs because the distal end of the gastrointestinal tract is

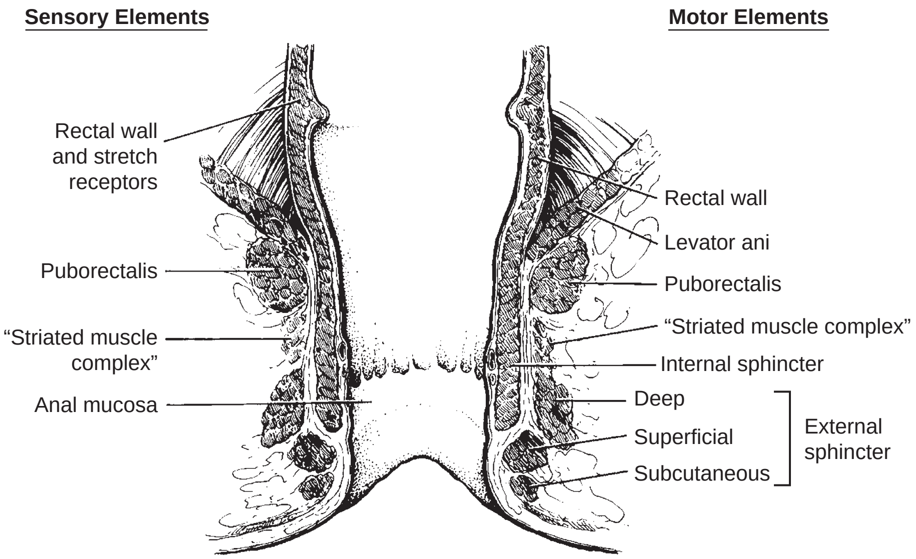


**FIGURE 104-1** The main anatomic components of the rectum and anus.

not a straight tube. The angulations in the sigmoid colon and the valves of Houston in the rectum impede the caudal movement of fecal contents. The 80-degree anorectal angle also assists fecal continence.[14] The longitudinal mucosal folds in the anus also contribute to continence of semisolid or fluid feces by the way they fold together, even when the internal sphincter partially relaxes.

The anal sphincters play an important role in maintaining continence, and both the voluntary external sphincter and the involuntary internal sphincter have a resting tone. Fecal continence requires a normally functioning IAS, external sphincter complex, and levator funnel, as well as intact sensory input from the rectum and anal canal.[15,16] The rectum has stretch receptors, which have an increasing sensitivity the more distal they are sited. The anal canal is richly endowed with sensory receptors for most modalities of sensation.[17] These receptors allow us to distinguish between flatus, fluid, and feces.

Gross continence, the ability to hold large volumes of solid or liquid feces, is a function of the intact anorectal angle and tonic contraction of both external and internal sphincter systems. Fine continence—the control of small volumes of feces or flatus—is the function of the coordinated action of the sphincters. The distal 2 cm of the anal canal above and at the dentate line is the critical site of fine continence.[18] This is the site where the "sampling reflex," discrimination between solid stool, liquid, or gas, is initiated.[19]

## Physiology of Defecation

The defecation sequence is a complex combination of involuntary actions and voluntary accomplishments that are controlled by higher cerebral centers. The rectum fills gradually by colonic action. The distension of the rectum stimulates stretch receptors in the rectal wall and levator and induces an initial contraction of the voluntary sphincter complex, retrograde emptying of the distal rectum, and relaxation of the IAS. This causes a sensation to desire to defecate that increases in intensity as the rectum fills. Stool is temporarily allowed to contact the sensitive mucosa of the anal canal and is sampled by the exquisitely sensitive sensory receptors in the anal mucosa, which allows evaluation of stool consistency and recognition of flatus. The need to defecate is appreciated, but this urge can be voluntarily inhibited. The external anal sphincter and puborectalis can be contracted voluntarily to abort the fecal expulsion. The rectum and colon stretch compliantly, decreasing the intrarectal pressure and the urge to stool.

As more stool is delivered to the rectum, the sensation increases and rectal waves intensify. The urge to defecate is increased, and the reflex inhibition of the sphincters becomes greater. The reflex suppression of the tonic contraction of the external anal sphincter and puborectalis begins; if time and place are appropriate, voluntary defecation can occur.

Young children have a shorter intestinal transit time than older children, and this correlates with the more frequent bowel movements in infants.[20] Infants who are fed by breast milk or cow's milk–based formula have one to seven bowel movements per day.[21] In children between 1 and 4 years of age, 85% pass stool once or twice per day.[22] Normal English school children[23] have mean transit times of 26 hours and constipated children of 80 hours. Healthy young adults have transit times from 30 to 48 hours.[24]

## Constipation

Constipation in children is a common condition, especially in the Western world. Unresolved constipation can lead to fecal retention and impaction, and finally to overf1ow incontinence. In the overwhelming majority of patients the exact cause of constipation remains obscure; in this case the condition is called *functional constipation.*

### DEFINITIONS

The consensus Rome III classification is most commonly used in the diagnosis of functional constipation in children.[25] Functional constipation in children is defined as constipation not associated with congenital abnormalities, acquired

diseases, or medication. The following criteria apply for children of all ages:

*Two or more* of the following must exist:

1. Two or fewer defecations in the toilet per week
2. At least one episode of fecal incontinence per week (after acquisition of toileting skills)
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large-diameter stools that may obstruct the toilet

Both constipation and soiling are common. Soiling has been reported in approximately 3% of children older than 4 years of age, and constipation accounts for at least 3% of all medical and 25% of pediatric gastroenterology referrals.[26–29] More than 50% of constipated children have a familial incidence, and most studies suggest a male predominance. The reported ratios range between 1.5:1 and 3:1.[30,31]

Because constipation during the neonatal period, usually associated with distention and vomiting, is never functional, anatomic or mechanical obstruction must be suspected. Most (94% to 98%) full-term and most (76%) preterm normal babies pass meconium during the first 24 hours after birth. All normal babies (100% of full-term and 99% of preterm) have a first stool with the first 48 hours of life.[32] During the first year of life, symptomatic constipation warrants an evaluation and organic causes for constipation should be ruled out.

During infancy, constipation is often initiated after dietary manipulations, often the change from breast-feeding to bottle-feeding or the introduction of solid foods.[33] Specifically, in children anal fissure or perianal dermatitis with group A *Streptococcus* causes a vicious cycle of stool withholding and painful defecation and chronic constipation. A suggested alternative etiology is cow's milk protein intolerance.[34] Dietary fiber is poorly associated with constipation except in older children.[35] Constipated parents are more likely to have constipated children.[36] Slow transit constipation is a major problem in adults and is probably important in a subset of children with constipation.[37,38] Psychologic problems are common in constipated children, but they are secondary to constipation in the majority of cases.[30,39]

## ACUTE CONSTIPATION

Acute constipation may be secondary to inactivity, changes of environment or diet, or an anal fissure. Presentation as acute abdominal pain is common. Acute constipation presenting with abdominal pain is usually relieved by one single enema. The management of acute constipation is usually straightforward, especially in infants and toddlers. Adding more water to the diet and restriction of cow's milk intake usually relieve the symptoms. Older children and those who have an acute anal fissure require bulk laxatives for a variable period of time.

## CHRONIC CONSTIPATION

Persistent constipation, which does not rapidly respond to dietary manipulation or simple laxative treatment, can be defined as chronic. A child with chronic constipation commonly presents with fecal soiling. Organic causes that should be taken into account in the diagnostic workup for chronic constipation are summarized in Table 104-1.

**TABLE 104-1**

**Differential Diagnosis of Chronic Constipation: Organic and Acquired Causes**

| |
|---|
| **Hirschsprung Disease and Allied Disorders** |
| Internal sphincter achalasia |
| Intestinal neuronal dysplasia (hyperganglionosis) |
| Hypoganglionosis |
| **Congenital Anomalies** |
| Anal stenosis |
| Anterior perineal anus |
| **Acquired Diseases** |
| Chronic anal fissure |
| Chronic anal fistula |
| Crohn disease |
| **Associated with Systemic Disease** |
| Hypothyreosis |
| Hypercalcemia |
| Cerebral palsy and other neurologic impairment conditions |
| Uremia |
| **Psychiatric Disease** |
| Depression |
| Anorexia nervosa |
| Primary encopresis |
| **Medication** |
| Anticonvulsive drugs |
| Psychiatric drugs |
| Anticholinergic drugs |

Studies of children with constipation and overflow soiling show that 40% were never completely toilet trained and that enuresis is an associated problem in more than 30%.[28] Chronic constipation and soiling typically present between ages 2 and 4 years[40]; however, up to 40% of the patients have the onset of symptoms during the first year of life. The diagnosis of chronic constipation relies on history and clinical examination. A detailed bowel history should focus on the age at which constipation first occurs; the frequency and description of stools; and therapeutic interventions previously attempted including any medications taken. Anticonvulsants, diuretics, antacids, and supplemental iron preparations are frequently associated with constipation. Family history can be important, particularly a history of Hirschsprung disease, cystic fibrosis, or familial constipation. The incidence of clinical findings in patients with chronic constipation is summarized in Table 104-2.

On clinical examination the child's abdomen is usually nontender and rarely distended. Stool masses are frequently palpable above the pubic symphysis and in the lower left abdomen. The perineum must be inspected carefully for the position and condition of the anus and the perianal skin, as well as for soiling marks. The normal position of the anus must be defined because malpositioning is a well-recognized cause of constipation.[41,42] Reisner and colleagues[43] defined normal values by using a ratio of the midanal to fourchette distance and the fourchette to coccyx distance in the female and midanal to posterior scrotum distance and the posterior scrotum to coccyx distance in the male. If the ratio is less than 0.34 in the female (usual values: newborn, 0.44; age 4 to 18 months, 0.40)

TABLE 104-2
Clinical Features of Severe Functional Constipation

| *Age at Onset* | |
|---|---|
| 0-1 yr | 20-25% |
| 1-5 yr | 70% |
| > 5 yr | 10-15% |
| Boys-to-girls | 1-3:1 |
| Previous attempts to treat | 80-90% |
| Soiling | 70-75% |
| Unsuccessful toilet training | 70-80% |
| Pain at defecation | 70-80% |
| Abdominal pain | 50-60% |
| Occasional blood in stool | 25-30% |
| Poor appetite | 20-30% |
| Wetting | 20-30% |
| Primary psychopathology | 15-20% |
| Rectal prolapse | 3% |

Data from references 28, 30, 36, 52, and 53.

and less than 0.46 in the male (usual values: newborn, 0.58; age 4 to 18 months, 0.56) the child should be investigated carefully, especially if constipation is present. To differentiate between anterior anus and perineal ectopic anus is often difficult, especially if the anterior position of the anus is associated with stenosis. Final diagnosis may require muscle stimulation in general anesthesia.

Perianal sensation to rule out neurologic disorders can be evaluated by stroking the perianal tissue gently with a cotton-tipped applicator, watching for the anal puckering, and ascent of the perineum. The child's underwear should also be examined for soiling.

It is advisable to perform a digital rectal examination at least once in a child with chronic constipation to rule out organic obstructing causes. The fecal mass that fills the rectum may have developed to a fecaloma that can be stone hard. The rectorectal space must be examined to feel masses within the hollow of the sacrum. The closing reflex should be seen when the finger is withdrawn. The absence of either the perineal cutaneous or closing reflexes suggests an underlying neurologic disorder.

If the clinical history and physical examination do not suggest organic etiology, a trial of medical treatment can be initiated. A small infant with a history of neonatal symptoms and early onset constipation should undergo barium enema without bowel preparation. An abnormal barium enema should be followed by rectal biopsy and possibly anorectal manometry to rule out Hirschsprung disease and allied disorders. In an older child without any history of significant neonatal constipation a primary barium enema or biopsies are not necessary[44,45] before the onset of medical management. Barium enema and other imaging such as plain abdominal radiography, transit time studies, or magnetic resonance imaging (MRI) are indicated in patients who have poor response to appropriate medical treatment or abnormal clinical findings such as neurologic symptoms. Patients who have a poor response to optimal medical therapy should undergo also rectal biopsy and anorectal manometry to rule out rare forms of dysganglionoses such as hypoganglionosis, intestinal neuronal dysplasias, and internal sphincter achalasia.

Barium enema usually shows dilatation of the rectosigmoid that extends to the anal canal. This rules out classic Hirschsprung disease but not internal sphincter achalasia.[46,47] Plain abdominal radiography may reveal spinal vertebral anomalies in patients who have clinical findings suggesting a neurologic disorder. In case of vertebral anomalies an MRI study should be performed to rule out intraspinal pathology such as tethering and intraspinal lipomas.[48] Transit time studies by radiopaque markers[37,49] or radioisotopes[38] have been used to assess colonic motility in patients with poor response to standard medical management. These studies have revealed that slow-transit constipation occurs in a significant proportion of patients with recalcitrant constipation. The main methodological problem with transit studies in children is the lack of standardized methods and normal values in healthy children.

Anorectal manometry is useful only for the diagnosis of Hirschsprung disease and internal sphincter achalasia. In both these conditions the rectoanal relaxation reflex is missing. In patients suffering from functional constipation, anorectal manometry does not improve diagnostic or therapeutic accuracy. Some constipated children with normal histology also have manometric evidence of anal outlet obstruction and paradoxically contract the sphincter complex with straining, so-called rectoanal dyssynergy.[46,50–52]

## MANAGEMENT OF CHRONIC IDIOPATHIC CONSTIPATION

The general approach to the management of a child with chronic constipation includes the following steps[39,53]:

- Provide parental counseling and education
- Determine whether a fecal impaction is present
- Disimpact the fecaloma if present
- Initiate oral medication

### Counseling and Education

Counseling and educating the family are the first steps in the management. The pathogenesis of constipation needs to be explained to the parents. If the patient has fecal soiling, the involuntary nature of overflow incontinence needs to be clarified to the parents. Parents are encouraged to maintain a consistent supportive attitude during the long period of treatment. Education of the child and parents, emotional support, and a commitment to continue to see the family until normal stooling is established are all important elements of the program.[51,53,54] The patient and the parents need to be aware that it may take 6 to 12 months or even years before a normal stooling pattern is achieved.

### Disimpaction

If the patient has fecal impaction, disimpaction is necessary before initiation of oral maintenance therapy. A fecal mass can be identified by physical examination in the lower abdomen, rectal examination, or radiographic methods. A typical symptom of fecal impaction is overflow incontinence. Disimpaction has been traditionally accomplished with bowel washouts, but oral medication is effective, too.[55,56]

Oral disimpaction can be accomplished by high doses of stimulant laxatives, docusate, mineral oil, and polyethylene glycol-electrolyte (PEG) solutions.[54,56] Osmotic laxatives such

as lactulose or sorbitol can be used in combination with other medication. Oral disimpaction is often associated with abdominal pain and colic, as well as an initial increase in fecal soiling.

Rectal washouts usually work faster than oral disimpaction. It is, however, invasive and painful, especially in patients who have associated anal pathology. Therefore rectal disimpaction is contraindicated in children with anal fissure. Saline, docusate, mineral oil, or phosphate enemas are recommended by different investigators.[53,57,58] When rectal disimpaction is used, it is essential that the number of enemas is kept minimal. Usually one to three washouts are required for complete disimpaction. In recalcitrant cases manual evacuation under general anesthesia may be considered.

### Maintenance Therapy

The goal of maintenance therapy is to produce one to two soft stools per day and prevent recurrent fecal impaction. This ensures that the vicious cycle of hard stools and painful defecation will be abolished. Treatment consists of dietary interventions, laxatives, and behavioral modification. Dietary changes are universally advised, particularly increased intake of fluids and fiber. The role of fiber may not be significant in children.[35] Too much milk is discouraged.[59]

There is no evidence that any particular drug treatment regimen is superior. Good compliance with the selected treatment is more essential. In the early phases of management after the disimpaction, more effective medication is often required. Stimulant laxatives (Senna, sodium picosulfate) should be used for short periods, as short as possible, and should be replaced by less harmful therapies. Osmotic laxatives (lactulose, docusate, PEG) can be safely used for months and years. A recent meta-analysis has shown that PEG is superior to lactulose for childhood chronic constipation.[60]

Having achieved regular pattern of bowel movements, the medication needs to be continued as long as needed. This usually means months and sometimes years. A good thumb rule is that the treatment continues as long as the patient has had symptoms before the management. The dosage of the medication needs to be tapered regularly; the goal is to use a minimum effective dose.

### Behavioral Therapy

Behavioral therapy varies with the age of the patient. In infants and toddlers, behavioral therapy has no role; it is important that too early and aggressive toilet training is discouraged. In young children younger than 2 to 3 years of age, the toilet should be avoided and diapers reinstituted as long as the child is ready to go back to potty or toilet.[53] Older children may benefit from regular toileting routines after a major meal during the day. Praise, rewards, and a diary may contribute to a successful outcome.[55]

### Long-Term Outcome

There are few studies of the long-term results of the management of chronic idiopathic constipation.[36,61] The reported final cure rates after 5 years of follow-up range between 50% and 70%. A recent longitudinal follow-up study showed that one third of children with chronic constipation continue to have severe complaints of constipation beyond puberty.[62]

### Surgical Options for Chronic Constipation

The majority of children with chronic constipation improve by appropriate medical therapy or with time. Most patients also comply even with aggressive medical therapy. However, a few children, despite optimal and maximal medical management, have persistent constipation, abdominal symptoms, and soiling throughout and beyond childhood. There are no controlled studies in children devoted to the surgery of pediatric idiopathic constipation.

For pediatric patients who are refractory to all medical therapy, there are some viable surgical options. It is essential that organic causes of constipation are ruled out. The MACE procedure[63] that has been originally used for neuropathic incontinence or incontinence following management of anorectal anomalies has been successfully used also for idiopathic constipation.[64,65] The MACE procedure can be easily reversed, which may make it an attractive alternative for enemas and laxatives, especially for pubertal and adolescent patients. Resection of the megarectum and megasigmoid has been performed for patients with functional constipation, but there is a complete lack of controlled studies and longer-term follow-up data. Moreover, high failure rates have been reported following colon resections.[66] Colostomy has been used in selected patients with significant patient and parent satisfaction.[66,67]

## Functional Fecal Soiling Without Constipation

There is a small subgroup of children with fecal soiling who are otherwise healthy without constipation or any other organic or neuropsychiatric underlying cause for the incontinence.[68–71] A typical age of presentation is between 4 and 8 years of age. The main symptom is involuntary passage of variable amounts of stool to the underwear one to several times a day. The patients rarely soil at school or during sport and social activities. Most have regular bowel actions. At least one third of these patients suffer from daytime or nighttime wetting.

The authors have encountered an increasing number of such patients during the past decade.[72] Most of these patients had had extensive but unsuccessful therapies to treat constipation. No signs of neuropsychiatric disorders or myelopathy in MRI were observed. Patients had normal barium enemas and spinal radiographs. All had developed normally and went to normal schools. The incidence of daytime or nighttime enuresis was 40%. The only measurable functional abnormality was an isolated impairment of rectal sensibility at anorectal manometry; sphincter performance was comparable with constipated control individuals. Treatment consisted of counseling, toilet training, and dietary modification. Some patients, especially those with accompanying enuresis, benefit from anticholinergic treatment with oral oxibutynin hydrochloride (5 to 15 mg/day). Most patients improved with decreased frequency of soiling. All the patients who have reached adolescence have experienced striking improvement of soiling. The most important issue with this subgroup of patients with encopresis is to keep in mind that childhood fecal soiling is not always related to constipation.

## Rectal Prolapse

Rectal prolapse is a relatively common, usually self-limiting condition in children. The peak incidence is between 1 and 3 years of age. Prolapse can be either partial or complete. In partial prolapse the rectal mucosa protrudes only about 1 to 3 cm from the anal verge with characteristic radiating folds from the center of the anal aperture. In complete prolapse, the full thickness of the rectum is involved; 5 cm or more of the rectum protrudes, and the prolapse is distinguished by the circular folds of the mucosa (Fig. 104-2). There is significant controversy as to whether rectal prolapse in children is partial or complete.

### PATHOGENESIS AND DIAGNOSIS

The vast majority of patients suffering from rectal prolapse do not have any predisposing factors. The children suffering from idiopathic rectal prolapse are usually otherwise healthy. The role of constipation as an etiologic factor is controversial; only 3% of patients suffering from severe chronic constipation have rectal prolapse.[30]

Several organic conditions predispose to rectal prolapse. Cystic fibrosis is associated with rectal prolapse.[73] More than a fifth of the patients with cystic fibrosis develop rectal prolapse.[74,75] The neuropathic causes of complete rectal prolapse excluding myelomeningocele are rare. Nevertheless, paralysis of the levator ani with raised intra-abdominal pressure leads to procidentia and prolapse. In ectopia vesicae there is wide separation of the symphysis pubis and the puborectalis muscle, and this wide hiatus predisposes to prolapse of the pelvic organs including the rectum. Besides severe malnutrition, connective tissue diseases (e.g., Ehler-Danlos) and behavioral disorders (e.g., Asperger) predispose to rectal prolapse.

Iatrogenic full-thickness rectal prolapse may occur following pull-through operations for high anorectal anomalies. Much more common is mucosal prolapse that is usually not circumferential.[76] Rectal prolapse and mucosal ectopia were much more common before the era of the PSARP procedure.[77] Rectal polyps may be a leading point for a prolapse.

FIGURE 104-2 Rectal prolapse in a 2-year-old boy.

The diagnosis of rectal prolapse is usually based on history. Most commonly a rosette of rectal mucosa is noted after defecation. The child complains that something comes out of the anus. Usually the prolapse reduces spontaneously but must be sometimes reduced manually. In mild forms the prolapse comes out occasionally following major straining or during diarrheal illness. The problem is more annoying and worrisome for the patient and parents if the prolapse occurs after every defecation.

Usually the prolapse cannot be provoked when the child is brought to consultation. Rectal examination is indicated to rule out rectal polyps and ulcers. If there is a history of rectal bleeding, colonoscopy may be necessary to look for higher polyps or other lead points. Dynamic defecography is warranted at least when a prolapse is associated with rectal ulcer, suggesting intussuscepting prolapse of the sigmoid colon or accompanying enterocele.

### TREATMENT

In acute prolapse, reduction may occur spontaneously on standing up. If not, the prolapse must be reduced as soon as possible. The parents often rush the child to a hospital when the prolapse appears for the first time. The tip of the herniated bowel can usually be gently pushed into the anus. If edema has formed, a gentle squeezing pressure may be required. Reduction technique must be taught to the parents.

There is spontaneous cure in most cases of recurrent prolapse.[78] In many cases the prolapse reduces spontaneously. In cases without spontaneous reduction the parents can reduce the prolapse gently if appropriately instructed. Accompanying constipation is treated with laxatives when present. Local transanal treatments such as injections of the prolapse, multiple linear thermocauterization to the mucosa, excision of redundant mucosa, or insertion of a subcutaneous suture around the anus are not tested in controlled trials.

Operation is indicated in rare cases with intractable prolapse and may be considered in patients who are not spontaneously cured in 12 to 18 months of follow-up. Patients older than 4 years of age require surgery much more often than younger children. There are several surgical methods that have been used with success for recurrent prolapse. We prefer laparoscopic suspension of the rectum to anterior sacrum with routine suture closure of the space between the rectum and the vagina or the urinary bladder in order to avoid development of enterocele.[79] An additional resection of the sigmoid colon may be performed in intussuscepting prolapse of the sigmoid colon and in recurrent cases. Laparoscopic approach has been successful in nearly 20 patients that have required surgery. The procedure is associated with minimal postoperative pain and short hospital stay. Patients benefit from laxative therapy during the early postoperative period. Posterior sagittal approach with muscle repair and suspension of the rectum to the sacrum,[80–83] posterior rectal plication,[84] and Ekehorn rectosacropexy[85] are also reported to be associated with a high cure rate.

Secondary operation is indicated for iatrogenic prolapse after a pull-through operation in symptomatic patients. Typical symptoms include bleeding and leak of mucus. In patients with mucosal prolapse treatment involves excision

of the mucosal ectopia and reconstruction of a skin-lined anal canal with a local skin flap. Patients with a complete prolapse require a repeat posterior reconstruction of the levator funnel and external sphincter complex, as well as rectal suspension.

# Anal Fissure

Anal fissure is a longitudinal tear or ulcer in the distal anal canal epithelium extending to the anal verge. Most acute fissures heal spontaneously within a few weeks, but a proportion become chronic. Anal fissure is the most common cause of hematochezia in childhood, and it is one of the most common lesions to consider in the differential diagnosis of anal pain. Anal fissures are common, although their exact incidence in children is unknown.

## PATHOGENESIS

Pathogenesis of idiopathic anal fissure is still incompletely understood, and it may differ in adults and children.[86] Anal fissures in childhood are often associated with secondary constipation due to painful passage of stools. The classic concept of mechanical tear caused by hard stools as a primary causative factor may be too simple and outdated. However, deliberate avoiding of defecation does cause rectal distension and leads to decreased rectal sensation, which in turn, results in infrequent, bulky, and hard stools that prevent healing of fissure. Fear of painful defecation may lead to fecal retention and gives rise to a vicious circle.

There is a widely accepted theory on the pathogenesis of anal fissure in adults.[86,87] According to this theory increased internal sphincter pressure and muscle spasm lead to impaired tissue perfusion and finally epithelial ulceration. Spasm of internal anal sphincter is so severe that the pain caused by fissure is thought to be due to ischemia. The most common site of idiopathic anal fissure is posterior midline, which is less vascularized than other areas of the anal canal. Anal canal resting pressure is increased in patients with anal fissure. Decrease of anal canal pressure after surgical or pharmacologic sphincter relaxation is accompanied with improved perfusion of anoderm and healing of chronic fissures. Currently, it is unknown whether this theory also applies to pediatric patients. In children a vast majority of idiopathic anal fissures heal without any specific therapy. This may be due to relatively better tissue perfusion of the anal canal, greater regenerative capacity in general, or different pathogenesis in children than in adults. An unhealed fissure may become inflamed due to bacterial infection and chemical and mechanical irritation. As a result of long-standing inflammation, chronic anal fissure may have hypertrophied anal papilla proximally and a sentinel skin tag distally. This kind of chronic anal fissure is only rarely seen in children and should raise the suspicion of underlying Crohn disease.[88]

## DIAGNOSIS

Anal fissure may occur in any age. Typical age of presentation is around 2 years. Most often anal fissures present with bright red rectal bleeding that may be associated with painful defecation. The child may cry with bowel movements and have stools streaked with bright-red blood. Anal fissure is often but not necessarily associated with constipation, which is caused by fear of painful defecation.

The diagnosis is made by direct inspection. The typical longitudinal tear distal to the dentate line can be visualized by retracting the perianal skin gently away. No further diagnostic modalities are necessary. The most common location of idiopathic anal fissure is posterior midline, but especially in infants it may be found anywhere in the anal circumference. In female infants a common site of anal fissure is the anterior midline. A sentinel pile or skin tag at the area of the fissure is associated with chronic or subchronic fissure. Atypical fissures may be multiple and often off the midline and are commonly large and irregular. Atypical appearance of fissure should initiate further investigations including biopsy, cultures, and colonoscopy to rule out Crohn disease, immunodeficiency states, tuberculosis, venereal infection, and malignancies.

## TREATMENT

Most idiopathic anal fissures in children heal without any specific treatment in a few months.[89,90] Only symptomatic fissures require treatment. If fissure is associated with constipation and/or painful defecation, stool softening with dietary modification and bulk laxatives is indicated. Lubricants ease painful passage of stools. The goal is to interrupt the vicious circle of painful defecation, fecal retention, hard stools, and prevention of healing of fissure. As expected, most fissures respond promptly to stools softening and heal in several weeks.[89] Hematochezia stops when fissure heals. Occasionally a child presents with typical history after the symptoms have disappeared and the fissure has healed. Initially, these patients may be treated expectantly unless no abnormal clinical signs are present and hematochezia has not recurred.

Botulinum toxin injection into sphincter muscles in order to overcome increased pressure is a novel treatment for chronic fissures. Quick and effective healing has also been reported in children.[91] We use botulinum toxin injections into the internal part of the sphincter complex with a dose of 15-25 U, depending on the patient's age, into each of the four quadrants. Usually healing occurs in several weeks and injections may be repeated in refractory cases. After encouraging initial results in adults, several recent randomized placebo-controlled trials have assessed efficiency of topical glyceryl trinitrate in anal fissure in children.[89,90,92,93] Two studies reported faster healing of fissures and relief of symptoms in children treated with glyceryl trinitrate,[90,93] whereas no benefit was found in one.[89] Few children experienced temporary incontinence, and none reported headache during glyceryl trinitrate treatment.[89,90,93] Taken together, topical glyceryl trinitrate for anal fissures is only marginally better than placebo.[92]

Surgical therapies reported for treatment of anal fissure in children include fissurectomy, anal dilatation under general anesthesia, and lateral internal sphincterotomy.[94,95] Lateral subcutaneous sphincterotomy also appears to be an effective procedure in children.[94] Fissure cure rates (80%) after fissurectomy combined with laxatives are comparable with simple laxative therapy.[89,95] Anal dilatation causes unpredictable degree of sphincter damage and should be avoided. In adult patients, lateral sphincterotomy is associated with an

incontinence rate of 10%.[96] Anal stretch has a significantly higher risk of minor incontinence than sphincterotomy.[96] Outcomes of different surgical procedures for fissures are poorly characterized in children. Thus lateral internal sphincterotomy should be reserved for those rare children whose anal fissure has progressed to a real chronic fissure after treatment with botulinum toxin has failed. In these cases a biopsy should be obtained to rule out possible Crohn disease.

## Perianal Streptococcal Dermatitis

Perianal streptococcal dermatitis is a common cause of anal complaints (e.g., pain, itching, anal discharge, constipation) in preschool-aged children. The clinical finding of sharply demarcated wet perianal erythema is usually characteristic (Fig. 104-3). A positive culture of group A or B β-hemolytic streptococci from a perianal swab confirms the diagnosis. The treatment includes oral antibiotics for 10 to 14 days with penicillin V or cephalosporin and topical antimicrobial therapy.[97]

## Perianal Abscess and Fistula in Ano

Perianal abscess is not uncommon in small infants. The vast majority of patients are male.[98] A congenital etiology has been suggested for infant anal fistulas.[99,100] A proposed relationship to androgens resulting in congenital deep, epithelialized crypts may explain the predominant occurrence in male infants.[100,101] A typical presentation is a perianal abscess in a child younger than 12 months (Fig. 104-4), in the majority before the age of 6 months. After initial incision the condition may progress to or recur as an anal fistula. The incidence of fistula formation in patients with perianal abscess may be as low as 10% to 20%.[102,103] The fistula may present alone without preceding perianal abscess. The fistula is typically subcutaneous and straight. It usually traverses from the affected crypt through the subcutaneous external sphincter to the perianal skin. The fistulas are usually distributed evenly around the anal circumference. Multiple lesions occur in 15% to 20% of cases (Fig. 104-5).[103,104]

The traditional management of perianal abscess is incision and drainage. This is associated with a significant recurrence rate.[104,105] However, at the end of the day most abscesses are cured by expectant treatment only.[104,105] Fistula-in-ano has been considered as an indication for surgical treatment. The traditional method has been identification of the affected anal crypt and fistulotomy by deroofing of the fistula tract. Recurrent fistulas occur in 10% to 20% of cases. Recent reports have advocated expectant treatment for asymptomatic

FIGURE 104-3 Perianal streptoccoccal dermatitis.

FIGURE 104-4 Typical perianal abscess in a male infant.

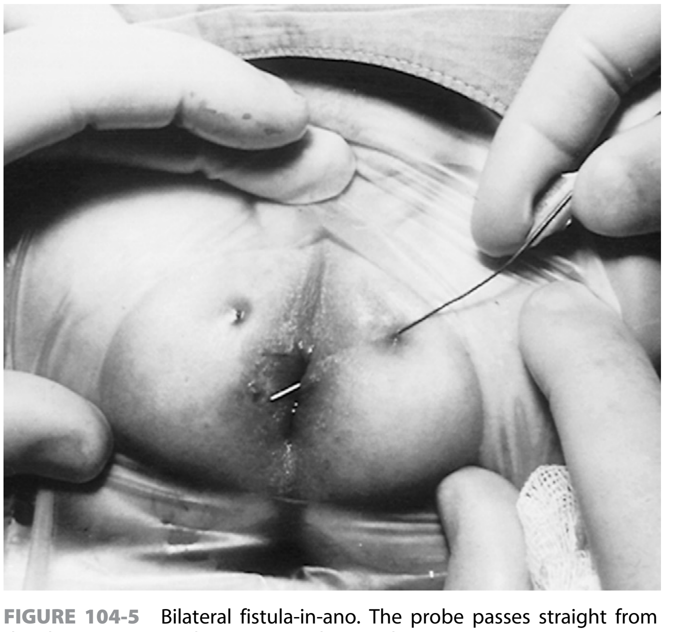

FIGURE 104-5 Bilateral fistula-in-ano. The probe passes straight from the skin opening to the corresponding anal crypt.

fistula-in-ano; most fistulas heal within 12 to 24 months without further sequelae.[104,105]

Fistulas in older children or adolescents are cryptoglandular or associated with inflammatory bowel disease, mainly Crohn disease. Crohn disease should be ruled out in all children who present outside the typical age groups, infants and adolescents. Treatment of adolescent fistula-in-ano should be along the same lines as in adults. The fistulous tract, once identified, is either incised and left open to granulate or excised with primary closure of the defect.

## Vascular Malformations

The classifications of intestinal vascular malformations have been confusing because different labels are laid on similar lesions without knowledge of their clinical and biologic properties. The classification of vascular malformations by Mulliken and Glowacki[106] is based on biologic properties of the lesion. The classification distinguishes between hemangiomas that are true neoplasms and usually regress spontaneously, and vascular malformations, which are nonproliferative lesions that do not regress. Intestinal bleeding from vascular malformations in children is rare. The most common sites are distal colon and rectum.[107] The vascular anomalies in the distal bowel are usually venous malformations and not hemangiomas as previously thought.[108] In the minority of cases the vascular lesion is part of a systemic disease such as Klippel-Trenaunay (congenital varicose veins, cutaneous hemangiomas, and ectatic hypertrophy of the lower limbs) and Osler-Rendu-Weber (multiple telangiectasia) syndromes.

A typical symptom of rectal vascular malformations is recurrent hematochezia that may sometimes be profuse. The patient may also present with hemorrhoids. The diagnosis of vascular anomalies may be difficult. In the distal bowel endoscopy may show findings that suggest localized inflammation. Dilated vessels are rarely visible. MRI and angiography are the best methods to diagnose and localize intestinal vascular lesions. Nonoperative methods may be used to control bleeding, but permanent cure is best achieved by complete resection of the lesion. Lesions that extend to the low rectum and anal canal are best treated by endorectal pull-through and colo-anal anastomosis.[109,110] This sphincter-saving operation eradicates bleeding episodes for long periods of time, if not permanently.

## Hemorrhoids

Hemorrhoids are uncommon in children unless in those with portal hypertension. One third of the children with portal hypertension have hemorrhoids. Hemorrhoids are more common in patients with extrahepatic portal hypertension than in those with intrahepatic disease.[111] Symptomatic hemorrhoids, however, are uncommon. Hemorrhoids in children may be associated with rectal vascular malformations.

Clinically detectable internal hemorrhoids with external extension occur also in otherwise healthy children but are rare (Fig. 104-6). We have seen approximately one to two healthy children with internal and external hemorrhoids per year during the past 15 years. Usually there are no symptoms, but the child or parents have noticed something to protrude


FIGURE 104-6 Hemorrhoids in a 5-year-old boy, without any underlying conditions. Note the typical adult type piles at 4, 7, and 11 o'clock.

from the anal opening. A more common finding, especially in constipated children, is a prominent venous plexus around the anal opening. This is a common source of rectal bleeding in constipated children. The venous sinuses of this venous plexus may rarely thrombose, causing similar symptoms as in adults with acute thrombosis of external hemorrhoids. Adult-type hemorrhoids begin to occur in adolescents and may be complicated by thrombosis of the external part of piles.

In otherwise healthy children hemorrhoids do not require surgical therapy. Major bleeding does not occur. Symptomatic patients with portal hypertension may require treatment. Banding or sclerotherapy controls the symptoms in most cases.[112]

## Solitary Rectal Ulcer

Solitary rectal ulcer syndrome (SRUS) is a chronic, benign disorder characterized by hematochezia, mucous discharge, tenesmus, and local perianal pain. It is rare in children but should be kept in mind in patients with local anal symptoms.[113,114]

In children the macroscopic finding at endoscopy is a thickened and edematous lesion that may have an ulcerative or polypoid appearance in the anterior rectal wall 2 to 5 cm above the anal verge. We have encountered 12 cases in the past 15 years. Some patients have a feeling of incomplete evacuation with frequent visits to the toilet associated with chronic straining at stool. Rectal or internal rectosigmoid prolapse has been reported to occur in a significant percentage of cases.[40] According to our experience, conservative management with stool softeners and local steroid suppositories is successful in most children. Open or laparoscopic rectopexy[113,115] has been suggested to correct the external or internal rectal prolapse that is often associated with SRUS; three of our patients have required rectopexy for recalcitrant symptoms.

## Infantile Proctocolitis

Apart from anal fissure, the most common cause of hematochezia in infants younger than 3 months of age is eosinophilic proctocolitis. The infantile proctocolitis typically presents at the age of 3 to 4 weeks with fresh blood streaks mixed in stools. The stools often contain mucus. Usually there are no other symptoms, and the growth and development of the infant is normal.[116] Colonoscopy shows colitis that is often patchy and rarely extends beyond the left colon. Histology reveals marked eosinophilic infiltrate. Some patients may also have an elevated eosinophilic count in peripheral blood. Allergic etiology has been suggested because of these findings but is found in a minority of cases.[117] The condition is self-limiting, and symptoms usually subside within a few weeks. Diet change has been also reported to be helpful in reversing the symptoms.[118]

## Proctalgia Fugax

Proctalgia fugax (PF) is a benign painful rectal condition that is defined as intermittent, recurring, and self-limiting pain in the anorectal region in the absence of organic pathology. There was also thought to be a male preponderance; however, more recently a female preponderance is reported.[119] The onset of symptoms is usually at school age or adolescence. The etiology of proctalgia fugax is unknown. Spasm of the anal sphincter complex is the most commonly suggested etiologic mechanism.

Rome III criteria define proctalgia fugax as recurrent episodes of pain that localize to the anus and lower rectum. The episode lasts from seconds to minutes, and there is no pain between episodes.[120] The condition is uncommon in children; the authors see approximately one to two new patients per year with proctalgia fugax. It is essential to rule out organic causes for anorectal pain before diagnosis of proctalgia fugax is made. Proctalgia fugax in children is a self-limiting condition that, however, may need treatment if episodes of pain are frequent and long lasting.

There no evidence-based management protocol for proctalgia fugax, but in most cases topical treatment with glyceryl nitrate cream or oral spasmolytics is helpful. Other options are oral clonidine or inhaled salbutamol. In recalcitrant cases local botulinum toxin injections may be helpful.[121]

## Sexual Abuse

Child sexual abuse is a common and worldwide problem. In Europe the incidence appears to be 6% to 36% of girls and 1% to 15% of boys younger than 16 years.[122] Sexual abuse rarely causes death, but its consequences can be serious and persist through adulthood. In child sexual abuse the significance of findings in the vagina and hymen are well recognized. In the context of anal abuse the findings are more controversial and difficult to verify.

Hobbs and Wynne[123] stated that "dilatation and reflex anal dilatation" are not seen in normal children and are signs of abuse. Reflex anal dilatation (even gross) was found on routine examination in 28 of 200 children (14%) examined consecutively in community health clinics, a pediatric outpatient clinic, a district hospital, and a rectal clinic.[124] Constipation or feces in the rectum, without associated sexual abuse, may often produce gaping of the anus on separation of the buttocks.[125] Hobbs and Wynne[126] also suggested that an anal fissure was a sign of abuse in 53% of 143 cases quoted. Pierce[127] found that the majority of children with strong or definite history of anal abuse had anal fissures or scars. However, an anal fissure is far too common a finding in routine clinical practice to be regarded as a cause for suspicion of sexual abuse.[128]

Obvious laceration, bruising around the anus or inner thighs, and scratches, especially with a suspicious or definitive history of abuse, are more conclusive. This sort of forensic evidence is rarely found in children because there is usually a significant time lapse between the abuse and medical examination.

If a child displays total passiveness and indifference to physical examination, or to inspection and examination of the anus, with no attempt to withdraw or tighten the striated muscle complex when a rectal examination is attempted, the clinician should be alert to the possibility of sexual abuse.

Perianal warts caused by the human papillomavirus should always raise the possibility of sexual interference because this is the most likely mode of transmission.[129,130] Although many studies suggest a high association with sexual abuse (60% to 90% of cases), recent studies have questioned this association, particularly in infants. Parents of children with condylomata often have warts on nongenital skin, and vertical transmission between mother and child has been well documented. The presence of condyloma acuminata in infants younger than 1 year of age may represent vertical transmission from the mother; older children must be treated with a high index of suspicion for child abuse.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 105

# The Jaundiced Infant: Biliary Atresia

Robert A. Cowles

## History

Biliary atresia was first described by John Thompson in 1892.[1] He detailed 49 clinical cases of congenital biliary obstruction and documented the autopsy findings in each case. In 1916 Holmes, a pediatrician and pathologist at Johns Hopkins University, reported his own case, reviewed previously reported cases, and concluded that successful surgical treatment for congenital atresia of the bile ducts was theoretically possible in at least 16% of cases.[2] Ladd was the first to report successful surgical correction of biliary atresia in cases where either the gallbladder or the common bile duct communicated with the liver.[3] This success led him to recommend a more aggressive surgical approach to cases of presumed biliary atresia. Despite this, a majority of infants do not have the favorable anatomy that was described by Holmes and Ladd and subsequent large series showed low success rates for surgery in cases of biliary atresia. From the late 1940s to the early 1960s several creative surgical approaches attempting to obtain bile drainage from the liver were used, but these were ultimately unsuccessful and subsequently abandoned.[4,5]

Diagnostic uncertainty made early surgery for biliary atresia an area of controversy during the 1960s. Thaler and Gallis felt that surgical manipulation was deleterious in cases of neonatal hepatitis and recommended a waiting period of 4 months before exploration for possible biliary atresia.[6,7] Other authors also reported that there was a possibility of spontaneous resolution of biliary atresia, further diminishing the potential merits of early operation. Finally, some believed that improved outcomes may be obtained after waiting for the course of the disease to progress with the hope that any ductal structures would enlarge, making repair more successful.[8–11] Outcomes for infants with "noncorrectable" biliary atresia remained dismal.

In the late 1950s Kasai and his colleagues in Japan noted that bile flow from the porta hepatis was possible after excision of the entire fibrotic extrahepatic biliary tree.[12–14] By surgically connecting the porta hepatis to the intestine (the duodenum in early cases), Kasai achieved the first long-term "cure" of a patient deemed to have the noncorrectable form of biliary atresia. Despite these encouraging initial results, Kasai's hepatic portoenterostomy did not gain immediate acceptance. Surgeons both in Japan and in the United States were initially skeptical of his results.[15,16] Over time, however, the outcomes associated with Kasai's hepatic portoenterostomy were confirmed[17,18] and in its most recent form, using a Roux-en-Y portoenterostomy, this procedure has become the standard operative treatment for biliary atresia.

Because many children develop progressive liver failure despite a technically well-executed hepatic portoenterostomy, salvage therapies are often necessary. Liver transplantation, popularized by Starzl in the early 1960s,[19] is the only readily available salvage treatment for children with biliary atresia and progressive liver dysfunction. In fact, biliary atresia is the most common diagnosis leading to liver transplantation in children.

## Incidence, Demographics, and Classification

Jaundice is a common finding in the newborn nursery and in young infants. In a majority of cases this hyperbilirubinemia is due to elevated unconjugated bilirubin and resolves spontaneously with no need for surgical consultation or intervention. It is important, however, to identify the rare infant who has persistent, pathologic jaundice beyond 2 weeks of life. These neonates should be presumed to have biliary obstruction due to biliary atresia or choledochal cyst or a cholestatic process due to a myriad of underlying causes, and a careful evaluation should be promptly undertaken.

Biliary atresia occurs in between 1 in 10,000 and 1 in 16,700 live births and this incidence has been consistent over time.[20–22] A slight predominance of females exists with a female-to-male ratio ranging between 1.4 to 1.7 to 1. No clear genetic factors have been associated with biliary atresia; however, the incidence of the disease appears to be higher in Asia than in Europe or North America.

Several systems have been proposed to classify the anatomy in cases of biliary atresia. The Japanese Association of Pediatric Surgeons proposed that cases should be classified according to the location of atresia. In their system, type I anatomy is

associated with atresia at the level of the common bile duct; in type II, atresia is at the level of the hepatic duct; and in type III, the most frequent type, atresia occurs at the porta hepatis.[22] The common anatomic variations are shown in Figure 105-1.

## Etiology

The exact etiology of biliary atresia is unknown and likely multifactorial. Theories implicating genetic, inflammatory, and infectious causes have been presented, but none has been proven. The higher incidence of biliary atresia in certain populations makes a genetic cause plausible. Moreover, the observation that up to 20% of biliary atresia cases are associated with other congenital malformations[22] (Table 105-1) implies a global developmental abnormality that may be under genetic control. Despite this, the occurrence of biliary atresia in twins is exceedingly rare, familial patterns have not been seen, and a clear genetic cause has not been found.

Theories suggesting an acquired, infectious etiology are supported by several findings. First, several viruses such as reovirus and rotavirus have been proposed as possible infectious agents responsible for the development of biliary atresia.[23,24] Animal models of perinatal viral infection produce biliary atresia,[25] although consistent viral isolation has not been possible in human cases.[26] In addition, given the high prevalence of these viruses, it would be expected that the incidence of biliary atresia would be higher if, in fact, viral infection was causative. Second, it appears that many cases of biliary atresia are acquired rather than congenital.[27] Up to 60% of infants who are found to have biliary atresia have been documented as having pigmented stools sometime during the postnatal period.[28] Third is the epidemiologic finding of seasonal clustering of biliary atresia cases during the winter months in some studies.[29]

Other proposed factors associated with biliary atresia include bile duct ischemia, abnormal bile acid metabolism, pancreaticobiliary maljunction, and the effect of certain environmental toxins.[30,31]

**TABLE 105-1**

| Congenital Anomalies Associated with Biliary Atresia |
|---|
| Malrotation |
| Preduodenal portal vein |
| Polysplenia |
| Interrupted inferior vena cava |
| Azygous continuation |
| Cardiac malformations |

## Embryology

The biliary system originates from the hepatic diverticulum of the foregut at 4 weeks' gestation. This structure differentiates into cranial and caudal components, which give rise to the intrahepatic and extrahepatic bile ducts, respectively. It is during this period that the bile ducts undergo recanalization, eventually leading to an intact biliary tree. Errors in the recanalization process constituted early theories regarding the etiology of biliary atresia, but this is no longer believed to be correct.

## Pathology

The pathologist plays a central role in the diagnosis of biliary atresia and provides an important assessment of the structures present at the fibrous biliary remnant. Inflammation is invariably seen in liver biopsies and in resected specimens.[32–35] In the appropriate clinical scenario, a percutaneous liver biopsy can reliably aid in the diagnosis of biliary atresia. The finding of bile ductular proliferation in the liver biopsy is considered diagnostic for biliary atresia.[36,37] Associated findings often include bile stasis, periportal inflammation, identification of giant cells, and varying degrees of fibrosis.

Histologic evaluation of the fibrous remnant can reveal patency or partial patency of ductal structures or complete absence of these structures. This may depend on whether excision of the remnant occurred before or after inflammatory obliteration of the extrahepatic ducts. Identifiable

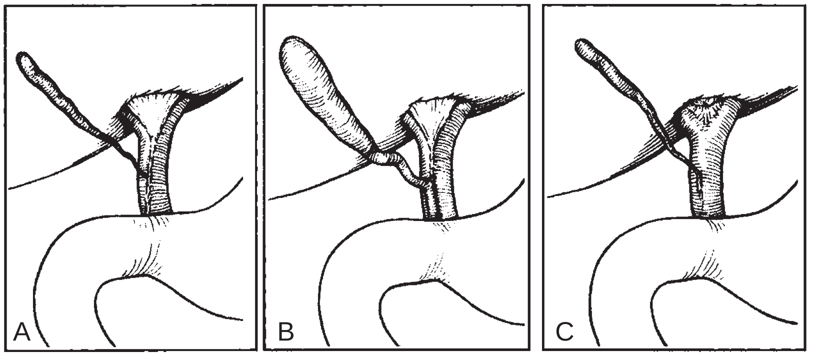


**FIGURE 105-1** Variants of ductal anatomy in biliary atresia. **A,** The most common pattern. Ducts are in continuity and obliterated from the porta hepatis to the common bile duct. **B,** The gallbladder, cystic duct, and distal common bile duct remain patent, but the hepatic ducts and porta are fibrotic. A cholangiogram in this case would show duodenal opacification, but no contrast would enter the intrahepatic ducts. **C,** Fibrous gallbladder with poor-quality tissue at the porta hepatis. (From Altman RP, Lilly JR, Greenfeld JR, et al: A multivariable risk factor analysis of the portoenterostomy [Kasai] procedure for biliary atresia: Twenty-five years of experience from two centers. Ann Surg 1997;226:348, discussion 353. Courtesy Lippincott & Wilkins.)

structures that can be found in the biliary remnant include bile ducts, collecting ductules, and biliary glands.[38] Of these, the ductules are ultimately responsible for bile drainage after the portoenterostomy procedure and, over time, these can form stable bile conduits (Fig. 105-2).

# Clinical Evaluation

## SIGNS AND SYMPTOMS

The combination of progressive jaundice, acholic stools, dark urine, and firm hepatomegaly in an infant should raise the suspicion for the presence of biliary atresia. Jaundice involves direct hyperbilirubinemia rather than the indirect hyperbilirubinemia seen in neonatal jaundice. In most cases, the perinatal course is unremarkable and meconium is described as normal. In more than 50% of cases, initial stools are considered pigmented.[28] Over time, stools take on a lighter color and become acholic due to biliary obstruction (Fig. 105-3). Eventually, signs of advanced liver disease such as palpable hepatomegaly and splenomegaly, ascites, failure to thrive, and malnutrition become present. If not treated, biliary atresia is fatal within the first 2 years of life with one study reporting a survival rate of less than 10% at 3 years.[20]

## DIAGNOSIS

Children with persistent jaundice, especially those with an elevated conjugated bilirubin, should be evaluated promptly to exclude the diagnosis of biliary atresia. No single test can reliably be used to differentiate biliary atresia from other causes of jaundice in the infant. For this reason, a combination of data obtained from a complete clinical assessment, blood tests, imaging studies, and pathologic evaluation is often used to arrive at a provisional diagnosis in almost all cases. The final diagnosis, however, is always confirmed at surgical exploration. The following evaluation is recommended as a useful guide.

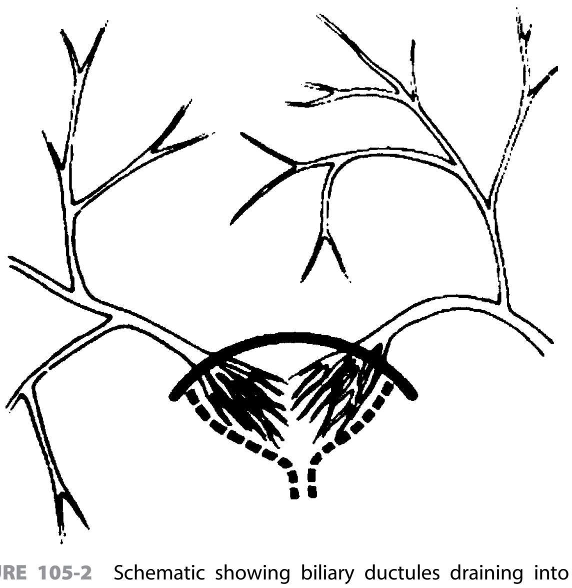

FIGURE 105-2 Schematic showing biliary ductules draining into the Roux limb as postulated to occur after successful hepatic portoenterostomy. (Courtesy M. Kasai, MD)

FIGURE 105-3 Gross appearance of acholic stool from an infant later confirmed to have biliary atresia.

## BLOOD TESTS

Standard serum “liver function tests” are uniformly obtained, but specificity is lacking. In biliary atresia both the direct and indirect bilirubin levels are elevated. The transaminases are also mildly to moderately increased. Alkaline phosphatase levels are often elevated in infants and children due to contribution from bone remodeling. For this reason, the gamma-glutamyl transpeptidase (GGTP) level can be used as a more specific indicator of hepatobiliary disease. Unless decompensated liver disease is present, tests of hepatic synthetic function such as the clotting cascade and serum albumin are normal.

In order to rule out conditions that can mimic biliary atresia, screening for perinatal infections due to members of the TORCH family (Toxoplasmosis, Other viruses, Rubella, Cytomegalovirus, and Herpes Simplex Virus) should be performed. In addition, screening for the presence of alpha-1 antitrypsin deficiency should occur.

## ULTRASOUND

Abdominal ultrasound is an easily obtained, simple, and noninvasive imaging study that can aid in the evaluation of infants suspected of having biliary atresia.[39,40] It should be obtained in the fasting state to allow for filling of the gallbladder, if patent, and the use of Doppler techniques can improve the accuracy of the study.[40] The echotexture of the liver, the presence of ascites, the patency of the hepatic vasculature, and the anatomy of the biliary structures can be assessed. Although the abdominal ultrasound does not secure a diagnosis in most cases, on occasion it can streamline the subsequent evaluation and management in specific situations. For example, the presence of a hilar cystic structure in the clinical setting of obstructive jaundice is sufficient information to proceed with surgical exploration with a presumptive diagnosis of cystic biliary atresia or choledochal cyst with obstruction.

In either scenario, relief of biliary obstruction should be provided as soon as feasible. Alternatively, an ultrasound appearance of dilated proximal bile ducts suggests the presence of inspissated bile syndrome, which may be treated by observation or, if needed, operative cholangiogram with or without biliary irrigation.

In almost all infants with biliary atresia, however, the ultrasound reveals that the gallbladder is either shrunken or normal appearing and the bile ducts are not easily delineated. In selected centers with extensive experience in the use of ultrasound in biliary atresia, an abnormal "cord" can be appreciated in the area of the portal plate.[41]

### HEPATOBILIARY SCINTIGRAPHY

Hepatobiliary scintigraphy relies on the use of isotopes of technetium 99m to assess excretion of bile from the liver into the small intestine and therefore biliary patency. The term "HIDA" (hydroxy iminodiacetic acid) scan is often used, but the technetium-labeled compound diisopropyl iminodiacetic acid (DISIDA) is more effective in the presence of significant cholestasis and therefore more commonly used. The usefulness of all hepatobiliary scintigraphy is diminished in the presence of severe jaundice, and this may cause errors in interpretation.

If time allows, all jaundiced infants undergoing hepatobiliary scintigraphy should be pretreated with phenobarbital (5 mg/kg/day) for 5 days before the study.[42] Presence of isotope in the intestine immediately confirms patency of the biliary system, and the diagnosis of biliary atresia can be excluded. Excretion of isotope may be delayed, however, in the presence of liver dysfunction. For this reason, a delayed assessment of isotope excretion at 24 hours is warranted. When no isotope is seen in the intestine after 24 hours, biliary obstruction is presumed and the diagnosis of biliary atresia must be further pursued.

## Liver Biopsy

A percutaneous liver biopsy can help differentiate biliary atresia from other cholestatic conditions with a high degree of reliability and should be considered the most accurate nonsurgical diagnostic test.[43,44] It is the most invasive of the diagnostic modalities but can be performed safely by an experienced pediatric hepatologist, or, if needed, by the surgeon. Typically, examination of several portal tracts by a well-trained pathologist will reveal important findings that can confirm or exclude biliary atresia. The presence of varying degrees of inflammation with ductular proliferation is considered compatible with the diagnosis of biliary atresia because these findings are not seen in other nonobstructive cholestatic syndromes. Further findings of bile stasis with plugging and giant cell transformation further support the diagnosis of biliary atresia. On the basis of the appearance of the liver biopsy, bile duct paucity syndromes can be readily differentiated from biliary atresia. In contrast, however, it can be difficult to differentiate between parenteral nutrition-associated cholestasis and biliary atresia on the basis of liver biopsy alone. This distinction should be made on the basis of the overall clinical assessment or, on rare occasions, at exploration when the diagnosis cannot be confirmed preoperatively.

## Other Tests

A combination of the previously described tests constitutes an adequate evaluation for biliary atresia, and operative therapy can be planned on the basis of these data. In some centers, however, other diagnostic modalities have been proposed. These adjunctive tests may be performed in certain circumstances but should not be considered part of the routine evaluation for biliary atresia.

Intubation of the duodenum via the nasoduodenal route with aspiration or prolonged collection of duodenal fluid can exclude biliary atresia if bile-stained fluid is obtained.[45] Although simple, this test is invasive, subjective, and similar in concept to the DISIDA scan, which is easily obtained in most centers.

Endoscopic retrograde cholangiopancreatography (ERCP) is a technique that is widely applied in the evaluation of biliary diseases in adults and older children. With improvements in endoscopic instrumentation, small side-viewing endoscopes that can be used in infants are available. Some authors have proposed ERCP as a useful adjunct in avoiding unnecessary exploration for presumed biliary atresia.[46] Because other less-invasive tests yield an accurate diagnosis in almost all cases, however, the practical use of ERCP is actually quite limited and is not currently recommended. Magnetic resonance imaging (MRI) techniques such as magnetic resonance cholangiopancreatography (MRCP) have superior accuracy in the diagnosis of biliary atresia.[47] MRI and MRCP, however, are expensive, sometimes require sedation, and have not been routinely used in most centers.

## Treatment

### PREOPERATIVE CARE

Infants with presumed biliary atresia should be prepared for exploration soon after diagnostic testing has been completed. Standard presurgical measures should be taken and, in general, children can be admitted on the day of surgery. A bowel preparation is not required, but a dose of broad-spectrum antibiotics should be administered before making the abdominal incision. Although most infants diagnosed with biliary atresia will have normal coagulation studies, poor absorption of the fat-soluble vitamin K can theoretically render them functionally vitamin K deficient. If possible, preoperative oral supplementation with fat-soluble vitamins (A, D, E, and K) or an intramuscular injection of vitamin K (1 mg) should be considered.

### SURGICAL TECHNIQUE

The Roux-en-Y hepatic portoenterostomy procedure (Kasai Procedure) is the standard initial operation for treatment of infants with biliary atresia. The operation involves excision of the entire extrahepatic biliary tree with transection of the fibrous portal plate near the hilum of the liver. Bilioenteric continuity is then reestablished with a Roux-en-Y limb.[13] The ultimate goal of the procedure is to allow drainage of bile

from the liver into the Roux limb via microscopic ductules in the portal plate. The conduct of the operation is described as follows.

The infant should be placed supine and on an operating table that will permit operative cholangiography, if deemed necessary. The exploration begins via a right upper abdominal incision. The left upper quadrant is examined, first searching for the spleen. Absence of the spleen or the finding of polysplenia can alert the surgeon to the presence of important associated anomalies such as malrotation, preduodenal portal vein, and interrupted inferior vena cava with azygous continuation. During evaluation of the left upper quadrant, adequate position of the tip of the nasogastric tube is also confirmed and the tube is secured by the anesthesiologist.

Next, the liver, biliary structures, and porta are inspected. The liver in biliary atresia can appear nodular and fibrotic with a greenish color. This finding is not common in neonatal hepatitis or bile duct paucity syndromes, where the liver is smooth and dark brown in color. Many infants with biliary atresia have a contracted, fibrotic gallbladder. If a rudimentary fibrous gallbladder is noted at initial exploration and if it clearly has no lumen, then the diagnosis of biliary atresia has been confirmed and the operation can proceed with dissection of the portal plate. If the gallbladder is normal-appearing or if it is felt to have a lumen, then additional intraoperative diagnostic maneuvers are warranted before dissecting the portal plate. In this situation, a purse-string suture can be placed in the fundus of the gallbladder and the fluid within the lumen of the gallbladder aspirated with an angiocath. If clear fluid (white bile) returns, then our approach has been to proceed with portal plate dissection without a cholangiogram. If, however, the aspirated fluid is darker in color or if there is any ongoing question regarding the diagnosis, then a cholangiogram should follow.

Although simple in concept, the cholangiogram can be difficult to perform and interpret successfully during this exploration. The following steps can be used to maximize the diagnostic yield of the intraoperative cholangiogram. First, a secure purse-string suture should be placed. A second purse-string suture can also be placed to prevent contrast leakage. Either an angiocath or a laparoscopic cholangiogram catheter can be placed into the lumen of the gallbladder before tying the purse-string suture(s). Diatrizoic acid (Hypaque or Gastrografin) is diluted 1:1 with normal saline and injected as the contrast agent via the cholangiogram catheter to assess for patency or obstruction of the biliary tree. Real-time, live fluoroscopy facilitates rapid intraoperative interpretation of the study. If contrast flows freely into the duodenum and into intrahepatic bile ducts, then patency of the biliary tree has been established and the diagnosis of biliary atresia excluded (Fig. 105-4). In this scenario, a wedge liver biopsy should be performed, the cholangiogram catheter removed, the cholecystotomy closed, and the operation concluded.

On occasion, contrast will flow freely into the gallbladder and down the distal common bile duct into the duodenum but not proximally into the intrahepatic bile ducts. This finding should be confirmed by occluding the distal common bile duct with an atraumatic "bulldog" clamp and reinjecting the cholangiogram catheter. This maneuver may encourage preferential filling of any patent proximal ducts that may have initially failed to opacify with contrast material when the distal resistance to flow was low. It is important to inject contrast gently because a speedy injection under pressure is likely to cause leakage of contrast around the purse-string suture, resulting in an obscured and confusing cholangiogram. Failure to delineate patent intrahepatic and extrahepatic biliary structures mandates that the surgeon proceed with portal dissection.

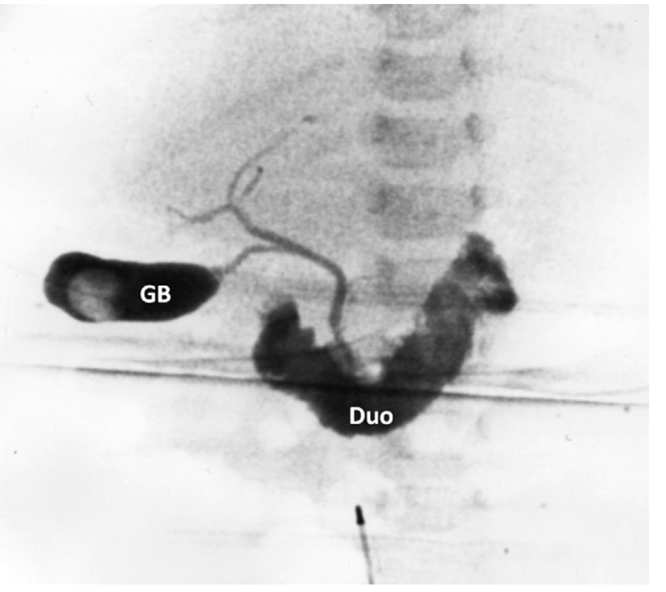


**FIGURE 105-4** Cholangiogram obtained during abdominal exploration for presumed biliary atresia. The gallbladder (*GB*) appeared normal, and an intraoperative cholangiogram revealed patency of the intrahepatic ducts to the duodenum (*Duo*). A liver biopsy was performed, and the procedure was concluded.

Regardless of the presence of a patent gallbladder or distal common bile duct, a direct Roux-en-Y hepatic portoenterostomy affords outcomes that are superior to other forms of reconstruction such as the portocholecystostomy.[48] Some surgeons gain exposure by dividing both triangular ligaments, thereby exteriorizing almost the entire liver.[49,50] This step is not necessary and likely disrupts lymphatics that may be responsible for the development of ascites. We have found that upward retraction of the liver to expose the porta affords excellent visualization of the critical structures and can be accomplished by assigning an assistant for retraction in the right upper surgical field or by carefully placing a fixed metal retractor with upward traction.

The peritoneum overlying the hepatoduodenal ligament is opened to allow identification of the structures in this area. The fibrous remnant of the distal common bile duct is often present here. It can be identified in the anterolateral aspect of the hepatoduodenal ligament, isolated and divided. Care should be taken to avoid injury to aberrant hepatic arteries that may be nearby. With traction on the cut end of the obliterated distal common bile duct, the fibrous biliary remnant can be dissected toward the porta. It is often necessary to dissect the right and left hepatic arteries away from the field in order to preserve them. During this dissection, the gallbladder remnant is also dissected away from the liver in continuity with the rest of the extrahepatic biliary remnant. As dissection continues proximally, the biliary remnant develops into a cone of fibrotic tissue that is located at the bifurcation of the main portal vein into its left and right branches. This constitutes the most important landmark during the dissection of the portal plate and should be the goal of every dissection.[51,52] In this

location it may be necessary to control several small portal vein branches to avoid inadvertent injury with subsequent bleeding. The absence of identifiable biliary remnant tissue or the finding of poor quality tissue at the expected location of the portal plate sometimes confuses the dissection. As stated earlier, the bifurcation of the portal vein should be used as a landmark and is especially important in such cases where the biliary remnants and portal plate are difficult to identify clearly.

Once the fibrous cone and portal plate region have been identified, the fibrous cone is placed on gentle traction and transected with sharp scissors or a knife. It is not beneficial to cut deeply toward the liver parenchyma because this may result in more scar formation and inhibition of bile drainage. Bleeding at the transected portal plate is controlled with pressure and placement of a surgical sponge in the area. Use of cautery on the portal plate is discouraged and should be minimized because this structure contains the fine ductules needed for success of the procedure. The resulting surgical specimen should be marked and submitted for routine pathologic evaluation. Careful measurement of the diameter of any biliary ductules by an experienced pathologist should be requested because this may provide important prognostic information. Although advocated by some,[53] we have not found frozen section to be helpful in guiding the level of transection.

With a completed portal plate dissection, the operation shifts to the construction of the Roux limb. The proximal jejunum is identified and transected about 10 centimeters distal to the ligament of Treitz. The distal end, destined for the right upper quadrant, is oversewn and the Roux limb is measured to 40 to 50 centimeters.[54] At this location, an end-to-side jejunojejunostomy is created with interrupted absorbable sutures. The oversewn end of the Roux limb is carefully brought into the right upper quadrant via a small defect created in the avascular portion of the transverse mesocolon.

The side of the Roux limb is opened, and the portoenterostomy is created. The posterior suture line is placed first using 6-0 absorbable suture with knots tied inside the lumen. Placement of these sutures must be exact with care taken to avoid injuring or impinging on the portal tissue. Once this posterior row is complete, the anterior sutures can be placed using similar care and precision. When complete, the entire surface of the portal plate must be contained within the jejunal lumen of the Roux limb. In this way, any bile drainage via biliary ductules at the portal plate will be contained within the Roux limb and proceed distally.

Before closure, it is advisable to close the mesenteric defect created by construction of the Roux limb and to anchor the Roux limb to the edges of the defect in the transverse mesocolon. These maneuvers are aimed at preventing internal herniation and at keeping the Roux limb in the right upper quadrant and without tension. A small closed suction drain is placed near the portoenteric anastomosis, and a wedge liver biopsy is routinely performed but likely not absolutely necessary. The abdomen is then closed using standard techniques. The completed operation is shown in (Fig. 105-5).

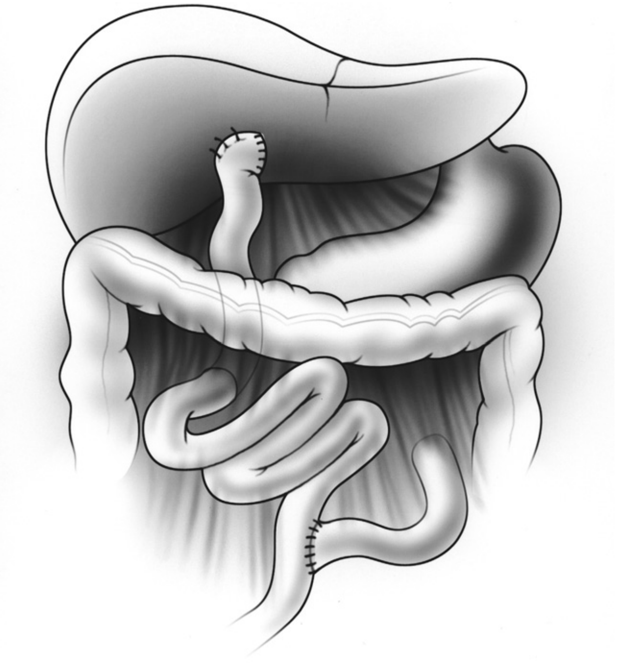

**FIGURE 105-5** Artist's rendition of the completed hepatic portoenterostomy procedure.

## SURGICAL CONTROVERSIES

Much of the controversy surrounding surgery for biliary atresia has subsided. Previously reported techniques with stomas to exteriorize the Roux Limb[28] or antireflux valves[28,55–57] have been subsequently abandoned either due to associated complications or lack of effectiveness.[58–60] Similarly, use of the appendix as a conduit between the liver and the small intestine has been proposed but its use has been limited with some reports suggesting an inferior surgical outcome.[61]

With the widespread application of minimally invasive techniques, even to the most complex operations, the laparoscopic Kasai procedure has been described and used at several centers worldwide.[62,63] Most reports, however, involve single cases or small series of carefully selected patients. A recent prospective trial confirmed the feasibility of the operation but revealed a significantly poorer outcome at 6 and 24 months, causing the trial to be stopped.[64] Outcomes of other series have been variable,[65] and therefore the laparoscopic Kasai procedure currently lacks support among general pediatric surgeons including those who specialize in minimally invasive pediatric surgery. Laparoscopic techniques may be used to perform the exploration and cholangiogram.

Some investigators have proposed that primary liver transplantation be considered the initial treatment for infants with biliary atresia, citing deleterious effects of the Kasai procedure on subsequent liver transplantation, if needed. This approach, however, would subject a percentage of children to the dangers of transplantation and its associated short- and long-term complications who would have been cured by the Kasai procedure. For this reason, primary liver transplantation has been reserved for selected cases such as delayed diagnosis with severe liver failure where a Kasai procedure would be risky and have a high failure rate.[66–68] For all other children with compensated liver function and a timely diagnosis, the Kasai procedure and liver transplant are considered by most to be sequential, complementary procedures.[69]

### POSTOPERATIVE CARE

Drainage of gastric secretions with a nasogastric tube should continue for the first 48 hours, and the tube can usually be removed at this point. By the second or third postoperative day, infants often have already passed gas and stool and an oral diet can be started. Intravenous antibiotics are administered until the child begins feeding, and this is subsequently converted to long-term oral antibiotics that are continued at discharge. The closed suction drain is removed before discharge, typically on the fifth postoperative day. Antibiotics, a choleretic agent, fat-soluble vitamin supplements, and an oral steroid taper have been the routine for our group (Table 105-2), although the support for the use of steroids is not universal as discussed in the next section.

### STEROID CONTROVERSY

Steroids are known to have antiinflammatory and immunosuppressive effects. Their use in patients with biliary atresia with its significant inflammatory component is therefore logical. In addition, steroids have been postulated to have a choleretic effect, making them even more attractive in this patient population. Despite this, definitive evidence for the beneficial effects of adjunctive steroids in biliary atresia has been elusive. First, attempts to prove the choleretic action of steroids were not successful.[70] Second, many studies commenting on the efficacy of steroids are retrospective and contain confounding factors that make it impossible to comment on the isolated effects of steroid treatment. Finally, studies often appear underpowered to allow definitive conclusions.[71,72] For these reasons, it is not surprising that one study found that perioperative steroids were used in less than 50% of patients in the United States between 2003 and 2008.[73]

The paucity of data regarding the utility of steroids may be changing, however. A recent randomized, double-blind, placebo-controlled trial of corticosteroids after hepatic portoenterostomy revealed that steroids resulted in accelerated clearance of jaundice but did not result in improved survival of the native liver.[74] A current study by the biliary atresia research consortium in the United States is also attempting to address this question systematically. The results are pending.

Adverse sequelae of steroid use are not commonly reported. Fluid retention and appetite suppression are minor side effects, but major steroid-related complications such as infection and wound breakdown have not been problematic. Given that the evidence supporting steroid use is currently stronger than the evidence against it, our group has incorporated a protocol for postoperative steroid administration (see Table 105-2).

**TABLE 105-2**
**Postoperative Medical Regimen After Hepatic Portoenterostomy**

| |
|---|
| Ursodiol (Actigall)—10-15 mg/kg/dose BID day |
| Trimethoprim-Sulfamethoxazole—2.5 mg/kg/day based on Trimethoprim component dosing |
| Vitamins ADEK drops—1 mL/day |
| Prednisone—2 mg/kg/day and taper over 6 weeks |

## Outcomes

Over the past 50 years, the hepatic portoenterostomy procedure has dramatically improved the outlook for infants diagnosed with biliary atresia. Before the introduction of the hepatic portoenterostomy, few surgical options were available for treating infants with biliary atresia. A review of 89 patients who were explored for biliary atresia before the advent of formal surgical correction revealed a "cure" rate of 1.1% (1 of 89) and a known mortality of 94% (84 of 89).[75] The current 30-day mortality is low, ranging between 0% and 5%, reflecting the safety of the hepatic portoenterostomy.[61,69]

An important initial observation is the color of the stool after hepatic portoenterostomy. Pigmented stools either immediately or within the first 10 to 14 days after surgery suggest successful bile flow from the liver to the intestinal tract. This occurs in two thirds of patients, on average.[59,61,69] Of these patients who have documented bile flow, half will continue to drain bile well, with efficient clearance of jaundice and normal development. This is considered a "cure," and liver transplantation is not necessary.

In the remaining patients who initially had good bile drainage, ongoing inflammation and scarring of the liver will lead to progressive liver failure. Jaundice, which may have initially cleared completely or partially, returns. Signs of portal hypertension and failure to thrive eventually appear, and liver transplantation is therefore required. In this patient population that had initial successful palliation, liver transplantation occurs at a mean age of 5.4 years.[69]

The remaining patients (15% to 30%) who continue to have acholic stools after hepatic portoenterostomy never experience clinically relevant bile drainage. Jaundice continues to worsen, and the liver fails within months. In these infants an evaluation for liver transplantation, either cadaveric or living related, should commence before the arrival of true end-stage liver disease.

The 10-year survival after hepatic portoenterostomy has improved over time. Initial improvements were likely due to refinement of the portoenterostomy procedure, while more recent gains have been made in the technique of liver transplantation and in immunosuppressive strategies and medications. A biliary atresia registry report from the United States in 1990 found 5- and 10-year survival rates of 48% and 30%, respectively,[20] while a report from our center in 1997 found a 20-year survival rate of 49%.[69] A recent multicenter study in the United States reported a 2-year overall survival rate of 91% with a 56% native liver survival and 40% liver transplant rate.[76] Studies from other countries including Japan quote similar statistics.[21,22,56,61,77]

Long-term patient outcomes beyond liver function are available. Abnormalities in menstruation and pubertal disorders occur and are closely related to liver function. These findings suggest that hepatic function is deteriorating and transplantation will eventually be necessary. When transplantation occurs, menstrual abnormalities have been shown to improve.[78] Pregnancy can be challenging for patients who have been treated with hepatic portoenterostomy for biliary atresia. Progression of liver disease with development of portal hypertension has been documented during gestation.[78] Newborns can be small but are generally healthy. The postpartum period has also been documented as complicated.[79]

These data suggest that great care should be taken in counseling former biliary atresia patients regarding pregnancy, and careful monitoring is indicated when pregnancy is being considered.

Psychosocial outcomes have been reported in long-term survivors of the hepatic portoenterostomy.[78] This study of 44 patients with long-term follow-up revealed that almost all patients (93%) are functioning well in society with high levels of employment and education. Psychologic morbidity was present, however, in 18% of this population.

### OUTCOME VARIABLES

A variety of factors appear to play a role in the outcome after hepatic portoenterostomy for biliary atresia. Age at operation, operative technique, severity of liver disease, gross and microscopic aspects of the biliary tree and portal plate, and the presence of comorbid conditions are a few of the many variables that can affect outcome.

Strong evidence suggests that age at operation is an important factor in outcome, and this is supported by multiple reports.[69,80–84] The exact cutoff, however, where outcome from surgery becomes predictably poor, is unknown. This may be due to the existence of several distinct pathologic forms of biliary atresia. In fact, recent studies suggest that age at surgery may be a factor only in certain subsets of children such as those with cystic biliary atresia or those with biliary atresia splenic malformation as compared with those who present with isolated biliary atresia.[85] In our series, infants operated on at 0 to 49 days had equivalent outcomes when compared with those who underwent operation at 50 to 70 days of age. Those explored at 71 days or older had a statistically higher rate of failure when compared with both of the younger groups.[69] In the Japanese experience, the better outcomes were seen until the age of 90 days with subsequent worsening outcome after 90 days.[22] Therefore it is the goal at most centers to accurately obtain a provisional diagnosis of biliary atresia and successfully operate before 70 to 90 days of life. It is important to note, however, that hepatic portoenterostomy is not contraindicated after 90 days of age. A study of older children ($\geq$100 days) revealed acceptable survival rates, supporting the use of the procedure, if possible, even in older infants.[86]

The gross appearance of the biliary tree appears to influence outcome. Patients with a patent gallbladder had better outcomes when compared with those with complete fibrosis or complete absence of the fibrous cone of the portal plate.[16]

The size of ductules that are present at the level of the portal plate seems to be related to prognosis. It is logical that larger ductules allow for more efficient drainage of bile and therefore would result in an overall better outcome. Our series found that bile drainage was universal in patients with ductules greater than 150 micrometers, occurred in 86% of those with ductules less than 150 micrometers, but was only seen in 12% of those with no identifiable ductules.[69] Other studies have supported these findings.[34,38,87–90]

The experience of the surgeon and the center has been suggested as a factor in outcome of hepatic portoenterostomy. Our study revealed inferior outcomes in patients who had surgery in the 1970s, possibly reflecting a learning curve regarding surgery and the care of these patients.[69] Recent studies in the United Kingdom[91] and in France[92] also suggest that experienced centers and centralization of care for patients with biliary atresia produce superior outcomes. These national health policies, however, have not been implemented in many countries and long-term outcome differences are pending.

## Complications

### NUTRITIONAL COMPLICATIONS

Nutrition with a well-functioning hepatic portoenterostomy follows a normal course. Specialty formulas and vitamin supplements, if used, can often be discontinued after several months without harm. In the face of ongoing or progressive liver dysfunction, however, weight gain can be affected and metabolic complications may occur.[93] Nutritional parameters, vitamin levels, and growth should be monitored over the long term. In fact, some authors suggest that growth failure is an important marker for liver disease and an indication for liver transplantation in biliary atresia.[94]

### CHOLANGITIS

Cholangitis is the most common complication of the hepatic portoenterostomy and occurs in 33% to 60% of patients.[54,77,95] Cholangitis occurs most frequently during the first several years after initial surgery. Because cholangitis causes liver injury and promotes accelerated development of cirrhosis, prevention and active treatment are important adjuncts during the postoperative period.

The exact cause of cholangitis is unknown, although reflux of intestinal contents via the Roux limb, portal venous infection, impaired lymphatic drainage at the porta, and bacterial translocation have been proposed. Intrahepatic biliary stasis due to the fibrotic ductal obstruction is also felt to play a role in the pathogenesis of cholangitis. The offending organisms have been identified as enteric gram-negative and anaerobic bacteria, further supporting an enteric source for the condition.[96]

The clinical signs of cholangitis include fever, diminished bile flow, jaundice, and sometimes abdominal pain. Blood testing will reveal leukocytosis, elevated serum bilirubin, elevated hepatic enzymes (transaminases, alkaline phosphatase, and GGTP), and inflammatory parameters such as C-reactive protein.

Treatment of cholangitis is aimed at the presumed infection and the ongoing inflammation. The mainstay of treatment includes intravenous fluids, broad-spectrum intravenous antibiotics including coverage of anaerobes, and choleretic agents. Steroids are indicated for their ability to decrease inflammation and edema of the periductular areas.[97]

Prevention of cholangitis is an important goal. An adequately constructed Roux limb is a surgical maneuver that aids in prevention of cholangitis. Similarly, postoperative use of oral antibiotics is generally felt to be efficacious as a preventative measure. Studies have shown that use of trimethoprim-sulfamethoxazole or neomycin appeared to delay the onset and reduce the number of episodes of cholangitis compared with historic controls.[98] The use of steroid pulses during the postoperative period has also decreased the frequency of this complication.[99]

A surgical approach to revise a failing hepatic portoenterostomy with recurrent jaundice or unrelenting cholangitis

has been attempted.[48,100] Hasegawa reported the results of attempted revision of the hepatic portoenterostomy in 25 patients who did not drain effectively after the initial operation.[101] Only five patients had improvement in jaundice, a similar result to a series from the United States in which two of seven children were helped by a re-do portoenterostomy.[48] A similarly low success rate has been shown for surgical revision of the hepatic portoenterostomy in children who develop severe, intractable cholangitis.[22,102] Given these discouraging outcomes, the possibility that repeated operations can negatively affect the eventual success of liver transplantation, and in an era where liver transplantation has improved dramatically, operative approaches to rescue a failed or failing portoenterostomy are not recommended.

## PORTAL HYPERTENSION

Portal hypertension occurs in 34% to 76% of children and young adults after hepatic portoenterostomy and can occur despite a seemingly excellent result from the point of view of bile drainage.[103,104] Ongoing intrahepatic inflammation, often manifested as recurrent cholangitis, is likely responsible even when jaundice clears.

The most common finding in patients with portal hypertension is ascites, occurring in more than 60%. Esophageal varices, the most feared sequela of elevated portal pressure, occur in nearly half of patients who are followed for more than 3 years. Surveillance endoscopy therefore is indicated, especially in cases where progressive liver dysfunction is suspected. No clear recommendations are available for the frequency of surveillance endoscopy; however, yearly or semiannual examinations have been recommended. When varices are identified endoscopically, prophylactic sclerotherapy has shown benefit in randomized trials.[105]

Bleeding from esophageal varices can be massive and life threatening. Treatment consists of endoscopic sclerotherapy, often requiring multiple sessions.[77] Other interventions that can aid in treatment include use of octreotide or beta-adrenergic blockers or variceal ligation.[106–108] Although concerning, variceal bleeding should not prompt urgent consideration of liver transplantation and does not signify the arrival of end-stage liver disease.[77]

Portal hypertension–associated hypersplenism occurs in 16% to 35% of patients after portoenterostomy, and the associated thrombocytopenia can complicate episodes of gastrointestinal bleeding from varices or other causes.[109] Although splenectomy, portosystemic shunting, and splenic embolization have been described,[110] evaluation for liver transplantation is the most prudent option in patients who develop this serious secondary complication of portal hypertension.

## LIVER TRANSPLANTATION

Liver transplantation is covered in a separate section of this textbook. Nevertheless, it is mentioned here because liver failure due to biliary atresia represents the most common indication for liver transplantation in the pediatric age group. The general indications for liver transplantation in biliary atresia include (1) failure of initial portoenterostomy with no bile drainage and progressive liver disease; (2) episodic or inefficient bile drainage with slow deterioration of liver function and development of growth failure; and (3) development of one or more complications of chronic liver disease such as cholangitis or portal hypertension that cannot be easily managed despite an apparently functional portoenterostomy.

Thankfully, death on the transplant waiting list is uncommon. Improvements in allocation of organs using the pediatric end-stage liver disease system, based on several markers of severity of disease, result in transplantation in the most severely affected first. In addition, two techniques have resulted in an increase in the number of available organs. First was the technique of splitting or rescuing the size of organs for use in children,[111] and the second is the development of living-related liver transplantation.[112] These techniques have been applied in liver transplantation programs worldwide with excellent success.[113–115]

With continual improvement in the outcomes of pediatric liver transplantation, some have questioned whether primary liver transplantation without an initial attempt at hepatic portoenterostomy is indicated.[68,116,117] At this juncture, however, most believe that a well-executed hepatic portoenterostomy is the best initial surgical treatment for biliary atresia. This opinion is based on several important observations: (1) Nearly half of infants who undergo hepatic portoenterostomy obtain bile drainage and maintain either excellent or adequate liver function after surgery. Even in those who eventually progress to end-stage liver disease, transplantation is delayed by having undergone hepatic portoenterostomy first; (2) The improved but still insufficient supply of donor organs would make primary liver transplantation logistically challenging; and (3) A subset of children who would have been "cured" by the hepatic portoenterostomy would be unnecessarily exposed to the morbidity (surgical, infectious, and oncologic) and mortality of liver transplantation. At this point, therefore, liver transplantation remains the most important rescue therapy for children with biliary atresia after portoenterostomy with 5-year survival rates expected to exceed 90%.[118,119]

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*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 106

# Choledochal Cyst

Kelly D. Gonzales and Hanmin Lee

Choledochal cyst is a congenital anomaly involving cystic dilation of various ducts of the biliary tree. They are relatively rare in the Western world but more common in Asia. Several hypotheses exist as to the etiology of choledochal cysts including pancreaticobiliary maljunction. Three patterns of presentation have emerged since Alonso-Lei and colleagues published their landmark paper describing their classification of ductal dilation. The first is a cystic mass in the abdomen identified prenatally, the second is jaundice presenting in infancy, and the third is ascending cholangitis, obstructive jaundice, or pancreatitis presenting later in childhood or in adulthood. Regardless of the time of presentation, surgical intervention is indicated to mitigate potential damage to the liver, prevent jaundice and pancreatitis, and prevent cancer.

## Epidemiology and Etiology

The incidence of choledochal cyst ranges from 1 in 100,000 to 150,000 live births in Western populations with the incidence in the United States reportedly as high as 1 in 13,500. Choledochal cysts are significantly more common in Asia, with rates as high as 1 in 1000 in Japan. There is a well-documented female dominance (3 to 4:1) that contributes to the belief that choledochal cyst is sex-linked.[1–3] Familial cases have been recognized, but no genetic basis has been evident. The majority (≈60%) of choledochal cysts are diagnosed in the first decade of life. Roughly 20% remain undiagnosed until later in childhood or adulthood, and the remaining 20% to 25% of cases are diagnosed prenatally. Prenatal diagnosis of choledochal cysts is increasing in frequency,[2] as is the number of cases diagnosed in adulthood in the United States and Europe, perhaps due to higher index of suspicion or improved imaging techniques.

The etiology of choledochal cyst remains unknown but is commonly accepted to be congenital in nature. Distal obstruction, weakness of the duct wall, or a combination of the two are the predominant hypotheses.[4–6] The etiologic basis for choledochal cyst is likely multifactorial. In 1852 Douglas reported that there is potential congenital weakness of the common bile duct in the common fusiform type.[5] In 1936 Yotsuyanagi reported that the defect is due to failed formation in the early embryologic development of the biliary system from an overproduction of epithelial cells, leading to a dilated common bile duct.[7] This hypothesis is now largely regarded as unlikely, however.

In 1916 Kozumi and Kodama recognized an anomalous junction between the bile and pancreatic ducts during an autopsy case with choledochal cyst.[8] In 1969 Babbitt described the "long common channel" theory, also known as *pancreaticobiliary maljunction* (PBM), which is commonly seen in association with choledochal cyst.[9,10] PBM is a rare congenital anomaly described as a proximal insertion of the pancreatic duct into the common bile duct as a result of incomplete migration of the choledochopancreatic junction into the duodenal wall, creating a "long common channel." In 1984 Todani and colleagues were able to show PBM through analysis of endoscopic retrograde cholangiopancreatography (ERCP).[11] In fetal development, PBM creates a nidus for reflux of pancreatic enzymes into the common duct that causes damage to the ductal wall and leads to cyst formation. Due to the reflux, PBM is also commonly associated with carcinoma of the bile duct and gallbladder. Distal obstruction at the level of the duodenum is an additional factor leading to damage of the ductal wall and causing formation of a saccular dilation.[11–15] Investigators have proposed various mechanisms related to distal ductal stenosis such as an abnormal ductal insertion into the duodenum, distal common bile duct stenosis, persistent epithelial web, valve dysfunction, or neuromuscular irregularity of the sphincter.[13] PBM has a reported 3% incidence.[16] PBM is commonly associated with choledochal cysts and carcinoma of the biliary duct and gallbladder. The majority of choledochal cysts are associated with PBM; however, PBM can be seen without an associated choledochal cyst in 20% to 30% of cases. Carcinoma of the gallbladder and, less frequently, the bile duct remains an association with PBM even without ductal dilation.[16]

Other types of choledochal cysts, specifically choledochocele and Caroli disease, have different proposed etiologies. Choledochocele has two main variations as described by Manning and colleagues.[17] In the most common variation, the common bile duct and pancreatic duct enter the duodenum separately. In the second variation, a common bile duct diverticulum arises at the level of the ampulla of Vater with the pancreatic duct entering the distal common bile duct in its normal anatomic variation. The formation of the diverticulum is thought to be due to either an obstruction of the ampulla and a low insertion or a congenital duodenal duplication. Caroli disease is believed to arise from an arrest in the twelfth

week of gestation in the ductal plate at the level of the large ducts of the hilum. This is distinct from Caroli syndrome, in which there is arrest of the small ductules of the periphery.[18,19] Caroli disease has been associated with polycystic kidney disease.[1,20–22] Overall, the etiologic background of choledochal cyst is congenital in nature, resulting from reflux of pancreatic enzymes causing damage to the bile duct wall and complete or partial distal obstruction of the bile duct.

## Embryology

In normal development the fourth week of gestation marks the formation of a hepatic diverticulum extending from the ventral aspect of the foregut. Thus the biliary structures are endodermal in nature. The diverticulum progresses to cranial and caudal buds. The liver and extrahepatic biliary tree form from the cranial bud and the caudal bud becomes the superior and inferior buds. The gallbladder and cystic duct are derived from the superior bud, and the inferior bud gives rise to the right and left ventral pancreas. There is some controversy regarding whether there is a solid phase to the biliary tree early in gestation and eventual recanalization or whether the biliary tree has a continuous lumen.[23] At the sixth week, the ventral pancreatic bud and common bile duct rotate around the duodenum clockwise by 180 degrees. The common bile duct at this point enters the duodenum at the left posterior surface. In the seventh week the main pancreatic duct (Wirsung duct) and common bile duct junction ends in the developing duodenum as closed cavities through elongation to form the ampulla of Vater. The junction retracts in the eighth week of gestation to reside in the submucosa of the duodenal wall. A concentric ring of mesenchyme forms around the junction of the pancreatic and biliary ducts, beginning the formation of the sphincter of Oddi. In the twelfth week of gestation, the main pancreatic and common bile ducts are obliquely arranged in the duodenum. PBM is believed to arise from a misarrangement of the pancreatic and common bile duct and not due to the pancreaticobiliary system or termination of the junction migration as once thought.[24]

## Anatomic Classification

The original anatomic classification of choledochal cysts included types I, II, and III.[4] After review of cholangiograms, Todani and colleagues broadened the classification into five types with some subtypes (Fig. 106-1).[25,26] Type I is by far the most common, accounting for 90% to 95% of cases,[4] and constitutes the cystic/saccular or fusiform dilation of the common bile duct.[27] Type I is divided into three subtypes (types Ia, Ib, and Ic). Type Ia consists of cystic dilation of the entire common bile duct. Type Ib is cystic dilation of a segment of the common bile duct, and type Ic is fusiform dilation of the common bile duct. Type II is a diverticulum of the common bile duct with no dilation of the common bile, extrahepatic, or intrahepatic ducts. Type III, also referred to as a *choledochocele* (Fig. 106-2), usually has a normal common bile duct and main pancreatic duct with cystic dilation of the distal common bile duct that is either intraduodenal or intrapancreatic in location. The ducts may either enter the choledochocele separately or in union at the wall of the duodenum, but are usually stenotic at their openings due to chronic inflammation. Type IV is composed of multiple cysts located intrahepatically, extrahepatically, or in both locations. Type V comprises single or multiple intrahepatic cysts without extrahepatic duct dilation. Type V cysts in conjunction with hepatic fibrosis are commonly referred to as Caroli disease.

## Pathology

The gross pathology of choledochal cysts is largely described in the anatomic classification section earlier. As described, choledochal cysts can occur in the intrahepatic ducts, the common bile duct, intraduodenally, or in a combination of

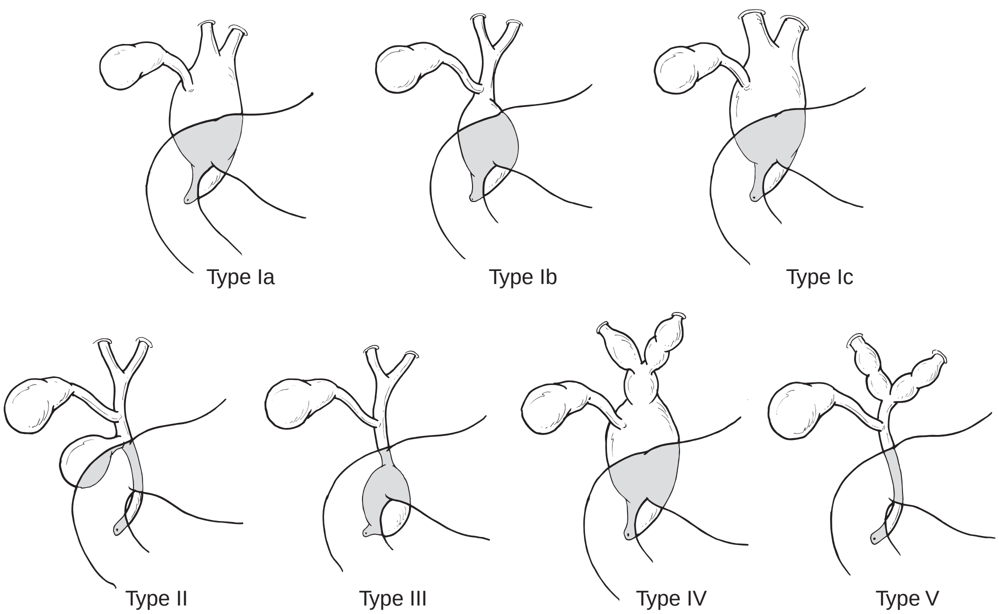


**FIGURE 106-1** Classification of the five major choledochal cyst forms and some subtypes.

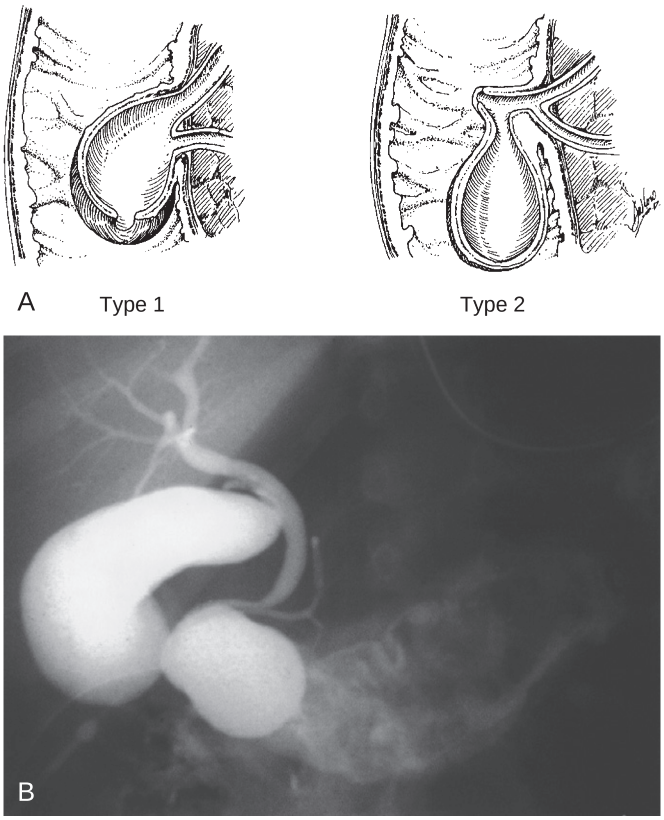


FIGURE 106-2 Two types of choledochoceles. (**A** from O'Neill JA: Choledochal cyst. Curr Probl Surg 1992;29:374. Used with permission.)

locations. The dilation is primarily fusiform. Pancreaticobiliary maljunction is common, as is stricture of the common bile duct. Sludge, cholelithiasis, or choledocholithiasis is commonly found with choledochal cysts.

The histopathology depends on patient age and severity of symptoms. The extrahepatic ducts are thickened with dense connective tissue intermixed with smooth muscle strands. Inflammatory reaction is usually present but may be minimal in the infantile stage. Generally, the inflammatory reaction increases with age and may lead to ulceration in the mucosa and submucosa. The inflammation can extend through the cyst leading to possible adherence to adjacent structures. The most marked inflammation is noted in the intrahepatic cysts. The lining of the cyst is not composed of typical biliary mucosa but rather is relatively acellular and may lack a typical mucosal lining. In the wall of the cyst, mucin-secreting cells are seen in intramural glands. A gastrointestinal mucosa-type composition of immunoreactive gastrin- and somatostatin-containing cells may also be found in the cyst wall due to repeated destruction and regrowth causing epithelial metaplasia. Small areas of columnar epithelium and bile ducts can be noted in the cystic wall of young patients.[28] The degree of epithelial metaplasia generally increases with age, as does the risk for adenocarcinoma.[1,29–31] These histologic changes are commonly seen in pancreaticobiliary maljunction as well. As mentioned, the distal common bile duct has various degrees of stricture, with a high-grade stricture commonly seen in the infantile stage. Older patients have stenosis of the distal common bile duct but not complete obstruction.

The histologic changes of choledochocele differ from those of the other forms of choledochal cysts that were described earlier. As these ducts are primarily intraduodenal, the cystic lining takes on a duodenal lining rather than biliary. The common bile duct, although normal on gross pathology, reveals inflammatory change on histologic examination. Sludge and stones may also be identified in the common bile duct extending into the extrahepatic and intrahepatic ducts, especially in older patients.

Liver pathology in a newborn is usually normal or reveals mild proliferation of intrahepatic ducts. Mild periportal fibrosis is often noted on liver histology of older patients. Congenital hepatic fibrosis has also been described in some patients.[32]

Chronic inflammation is the likely cause of carcinoma in the choledochal cyst wall found in older patients. PBM with or without the presence of choledochal cysts increases the risk factor for carcinoma of the biliary tract.[28,33,34] Adenosquamous carcinoma is the most common type of carcinoma found in the wall, although small-cell carcinoma has also been reported. The choledochal cyst wall is the primary location of carcinomas, but the gallbladder and pancreatic head are other common sites. The location of carcinoma in the head of the pancreas is usually associated with the presence of PBM.[2,10,35]

## Prenatal Diagnosis

Choledochal cysts are being diagnosed with increasing frequency on prenatal anatomic ultrasounds in the second and third trimesters.[36–42] The typical finding on high-resolution ultrasound is that of a cyst in the porta hepatis. The differential diagnosis includes hepatic cysts, duodenal atresia, mesenteric or omental cysts, intestinal duplication, gallbladder duplication, and ovarian cysts.[43] Because choledochal cysts are rare anomalies, prenatal diagnosis can be challenging.[44] Having a skilled and experienced sonologist performing the prenatal ultrasound has, in our experience, been critical in increasing both the sensitivity and specificity of prenatal ultrasound for choledochal cysts.

Fetal magnetic resonance imaging (MRI) has also been performed to aid in the diagnosis.[45] Our group has not found that MRI adds significantly to the information found on ultrasound, but as both imaging techniques evolve, they may increase diagnostic yield in a complementary fashion.

As discussed in further detail later in this chapter, choledochal cysts historically presented in two broad categories: (1) the infantile form indicated by obstructive jaundice and (2) the adult form generally presenting with obstructive jaundice, pancreatitis, or ascending cholangitis.[46] Prenatally diagnosed choledochal cysts could fall into either of these categories. The true natural history of choledochal cysts diagnosed prenatally is impossible to accurately delineate due to widespread support for early surgical management to avoid the high risk of potential complications from untreated choledochal cysts. Clearly, those with an infantile form need surgical excision and reconstruction within the first several weeks of life. Many of these neonates may have choledochal cysts in conjunction with complete or nearly complete biliary obstruction. Some categorize these patients as having biliary atresia in association with choledochal cyst, whereas others may term

these patients as having what was historically called *surgically correctable biliary atresia*. Some overlap between the two diseases is likely.

In those patients with prenatally diagnosed choledochal cysts that are asymptomatic, opinions differ in management. Some have advocated for repair within the first several months of life to avoid potential complications of cholangitis and hepatopathy.[39,47] These papers compare infants diagnosed prenatally who underwent surgery within the first 6 months of life to children diagnosed later who underwent surgery at an average age of 4 to 6 years. In one series, children in the older group had greater hepatic fibrosis, as well as a higher incidence of preoperative clinical manifestations of choledochal cysts. However, no long-term follow-up was conducted to provide data on long-term liver function and quality of life in order to compare these two different cohorts. In our center, our general recommendation has been to perform laparoscopic operation for asymptomatic choledochal cysts diagnosed prenatally within the first year of life.

# Clinical Presentation

Patients with choledochal cysts can manifest clinical symptoms at any time during their life, with 80% of patients being symptomatic before the age of 10 years.[48] Abdominal pain, jaundice, and a palpable right upper quadrant abdominal mass is the classic triad described for patients with choledochal cyst. The triad is only reported in about 20% of patients diagnosed. Two of the three symptoms are seen in two thirds of patients at the time of diagnosis.[48] Some have applied a classification according to age at presentation. The infantile form occurs before 12 months of age, and these patients tend to present with obstructive jaundice, acholic stools, and hepatomegaly similar to biliary atresia.[49] The adult form occurs anytime after 12 months of age and usually has a greater number of symptoms including fever, nausea, vomiting, and jaundice.[4] As previously mentioned, choledochal cysts diagnosed prenatally may fall into either category.

Signs of hepatic fibrosis may be present in the infantile form, and these patients benefit the most from early treatment. Delayed treatment of asymptomatic infants is advocated by some; however, the risk of progressive hepatic fibrosis exists. In the infantile form, patients with the fusiform type of choledochal cyst tend to present with transient jaundice. Perforation of the choledochal cyst is rare (1% to 12%) and thought to be due to a fragile cystic wall from inflammation, increased ductal pressure, or increased intra-abdominal pressure. The site of rupture is at the low-flow region of the junction of the cystic and common bile ducts. These patients present with abdominal pain, sepsis, and peritonitis.[50]

The adult form usually presents after 2 years of age. These patients tend to have a fusiform dilation of the common bile duct without complete obstruction of the distal common bile duct and present with intermittent symptoms from a mucous plug or biliary sludge. Patients with the adult form are more likely to present with the classic triad of abdominal pain, jaundice, and a palpable right upper quadrant abdominal mass compared with the infantile form.

Symptoms arise from biliary obstruction leading to ascending cholangitis and complications of pancreatitis.[3,27,46,48,51,52] Bile stasis, sludge, stone formation, inflammation, and recurrent superinfection have all been identified as complications leading to intermittent jaundice and abdominal pain in the right upper quadrant. Mucous or protein plugging is likely due to chronic inflammation leading to formation of albumin-rich exudates or dysplastic epithelium with hypersecretion of mucin.[53] Persistent bacterial colonization of intrahepatic ducts in type IV and V cysts is exacerbated by bile stasis, sludge, and stone formation and is one theory for recurrent cholangitis. Secondary biliary cirrhosis is noted in 40% to 50% of patients due to obstruction and inflammation and leads to portal hypertension in some patients.[48] In cases of choledochal cyst not diagnosed until adulthood, patients may present with cholelithiasis and symptoms mimicking biliary colic or cholecystitis. If imaging has been inadequate, the diagnosis of choledochal cyst may only be made intraoperatively by visual inspection or cholangiography. In some, cholecystectomy may be performed without diagnosis of the choledochal cyst. Pain similar to recurrent pancreatitis has been described by some patients, which has led to a misdiagnosis of abnormal amylase clearance; however, after further work-up, an elevated serum amylase is noted.[54,55] However, these patients may truly be having pancreatitis as a result of mucous plugging in the PBM.

# Diagnosis

## LABORATORY STUDIES

Laboratory data are usually obtained in patients with choledochal cysts in the diagnostic workup but are reserved primarily for evaluating the clinical condition of the patient and not diagnosis. Serum markers of obstructive jaundice (e.g., conjugated hyperbilirubinemia and increased serum alkaline phosphatase) are usually present. An elevated conjugated bilirubin is typical in the infantile form but may or may not be present in the adult form due to intermittent or incomplete biliary obstruction. In chronic cases an abnormal coagulation profile may be evident due to hepatic injury.

## IMAGING STUDIES

Diagnosis of choledochal cysts is made by imaging studies. An abdominal ultrasound is the first imaging modality used because it is noninvasive, inexpensive, and provides excellent detail of the portal structures. Choledochal cyst on ultrasound is commonly identified as a cystic mass that is not part of the gallbladder in the right upper quadrant and is usually in the porta hepatis. The cyst needs to be in continuity with the biliary tree to be diagnosed as a choledochal cyst because other cystic abnormalities such as pancreatic pseudocyst, biliary cystadenomas, or echinococcal cysts can exist in this area.[18] The diagnosis of choledochal cyst on ultrasound carries a 71% to 97% sensitivity.[56] Ultrasonography is an excellent screening tool and is used by some as the only imaging study in infants.

In the event that choledochal cyst is suspected on ultrasound, a technectium-99 HIDA scan may provide more definitive data. Photopenia is initially evident at the cyst followed by filling and delayed emptying. The HIDA scan has varying sensitivities, with 100% for type I cysts and 67% for type IV.[56]

A HIDA scan has decreased sensitivity for intrahepatic cysts. A HIDA scan may also be helpful for distinguishing between choledochal cyst and biliary atresia. Biliary atresia on a HIDA scan is characterized by lack of contrast emptying into the duodenum, whereas a choledochal cyst will have contrast entering the duodenum. A HIDA scan may also be useful in the diagnosis of cystic rupture, in which case contrast would empty into the peritoneal cavity.[48]

An abdominal computed tomography (CT) scan may be another useful modality. A CT can show the intrahepatic ducts, distal common bile ducts, and the pancreatic duct, features that are not reliably identified on ultrasound, making CT scan highly useful in identifying type IV and type V cysts. The full anatomy of the biliary tree can be delineated using CT cholangiography, a valuable modality in preoperative planning. The sensitivity of CT cholangiography is 93% for biliary tree visualization and diagnosing lithiasis, 90% for diagnosing choledochal cysts, and only 64% for characterizing the pancreatic duct.[57] The risk of using CT or CT cholangiography is contrast toxicity that can cause nephrotoxicity or hepatotoxicity and radiation exposure.

Invasive imaging studies also play a role in diagnosis and evaluation of the biliary anatomy. These modalities include cholangiography through endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and intraoperative cholangiogram. Cholangiography will delineate the anatomy and locate abnormalities such as PBM and filling defects caused by stones, stenosis, or carcinomas.[58,59] The risk of cholangitis and pancreatitis after invasive cholangiography is higher than in the general population, with reported incidences as high as 87.5%[48] due to the frequency of PBM, dilated ducts, and dysfunctional sphincters in patients with choledochal cyst. Due to recurrent inflammation and scarring, ERCP can be challenging with respect to cannulization of the ampulla. A high volume of dye load is often required for adequate visualization, especially in the setting of large cysts.[48]

Magnetic resonance cholangiopancreatography (MRCP) is now considered the gold standard for imaging choledochal cyst, especially given the complications and concerns with invasive cholangiography (Fig. 106-3). The diagnostic sensitivity of MRCP is 90% to 100%.[60] Administration of secretin increases pancreatic secretion and dilates the pancreatic duct. Thus some centers administer secretin before MRCP to increase diagnostic yield.[61] As the technology for MRCP has improved, smaller ductal structures are being visualized with finer detail. This has allowed for increased diagnosis of PBM and pancreatic divisum and usually gives accurate information as to the location of insertion of the pancreatic duct. The type and extent of the choledochal cyst are well visualized, and images can be reconstructed in three dimensions (Fig. 106-4). MRCP avoids radiation associated with CT scan and ERCP and avoids the potential post-ERCP complications of cholangitis and pancreatitis.

Choledochoceles (type III cysts) can be diagnosed with various imaging modalities such as upper gastrointestinal series (UGIS), endoscopy, ERCP, MRCP, and CT cholangiography. On UGIS for choledochoceles, a filling defect is noted at the level of the cyst entering the duodenum. The papilla will have a smooth bulging on endoscopy and ERCP. The advantage of ERCP over MRCP and CT cholangiography for choledochoceles is the ability to perform a therapeutic procedure such as a sphincterotomy. Endoscopic ultrasound is also well-suited to diagnosing choledochoceles because this modality can reach close to the cyst for appropriate visualization. The best imaging techniques for Caroli disease (type V cysts) are ultrasound, CT, and MRI.[48] The "central dot sign" has been described for Caroli disease but is not pathognomic.[62] On HIDA scan a beaded appearance due to intraductal bridging may be indicative of Caroli disease.

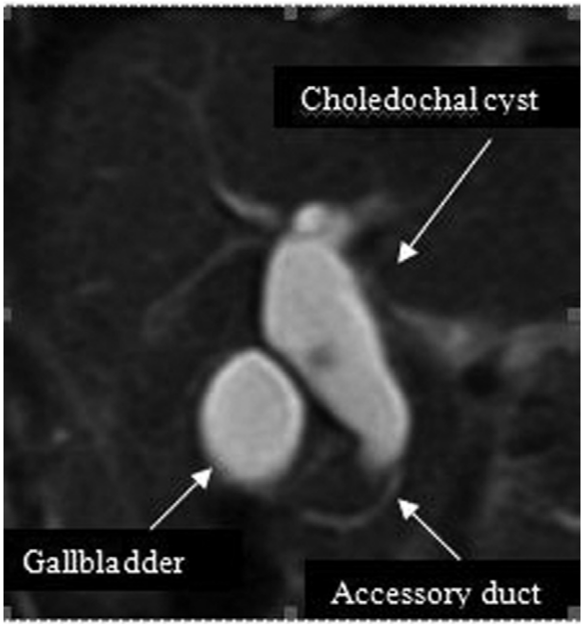


**FIGURE 106-3** A magnetic resonance cholangiopancreatography of a patient with type I choledochal cyst and an accessory pancreatic duct entering the duodenum.

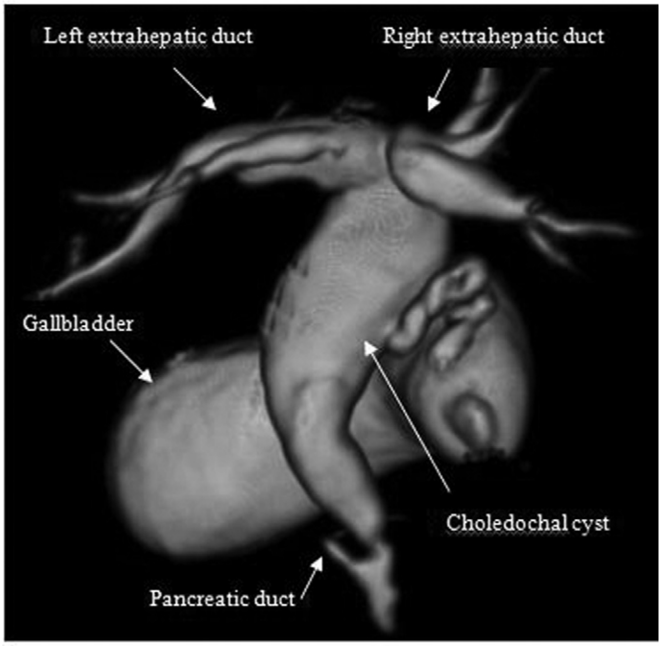


**FIGURE 106-4** Three-dimensional reconstruction of a magnetic resonance cholangiopancreatography image of a choledochal cyst with mild dilation (6 mm) of the right and left extrahepatic ducts. Pancreatic duct is seen entering the normal caliber distal common bile duct.

Our preference for imaging for all types of choledochal cysts is ultrasound followed by MRCP. If the MRCP does not give sufficient anatomic detail to guide therapy, we perform either an ERCP before operation or an intraoperative cholangiogram at the time of cyst resection.

## Surgical Management

The management of types I and IV choledochal cysts has evolved from either internal or external drainage to cyst excision and hepaticojejunostomy to a Roux-en-Y limb (Fig. 106-5). Due to the relatively complex nature of cyst excision, early attempts at treatment focused on external drainage to avoid complications of biliary tract obstruction. However, an external biliary fistula proved to have high morbidity and mortality.[4] As surgical techniques advanced, subsequent attempts focused on cyst duodenostomy or cyst jejunostomy to a Roux-en-Y limb to internalize biliary drainage.[15,27,63,64] However, complications of cholangitis and progressive liver damage and the high risk of cancer in the choledochal cyst led to the current surgical strategy of cyst excision with Roux-en-Y jejunostomy as advocated by Kasai and colleagues[65] and Ishida and colleagues.[66–68] This operative approach eliminates the potentially premalignant epithelial cyst lining and also separates the pancreatic drainage from the biliary drainage. This strategy is summarized in Figure 106-6. This technique is essentially identical to our laparoscopic technique for treatment for type I and type IV cysts and is described in detail later in the laparoscopic section. Some surgeons prefer cyst resection with hepaticoduodenostomy, which yields similar outcomes to that of drainage with a Roux-en-Y limb.[69]

In previous series of choledochal cysts, diagnosis was often delayed, leading to patient presentation with repeated episodes of cholangitis. Delayed diagnosis led to inflammation of the cyst and adherence to the periportal structures, particularly the portal vein. In patients such as these, for whom excision of the full thickness of the cyst may carry an unacceptably high complication rate, the technique described by Lilly can be performed[70,71]: The cyst can be incised anteriorly away from the hepatic artery and portal vein, allowing the inner epithelial lining of the entire choledochal cyst to be excised while avoiding the difficult and potentially dangerous plane of dissection between the outer cyst wall and the portal vein. This removes the potentially premalignant aspects of the cyst while minimizing potential operative complications.

Type II choledochal cysts are rare but appear to have a low malignant potential. This type requires simple cyst resection and is easily amenable to a laparoscopic approach because complicated dissection and reconstruction are not required. In fact, the first laparoscopic treatment for a choledochal cyst in the pediatric population was reported in a child with a type II cyst.[72]

Type III choledochal cysts, or choledochoceles, are intraduodenal or intrapancreatic dilations of the distal common bile duct, as outlined previously. Management has traditionally been operative marsupialization of the cyst, usually through a transduodenal approach.[73] Increasingly, however, choledochoceles are being treated by sphincterotomy or cyst marsupialization during an ERCP.[74–76] The incidence of cancer is unclear due to the rarity of this type of cyst but is likely significantly elevated.[77] It is unclear to what extent drainage with either an operative approach or via ERCP minimizes the malignant potential for choledochoceles.

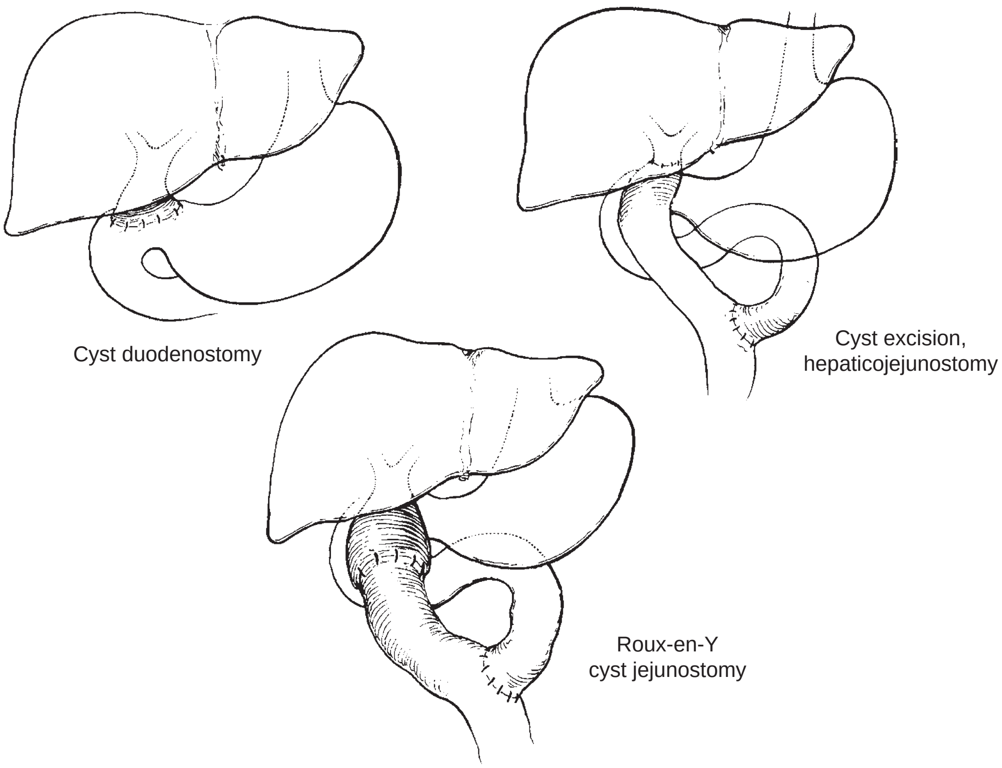


**FIGURE 106-5** Surgical operative management of choledochal cyst and the types of anastomoses that can be created.

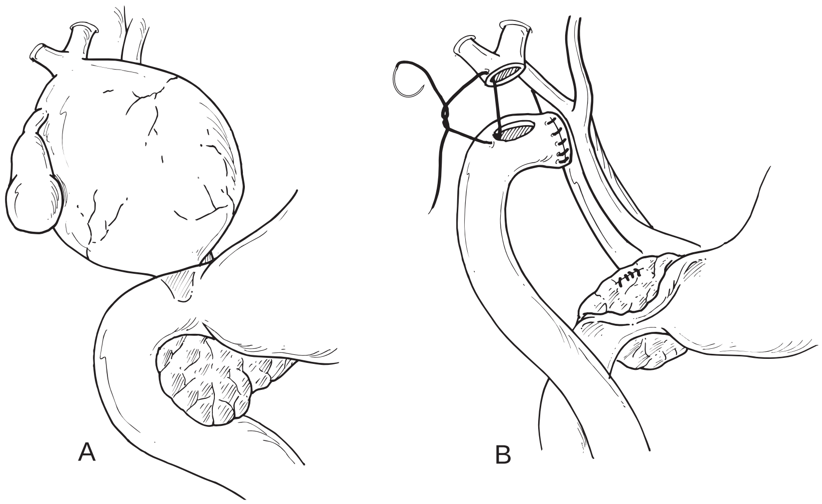


**FIGURE 106-6** Diagram reveals preoperative anatomy **(A)** and postoperative anatomy **(B)** after cyst excision and Roux-en-Y reconstruction.

For patients with type IV disease, most surgeons recommend cyst resection to the hepatic ducts, leaving in place the dilated intrahepatic ducts because they may decrease in size without distal obstruction. However, careful long-term follow-up is required to monitor the relative size of the intrahepatic ducts and for the possibility of symptomatic lithiasis and cholangitis. Surgical treatment of type V (Caroli disease) is challenging. Segmental resections can be performed if the disease is localized to a portion of the liver. Liver transplantation has also been performed.[78,79]

We and others have reported laparoscopic excision of choledochal cysts with either Roux-en-Y reconstruction or hepatico-duodenostomy.[80–83] The largest series, from Tang and colleagues,[83] was a retrospective review of 62 children undergoing laparoscopic resection of choledochal cysts. They reported outcomes comparable with those of published open series with a low rate of complications including only one case of a biliary leak. Long-term outcome for laparoscopic surgery for choledochal cyst in the pediatric population has not been well-reported, and data are similarly scarce for outcomes of open surgery. A recent series from the long-term follow-up data reported by Ono and colleagues is discussed in "Outcome and Complications" later and provides the best overall long-term data from open cases.[84]

Techniques for laparoscopic repair including ours are all similar. This next section describes in detail our technique for laparoscopic excision of type I choledochal cysts with Roux-en-Y reconstruction, as previously reported.[81]

Detailed preoperative workup including an MRCP is essential in determining the type of cyst and the insertion of the pancreatic duct(s) for safe resection. Particularly in instances in which the pancreatic duct inserts near the distal extent of the choledochal cyst, care must be taken to avoid the pancreatic duct in the distal dissection. Intraoperative cholangiography may also be performed by placing a catheter in the gallbladder if MRCP is inadequate or not available. The placement of four ports for the procedure is illustrated in Figure 106-7. A 5-mm port is placed through the umbilicus for the camera. Typically, we prefer a 4-mm or 5-mm 30-degree endoscope due to the improved optics as compared with smaller endoscopes. A 3-mm port is placed in the right abdomen between the midaxillary line and the midclavicular line just inferior to the level of the umbilicus. This is the

**FIGURE 106-7** Port placements for laparoscopic choledochal cyst excision and Roux-en-Y hepaticojejunostomy.

left-handed working port for the primary surgeon. A 5-mm port is placed in the left midclavicular line just superior to the level of the umbilicus for the right-handed working port for the primary surgeon. The fourth port is located in the left anterior axillary line just below the costal margin. This port is used by the assistant to retract the gallbladder and liver superiorly. The location of this port, although it may seem counterintuitive, has proven to be the optimal location for retraction and affords adequate distance from the other instruments. Placing two ports in the right abdomen, as one would typically do for a cholecystectomy, results in inadequate distance between instruments placed through these ports. After laparoscopically confirming the diagnosis of a choledochal cyst, a cholangiogram is performed, if necessary, by placing an angiocatheter into the gallbladder and installing water soluble contrast (Fig. 106-8).

The gallbladder is then divided at the cystic duct junction with clips or ties (Fig. 106-9). This allows the assistant to retract the gallbladder superiorly through the left subcostal port and expose the porta hepatis. If the cyst is large enough that the hepatic hilum is obscured, it may need to be decompressed. Next, the hepatic duct is divided just superior to the

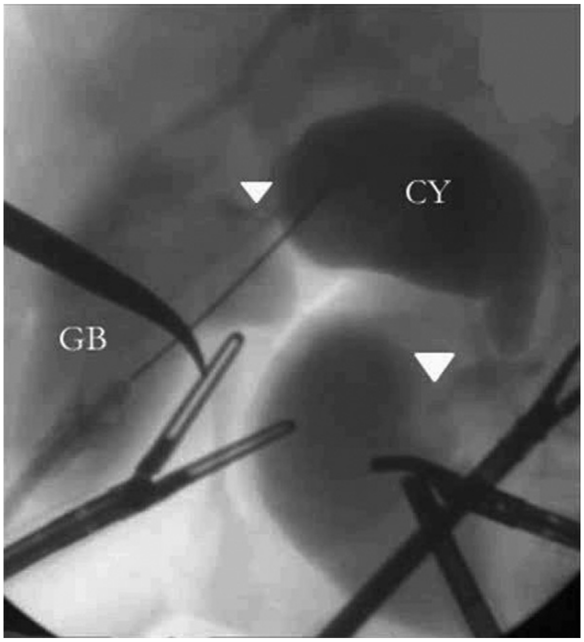


**FIGURE 106-8** Intraoperative cholangiogram during laparoscopic cyst excision and Roux-en-Y hepaticojejunostomy revealing the gallbladder (*GB*) and the choledochal cyst (*CY*).

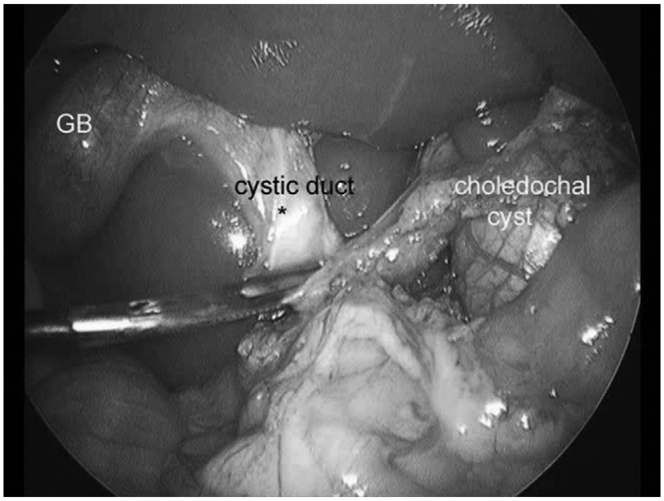


**FIGURE 106-9** Intraoperative laparoscopic view of the gallbladder (*GB*) and cystic duct in relation to the choledochal cyst.

most cephalic extent of the choledochal cyst. Care should be taken to identify the right and left branches. In some instances, separate anastomoses may be required from the right and left ducts to the Roux-en-Y limb. Dividing the hepatic duct early in the operation allows the surgeon to manipulate both the superior and right lateral aspects of the choledochal cyst to aid in the dissection. The cyst is then carefully dissected away from the hepatic artery and the portal vein. At this point, the cyst is attached only to the distal common bile duct within the pancreas. Dissection continues distally, dissecting closely on the cyst wall to avoid damage to the duodenum or pancreas until the cyst begins tapering in size to become a normal-sized common bile duct. Again, the MRCP can be valuable in guiding the distal dissection with respect to the location of the pancreatic duct insertion. The common bile duct is excised, and the distal common bile duct is ligated with a tie or occluded with a clip. If the cyst is not leaking bile, we prefer to place the cyst on the lateral aspect of the liver and remove it subsequently along with the gallbladder.

We then begin the creation of the Roux-en-Y limb. The ligament of Treitz is identified by elevating the transverse colon. The area of the jejunum that will be divided for the Roux-en-Y limb is identified approximately 15 cm from the ligament. We prefer to mark this area by placing vessel loops of different colors separated by 1 to 2 cm. Marking the jejunum in this manner allows easy identification of the proximal and distal aspects of the jejunum when the bowel is exteriorized. Next, the umbilical incision is extended to approximately 1.5 cm and the marked jejunum is exteriorized. A 30- to 40-cm Roux-en-Y limb is then created in the standard fashion, the bowel is then returned intracorporeally, and the umbilical port is replaced. The Roux-en-Y limb is brought to the porta hepatic in a retrocolic fashion, and then an end-to-side anastomosis is performed from the hepatic duct to the Roux-en-Y limb. We use fine absorbable monofilament suture material. We have found that using a continuous suture on the posterior aspect of the anastomosis and interrupted sutures on the anterior and lateral aspects is simplest. All knots are tied on the outside of the anastomosis to prevent the potential for a focus of formation or collection of biliary sludge on the knots. Finally, a cholecystectomy is performed and the gallbladder and the choledochal cyst are removed through the umbilical port site.

## Outcome and Complications

In past operative treatment of cystenterostomy, there was a high rate of complications such as anastomotic stricture, recurrent ascending cholangitis, bowel obstruction, portal hypertension, and malignancy. However, the advancement of surgical treatment to include cyst excision resulted in minimal morbidity and mortality and reduced the number of late complications. The most common late complication continues to be anastomotic stricture. Early diagnosis and cyst excision results in low complication rates in most experienced centers. The type of internal drainage after cyst excision has not been shown to affect postoperative complications. The technique of Roux-en-Y hepaticojejunostomy is favored by most, although comparable results can be achieved by hepaticoduodenostomy. Either procedure can be performed laparoscopically as well.

Although late complications are reduced with current surgical management, studies suggest that long-term follow-up to 17 years or beyond is indicated due to the potential for problems such as anastomotic stricture, cholangitis, intrahepatic stone formation, and malignancy.[85] This is particularly important for patients with type IV disease because malignancy can occur in incompletely resected cystic hepatic ducts or recurrent cysts.[85] The risk of malignancy is greatly reduced after cyst excision but is still elevated as compared with the general population. Intrahepatic stone formation in the intraoperative setting has been evaluated and reported in the literature and seen in patients who showed no stone formation in the preoperative course. Stone formation has been reported to occur

anywhere from 3 to 22 years postoperatively.[86] However, if the duct is patent and there is no stenosis of the hepaticojejunostomy, stones are likely to pass spontaneously. Intrahepatic stones usually present in cases of stenosis that initially cause bile stasis and lead to stone formation.[85] Todani and colleagues[87] reported a 25-year review with the identification of biliary complications primarily associated with either anastomotic stricture or primary ductal stricture and recommended a wide hepatic hilum anastomosis to prevent biliary complications.

The long-term complication of malignancy can be avoided with cyst excision. In addition, any cause of chronic inflammation and stasis, as seen with PBM, has to be treated appropriately.[34] The incidence of malignancy of the gallbladder and bile ducts remains high in patients with PBM compared with the general population and occurs at a younger age. Further studies reviewing the genetic changes of PBM have revealed KRAS gene mutations early in epithelial hyperplasia and metaplasia. In the late progression of adenocarcinoma of the biliary tract, inactivation of DPC4 gene occurs.[28,44,88]

# Conclusion

The management of choledochal cysts is performed predominantly by pediatric surgeons. Generally considered a congenital abnormality, most cases are diagnosed in infancy with many now being diagnosed prenatally, though presentation may be delayed until adulthood. Because of the high risk of serious sequelae including malignancy, early surgical excision is warranted even in asymptomatic patients. Adequate imaging with MRCP helps map the extent of the dilated biliary tree, as well as the insertion of the pancreatic duct(s), ensuring safe resection. Increasingly, surgery is being performed with minimally invasive techniques with good outcomes. Because of the rare nature of this disease, extensive knowledge of the different variants and experience with advanced biliary tract surgery is critical in attaining good outcomes.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 107

# Gallbladder Disease and Hepatic Infections

George W. Holcomb III and Walter S. Andrews

## Gallbladder Disease

Cholelithiasis and biliary dyskinesia are being increasingly diagnosed in children. Whether their incidence is actually escalating or the diagnostic accuracy is improving because of the increasing use of ultrasonography (US) and cholescintigraphy remains unclear. Moreover, hemolytic disease is no longer a prerequisite for the development of gallstones.[1–3]

### NONHEMOLYTIC CHOLELITHIASIS

Several factors are known to cause cholelithiasis in children. By far, the most commonly reported condition associated with the development of nonhemolytic cholelithiasis, particularly in neonates and infants, is the use of total parenteral nutrition (TPN).[4–6] Up to 43% of children receiving long-term TPN develop gallstones.[7] The mechanism of gallstone formation related to TPN remains unclear but may be associated with changes in bile composition caused by the amino acid infusion. Also, the lack of enteral feeding leads to ineffective gallbladder contraction and results in reduced enterohepatic circulation of bile. The administration of fat is believed to ameliorate the deleterious effects of the amino acids in the TPN.

Because many infants receive TPN and only a few develop gallstones, other factors are probably necessary for the development of cholelithiasis in this patient population. Septicemia, dehydration, chronic furosemide therapy, cystic fibrosis, short-bowel syndrome, and ileal resection for necrotizing enterocolitis also may be important contributing factors.[6,8–10] The cause of gallstone formation is probably multifactorial. Stasis, sepsis, a lack of enteral feedings, and some alteration of the enterohepatic pathway for the recirculation of bile are all important for stone development. Moreover, neonates and, particularly, premature infants are susceptible to the cholestatic effects of TPN because of the immaturity of their enterohepatic circulation of bile salts. Finally, the composition of gallstones in children may be different than that found in adults. Whereas stones in adults are primarily cholesterol in composition, calcium carbonate and black pigment stones are often found in pediatric patients, especially those younger than 10 years of age.[11–13]

Causes associated with gallstones in older children include the use of oral contraceptives, cystic fibrosis, pregnancy, obesity, and ileal resection.[14–17] Cholelithiasis has also been reported in children undergoing cardiac transplantation who are receiving cyclosporine and in patients who have previously required extracorporeal membrane oxygenation as a newborn.[18–21]

### HEMOLYTIC CHOLELITHIASIS

Although the incidence of nonhemolytic cholelithiasis is increasing at many centers, hemolytic cholelithiasis (usually secondary to sickle cell disease [SCD]) remains the most common cause of gallstones in children at many academic institutions, especially in urban areas where an active sickle cell program exists. The prevalence of pigment gallstones associated with sickle cell disease appears to be age dependent. Fifty percent of patients with sickle cell anemia develop gallstones by 20 years of age.[22–24] Interestingly, in one study, patients with sickle cell disease and gallstones had rates of bilirubin production, bilirubin clearance, and plasma levels of unconjugated bilirubin similar to patients with sickle cell hemoglobin and no gallstones.[25] Thus the researchers suggested that excessive unconjugated hyperbilirubinemia alone is not sufficient to produce pigment gallstones. In that study, enlarged fasting and postprandial gallbladder volumes were found in patients who developed stones. It was hypothesized that stasis occurs as a result of incomplete emptying and leads to sludge and later to gallstone formation. In addition, genotyping may become a screening tool for predicting SCD children who are most likely to develop gallbladder disease.[26] Because gallbladder sludge is frequently documented in patients with sickle cell anemia, elective cholecystectomy has been recommended when evidence suggests the presence of sludge, with or without stones.[27] In one study of 35 patients with sickle cell disease and biliary sludge, 23 (65.7%) went on to develop gallstones.[28]

### COMPLICATIONS

Patients with SCD represent the largest group of patients at risk for postoperative complications after cholecystectomy. In a report of 364 cases from a national sickle cell disease

study group, the total complication rate was 39%, with sickle cell events representing 19%; intraoperative or recovery room problems, 11%; transfusion complications, 10%; postoperative surgical events, 4%; and death, 1%.[29] The open operation was performed in 58% of the patients, and the laparoscopic route was used in 42%. The complication rates were similar between the two groups. From that study, it was believed that the incidence of sickle cell events may be higher in patients who were not preoperatively transfused. Moreover, the laparoscopic approach is now recommended for this patient population.[30]

The acute chest syndrome can be seen in up to 20% of sickle cell patients undergoing abdominal operation. The laparoscopic approach did not decrease the incidence of this complication.[31] Meticulous attention to perioperative management, transfusion guidelines, and pulmonary care may reduce the incidence of the acute chest syndrome.

Two other hemolytic conditions commonly associated with gallstones are hereditary spherocytosis and thalassemia. The incidence of cholelithiasis in patients with hereditary spherocytosis ranges from 43% to 63% and is slightly more common in girls than boys.[32,33] Because of this association, US is recommended before elective splenectomy to determine whether concomitant cholecystectomy should be performed at the time of the splenectomy. Previously, patients with thalassemia major comprised a group of children at risk for cholelithiasis.[34] However, the incidence of cholelithiasis has markedly decreased in this patient population. This reduction has been attributed to a hypertransfusion regimen that blocks the bone marrow so that the fragile cells of thalassemia major are not produced.[35] Currently, patients with this disorder are rarely seen with cholelithiasis.

## CLINICAL PRESENTATION

Gallbladder disease in infants usually occurs during a systemic illness or following TPN use. Some infants will also have undergone ileal resection because of acquired diseases such as necrotizing enterocolitis or congenital anomalies. Jaundice may occur before gallstones are detected with US. Most of these stones are composed of calcium bilirubinate.

Gallstones that develop between 2 and 12 years of age are primarily composed of mixtures of calcium bilirubinate, with varying amounts of calcium carbonate and cholesterol. Opaque gallstones are sometimes detected on plain radiographs (Fig. 107-1), but the diagnosis is usually determined with US. Unfortunately, the diagnosis may be delayed in this young age group despite abdominal pain, nausea, emesis, and, occasionally, fever. Abdominal pain may vary from the typical right upper abdominal location to vague and poorly localized pain, especially in younger children. Older patients are usually more specific in localizing their pain to the right subcostal region.

The symptoms and physical findings in teenagers are similar to those found in adults. The pain is usually described as right subcostal with some radiation to the subscapular area. Nausea and vomiting commonly occur, and intolerance to fatty foods is often mentioned.

The primary reason for elective cholecystectomy in patients with cholelithiasis is to prevent associated complications. Four major complications can occur: cholecystitis, jaundice, cholangitis, and biliary pancreatitis. The incidence of acute cholecystitis seems to be increasing. In one report of 100 patients undergoing laparoscopic cholecystectomy, 22% presented initially with complications related to gallstones.[19] Seven presented with acute cholecystitis, six presented with jaundice and pain, five developed gallstone pancreatitis, and four had acute biliary colic without evidence of cholecystitis. Others have also reported a large number of patients presenting with symptomatic choledochal obstruction.[36,37] In such patients, management should be initially directed at trying to reduce the inflammation in the region, followed by laparoscopic cholecystectomy several days later.

## ACALCULOUS CONDITIONS

Hydrops of the gallbladder, acalculous cholecystitis, biliary dyskinesia, and gallbladder polyps are being seen more frequently. Hydrops is characterized by massive distention of the gallbladder in the absence of stones, infection, or congenital anomalies. It has been most frequently reported in association with Kawasaki disease and is usually due to a transient obstruction of the cystic duct or to increased mucus secretion by the gallbladder resulting in poor emptying.[38–42] With additional gallbladder distention, further angulation of the cystic duct may increase the obstruction.[43] Conservative treatment is initially recommended in this setting. Appropriate antibiotics for septic patients and early initiation of enteral feedings to stimulate gallbladder emptying often lead to resolution of this condition. If serial US examinations show progressive gallbladder distention with increasing pain, or if the gallbladder appears gangrenous, cholecystectomy is recommended.

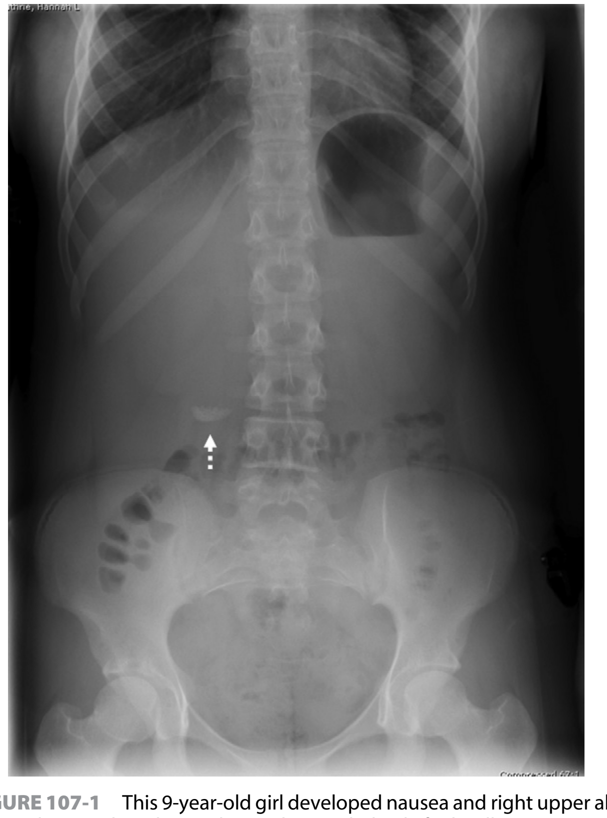

FIGURE 107-1 This 9-year-old girl developed nausea and right upper abdominal pain. This plain radiograph revealed calcified gallstones (*arrow*) that had settled in the dependent portion of the gallbladder on this upright abdominal film.

Acalculous cholecystitis commonly occurs in association with severe illness such as sepsis, burns, or trauma that results in dehydration, hypotension, and ileus. In this setting, TPN is often administered and, if prolonged, may be followed by decreased gallbladder contractility with progressive distention, stasis, and possible infection. In a small report of 12 patients, the investigators used daily US criteria for clues to indicate the need for cholecystectomy. In the three patients who underwent operation, there was progressively increasing gallbladder wall thickness and distention along with pericholecystic fluid. In the other patients, the daily US examinations found progressive improvement from the previous day's findings. These patients all recovered uneventfully.[44]

Biliary dyskinesia is now a common diagnosis in children.[45–56] In some centers, it has become the most common reason for cholecystectomy.[57–59] This disorder is characterized by poor gallbladder contractility and the presence of cholesterol crystals within the bile. It should be considered when patients present with typical biliary pain but no evidence of gallstones on US. Gallbladder contractility can be assessed with radionuclide scanning during cholecystokinin (CCK) injection. Recently, Lipomul has been shown to provide similar findings.[49] Most surgeons use a gallbladder ejection fraction of less than 35% as an indicator for cholecystectomy in a patient with symptoms.[53,59–62] Laparoscopic cholecystectomy has been shown to be an effective treatment for this disorder, with expected resolution of symptoms in more than 80% of the patients using this benchmark.* Chronic cholecystitis is often documented on histologic examination of the gallbladder specimen.[63] A few centers use a lower benchmark for operation. In a review of 51 patients who underwent laparoscopic cholecystectomy for symptoms consistent with biliary dyskinesia, it was found that nausea, pain, and a decreased gallbladder ejection fraction of less than 15% most reliably (93% PPV, 81% NPV) predicted which children will benefit from cholecystectomy for this condition. In that report, children with an ejection fraction greater than 15% did not have predictable resolution of symptoms.[46]

In a recent report from our institution, we have found that children with biliary dyskinesia have a marked increased number of mucosal mast cells in the gallbladder mucosa compared with patients with stone disease.[64] In a follow-up study, a moderate to high degree of mast cell activation was also found in children with both biliary dyskinesia and gallstones.[65] These findings provide biologic credibility for cholecystectomy in both patient groups.

Gallbladder polyps are being described more frequently in children.[66,67] Cholecystectomy is advisable if there are biliary symptoms or if the polyp is greater than or equal to 1 cm.[68,69]

Several unusual conditions merit attention. First, partial external biliary diversion interposing a jejunal loop between the gallbladder and abdominal wall has been described to treat the intractable pruritus in patients with progressive familial intrahepatic cholestasis.[70] We have used this technique as well with resolution of the pruritus. Thus in these children, cholecystectomy should be avoided. Second, ventriculo-gallbladder shunts have been performed in patients with a scarred peritoneal cavity from multiple previous operations or severe peritonitis.[71] We have performed one ventriculo-gallbladder shunt with a good result.

*References 45–48, 50, 51, 53, 59, 61–62.

## RADIOGRAPHIC EVALUATION

Although a plain abdominal radiograph is often the initial imaging study used to evaluate abdominal pain in children, it is rarely helpful with gallbladder disease unless the gallstones are calcified (see Fig. 107-1). The incidence of radiopaque stones has been reported to be as high as 50% in patients with hemolytic disorders compared with approximately 15% in adolescents with cholesterol stones.[72] Oral cholecystography is rarely used today because of the superior accuracy of US. Real-time US has an accuracy of approximately 96% for gallbladder disease and is effective in determining hepatic and common bile duct involvement, the presence of thickening of the gallbladder wall, and any abnormalities in the liver or head of the pancreas.[73] The most useful procedure for diagnosing acute cholecystitis is cholescintigraphy that uses technetium-99m-labeled iminodiacetic acid analogues. With this study, the gallbladder is not visualized in patients with acute cholecystitis. In critically ill patients, especially infants who are fasting, have severe associated illnesses, or are receiving TPN, there may be a false-positive result. Intravenous morphine may be useful in this setting because it causes spasm at the sphincter of Oddi, resulting in increased bile duct pressure. The latter, in turn, enhances visualization of the gallbladder and helps reduce the rate of false-positive studies.[74] Cholecystokinin-assisted or Lipomul-challenged cholescintigraphy is an accurate predictor of biliary dyskinesia and also suggests the likelihood of symptomatic relief with cholecystectomy.[45,46,48,49,75,76]

## NONSURGICAL TREATMENT

Nonsurgical treatment for gallstones in children or adults is of historical interest only. Previously, attempts at oral dissolution therapy or extracorporeal shockwave lithotripsy were attempted in adults with minimal success.[43,77,78] In one adult study evaluating lithotripsy, the duration of treatment, the high cost, and the 50% risk of recurrent gallstones within 5 years were significant disadvantages.[77] In these studies, children were not included for a variety of reasons including the fact that pigmented stones would not be amenable to these therapies. Currently, observation is not recommended for children older than age 2 or 3 years with gallstones. In some reports, gallstones that developed in infants secondary to prolonged TPN have been found to resolve spontaneously.[79–82] Thus a 6- to 12-month period of observation in this age group is not unreasonable after cessation of the TPN and initiation of enteral alimentation.

In a study of 55 patients with biliary dyskinesia comparing observation versus laparoscopic cholecystectomy, there was no difference (74% vs. 75%) in resolution of pain at 2 years between groups.[83] However, of those patients whose symptoms improved, those who underwent laparoscopic cholecystectomy had a much quicker resolution of pain compared with those who were observed.

## SURGICAL TREATMENT

Surgical treatment for symptomatic cholelithiasis consists of either cholecystectomy or cholecystolithotomy. In a preliminary report, one group reserved laparoscopic cholecystolithotomy for symptomatic cholelithiasis in patients before the onset of puberty.[84] However, long-term outcome data from

this approach are lacking. In another report of 10 patients undergoing cholecystolithotomy over 25 years with a mean follow-up of 5 years, 30% of the patients undergoing cholecystolithotomy were reported as having recurrent right upper abdominal pain and recurrent stones.[85] Because of the high recurrence rate, these authors believe that cholecystectomy is preferred in children.

The laparoscopic approach has become the standard method for cholecystectomy in children over the past 20 years. The major advantages of this approach include decreased discomfort and reduced length of hospitalization, an improved cosmetic result, and a faster return to routine activities such as work, school, play, or participation in athletic activities. These advantages result from less muscle disruption from the small incisions and reduced trauma to the tissue, leading to less discomfort and ileus than with the open approach. In most reports, children without complications undergoing laparoscopic cholecystectomy are ready for discharge on either the first or the second postoperative day.[19,53,75,86–88] However, there are recent reports of laparoscopic cholecystectomy being performed in children as an outpatient procedure.[59,89] Patients with sickle cell disease require special preoperative care to prevent postoperative complications. Several authors have reported favorable results with cholecystectomy in this patient population and have emphasized the need for preoperative transfusion.[29,31,90–92] From recent reports, the laparoscopic approach does not appear to be more hazardous for these patients and may be preferred.[19,29–31,91]

Several special circumstances merit attention. The first is the child with hereditary spherocytosis who is undergoing splenectomy. In these patients, a gallbladder US is recommended before the splenectomy. If gallstones are present, then cholecystectomy should be performed at the time of the splenectomy, regardless of whether the laparoscopic or open approach is used. Whether splenectomy protects these patients from the future development of cholelithiasis is unclear. However, in a study of 17 patients undergoing splenectomy alone in which cholelithiasis was not seen at the time of the splenectomy, none of the patients subsequently developed symptoms of cholelithiasis with a mean follow-up of 15 years.[93] Thus prophylactic cholecystectomy at the time of splenectomy is probably not indicated in patients with hereditary spherocytosis who do not have gallstones.

The second situation is that of the patient who presents with known or suspected choledocholithiasis in addition to cholelithiasis. A number of management strategies for such patients are available.[94–97] Options include preoperative endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and stone extraction, laparoscopic or open common duct exploration at the time of laparoscopic cholecystectomy, or postoperative endoscopic sphincterotomy with stone extraction, which is the approach commonly used in adults. This decision analysis appears to be related to two factors: the surgeon's experience with laparoscopic common duct exploration and the availability of ERCP and sphincterotomy in children and adolescents at the treating institution. For those pediatric surgeons who are facile with laparoscopic common duct exploration, this may be an attractive approach with postoperative endoscopic sphincterotomy reserved for the unsuccessful cases. However, for most pediatric surgeons, this is probably not the best option because postoperative endoscopic sphincterotomy is a rarely performed procedure in many pediatric surgical centers. Thus in this setting, it would appear best to perform preoperative ERCP with sphincterotomy and stone extraction if stones are found. If successful, the surgeon can then proceed with uncomplicated laparoscopic cholecystectomy in the next few days. However, if the endoscopic sphincterotomy and stone extraction are not successful, then the surgeon will know at the time of the operative procedure whether a laparoscopic or open common duct exploration is necessary (Fig. 107-2). Both approaches have been used at our institution.

A final preoperative concern is whether to perform an intraoperative cholangiogram. In the early to mid-1990s, when there was not much experience with laparoscopic cholecystectomy in children, it was suggested that most, if not all, children undergo a cholangiogram for surgeon-training purposes and to ensure that the correct anatomy has been visualized. A third reason was to evaluate for the presence of common duct stones, although this is often suspected preoperatively either from symptoms, US, or laboratory studies. As pediatric surgeons have gained more familiarity with the technique of laparoscopic cholecystectomy, routine intraoperative cholangiography for surgeon-training purposes does not appear necessary once the surgeon has become familiar with the technique. Thus in our minds, intraoperative cholangiography is useful primarily to ensure that the correct anatomy is visualized and to evaluate for choledocholithiasis. We often obtain a US evaluation a few days before the laparoscopic

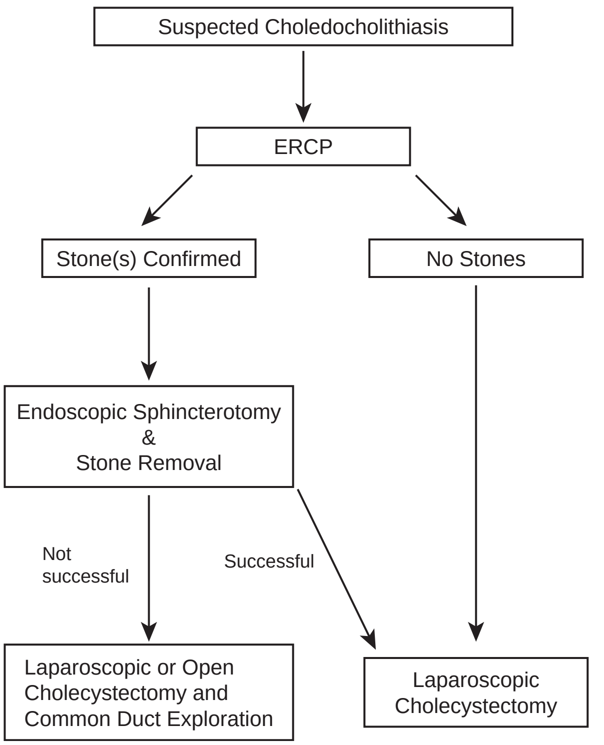


FIGURE 107-2 This algorithm depicts the authors' preferred strategy for managing patients with suspected choledocholithiasis. Preoperative endoscopic retrograde cholangiopancreatography (ERCP) is favored with stone extraction and sphincterotomy, if necessary, before the laparoscopic cholecystectomy. If the ERCP does not show evidence of choledocholithiasis, then laparoscopic cholecystectomy is performed. The reason this approach is favored is that, at the time of the laparoscopic cholecystectomy, the surgeon knows whether a laparoscopic or open choledochal exploration is necessary.

**TABLE 107-1**

**Financial Analysis of Preoperative Ultrasonography Versus Intraoperative Cholangiography for Detection of Choledocholithiasis at Children's Mercy Hospital, Kansas City, MO**

| *Immediate Preoperative Evaluation with Ultrasound* | *Charges* | *Intraoperative Cholangiography* | *Charges* |
|---|---|---|---|
| Ultrasound study (including radiologist's fee) | $307.67 | 15 minutes operating room time | $734.25 |
| | | C-arm with radiologist's fee | $365.41 |
| | | Sterile drape for C-arm | $20.00 |
| | | Cholangiocatheter | $83.50 |
| | | Contrast agent for cholangiogram | $40.00 |
| Total | $307.67 | Total | $1,243.16 |

cholecystectomy to confirm the presence of gallstones and to evaluate for common duct obstruction. This approach reduces the operative time and is cost effective (Table 107-1). Thus at the time of the operation, the primary need for cholangiography is to ensure the anatomic roadmap. If the anatomy appears clear at the time of the laparoscopic operation and there is no suspicion of common duct stones, routine cholangiography is not performed. If cholangiography is necessary, we still prefer the Kumar clamp technique, although a number of other techniques in which a catheter is introduced into the cystic duct through a transcystic incision are certainly appropriate.[1,98] Fluoroscopy is also useful because it is more time efficient than static radiography and allows dynamic assessment of the biliary tree (Fig. 107-3).

Another modification in the authors' technique over the past several years merits mention. For many laparoscopic operations including cholecystectomy, we have adopted a "stab incision" technique for instruments that are not continually exteriorized and reinserted into the abdominal cavity during the operation. In a study of 511 patients undergoing a variety of laparoscopic procedures in which only one or two Step (Covidien, Norwalk, Conn.) cannulas were used, a reduction of $187,180 was noted in the patient charges.[99] If the Ethicon (Ethicon Endosurgery, Cincinnati) disposable cannulas were used, patient savings of about $123,000 would have been realized. For cholecystectomy, the instruments placed through the two right-sided incisions are not routinely changed. Thus these two sites are optimal for the stab incision technique (Fig. 107-4). The telescope is introduced through the umbilical cannula, and the main working port is in the upper abdomen, so two Step cannulas are still used in these sites.

## LAPAROSCOPIC CHOLECYSTECTOMY

### Four-Port Technique

The patient is placed supine on the operating table with two video monitors situated at the head of the table. After induction of anesthesia, an orogastric tube is inserted for gastric decompression and the urinary bladder is evacuated using a Credé maneuver. A two-cannula and two "stab-incision" technique is used, but the location of the incisions and the cannulas depends on the patient's age and size (Fig.107-5). For infants and small children, the right lower abdominal incision can be positioned in the inguinal crease region and the epigastric cannula should be situated more on the patient's left to allow adequate working space between the instruments.

A 10-mm incision is made in the umbilicus, through which a 10-mm cannula is inserted into the abdominal cavity and abdominal insufflation is initiated. After creation of an adequate

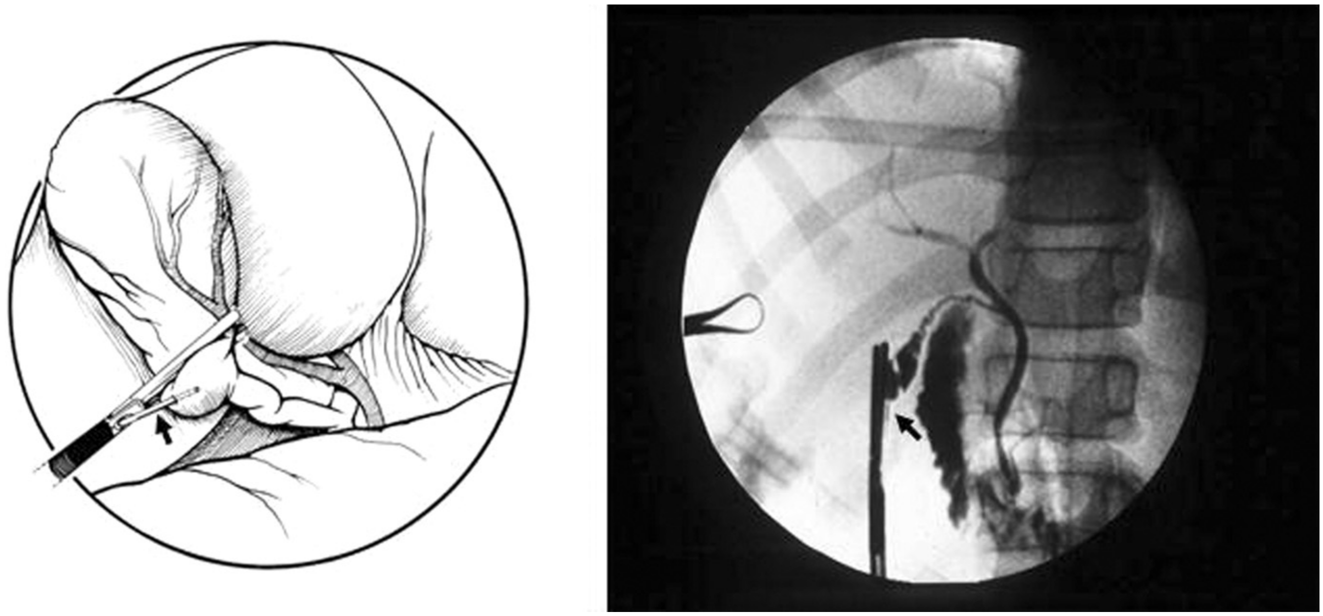

**FIGURE 107-3** The Kumar clamp technique for cholangiography in infants and small children is depicted. Note the clamp across the infundibulum and the sclerotherapy needle (*arrow*), which exits the side arm of the clamp and is introduced into the proximal infundibulum. The advantage of this technique is that lateral incision and cannulation of the small cystic duct are not necessary.

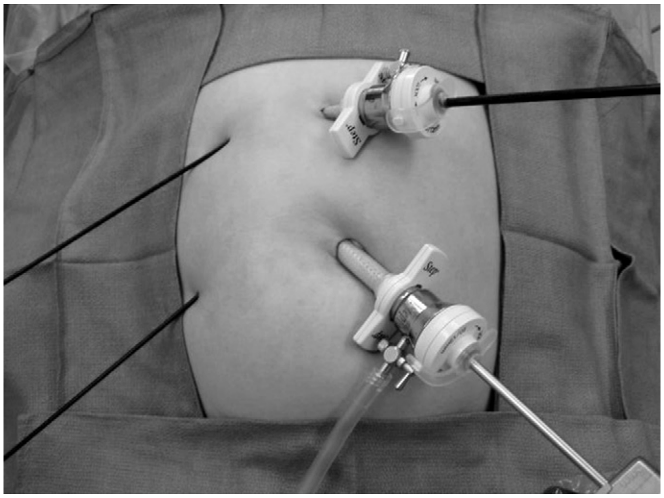

FIGURE 107-4 This operative photograph depicts the stab incision technique in a 5-year-old undergoing laparoscopic cholecystectomy. On the patient's right side, the two 3-mm instruments were introduced through the stab incision technique without the use of cannulas. A 5-mm cannula has been placed in the epigastric region, and a 10-mm cannula is introduced into the umbilicus. This is the site of extraction of the gallbladder. One advantage of the stab incision technique is cost savings because two additional cannulas are not necessary.

pneumoperitoneum, a 5- or 10-mm 45-degree telescope is inserted through the umbilical cannula and connected to the camera. The image is then displayed on the video monitors. The right lower abdominal stab incision is created with a No. 11 blade, and a locking, grasping forceps is introduced for retraction of the gallbladder superiorly over the liver by the assistant. Usually this is a 5-mm instrument, but a 3-mm instrument can be used in small children. Through the right upper abdominal stab incision, a nonlocking, grasping forceps is inserted for lateral retraction of the infundibulum of the gallbladder by the operating surgeon. The epigastric port is usually 5 mm in diameter and is the main working site. Occasionally, in larger adolescents, a 10-mm port may be necessary if a 10-mm endoscopic clip is required to completely occlude the cystic duct. Once the location of the cannulas is individualized according to the patient's size, the remaining principles of the procedure are similar to those used in adults.

For improved exposure, the patient and table are usually rotated into reverse Trendelenburg and left-dependent positions, which helps the adjacent viscera fall away from the surgical area. In addition, lateral retraction of the infundibulum is important because the cystic duct is then positioned at more of a 90-degree orientation to the common duct rather than an oblique or even parallel orientation, which occurs without such lateral retraction (Fig. 107-6). This parallel orientation may lead to misidentification of the cystic and common bile ducts resulting in injury to the common duct.

The initial surgical maneuver is to expose the cystic duct and identify the cystic artery. Adhesions between the duodenum and stomach often require lysis for access to the infundibulum and triangle of Calot. Once the cystic duct is identified, two options are available. One is to proceed with cholangiography as previously discussed. If the anatomy is clear and there is no evidence of choledochal obstruction on a preoperative US, we proceed with ligation and division of the cystic duct. Usually 5-mm clips are adequate, although a 10-mm clip may be required in larger patients. Two clips are placed on the cystic duct approximately 5 mm from its insertion into the common bile duct (Fig. 107-7). Another one or two clips are placed on the cystic duct near the infundibulum to prevent spillage of stones from the gallbladder. The cystic duct is then divided, and the cystic artery is similarly ligated and transected. Once these two structures are divided, the gallbladder is detached in a retrograde manner using one of several instruments: the hook cautery, spatula cautery, or endoscopic scissors attached to the cautery.

Before the gallbladder is completely separated from the liver bed, the triangle of Calot should be carefully inspected to ensure that all clips are secure and that there is no evidence of bleeding. After complete detachment of the gallbladder, the telescope is rotated from the umbilical port to the epigastric port. If the epigastric port is 5 mm, then a 5-mm telescope is used to visualize the gallbladder and a locking, grasping instrument is introduced through the umbilical cannula to secure the gallbladder. The gallbladder is then extracted through the umbilical port. In older patients, the gallbladder may be too large for removal without further incising the umbilical fascia. This opening should be enlarged in patients with large gallbladders to prevent rupture with spillage of stones and bile during removal of the gallbladder. These gallstones, if spilled, should be removed because complications from retained stones have been reported in adults.[15,100,101] After the gallbladder is extracted, the area of dissection is again

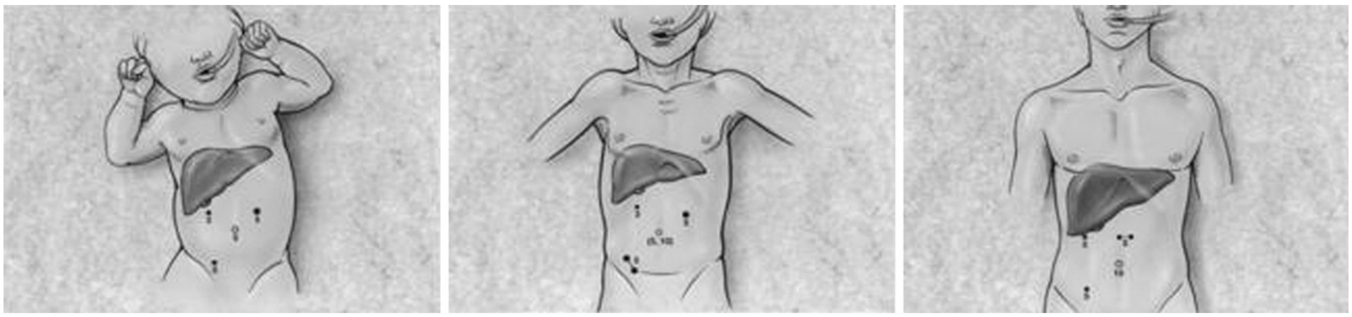

FIGURE 107-5 Placement of the cannulas and instruments in patients undergoing laparoscopic cholecystectomy depends on the patient's age and size. In an infant, 3- and 5-mm ports/instruments can be used. Also, the ports/instruments should be separated as much as possible to create an adequate working space for the operation (*left*). In a prepubertal child the port/instruments should be widely spaced as well. A 3-mm instrument can often be used in the surgeon's left hand. In younger patients in this age range, a 5-mm umbilical cannula may be possible. However, for most patients, a 10-mm umbilical cannula is necessary to extract the gallbladder through this incision (*middle*). In a teenager, the port placement more closely resembles that seen in adults (*right*).

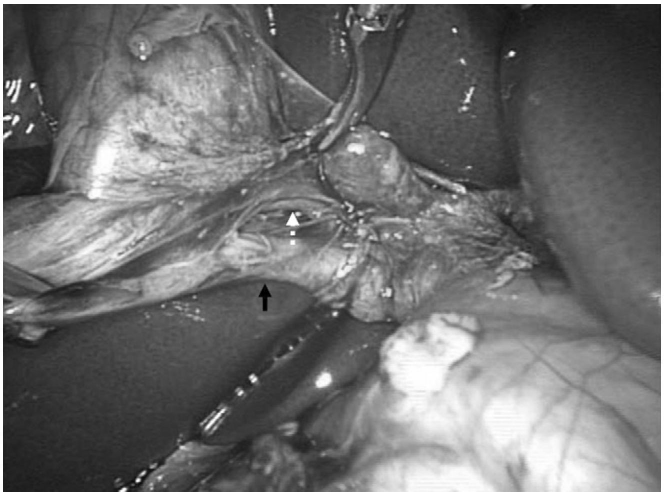

**FIGURE 107-6** During the initial stages of the laparoscopic cholecystectomy, it is vitally important to retract the infundibulum directly lateral so as to create a 90-degree angle between the cystic duct (*solid arrow*) and common duct. Note the cystic artery (*dotted arrow*) cephalad to the cystic duct.

carefully inspected to ensure adequate hemostasis. All irrigant is evacuated, and bupivacaine is injected into the incisions for postoperative analgesia. In smaller patients, the fascia surrounding the 5-mm cannula sites should be closed. In larger patients, fascial closure for the 5-mm ports or stab incisions is usually unnecessary, but the fascia surrounding the 10-mm cannula sites should be approximated carefully to prevent herniation. For the stab incisions, skin closure is usually all that is necessary. The patients are usually hospitalized after the procedure and discharged the next morning.

### Single-Site Umbilical Laparoscopic Cholecystectomy

Single-site umbilical laparoscopic surgery (SSULS) is being used more and more frequently for common surgical procedures such as cholecystectomy and appendectomy. It has also been used for splenectomy, pyloromyotomy, and ileocecectomy for Crohn disease. When compared with traditional three- and four-port/incision laparoscopic surgery, the only advantage of SSULS appears to be cosmesis. SSULS has become an attractive alternative between traditional laparoscopic surgery and natural orifice transluminal endoscopic surgery (NOTES) because there are a number of real and potential complications with access to the abdominal cavity with NOTES. Similar to SSULS, the only advantage of NOTES over traditional laparoscopic procedures is cosmesis.

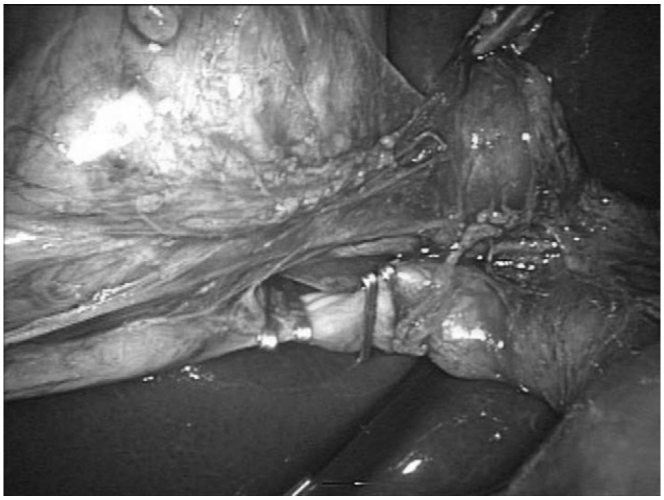

**FIGURE 107-7** After identification and isolation of the cystic duct, the duct is doubly ligated with two clips proximal and two clips distal. The duct will be divided between the two middle endoscopic clips.

For single-site laparoscopic cholecystectomy, an umbilical incision of approximately 2 cm is necessary. For this particular indication, our group uses either the SILS port (Covidien, Norwalk, Conn.) or the Tri-Port (Olympus America, Center Valley, Pa.). The SILS port is a foam port with three channels through which the telescope and instruments are introduced. A fourth instrument is then introduced along the side of the foam port for retraction of the gallbladder (Fig. 107-8, *A*). There is also a channel for insufflation. The TriStar port is designed for three instruments, but a fourth 3-mm instrument can be introduced through one of the insufflation portals (Fig. 107-8, *B*). As with other SSULS procedures, it is helpful to have a long telescope so that the telescope/camera holder can stand away from the operating surgeon. Once the telescope and instruments are introduced, the operation proceeds

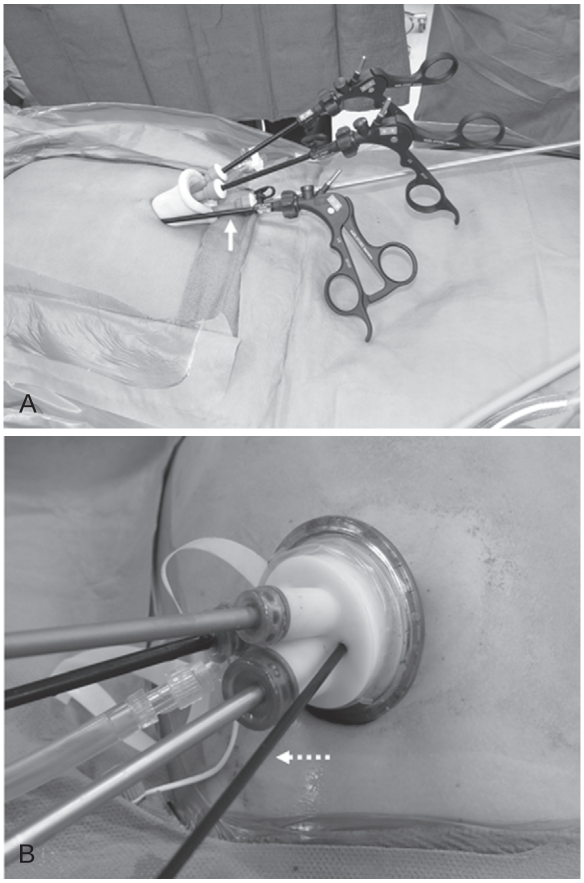


**FIGURE 107-8** For single-site laparoscopic cholecystectomy, an umbilical incision of approximately 2 cm is necessary. Our group uses both the Covidien SILS port (**A**) and the Olympus Tri-Port (**B**). The SILS port is a foam port with three channels through which the telescope and instruments are inserted. A fourth instrument (*arrow*) is then introduced along the side of the SILS port for retraction of the gallbladder over the liver. The Tri-Port is designed for single-site umbilical surgery as well. We insert a fourth 3-mm instrument through one of the insufflation ports (*dotted arrow*), if necessary.

exactly like a traditional four-port laparoscopic cholecystectomy. The instrument used to grasp the dome of the gallbladder is introduced at approximately 9 o'clock in the SILS or TriStar port, and another instrument is used to retract the infundibulum. With the SILS port, this instrument is introduced along the side of the port in the umbilical incision. The telescope should be angled at 30 to 45 degrees. As with traditional laparoscopic cholecystectomy, it is important to retract the infundibulum of the gallbladder laterally to create a right-angle orientation of the cystic and common bile ducts. Following identification and dissection of the cystic duct and cystic artery, the duct is ligated with endoscopic clips (Fig. 107-9, *A*). In a similar fashion, the cystic artery is divided as well (Fig. 107-9, *B*). After division of the cystic duct and cystic artery, the gallbladder is dissected free from its liver attachment using electrocautery. A number of instruments can

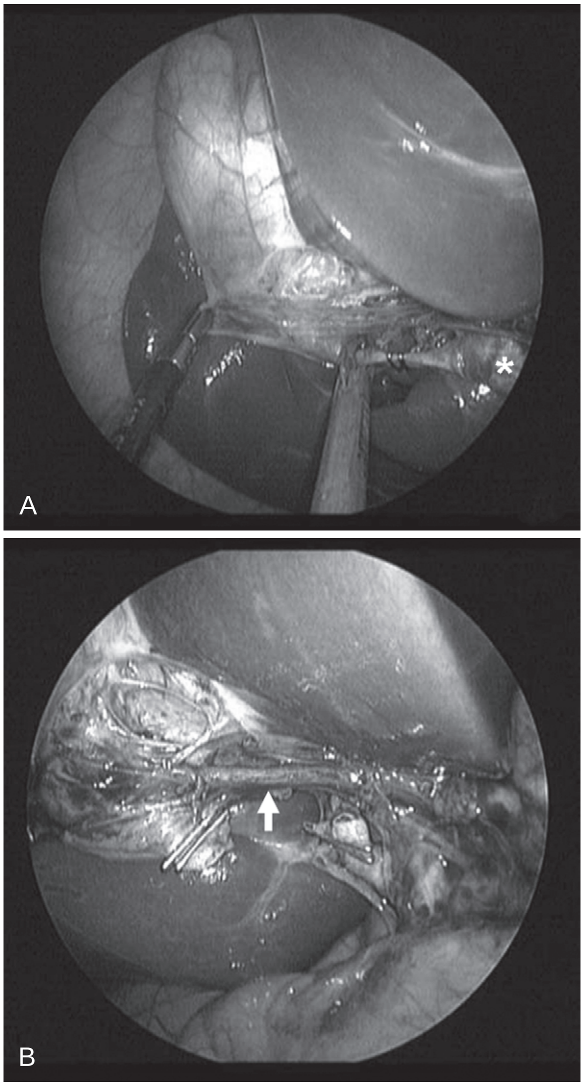


**FIGURE 107-9** Once the telescope and instruments are introduced, the operation proceeds exactly like the traditional four-port laparoscopic cholecystectomy. It is important to retract the infundibulum of the gallbladder laterally to create a right-angle orientation of the cystic and common bile ducts. In the top photograph (**A**), the endoscopic clips are being applied to the cystic duct. Note the right-angle orientation of the cystic and common bile ducts (*asterisk*). Following ligation and division of the cystic duct (**B**), the cystic artery (*arrow*) is well visualized and will be similarly ligated and divided.

**FIGURE 107-10** This teenager underwent a single-site umbilical laparoscopic cholecystectomy and was discharged the following day. She has achieved a nice cosmetic appearance at 1 month postoperatively. (She removed her belly-button ring for this photograph.)

be used for this purpose including the hook cautery, spatula cautery, or a Maryland dissector attached to cautery. After complete mobilization of the gallbladder, it is then grasped with an instrument placed through one of the channels in the umbilical port and exteriorized through the umbilical incision along with the port. Before extracting the gallbladder, it is helpful to assess for bleeding and to irrigate/suction because it would be necessary to reintroduce the umbilical port to recreate the pneumoperitoneum to perform these functions after removing the gallbladder.

The umbilical fascia is then closed with 0 absorbable suture in an interrupted or continuous fashion. We prefer to close the skin with interrupted 5-0 plain sutures, which is our usual practice for umbilical skin closure for traditional laparoscopic surgery. A nice cosmetic result is achieved using this SSULS approach for cholecystectomy (Fig. 107-10).

## CHILDREN'S MERCY HOSPITAL EXPERIENCE

Despite the widespread use of laparoscopic cholecystectomy in children, there are surprisingly few reports in the literature describing a series as large as 100 patients.[19,37,53,58,61,94] In a 1999 review of 100 patients undergoing laparoscopic cholecystectomy at Vanderbilt University Medical Center, one of the authors (GWH) described 78 children who underwent an elective operation and 22 who required an urgent operation for acute complications of cholelithiasis.[19] In that series, 19 patients had hemolytic disease and two patients had biliary dyskinesia. The six patients who presented with jaundice underwent ERCP before the laparoscopic cholecystectomy. Stones were extracted in two patients, and the other studies were normal. In that report, two patients required laparoscopic choledochal exploration. The operating time and postoperative hospitalization were significantly longer for the complicated group when compared with the elective patients. No significant complications occurred such as the need for reoperation, injury to the choledochus or other viscera, bile leak, or retained choledocholithiasis.

Recently, our group reported a 6-year experience with traditional four-port laparoscopic cholecystectomy at Children's Mercy Hospital (Table 107-2).[53] Between September 2000 and June 2006, 224 patients underwent laparoscopic

**TABLE 107-2**
**Patients Undergoing Laparoscopic Cholecystectomy at Children's Mercy Hospital (September 2000 to June 2006)**

| *Symptomatic gallstones (Hemolytic Disease)* | *166 (29)* | *Mean Age (Yr)* | *12.9 (0-21)* |
|---|---|---|---|
| Biliary dyskinesia | 35 | Mean weight (Kg) | 58.3 (3-121) |
| Gallstone pancreatitis | 7 | Mean operating time (min) | 77 (30-285) |
| Concomitant splenectomy | 6 | Major complications | 1 |
| Calculous cholecystitis | 5 | | |
| Miscellaneous | 5 | | |
| | 224 | | |

From St. Peter SD, Keckler SJ, Nair A, et al: Laparoscopic cholecystectomy in the pediatric population. J Laparoendosc Adv Surg Tech A 2008;18:127-130.

cholecystectomy.[53] The mean age was 12.9 years (range 0 to 21 years) with a mean weight of 58.3 kg (range 3 to 121 kg). One hundred and sixty-six children had symptomatic gallstones, 35 children had biliary dyskinesia, seven patients presented with gallstone pancreatitis, six patients were undergoing splenectomy and found to have gallstones, five patients had calculous cholecystitis, and one patient each had choledocholithiasis, gallbladder polyp, acalculous cholecystitis, and congenital cystic duct obstruction. In this series there were only 29 patients with hemolytic disease. Eighteen patients had sickle cell disease, and 11 had hereditary spherocytosis. The mean operative time (excluding patients undergoing a concomitant operation) was 77 minutes (range 30 to 285 minutes).

Due to preoperative concerns about choledocholithiasis, a preoperative ERCP was performed in 17 patients. Stones were retrieved endoscopically in eight of these patients. Additionally, an operative cholangiogram was performed in 38 patients and common duct stones (CBD) were identified in 9 patients. CBD stones were cleared intraoperatively in five patients, while the other four patients required postoperative endoscopy and sphincterotomy to retrieve the stones. Because of a postoperative rise in direct bilirubin, two patients who did not have an intraoperative cholangiogram underwent a postoperative ERCP. The ERCP was normal in both cases.

There were no conversions, ductal injuries, bile leaks, or mortality. However, one sickle cell patient developed a postoperative hemorrhage, which required laparotomy for control. Interestingly, biliary dyskinesia was diagnosed in only 10% of the first 30 patients in this series but was diagnosed in 40% of the last 30 patients studied. The mean ejection fraction in these patients was 21%. All of these patients had improvement in their symptoms following the laparoscopic cholecystectomy.

Over the past 10 years, laparoscopic cholecystectomy has become the accepted standard for removal of the gallbladder in children and adolescents. Reported complications have been rare. There are no reports of choledochal injury in children, although some have undoubtedly occurred. As additional experience is gained, pediatric surgeons may use intraoperative US rather than cholangiography to assess the correct anatomy and the presence of choledocholithiasis.

SSULS is also being used for gallbladder removal at our institution. A prospective, randomized trial is under way at our hospital comparing single-site umbilical laparoscopic cholecystectomy with traditional four-port laparoscopic cholecystectomy. Operative time is the primary outcome variable. Using an alpha of 0.05 and a power of 0.80, a total of 60 patients will be enrolled. To date, 42 patients have participated in this trial.

# Hepatic Infections

Various hepatic infections occur in infancy and childhood (Table 105-3). The focus in this section of the chapter is on hepatic infections that often require surgical consultation for either diagnosis or treatment. This group includes hepatic abscess and nonviral causes of liver infection. In most pediatric series, more than half of liver abscesses are found in patients younger than 5 years of age and more than 25% occur during the first year of life.[102–104]

## PATHOPHYSIOLOGY

Bacteria and other organisms may enter the liver through various routes, the most common being the biliary tract, the portal vein, and the hepatic artery. Also, organisms may directly invade the liver during penetrating trauma. In one report, a liver abscess occurred in 4 of 16 patients with unruptured post-traumatic intrahepatic hematomas.[105]

The clinical signs and symptoms of liver abscess are usually nonspecific. The most common signs and symptoms are fever, abdominal pain, and hepatomegaly. Abnormalities in leukocyte count, liver enzyme levels, or bilirubin levels vary in degree. Symptoms may last from days to months. The diagnosis of an hepatic abscess with imaging techniques has improved markedly with the availability of US and computed tomography (CT) (Figs. 107-11 and 107-12).[102,103]

## PYOGENIC LIVER ABSCESS

Pyogenic liver abscess (PLA) is uncommon in children, with a reported incidence varying from 3 to 25 per 100,000 pediatric hospital admissions.[106] Its incidence has decreased since the introduction of antibiotics. In contrast to adults, in whom

**FIGURE 107-11** Computed tomography scan demonstrating several hepatic abscesses (defects) in a child with staphylococcal infection related to chronic granulomatous disease.

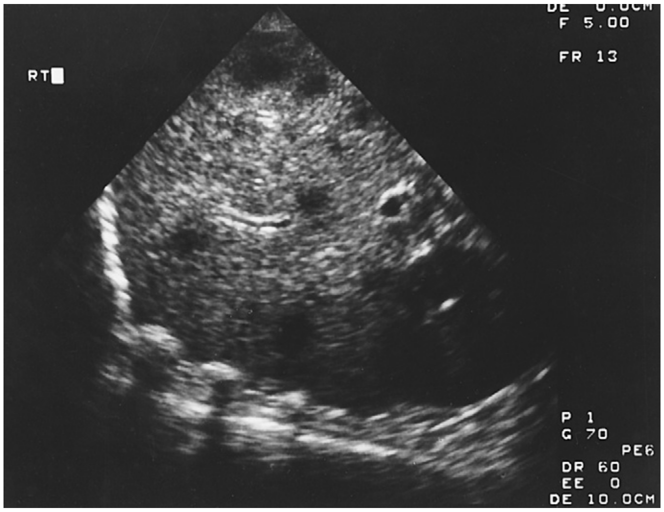


**FIGURE 107-12** Sonogram demonstrating several hepatic abscesses (echolucent areas) in the same patient as in Figure 107-13.

biliary tract disease is the primary cause of hepatic abscess, pyogenic liver abscess in children can be caused by a number of different conditions. Historically, the most frequent cause of hepatic abscess in children was perforated appendicitis. The development of hepatic infection in this setting was presumed to be due to pylephlebitis of the mesenteric and portal veins with ascending migration of bacteria into the liver. An intra-abdominal source of bacteria is still a common etiology of PLA, but liver abscesses are also seen in children with chronic malnutrition, granulocyte dysfunction, sickle cell disease, and with congenital or acquired immunosuppression.

Chronic granulomatous disease of childhood is one of the more common immunodeficiencies. Also, acquired impairment in host resistance, such as that caused by chemotherapy or transplantation immunosuppression, can predispose patients to hepatic abscess formation. In immunocompetent children, causes for PLA include an intestinal source (i.e., appendicitis, Crohn disease), chronic cholangitis with intrahepatic abscess formation in patients with biliary atresia or choledochal cysts, umbilical vein catheterization (neonates), and systemic bacteremia of any cause.[107] Abdominal trauma, either penetrating or blunt, with liver injury is also associated with an increased incidence of hepatic abscess.[108,109] Abscesses in such cases are presumed to be secondary to bacterial seeding of the devitalized liver parenchyma and are often associated with a hematoma. It must be remembered, however, that liver abscesses do occur in otherwise normal children without any obvious predisposing conditions.[110,111] In 20% of these patients, the infectious source of the hepatic abscess is never found.[112]

The diagnosis of a PLA is often dependent on its being considered as part of the differential diagnosis. The low incidence of liver abscess in childhood leads to a low index of suspicion and sometimes delays the diagnosis for weeks to months. The overall mean age of presentation for PLA is reported to be 7.5 years with children from developing countries presenting at younger ages and children from developed countries presenting at older ages.[113] The classic signs and symptoms of fever, abdominal pain, jaundice, and liver enlargement occur infrequently, which is why the diagnosis is often missed. These symptoms can develop slowly and, if associated with weight loss, can lead initially to the suspicion of cancer. Usually the presenting symptoms are nonspecific, with the major symptom being abdominal pain.[106,110] The duration of symptoms is highly variable, but usually patients present between 1 week and 1 month after they become ill. Most patients are febrile, but an enlarged liver is rarely found on physical examination. Right upper quadrant tenderness is only found in about 40% of patients.[107] Hematologic studies are usually not helpful because only mild leukocytosis is seen. Elevated liver function studies are found in only one half of the patients. Inflammatory markers, however, are frequently elevated in patients with a PLA.[113]

When the bacteriology of pyogenic abscesses is examined in children, *Staphylococcus aureus* is the primary infecting agent in 37% to 50% of the children.[106,110,112,114] Most hepatic abscesses, however, tend to be polymicrobial with gram-positive cocci and gram-negative rods including *Escherichia coli, Klebsiella, Enterobacter,* and *Pseudomonas.* Recently, anaerobes have also been cultured from these abscesses in at least 20% of the cases.[114–116] Blood cultures are positive in about 50% of patients. However, blood cultures often grow fewer bacterial types than are subsequently recovered from direct cultures of the abscess. As a cautionary note, in a third of the blood cultures, the organisms that were recovered from the blood were not subsequently recovered from the cultures of the liver abscess. Unfortunately, whereas Gram stains of a direct aspirate from a liver abscess are highly accurate for gram-positive cocci, they have only a 50% sensitivity for gram-negative organisms.[117] Fungal abscesses have been found with an increasing incidence in children who become febrile and neutropenic while being treated for acute leukemia.[118] One prospective series reported a 29% incidence of fungal hepatic and/or splenic abscesses in this population.[119] A specific ultrasonographic appearance for hepatic and splenic candidiasis has been described.[120]

Neonates comprise another special subpopulation of patients. In the perinatal period, direct transplacental bacterial seeding of the liver can occur. This seeding may be associated with premature rupture of membranes. Omphalitis, with or without catheterization of the umbilical vein, has been rarely associated with bacterial hepatitis or abscess. Most of the time these abscesses are miliary. There is a disproportionately high representation of gram-negative organisms in the neonatal hepatic abscess. Because they are usually miliary, they are not amenable to percutaneous drainage. Therefore high-dose, long-term antibiotic treatment is necessary.

In those neonates who presented with a solitary hepatic abscess, the offending organism is usually *S. aureus.* These patients present with an enlarging right upper quadrant mass that is often confused with a tumor. Treatment of these solitary abscesses has often been resection because of the difficulty in distinguishing between an abscess and a solid tumor.[121]

## RADIOLOGIC EVALUATION

The radiologic studies that are most helpful in the diagnosis of PLA are abdominal US and CT. US is usually preferred as the initial screening tool because of the lack of need for sedation and the absence of ionizing radiation. CT, however, is more sensitive and can discover lesions that are missed by US. In addition, CT is usually the preferred radiologic modality for localization of the abscess for percutaneous drainage.[106]

On radiologic evaluation, PLAs can present as either a solitary lesion or as multiple lesions. There is also a predisposition for the lesions to be in the right lobe of the liver.[122]

## TREATMENT

The initial treatment of a PLA should be with broad-spectrum antibiotics with coverage for gram-positive, gram-negative, and anaerobic organisms. As part of the gram-negative spectrum, *Pseudomonas* coverage must be included. The preferred therapeutic and diagnostic intervention is percutaneous drainage/aspiration of the abscess under either CT or US guidance. After the abscess has been drained and specific bacteria have been recovered, antibiotic therapy can then be tailored to cover these organisms. The recommended duration of intravenous antibiotic therapy is 4 to 6 weeks, followed by oral antibiotics for an additional 4 to 8 weeks.[104] The complication rate of percutaneous drainage has been reported to be about 4%, with a failure rate of 15%.[123] However, if the patient does not respond to percutaneous drainage or if percutaneous drainage is not possible, then an operative approach is warranted.[110,124] One study reported the laparoscopic approach for drainage of a pyogenic liver abscess.[125] With an aggressive approach to treatment of pyogenic liver abscess, the mortality of this condition has dropped from 36% in the 1970s to 15% in the late 1980s and 10% now.

One complication of PLA that has been reported in the adult population is endophthalmitis. In one series, there was a 3.5% incidence of this complication, which can lead to a variety of devastating visual problems, ranging from decreased visual acuity to complete blindness.[126] The best results for recovery were associated with initiation of treatment within 24 hours of any visual symptoms. Therefore a child who appears to be having any visual difficulties with a pyogenic abscess should undergo an ophthalmologic evaluation.

## CAT-SCRATCH DISEASE

Cat-scratch disease is a subacute illness preceded by exposure to an infected cat. It is characterized by regional lymphadenitis but may involve other organ systems including the liver, brain, and bone. This disorder was first described as oculoglandular syndrome in 1889, and the association with a scratch by a cat was reported in 1950 by Debre.[127] Since then, various infectious organisms have been postulated as the etiologic agent. Cat-scratch disease is now known to be caused by *Bartonella henselae* and is seen throughout North America with most cases occurring in late summer to fall. The disease primarily affects children and adolescents (75% to 80% of cases). A primary lesion develops at the site of inoculation in most cases, usually within 1 to 2 weeks of inoculation. This lesion is typically a single papule 2 to 5 mm in diameter. Regional lymphadenopathy develops approximately 3 weeks later and frequently involves axillary, inguinal, and cervical nodes. The primary skin lesion has often resolved by the time the adenopathy occurs. Other associated symptoms are fever, anorexia, malaise, fatigue, and headache. Traditionally the diagnosis has been confirmed by acute/convalescent IgG titers. Recently, polymerase chain reaction (PCR) of tissue, lymph node, or peripheral blood has been found to be both sensitive and specific for *B. henselae,* as well as having a rapid turn-around time.[128]

It is estimated that 5% to 10% of patients present with significant systemic symptoms or atypical manifestations of the disease. In these patients, the typical regional adenopathy may be absent.[129] Patients who are immunosuppressed are also at risk for cat-scratch disease. There have been several recent reports documenting cat-scratch disease causing liver masses in patients after liver transplantation.[130–132]

Liver involvement is the third most common clinical manifestation of cat-scratch disease after fever and lymphadenopathy.[133] It is usually diagnosed by abdominal CT, which is performed as part of the evaluation for fever of unknown origin. This test typically shows multiple lesions in both lobes of the liver and, sometimes, associated splenic involvement.[127,134] The diagnosis is confirmed by liver biopsy, either open or guided by laparoscopy. The histologic features consist of a granulomatous reaction with necrosis. Cultures of the lesions are usually negative for bacteria and fungi. Treatment of cat-scratch disease remains controversial because most untreated cases resolve without sequelae. Patients with marked symptoms or visceral involvement are usually treated with antibiotics (e.g., gentamicin, ciprofloxacin, rifampin, or azithromycin).[135] Currently azithromycin is the agent of choice for uncomplicated disease. For hepatic involvement, a multidrug regimen (gentamicin and rifampin) has been used for 2 to 3 weeks.[136]

## PERIHEPATITIS

In the pediatric population, bacterial liver infection with either *Neisseria gonorrhoeae* or *Chlamydia trachomatis* tends to occur most frequently in teenage girls. The initial pelvic infection travels cephalad in the abdomen, resulting in the perihepatitis. If the perihepatitis is untreated, then the classic "violin string" adhesions develop between the liver and the peritoneal cavity that are associated with the Fitz-Hugh-Curtis syndrome.

In addition to the typical symptoms of pelvic inflammatory disease including dysmenorrhea, vaginal discharge, and lower abdominal pain, these patients also present with severe pleuritic right upper abdominal pain that often radiates to the right shoulder. It is not unusual for the patient to complain of left upper quadrant pain as well. In these patients, the liver is often tender to palpation and a rub may be audible near the costal margin. Pelvic findings of acute salpingitis are usually present. Laboratory findings include leukocytosis, elevated aminotransferase levels, and occasional hyperbilirubinemia.

Perihepatitis can mimic a variety of other conditions in the upper abdomen including cholelithiasis, hepatitis, a perforated peptic ulcer, appendicitis, or pancreatitis. In female adolescents with a history of pelvic inflammatory disease, perihepatitis must be part of the differential diagnosis when these patients present with right upper quadrant pain. Recently, dynamic abdominal CT scanning including the arterial phase has been reported as an important tool in the diagnosis of this syndrome.[137] If the arterial phase of the scan shows hepatic capsular enhancement (secondary to increased blood flow in the inflamed hepatic capsule), then the diagnosis of Fitz-Hugh-Curtis syndrome can be made without further invasive studies.

In patients in whom the diagnosis is uncertain or in patients who have persistent symptoms, diagnostic laparoscopy can allow direct visualization of the perihepatic space.

If found, the classic adhesions can be lysed, which often results in a significant improvement in pain.[138]

Recent reports have implicated *C. trachomatis,* in addition to *N. gonorrhoeae,* as a cause of this syndrome.[137,139] Therefore a treatment regimen that is effective against both chlamydial infection and gonococcus is necessary. This would include tetracycline or doxycycline or erythromycin for patients in whom tetracycline is contraindicated.[140]

## AMEBIC ABSCESS

The incidence of amebic liver abscess in the United States seems to have gradually increased. Hepatic involvement by *Entamoeba histolytica* is primarily a disease of adults but does occur in younger patients, most commonly in early childhood.[141] Poor sanitation and crowded conditions help foster the development and spread of amebiasis. In patients with amebic colitis, trophozoites from colon ulcers travel through the portal vein to the liver, where they initiate a necrotizing process with subsequent abscess formation. In the adult population, liver involvement with an amebic abscess occurs in 10% to 50% of adults with a 90% male predominance. In children, however, liver involvement occurs in only 1% to 7% of the patients with an equal distribution between males and females.[142–144] Corticosteroids and immunosuppression seems to predispose patients to amebic abscess formation.

More than 80% of amebic liver abscesses occur in the right lobe of the liver. Symptoms include fever, chills, nausea, weight loss, and abdominal distention. On physical examination, the children tend to have hepatomegaly, but abdominal pain and liver tenderness are relatively infrequent. Breath sounds are often decreased in the lower right chest, and right-sided pleural effusions are common. Clinical jaundice is uncommon. A history of exposure or travel to endemic areas (Mexico, South America, or Southeast Asia) is often a better indicator of amebiasis than are the imaging studies.[145] In the United States the typical patient is a child of immigrants who come from an area that is endemic for amebiasis but are not necessarily living in poverty.[146]

Laboratory findings include leukocytosis without eosinophilia, mild anemia, and normal or mildly abnormal liver function studies. Abdominal US and CT are useful for defining the location and number of lesions. The characteristic US appearance is a hypoechoic, thin-walled abscess that sometimes contains air. CT shows a nonspecific picture of a well-circumscribed, low-density lesion that is usually solitary and has predominance for the right lobe of the liver. Also, with modern imaging techniques, it is now clear that multiple amebic abscesses can be found within the liver.[147]

The diagnosis of an amebic liver abscess relies on the identification of a space-occupying lesion in the liver and the presence of positive amebic serology. Amebic serology (indirect hemoglobin assay or agar gel immunodiffusion precipitant) has been found to be highly sensitive (>94%) and highly specific (>95%) for the diagnosis of amebic liver abscess.[148] PCR analysis for *E. histolytica* and *E. dispar* has become available and may prove to be more sensitive and specific than the previous assays.[149] If it is not possible to distinguish clinically between a pyogenic versus an amebic liver abscess, if the abscess does not respond to appropriate medical treatment, or if serologic tests for ameba are inconclusive, then aspiration of the abscess is indicated for culture.

The current treatment for an amebic abscess is oral metronidazole (30 to 50 mg/kg/day divided 3 times a day for 7 to 10 days). Most patients will respond to this therapy with resolution of their fever and abdominal pain. Currently there is no indication for aspiration of an uncomplicated amebic abscess because the majority of these will resolve with medical management alone.[147,150–152] If the patient does not respond to medical management within 4 days, if the liver abscess is greater than 5 cm in diameter, if it is located in the left lobe of the liver, or if it is believed to be in danger of rupture, then aspiration and percutaneous drainage is advisable. In addition, percutaneous catheter drainage is also indicated in patients who have had rupture of an amebic abscess into the right pleural space. Total resolution of the abscess may take months to years and can be followed by US.

The most common complication of an amebic liver abscess is erosion through the diaphragm and rupture into the right chest. The rupture rate of a right lobe amebic liver abscess is relatively low, but the rupture rate of a left lobe abscess has been reported to be as high as 22%.[153] Intraperitoneal rupture of an amebic abscess carries a 20% to 75% mortality, and the patients who are at the highest risk are those who present with acute peritonitis.[154,155] Intraperitoneal rupture results in a clinical picture of peritonitis and shock. If this develops, fluid resuscitation, antibiotics, antiamebic drugs, and surgical exploration are necessary. Erosion into the pericardial sac is less frequent but may cause cardiac tamponade. Erosion into intra-abdominal organs including the stomach has also been reported.[146,156]

There have been attempts at developing a vaccine for *E. histolytica* in an attempt to eradicate amebiasis. However, unfortunately in some cases, a natural infection with *E. histolytica* does not seem to result in long-term immunity. In fact, recurrent amebic liver abscesses are a well-known problem in areas where *E. histolytica* is endemic.[157–159]

## ECHINOCOCCAL CYST

Hydatid disease is generally caused by infection with the larval stage of the dog tapeworm *Echinococcus granulosis.* The ingested ova burrow through the intestinal mucosa and travel to the liver through the mesenteric veins. A few ova may bypass the liver and be trapped in the lung. The reported peak incidence of echinococcal infection in children is between 5 and 15 years of age.[160,161] The liver is involved in about 60% of the cases, the lung in about 20%, and other organs (kidney, brain, bone, or muscle) in about 20% of the cases. A solitary cyst will develop in one organ about 80% of the time.[162] The host organ separates itself from the parasite by forming a pericyst, which is a capsule of native connective tissue. For most surgical procedures, the pericyst is left behind and the intraluminal contents of the cyst are removed.

The usual presenting symptoms include right upper quadrant pain, a mass, and right pleuritic type chest pain in about one half of the patients. Interestingly, about a fourth of the patients are asymptomatic at presentation. Untreated cysts tend to grow until they reach the surface of the liver, where they can then spontaneously rupture, resulting in dissemination of the parasite into the peritoneal cavity and possible anaphylaxis.[163] In one fourth of the cases, the cyst can become secondarily infected with bacteria.[147] Echinococcal liver abscess is best diagnosed by serologic testing. The indirect hemagglutination

assay is the most specific test, but it lacks sensitivity for echinococcal disease. Results are considered positive for tissue invasion at a titer of 1:512, suspicious at a titer of 1:128, and negative at a titer of 1:32. Additional tests include an enzyme-linked immunosorbent assay (ELISA), which has been reported to be positive in 96% of patients, or a compliment fixation test, which has an 89% positivity rate.[162] Sunita and colleagues have also reported excellent results using urine and saliva for ELISA antibody testing. The combination of two positive serologic tests provides a laboratory diagnosis in more than 94% of patients with echinococcal disease.[163a]

Diagnostic aspiration is indicated if there is concern that the cyst could be a pyogenic or amebic abscess, but it is not indicated for echinococcal disease. Abdominal US or CT is the diagnostic imaging modality of choice.[164] A plain film of the abdomen or abdominal CT may show calcification of the rim of an echinococcal cyst or daughter cysts that is not found in amebic liver abscess (Fig. 107-13).

The definitive treatment of hepatic hydatid disease is surgical. Medical treatment of hydatid cyst includes the second-generation anthelmintic albendazole. Albendazole has been shown to be most effective in decreasing recurrent disease when it is given both preoperatively and postoperatively.[161,166,167]

Successful operative management starts with isolation of the liver from the rest of the abdomen, usually with sponges soaked in hypertonic saline or a povidone-iodine (Betadine) solution to prevent spillage of the cyst material. The cyst fluid is then aspirated. The cyst is then opened 2 to 3 cm and the remaining contents including the laminated membrane are removed. The cavity is then flushed with 20% saline; however, the effectiveness of this step has been questioned.[168] The cavity then needs to be obliterated using one of several different techniques: closed suction drainage (cystostomy with drainage), obliteration with absorbable sutures (cystostomy with capitonnage), placement of an omental flap over the residual cavity (cystostomy with omentoplasty), or total excision of the entire cyst (cystectomy).[167,168] When cystostomy is performed, the cyst wall needs to be carefully inspected for any open biliary radicals. If found, they are individually sutured closed.[161] Recurrence rates after surgical excision of hepatic hydatid cysts have been reported to range from 1.1% to 9.6%.[169] When surgery and albendazole treatment are combined, the hepatic recurrence rate can be lowered to 2%.[161,165–168]

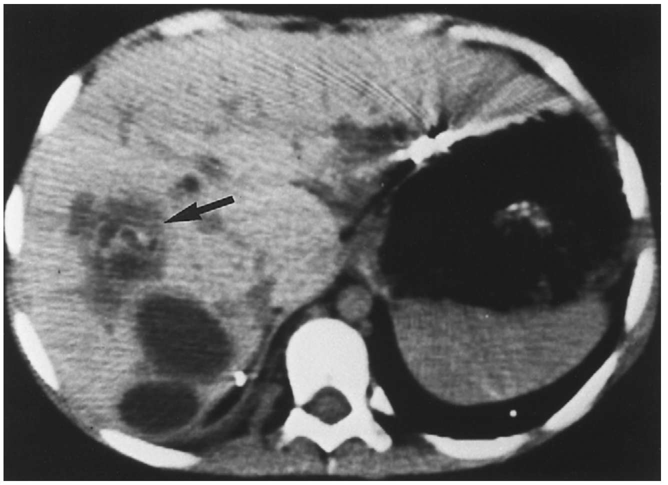

**FIGURE 107-13** Computed tomography scan demonstrating several hepatic abscesses with one (*arrow*) containing daughter cysts characteristic of hydatid disease.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 108

# Portal Hypertension

Riccardo Superina

*A man who thinks that a science can perform what is outside its province, or that nature can accomplish unnatural things, is guilty of ignorance more akin to madness than to lack of learning. Our practice is limited by the instruments made available by Nature or by Art. When a man is attacked by a disease more powerful than the instruments of medicine, it must not be expected that medicine should prove victorious.*

**—Hippocrates**

The treatment of portal hypertension in children is always evolving as the nature of underlying disorders is better understood. Treatment is often successful, Hippocrates notwithstanding, and the strategy usually involves medical, surgical, or combined therapy. This improved outlook is a departure from past years because of the improved understanding of the underlying pathophysiology. More effective imaging techniques and a wider array of options in pharmacologic management have resulted in opportunities to apply both established and newer surgical techniques precisely and deliberately to address underlying disease processes that cause portal hypertension.

## Historical Background

The Italian physician and pathologist Guido Banti first described the relationship among splenic enlargement, anemia, and cirrhosis of the liver. The first splenectomy done for hypersplenism was done in Florence in 1903 on his advice. The constellation of symptoms later became known as *Banti syndrome*.[1]

Earlier, Nikolai Eck, a German anatomist, had produced a connection between the portal vein and the inferior vena cava in a dog.[2] Later studies described the association between the direct communication of portal and systemic venous blood and the onset of encephalopathy associated with hyperammonemia and protein ingestion.[3–5]

The first applications of portosystemic shunting in patients were reported in the 1950s and 1960s. More selective shunting procedures were devised when it was discovered that diversion of mesenteric blood flow into the systemic circulation could precipitate severe encephalopathy. Nonshunt procedures aimed at interrupting the blood flow to gastric and esophageal varices were also described.

Finally, with the advent of liver transplantation, portal hypertension caused by advanced liver disease was treated by replacement of the diseased organ, rather than palliative procedures that produced significant morbidity and often hastened the demise of the patient.

## Embryology and Anatomy

The portal vein develops through a complex system involving the formation and involution of primitive vessels, followed by circulatory changes at birth that affect the flow of blood in the mature portal circulation (Fig. 108-1).

The left and right omphalomesenteric veins drain the developing gut as it is formed from the yolk sac during the fourth to sixth weeks of embryonic life. At the same time, the umbilical veins transport blood from the placenta to the embryo. Blood from both the umbilical and the omphalomesenteric veins drains through the nascent hepatic sinusoids in the developing liver and into the hepatic veins back to the developing heart. Some of the blood from the umbilical veins bypasses the liver and drains into the sinus venosus through the ductus venosus. Although the omphalomesenteric veins communicate by a series of intermediary vessels early in embryonic life, the right one involutes and disappears by the sixth week of gestation. The left one develops into the permanent portal vein, which drains the mesenteric venous bed through the superior mesenteric vein and its branches. The right umbilical vein also involutes, and the left remains patent until shortly after birth, when it thromboses and becomes the ligamentum teres.

The portal vein is formed by the confluence of the splenic and superior mesenteric veins posterior to the head of the pancreas. The coronary vein draining the gastric venous bed inserts into the portal vein at or just distal to the splenomesenteric confluence, and the inferior mesenteric vein drains into the splenic vein anywhere along its length, also behind the pancreas.

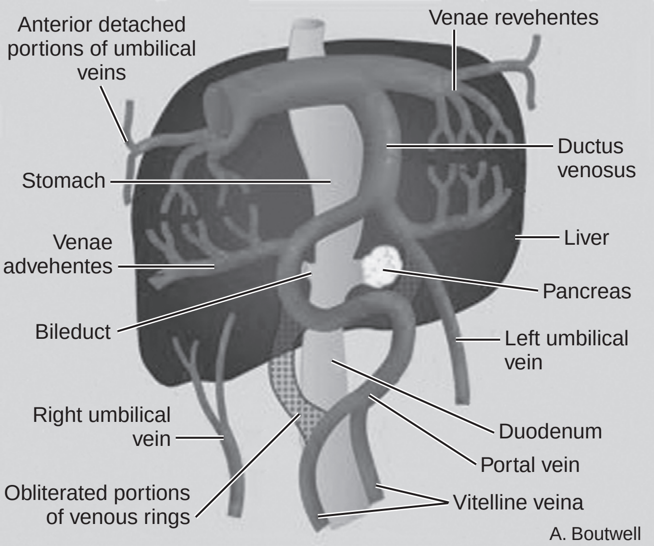


**FIGURE 108-1** The portal vein forms from the union of the two vitelline veins draining blood from the yolk sac. The left vitelline vein joins with the splenic vein to form the extrahepatic portion of the portal vein. The intrahepatic portal vein forms from the umbilical veins. In addition, the left umbilical vein communcates with the sinus venosus, allowing placental blood to bypass the liver during intrauterine life. The right vitelline and umbilical veins involute.

Despite the relative variability in the anatomy of the liver's arterial supply, the portal vein anatomy varies little. The principal extrahepatic vein divides into a left and a right branch. The left branch supplies the left lobe as it courses under the surface of segment IV of the liver; turns anteriorly in the recessus of Rex among segments II, III, and IV; and ends by dividing into the branches that supply those segments. The right branch divides into the posterior and anterior sectoral branches at or just before the liver plate at the capsule.

A cavernous venous malformation may be the result of a disordered sequence of biologic steps. Thrombus in the postnatal umbilical vein may also propagate into the hepatic portal vein and occlude flow in the extrahepatic portion of the vein. Both processes may lead to the syndrome of extrahepatic or prehepatic portal hypertension.

## Definition

Portal hypertension occurs whenever the resistance to the flow of blood from the mesenteric venous circulation through or to the liver increases. The causes of portal hypertension are most commonly obstructive in nature. That is, there is an impediment to the forward flow of blood from the omphalomesenteric vascular bed through the liver and toward the heart. However, portal hypertension can also be caused by an increase in the volume of blood going to the liver or by a direct communication between the arterial and venous supplies to the liver that exposes the venous bed to abnormally high pressures.

Portal hypertension may be defined as pressure in the portal venous bed that exceeds 5 to 8 cm $H_2O$ or a pressure gradient of more than 5 cm $H_2O$ between the hepatic veins and the portal circulation. When the pressure in the portal circulation exceeds those values, a series of physiologic changes leads to the symptoms common to all forms of portal hypertension, regardless of the cause.

## Collateral Circulation

As a consequence of the resistance to flow and the increase in pressure in the mesenteric venous circulation that includes the superior mesenteric, inferior mesenteric, splenic, and coronary veins, blood that normally goes to the liver from the portal vein must find alternative or additional routes back to the heart. The abnormal communications that form between the mesenteric and systemic venous systems are called varices or "shunts" because blood is shunted away from the liver and back to the heart. The hemorrhoidal plexus in the rectum, the paraumbilical network between the portal vein and the paraumbilical veins that form through the recanalization of the umbilical vein and ligamentum teres (forming the "caput medusa" around the umbilicus), and the communications in the gastroesophageal area between the coronary and splenic veins through the esophageal and paraesophageal veins back to the hemiazygous system are the typical areas where the abnormal shunts between the systemic and mesenteric venous systems occur.

Other locations of spontaneous shunts are between the veins of the colon and duodenum and the left renal vein; the accessory portal system of Sappey, whose branches in the round ligament unite with the epigastric and internal mammary veins through the diaphragmatic veins to unite with the azygos vein; the veins of Retzius, which connect the intestinal veins with the inferior vena cava and its retroperitoneal branches; the inferior mesenteric veins and the hemorrhoidal veins that open into the hypogastrics; and, rarely, the patent ductus venosus, affording a direct connection between the portal vein and the inferior vena cava.

## Causes: A Spectrum of Disorders

Portal hypertension can be divided into two categories: (1) portal hypertension from hepatocellular injury and liver fibrosis and (2) portal hypertension from primary vascular causes (Table 108-1).

### HEPATOCELLULAR INJURY

Table 108-2 illustrates some of the common liver disorders in children that can lead to portal hypertension. Hepatocellular injury from a variety of toxins leads to cell death, initiation and progression of fibrosis, and ultimately cirrhosis. Progressive injury to hepatic tissue and replacement of normal liver with fibrous tissue lead to increased resistance to blood flow through the liver. The process of deposition of collagen in response to hepatocyte injury appears to be a complex process mediated through the transcription of proinflammatory cytokines such as osteopontin and through stellate cells.[6] The stellate cell, a normal constituent of hepatic sinusoids, is the primary source of excess extracellular matrix proteins in liver fibrosis.[7] It can change its phenotype from one that is fairly quiescent during normal liver homeostasis to one that

**TABLE 108-1**
**Classification of Portal Hypertension**

| *Type* | *Description* |
|---|---|
| Hepatocellular | Intrinsic liver disease with increased liver fibrosis (see Table 108-2) |
| Vascular | |
| Prehepatic | Extrahepatic portal vein thrombosis |
| | Cavernous transformation of portal vein |
| | Extrinsic compression of portal vein |
| Posthepatic | Budd-Chiari syndrome |
| | Intrinsic web |
| | Stenosis of hepatic vein orifice |
| High-flow (hyperkinetic) | Arteriovenous communication—intrahepatic or extrahepatic |
| | Congenital |
| | Acquired |

**TABLE 108-2**
**Hepatocellular Diseases Leading to Portal Hypertension**

| |
|---|
| Biliary atresia |
| Postinfectious cirrhosis |
| Congenital hepatic fibrosis |
| Congenital disorders of bile acid metabolism |
| Sclerosing cholangitis |
| Autoimmune hepatitis |
| Drug toxicity |
| Metabolic diseases (e.g., alpha-1 antitrypsin deficiency) |

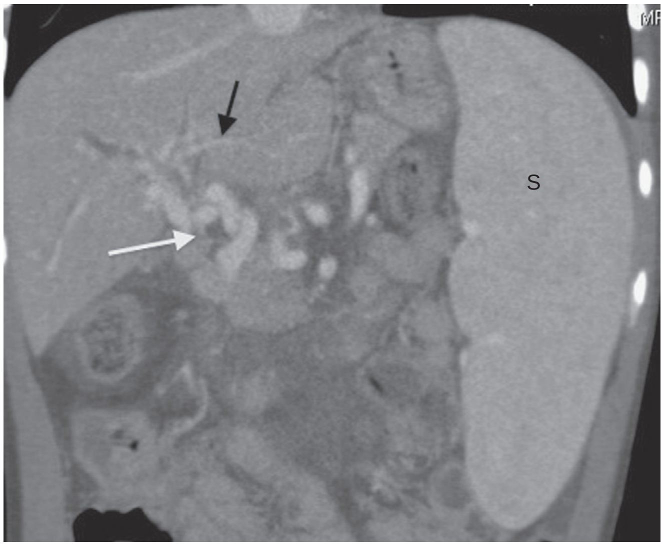


FIGURE 108-2 Preoperative computed tomography scan of a child with extrahepatic portal vein thrombosis showing the typical cavernoma, the tangle of varices in the hilum of the liver (*white arrow*) that replaces the normal portal vein. Also of note is the typically small size of the intrahepatic portal vein branches (*black arrow*) and the large spleen (*S*) that appears larger than the liver.

undergoes myofibroblastic differentiation or activation during episodes of hepatocyte injury. Dysregulation in the activity and number of stellate cells through faulty apoptosis or perpetuation of the insult that led to hepatocyte injury leads to ongoing deposition of proteins in the extracellular compartment of the liver. Ultimately, excess deposition of collagen in sinusoids results in portal hypertension.

## VASCULAR CAUSES

### Prehepatic Portal Hypertension

Prehepatic portal hypertension is caused by obstruction at the level of the portal vein proximal to its branching at the liver plate. Extrahepatic portal vein thrombosis has been recognized and treated in both adults and children; it may be a congenital lesion or acquired at a later time. Even though the symptoms may be dramatic, patients, particularly children, tolerate the bleeding from varices well because of the well-preserved hepatic function.[8] Occlusion of the main trunk of the portal vein may lead to recanalization of the vein and its transformation into a series of smaller collateral veins that assume the appearance of a venous cavernoma visible on ultrasonography or CT scanning (Fig. 108-2). In most instances the intrahepatic architecture of the portal vein is preserved. Thrombosis of the portal vein is associated with omphalitis, instrumentation and cannulation of the umbilical vein at birth including umbilical vein catheters for intravenous access,[9,10] sepsis and dehydration in infancy, and mass lesions that exert extrinsic compression on the vein. These lesions may be inflammatory or malignant; examples include reactive enlargement of the lymph nodes in the hilum of the liver from histoplasmosis or compression from non-Hodgkin lymphoma involving the hilum of the liver.

Unlike children with preexisting liver disease, children with extrahepatic portal vein thrombosis are usually completely well before the sudden onset of symptoms. More than 50% of children present with unheralded hematemesis or hematochezia from gastroesophageal varices.[11] Others are diagnosed with splenomegaly of unknown cause and may be referred to an oncologist for suspected hematologic malignancy.

### Posthepatic Portal Hypertension

Posthepatic portal hypertension is caused by occlusion of large or small veins draining blood from the liver into the inferior vena cava. Obstruction at this level leads to passive congestion of the liver and necrosis of the hepatocytes in the central areas of the hepatic lobule. Acute venous obstruction may lead to massive hepatic necrosis and cell death unless it is relieved in an urgent fashion. The Budd-Chiari syndrome, sometimes referred to as *Chiari disease,* was first described in 1845.[12,13] It is uncommon in children.[14] Outflow occlusion is caused by congenital venous webs in the hepatic veins, hydatid disease,[15] myeloproliferative diseases, hypercoagulable states, and increased estrogen levels, most commonly from oral contraceptives. It can also occur after liver transplantation (Fig. 108-3).

Microvascular nonthrombotic occlusion of hepatic venules is termed venoocclusive disease, and it is being seen with increasing frequency in patients following bone marrow transplantation.[14,16] Cytoreductive regimens involving busulfan and cyclophosphamide are thought to induce obliterative phlebitis in the small veins of the liver, and damage to the endothelial cells is induced through the depletion of endogenous

FIGURE 108-3 Acute hepatic venous obstruction after split liver transplantation, caused by a blood clot in the left hepatic vein of a segment II-III transplant that resulted in hepatic necrosis. The child was retransplanted.

glutathione S transferase stores within the cells.[17] Other causes of venoocclusive disease such as ingestion of herbal teas containing pyrrolizidine alkaloids have been described. Other diverse agents including contrast media, estrogen, and thioguanine have also been associated with the development of venoocclusive disease. This disease has a high mortality rate, and treatment is limited to withdrawal of the offending agents, if possible, coupled with implementation of thrombolytic therapy and transjugular intrahepatic portosystemic shunting if feasible.[18–20]

### High-Flow States

A congenital or acquired communication between an artery and vein in the mesenteric circulation is a rare but known cause of portal hypertension (Fig. 108-4). Portal hypertension from such abnormal communications between arteries and veins in the portal circulation is termed *hyperkinetic*[21] because of the hyperdynamic circulation responsible for the increased portal pressure. Patients have well-preserved liver function and present with bleeding from gastrointestinal (GI) varices, ascites, or splenomegaly. The site of the communication between the artery and vein is quite varied. The splenic and gastric arteries have been reported as sites of these fistulas, as well as the more common site of the hepatic artery within the parenchyma of the liver. Arteriovenous fistulas causing portal hypertension have been reported in all age groups.[22–24] Most often they are congenital, but some are thought to be acquired through a pathologic process or iatrogenically.[25,26] Patients may present with varied symptoms that depend on the site of the arteriovenous communication. Bleeding from varices may be severe, and because of the exposure to arterial pressures, the usual therapeutic maneuvers may be inadequate to control it.[27]

Treatment of high-output fistulas requires interruption of the abnormal communication between the artery and vein. Although surgical procedures including hemihepatectomy[22] and surgical ligation of extrahepatic fistulas[27,28] have been described as a means of removing the fistula, access by radiologic means and the use of selective transcatheter embolization to interrupt flow has become the treatment of choice for this condition.[29,30]

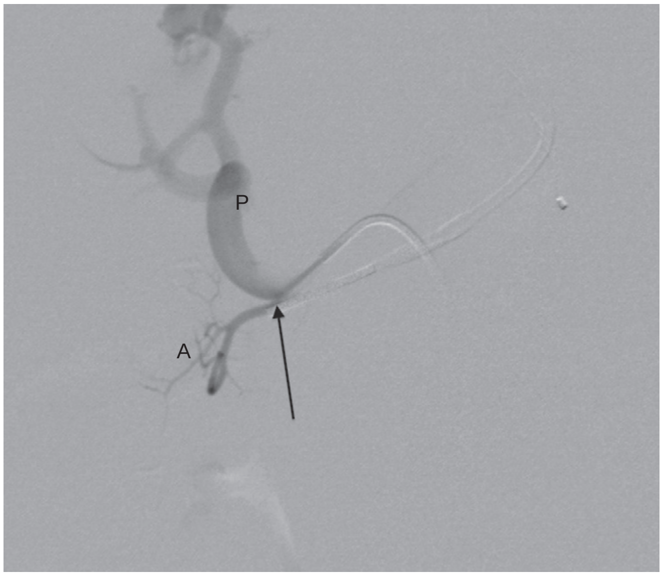


FIGURE 108-4 Contrast flow directly from the smaller hepatic artery (*A*) into the larger portal vein (*P*) without traversing the parenchyma of the liver. This child had an arteriovenous fistula of unknown etiology resulting in esophageal and gastric varices. The fistula was treated by embolizing the branch of the hepatic artery.

# Clinical Presentation

## GASTROINTESTINAL HEMORRHAGE

Bleeding from the GI tract is one of the most common, dramatic, and ominous signs of portal hypertension. Bleeding most commonly occurs from varices in the distal esophagus and gastric cardia. Although the incidence of bleeding in adults with portal hypertension from nonvariceal sites may be as high as 25%, there is no evidence that the same holds true in children. In one study of children presenting with upper GI bleeding, the vast majority of unselected patients had bleeding from varices secondary to portal hypertension, with no other source.[31] The importance of portal hypertension as a cause of upper GI bleeding in children may vary in different parts of the world. Peptic ulcer disease is still a frequent finding at endoscopy in children in the Western Hemisphere.[32] In children with portal hypertension of any cause, upper GI bleeding is almost universally caused by variceal hemorrhage, although portal hypertensive gastropathy may cause less acute bleeding. Therefore variceal hemorrhage is usually the only source of bleeding in children with portal hypertension, and it is the most common cause of bleeding from the upper GI tract in nonhospitalized children older than 2 years.

Variceal hemorrhage may take the form of hematemesis, hematochezia, melena, or chronic anemia. Bleeding most commonly originates from the lower esophagus and the cardia of the stomach. Thin-walled varices that contain blood under raised venous pressure are eroded from gastric acid or medications such as aspirin or nonsteroidal antiinflammatory drugs, and blood fills the stomach. In the absence of advanced liver disease, the blood clots and gathers in the stomach, producing gastric distention and eventually hematemesis.

The bleeding may be sudden and dramatic and is usually not accompanied by abdominal pain. A previously well child can vomit large quantities of altered or fresh blood. Although this can be extremely frightening to both the child and the parents, the bleeding usually stops spontaneously. Varices may be present in the lower GI tract as well. Rectal bleeding is less common and occurs from rectal and sigmoid varices. Melena or the passage of gross blood through the rectum or accompanying a bowel movement may occur in the absence of hematemesis.

Although most patients with portal hypertension have varices, not all varices bleed. Predicting the risk of bleeding from varices is based on Laplace law, which states that the transmural tension in the wall of a vessel is directly related to the pressure inside the vessel and inversely related to the thickness of the vessel. Unfortunately, intravariceal pressure cannot be easily measured[33]; therefore the risk of bleeding in adults has been linked to the size of the varix, the severity of liver disease, and the appearance of red wale markings on the vessel wall, which may indicate epithelial thickness.[34] More recently, detailed measurements of the cross-sectional diameter of the varices have been correlated with the risk of bleeding[35] in adults. Similar studies are necessary in children.

Predicting which patient is likely to bleed from varices is important in determining treatment options, particularly for those who may be candidates for prophylactic therapy of any kind.[36] It is estimated that 30% to 50% of patients bleed from varices once they are diagnosed[37] and that 10% to 50% of patients with liver disease die every year after the first hemorrhage.[38]

Aggressive therapy is indicated after the first bleed in patients with or without liver disease. This may include medical therapy in addition to local control of varices with banding or sclerotherapy, portosystemic shunting in patients with stable and well compensated cirrhosis, or liver transplantation in those with more advanced disease. There may be a role for noninvasive or even invasive surgical therapy in those who are at high risk for bleeding but have not yet bled, provided the morbidity and mortality associated with bleeding can be reduced with an acceptably low risk of complications.

In children with portal hypertension from extrahepatic portal vein thrombosis, mortality from bleeding is much less than in those with liver disease and bleeding is generally well tolerated. However, the same principles apply: early intervention and implementation of a long-term plan to reduce hospital admissions and invasive procedures. Because these children have a vascular problem rather than hepatic disease, they are more amenable to surgical intervention and generally obtain excellent long-term results.

### Portal Hypertensive Gastropathy

The gastric mucosa develops distinct pathologic changes in the presence of portal hypertension and liver disease. The symptoms include chronic blood loss and iron deficiency anemia, but occasionally portal gastropathy may also cause acute GI bleeding and hematemesis. The diagnosis is generally made during endoscopy, when the severity of the lesion can also be graded. The severity of the lesion has been correlated with the severity and frequency of bleeding and the necessity of treating the consequent anemia.

### Hypersplenism

Silent splenomegaly without any other history suggestive of portal hypertension is often the first sign of a serious underlying disorder. Splenomegaly may be detected in infancy or early childhood and can easily be misinterpreted as a sign of hematologic malignancy, particularly in children with extrahepatic portal vein thrombosis and no other stigmata of liver disease. With the advent of Doppler ultrasound examinations of the abdomen, portal vein thrombosis is more readily diagnosed and can be appropriately monitored. In addition to splenic enlargement, patients may present with severe thrombocytopenia and leukopenia from splenic sequestration of platelets and white blood cells. Children are often prevented from engaging in sporting activities for fear that even slight trauma to the abdomen may result in splenic rupture and catastrophic intra-abdominal bleeding, exacerbated by raised venous pressure and low platelet counts. It is hard to find documented cases of splenic rupture in which the underlying portal hypertension contributed to massive bleeding and death.[39] Splenic artery aneurysm is a rare complication in patients with portal hypertension and spontaneous hemorrhage, and suggested treatments have been reported.[40]

### Encephalopathy

Encephalopathy is extremely unusual in the absence of signs of advanced liver disease such as jaundice and low levels of liver-dependent coagulation factors or low albumin levels. Learning disabilities and behavioral abnormalities are manifestations of encephalopathy in children, in contrast to the traditional signs of disorientation, memory loss, and drowsiness commonly seen in adults. Children may also have accompanying hyperammonemia.[41]

### Bleeding from Nongut Sites

Severe thrombocytopenia can lead to hematuria, menorrhagia in adolescent girls, epistaxis, and hematochezia. In severe cases, spontaneous intracranial bleeding can also occur, with serious neurologic consequences. Liver-dependent coagulation factor deficiencies also lead to bleeding, typically from the genitourinary tract or from the nose. In cases of advanced liver disease, hemorrhagic complications in the lungs may cause severe respiratory compromise.

### Ascites

Children with ascites may have advanced liver disease with synthetic failure. Ascites may be accompanied by a low serum albumin level and decreased plasma oncotic pressure. Dilated lymphatics in the abdomen from increased hydrostatic pressure in all portal tributaries can lead to transudation of fluid across capillary membranes and accumulation of fluid in the abdominal cavity. Additional mechanisms include increased nitric oxide production in capillaries, causing vasodilatation, and an increase in renal tubular absorption of sodium in patients with decompensated cirrhosis. Ascites can also occur in the setting of Budd-Chiari syndrome and outflow obstruction. Ascites is an alarming symptom that may herald the onset of liver decompensation on a wider scale.

### Pulmonary Disorders

Pulmonary hypertension can occur in children with both cirrhotic and noncirrhotic forms of portal hypertension.[42,43] Pulmonary hypertension may be secondary to an increase in vasoactive substances that exert a vasoconstrictive or direct toxic effect on pulmonary vessels.[43a] An increase in blood levels of prostaglandin $F_{2\alpha}$, thromboxane, and angiotensin I in patients with portal and pulmonary hypertension suggests that these agents play a role in mediating pulmonary hypertension by reaching the pulmonary circulation in blood shunted around the liver. In experimental studies, portal hypertension induced by portal vein ligation was associated with increased amounts of inducible nitric oxide synthetase and heme oxygenase-1 messenger RNA and protein in the lungs, compared with animals in the control group.[44] This suggests that the pulmonary pathology seen with portal hypertension is associated with the production of nitric oxide and carbon monoxide in the lung.

Patients with both pulmonary and portal hypertension may develop pulmonary symptoms before there is any evidence of bleeding from portal hypertension. Symptoms may include exertional dyspnea or chest pain, or there may be no symptoms other than unheralded syncope or sudden death.[45] Treatment of portal hypertension may be problematic in children with advanced pulmonary hypertension, and medical treatment for both conditions may be limited in scope and duration.[46]

The hepatopulmonary syndrome includes persistent hypoxemia from arteriovenous shunting in the lungs. Both pulmonary hypertension and arteriovenous shunting are potentially reversible after the portal hypertension and shunting are eliminated, although in cases of cirrhosis, a liver transplant may be necessary.[47,48]

# Diagnosis

The diagnosis of the underlying cause of portal hypertension depends on the synthesis of the clinical information gathered from the parents and the child and the results of imaging tests and laboratory investigations.

## CLINICAL INFORMATION

### Hepatomegaly

An enlarged liver is usually a sign of hepatocellular disease, although patients with cirrhosis may present with impalpable shrunken livers. If the liver is hard or nodular to palpation, this is further evidence that the cause of the portal hypertension is a diseased liver. Children with congenital hepatic fibrosis often present with enlarged livers that may extend as far as the iliac crest on palpation. Children with venous outflow obstruction may also present with easily palpable liver enlargement.

### Splenomegaly

Enlargement of the spleen is a common finding in children with portal hypertension and is often the first abnormality found on a routine physical examination before the onset of bleeding. Splenomegaly occurs in all forms of portal hypertension and is not helpful in diagnosing the cause.

### Jaundice

Jaundice and portal hypertension usually do not occur together unless there is advanced liver disease. Children with extrahepatic portal vein obstruction may have mild elevation of the total bilirubin level, but jaundice is not a clinical feature. If jaundice is a prominent symptom in a child with portal hypertension, it may indicate that the liver function is severely compromised and consideration should be given to a liver transplant evaluation.

### Abdominal Examination

Patients with portal hypertension often have protuberant abdomens. Causes include splenomegaly, ascites, and enlargement of the liver. Distended abdominal veins are a frequent finding, and the direction of blood flow away from the abdomen or umbilicus is easily demonstrable. In patients with congenital hepatic fibrosis, the combination of enlarged liver and spleen and often large polycystic kidneys contributes to making the abdomen extremely protuberant.

### Encephalopathy

Clinically evident encephalopathy is a sign of advanced liver disease. Signs of encephalopathy may be hard to discern or quantify in young children. Advanced psychometric testing may detect subclinical encephalopathy that may be manifest as impaired attention span, poor school performance, or behavioral issues that may be present even in children with no underlying liver disease or patients with well-compensated cirrhosis.[49] Although advanced encephalopathy may be exacerbated or unmasked by acute bleeding because of the increased protein load in the gut, it usually signifies advanced hepatocellular disease that may require the patient to be evaluated for liver transplantation.[50]

## LABORATORY INVESTIGATIONS

Laboratory tests are useful adjuncts in evaluating patients with portal hypertension. Tests may indicate the severity of the accompanying liver disease or may indicate the cause of the underlying liver disease in many instances. In the acute setting of a GI bleed, a complete blood count and electrolyte levels will be necessary as a guide to blood and fluid replacement. A complete metabolic panel including renal function tests is helpful in guiding fluid resuscitation and to assess the underlying status of the kidneys. In patients with established cirrhosis from underlying systemic diseases like cystic fibrosis, blood gases may be necessary. Low blood glucose levels may indicate impending liver decompensation or an underlying glycogen storage disorder.

Children with long-standing portal hypertension may have nothing more than thrombocytopenia and leukopenia, particularly those with extrahepatic portal vein thrombosis. An increase in the direct bilirubin fraction, a low albumin level, and a long prolongation in prothrombin time all indicate significant hepatocellular disease and possible cirrhosis as the underlying cause of the portal hypertension. A raised serum ammonia level indicates significant portosystemic shunting and may occur with all forms of portal hypertension, although severely increased ammonia levels are generally only seen in patients who have decompensated cirrhosis or those in fulminant hepatic failure.

Children with extrahepatic portal vein thrombosis may have laboratory evidence of disordered synthesis of liver-dependent coagulation factors in both the procoagulant and plasminolytic pathways, but this is generally not evident clinically without detailed testing.[51]

## ENDOSCOPY

Endoscopy is indispensable in establishing the cause of GI bleeding and to confirm the presence of varices in the esophagus and stomach. In cases of acute bleeding and after stabilization in the intensive care unit, upper GI endoscopy provides direct confirmation of the bleeding source. Varices, if present, will be most prominent in the distal third of the esophagus and in the cardia of the stomach. Endoscopy should be done only by those who are well trained in the procedure and familiar with the equipment. Endoscopy provides an opportunity to intervene therapeutically, as well as to rule out other sources of bleeding such as peptic ulcers, Mallory-Weiss tears of the esophagus, or hemorrhagic gastritis.

If endoscopy is done before the onset of bleeding because of suspected portal hypertension, the appearance of the varices provides valuable clues about the likelihood of future bleeding. Variceal diameter greater than 5 mm, the appearance of red wale markings, and more advanced liver disease based on Child-Pugh class indicate a greater chance for future bleeding and may justify the institution of prophylactic treatment.[52–54]

## IMAGING

The first imaging study in any child who presents with hematemesis should be abdominal ultrasonography. The status of the portal vein is one of the most important radiologic considerations in arriving at a diagnosis. Cavernous transformation of the portal vein and portal vein thrombosis are best diagnosed by ultrasonography with Doppler interrogation of the vessels of the liver. A complete evaluation of the intra-abdominal vasculature including the hepatic veins, the patency of the splenic and superior mesenteric veins, and the inferior vena cava is possible. In addition, information about the size of the spleen can be obtained to confirm the clinical examination. Liver parenchymal abnormalities such as nodularity, inhomogeneity, or the presence of cysts can be seen. The appearance of the kidneys can yield useful diagnostic clues because children with congenital hepatic fibrosis may also have autosomal dominant polycystic kidney disease and other renal abnormalities.

Computed tomography (CT) and magnetic resonance (MR) angiography are excellent diagnostic tools and have supplanted conventional digital angiography for most purposes. Both modalities provide excellent information about all the intra-abdominal vessels and detailed information about the liver anatomy including the bile ducts. CT-angiography has several advantages; it can be done more quickly and is less prone to image degradation from motion artifact than is MR angiography, unless the MR study is done under general anesthesia with ventilatory arrest for the duration of the study.

Conventional angiography is an invasive modality that has few indications as a diagnostic tool in children with portal hypertension. The exceptions are rare cases of unusual vascular malformations such as arteriovenous communications in the abdomen or liver that may best be delineated by angiography. Also, angiographic visualization is essential as a prelude to angiographic embolization or stenting of a vascular abnormality.

Splenoportography is a technique that was written about extensively in the past but is almost never used for diagnostic purposes today.

Transjugular hepatic venography is a test that can be used to measure free and wedged hepatic vein pressures indicating the gradient across the hepatic veins. This technique is limited in small children where the size of the child and the veins makes the performing of this test more challenging. Wedge hepatic vein pressure can rule out parenchymal disease and high sinusoidal pressure as a contributing factor to portal hypertension. Sinusoidal pressures are normal in cases of prehepatic portal venous obstruction.

Retrograde transjugular portal venograms can also be used to obtain high-quality definition of the intrahepatic portal vein (Fig. 108-5). Hepatic vein angiography can also be used therapeutically for the placement of a transjugular intrahepatic portosystemic shunt (TIPS) or the dilatation of congenital or acquired strictures causing venous outflow obstruction.

## LIVER BIOPSY

Many children who present with portal hypertension do not need a liver biopsy to establish a diagnosis. For example, in children with biliary atresia a biopsy is not necessary as an adjunctive test after the onset of portal hypertension. In children with a known underlying metabolic disease such as cystic fibrosis or alpha-1 antitrypsin deficiency, a biopsy will not necessarily add useful information to aid in formulating a treatment plan.

However, if a biopsy is considered helpful, it can be done percutaneously in most cases. In children with mild coagulopathies that can be corrected with vitamin K, fresh frozen plasma, and platelets, the procedure can be performed with close monitoring, where any bleeding from the biopsy site can be treated promptly. Children with more profound

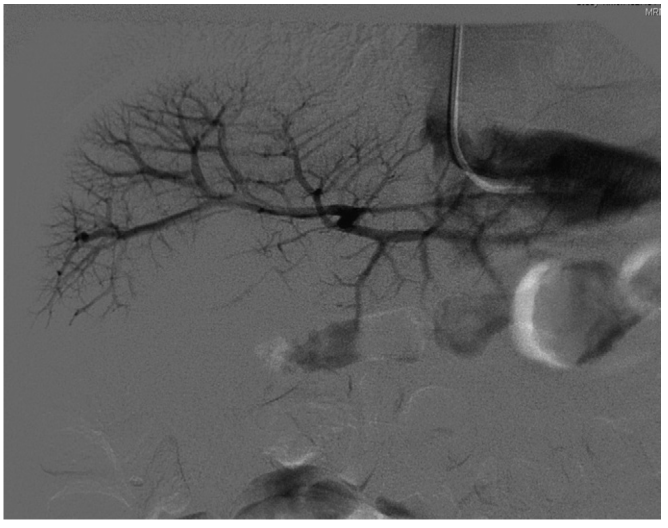

**FIGURE 108-5** A catheter has been advanced into the left hepatic vein, and contrast is injected under pressure filling the entire intrahepatic portal vein.

coagulopathies, as manifested by a prothrombin time in excess of 20 seconds, should have a transjugular biopsy in the interventional radiology suite or an open biopsy in the operating room. In general, the limiting factor in the radiologist's ability to do a transjugular biopsy is the patient's size. The difficulty and technical limitations are greatest in infants and babies.

# Treatment

The treatment of a child with portal hypertension is predicated first on the underlying pathophysiology of the disease and then on the severity of the symptoms.

Children with liver disease and portal hypertension do not tolerate bleeding as well as those with essentially normal livers whose portal hypertension is caused by primary vascular malformations. Acute hemorrhage adversely affects liver function, which may already be abnormal. The prognosis of a child with liver disease and portal hypertension depends entirely on the hepatic reserve. Children with relatively stable cirrhosis and preserved synthetic function require a completely different therapeutic approach from those with hypoalbuminemia, growth failure, and coagulopathy. The Child-Pugh score[55] was devised in an attempt to categorize patients according to degree of hepatic reserve and thus arrive at a prognosis for survival if left untreated or with surgery.[56] More recently, a pediatric-specific score (pediatric end-stage liver disease [PELD]) has been developed to stratify children on liver transplant waiting lists in a way that accurately reflects the severity of the underlying liver disease.[57] Children with age-appropriate growth, normal coagulation, and no jaundice have low PELD scores; their treatment for the complications of portal hypertension is different from that of children with high scores, who would be better served by liver transplantation.

In children with Child-Pugh scores of 5 or 6 or PELD scores lower than 10 who have a predicted 1-year survival of more than 90%, it is justified to consider complex surgical therapy to alleviate the symptoms of portal hypertension. The expectation is that these children will survive the surgery and have a good long-term prognosis without the need for liver transplantation in the short term. For children with portal hypertensive bleeding from varices and who also have ascites, advanced coagulopathy or poor synthetic function as indicated by hypoalbuminemia, endoscopic banding or sclerosis of esophageal varices in addition to aggressive medical therapy of portal hypertension is indicated as they await transplantation. Operation is not indicated in children with advanced liver disease because it would be poorly tolerated and not address the underlying issue of poor hepatic reserve.

Pediatricians and pediatric gastroenterologists closely follow all patients with portal hypertension and liver disease. When portal hypertension becomes symptomatic, it is rarely a surprise and the parents are usually well versed in the medical issues. Under ideal circumstances, surgery can be considered for the control of symptoms when bleeding is imminent or likely to recur. Selective shunting is generally the procedure of choice, as discussed later.

In contrast, patients with noncirrhotic forms of portal hypertension can develop symptoms quite unexpectedly and as the first manifestation of a serious underlying condition.

## MEDICAL MANAGEMENT OF BLEEDING VARICES

Patients admitted with acute variceal hemorrhage require intense resuscitation with blood and crystalloids, replacement of coagulation factor deficiencies with fresh frozen plasma, and control of the bleeding. Bleeding from varices may be exacerbated by disseminated intravascular coagulation, fibrinolysis, and a decrease in circulating platelet counts. The availability of exogenous recombinant factor VII to treat those with compromised liver synthetic function has enhanced the care of these patients. Factor VII replacement decreases the amount of sodium and fluid necessary to correct the liver-dependent factor deficiencies, although its use is limited to some extent by its cost.[58]

Patient care is best delivered in the intensive care unit, where vital signs including central venous and arterial pressures, hourly urine output, and oxygen saturation can be monitored. Monitoring of mental status is also essential in those with cirrhosis because bleeding into the GI tract may exacerbate or unmask encephalopathy.

Cessation of bleeding is the most important therapeutic goal, along with the replacement of extracellular fluid and blood. In the past, Sengstaken-Blakemore tube tamponade of varices was the most effective method of short-term control of blood loss. Pharmacologic therapy has proved to be just as effective in adults,[59] rendering the balloon method almost obsolete. Pharmacologic control of variceal bleeding has improved greatly with the use of intravenous octreotide, the octapeptide analogue of somatostatin. It has a longer half-life than somatostatin and fewer side effects. Octreotide has largely replaced vasopressin in the management of acute variceal bleeding because of the severe vascular side effects of the latter drug.

Octreotide and other somatostatin analogues such as vapreotide reduce hepatic blood flow and wedged hepatic vein pressure and constrict splanchnic arterioles by a direct effect on arteriolar smooth muscle. Somatostatin analogues are effective in reducing and temporarily stopping the bleeding from portal hypertension and can be used in the initial 24 to 72 hours while awaiting direct endoscopic management of varices.[60–63] More recently, terlipressin, a vasopressin derivative, has also been proven effective in the acute bleeding situation, although experience in children is limited.[62,64,65] Octreotide is started as a continuous infusion at 1 to 2 μg/kg/hr, up to a maximum of 100 μg/hr, and continued for as long as symptoms of bleeding persist. Antibiotics and acid suppression are also recommended.[62]

The long-term medical management of children with portal hypertension includes the use of nonselective beta blockers such as propranolol or nadolol, either alone or in combination with nitrate vasodilators such as isosorbide-5-mononitrate. Some authors, however, have shown that local control of varices with banding is equivalent to long-term pharmacologic management. In a majority of patients, surveillance endoscopy and intermittent banding may be sufficient,[37] with equivalent survival and rebleeding rates in endoscopically managed and pharmacologically managed groups. The role of beta blockers in reducing splanchnic blood flow and wedge hepatic vein pressure is well documented; their use may decrease the incidence of recurrent bleeding by as much as 50% and lessen the need for liver transplantation in patients with liver disease.[66]

Assessment of wedge hepatic vein pressure reduction has been promoted as the best way to determine the impact of medications on portal pressure and to guide and refine pharmacologic management,[67] but these studies are all adult based and may represent a less practical approach in children.[68]

## PROPHYLACTIC TREATMENT OF VARICES

Intervention of any kind before the onset of bleeding is controversial. However, the benefit to the patient of preventing a first bleed may be considerable and justifies early prophylactic management. Studies in both adults and children have demonstrated that prophylactic treatment of varices by pharmacologic means and with endoscopic ligation reduces the frequency of bleeding but may not diminish mortality in patients with advanced liver disease without transplantation.[69,70] Primary procedures for the prevention of an initial bleed are more controversial if there is no other primary goal such as the treatment of severe hypersplenism.

## ENDOSCOPIC SCLEROSIS OR BANDING OF VARICES

Surgeons were involved in the earliest attempts to control variceal bleeding by injecting sclerosing solutions into the tissue around a varix or directly into a varix to obliterate the vessel lumen.[71] This method has proved to be effective and safe in children in the acute phase of bleeding.[52–54,72–81] Sclerosing solutions include sodium morrhuate, ethanolamine, sodium tetradecyl sulfate, and polidocanol. Long-term follow-up in children after sclerotherapy for the control of initial bleeding has demonstrated success in almost 90% of patients. Initial sclerotherapy should be followed by repeat endoscopy at regular intervals until all the varices are obliterated or too small to inject and then at longer (yearly) intervals for at least 4 years to check for reappearance of varices. Generally, two to three injections at 1 mL per injection are required for each varix, up to a maximum of 10 to 15 mL per session. The endoscopist should proceed circumferentially from the distal esophagus at the gastroesophageal junction to the more proximal esophagus.

Sclerotherapy is associated with a fairly high incidence of complications, both major and minor, in at least one third of patients. Acute complications include chest pain, esophageal ulceration, and mediastinitis; chronic ones include esophageal strictures from fibrosis after multiple injection sessions.

Esophageal banding has become an increasingly popular method of treating varices. In one prospective trial in children with portal hypertension from extrahepatic portal vein thrombosis, banding was found to be a more effective, more rapid, and safer method of reducing the chance of bleeding from varices.[82] The incidence of complications and of long-term rebleeding was lower with banding. New technology, such as the multiband ligator scope, has made it possible to apply bands to multiple varices; this method was first used in adults but has recently been extended to children.[83,84] This technique increases the speed and safety with which esophageal varices can be ligated in children as young as 3 months old; obliteration of varices was accomplished in almost 100% of children after only two sessions.

Esophageal banding in concert with pharmacologic control has become the procedure of choice in the early therapy of bleeding esophageal varices. Subsequent sessions are aimed at ligating residual varices or varices that arise after the larger ones are tied off. Ligation is effective in most children and is not associated with many of the adverse side effects of sclerotherapy.

## INJECTION THERAPY FOR GASTRIC VARICES (TIPS)

With the advent of more effective means of controlling esophageal varices, bleeding from varices lower in the GI tract has become more problematic. Injection with N-butyl-2-cyanoacrylate has had modest success in adults with bleeding from gastric varices and results in children have been encouraging.[85,86] Gastric varices may coexist with esophageal varices in up to 15% to 20% of patients, or they may be isolated. Gastric varices may emerge after the obliteration of esophageal varices, or they may persist after esophageal varices have been ligated. Experience in adults suggests that in patients with gastric varices, cirrhosis, and advanced liver disease, bleeding can be controlled with minimal morbidity, but there is a high incidence of rebleeding at 1 year after treatment.[87] In adults, injection of gastric varices results in relatively poorer control of bleeding in patients with extrahepatic portal vein thrombosis (35%) than in those with liver disease (75%).[88] Given the fact that extrahepatic portal vein thrombosis is a more important cause of bleeding varices in children than in adults, injection therapy for gastric varices in pediatric patients is not justified, except in the setting of a formal study to determine its safety and efficacy compared with surgery or other medical therapies.

## TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNTS

The percutaneous insertion of vascular stents to create channels between the portal vein and hepatic veins within the parenchyma of the liver heralded a new way of treating patients with advanced liver disease and portal hypertension.[89,90] The main indication for TIPS is variceal hemorrhage recalcitrant to more conservative therapy with endoscopy or octreotide. It is usually reserved for patients with advanced liver disease and serves as a bridge to transplantation.[91] Other indications include refractory ascites, hepatic venous outflow obstruction in both transplant and nontransplant patients, and hepatorenal syndrome.

In children, the experience is limited. TIPS may act as a bridge to transplantation in children with portal hypertensive gastropathy or in those whose variceal bleeding is difficult to control by other means. The TIPS method has been used in children with cystic fibrosis,[92] biliary atresia,[93] and congenital hepatic fibrosis[94] with apparent success and in infants as young as 1 year.

Its primary limitation is the high rate of shunt thrombosis. Vigilance is required to monitor shunt patency and to declot the shunt when it is thrombosed. The other limitation is the aggravation of preexisting encephalopathy in approximately 20% of patients and the hastening of liver failure in patients whose livers are already borderline; TIPS facilitates the

shunting of blood without the benefit of hepatic clearance in these extremely debilitated patients.[95]

Hepatic encephalopathy is less common after TIPS in children than in adults, but the incidence of shunt occlusion is higher because of the smaller shunt diameter.

## SHUNT SURGICAL PROCEDURES

Early shunt operations diverted all the mesenteric blood flow into the systemic circulation, as first described by Eck.[2] Later authors reported the application of portacaval shunting in the setting of severe bleeding from portal hypertension in adults with advanced liver disease,[55,96–99] as well as in children with prehepatic and intrahepatic causes of portal hypertension.[100–104]

Shunts can be described as nonselective or selective. Selective shunts preserve the majority of portal or mesenteric blood flow to the liver while shunting blood from high-pressure gastroesophageal varices into the low-pressure systemic venous circulation. In essence, selective shunts divide the portal circulation into two separate entities, although it is impossible to fully divide all communications. In contrast, nonselective shunts divert a large proportion of mesenteric blood flow away from the liver so that the entire GI tract including the spleen and pancreas is decompressed. Nonselective shunts can be further subdivided into total or partial portal diversions.

### Nonselective Shunts

***Total Diversion*** The end-to-side portacaval shunt as first described by Eck is the classic example of a total portal diversion. Portal blood is completely redirected into the inferior vena cava below the liver, and the hepatic end of the portal vein is oversewn. That operation is almost never done in children and bears no further discussion. All nonselective large-caliber shunts deprive the liver of virtually all mesenteric venous blood flow and increase the danger that the undesirable side effects of portosystemic shunting will be produced. Encephalopathy, pulmonary hypertension, and formation of regenerative nodules in the liver are some of the long-term side effects of complete mesenteric venous diversion away from the liver and can happen even in children with ostensibly normal liver function and no intrinsic liver disease.

***Proximal Splenorenal Shunt*** The proximal splenorenal shunt is another example of a shunt that results in total diversion of mesenteric venous blood into the systemic circulation. The pancreas is mobilized cephalad, exposing the underling splenic vein. All branches between the pancreas and the splenic vein must be tied off meticulously. The splenic vein is divided close to the spleen, and the spleen is removed. The left renal vein is isolated, and the mesenteric end of the splenic vein is sewn to the side of the left renal vein so that all the blood from the superior and inferior mesenteric veins is shunted into the systemic venous circulation through the left renal vein.[105,106] This procedure almost invariably includes a direct attempt to ligate the varices of the esophagus and stomach in the region of the coronary vein.

Although the operation is effective in relieving the symptoms of portal hypertension, it should be used sparingly because it not only exposes the child to the potential drawbacks of complete mesenteric diversion, as outlined earlier, but also results in the loss of the spleen.

***Mesocaval Shunt*** Wide-diameter mesocaval shunts also completely divert mesenteric blood away from the liver. This procedure can be done directly as a side-to-side anastomosis between the two veins or with the interposition of a short autologous vein graft or prosthetic graft.[107,108] Use of an interposition graft is the more common method. Exposure of both the superior mesenteric vein at the root of the bowel mesentery and the inferior vena cava below the duodenum is required.

Mesocaval shunting has been used in children in a wide variety of settings and diseases, with uniformly acceptable results.[109–111] Some prefer this method because it allows an anastomosis between two large-diameter vessels and because the length of the anastomosis can be increased to some extent to facilitate the creation of a large venous fistula, which is technically easier to perform than a proximal splenorenal shunt. In addition, in contrast to the proximal splenorenal shunt, the spleen is preserved, which is thought to be important in preventing postsplenectomy sepsis.

***Side-to-Side Portacaval Shunting*** The side-to-side portacaval shunt allows blood from the intestine and spleen to flow easily into the vena cava. In addition, and unlike with the end-to-side portacaval shunt, the hepatic end of the portal vein is changed into an outflow tract. In cases of Budd-Chiari posthepatic portal hypertension, the liver is decompressed by this operation; this may result in long-term palliation of the disease, with arrest or delay in the progression of hepatic fibrosis and ultimate failure.[14,112,113] Other effective operations for Budd-Chiari syndrome are mesocaval and central splenorenal shunts, which allow portal blood in the liver to empty in a retrograde fashion through the patent portal vein.

***Partial Diversion*** Partially diverting shunts depend on a fixed, narrow communication between a vessel in the portal circulation and one in the systemic venous circulation. The Sarfeh shunt can divert enough blood from the portal circulation to drop mesenteric pressure below 12 cm $H_2O$, thus decompressing the varices and reducing the chance of bleeding while maintaining enough pressure in the portal bed to allow hepatopetal flow and hepatic blood flow preservation.[114] Although there may be less encephalopathy with the Sarfeh shunt because of sustained hepatic portal flow, it is associated with a higher incidence of thrombosis and recurrence of hemorrhage and rarely used in children.[115]

The relationship between deprivation of portal blood to the liver and encephalopathy has long been noted following portacaval shunt surgery. Sarfeh was able to determine the diameter shunt that would preserve forward flow in the portal vein, decompress the portal circulation so that bleeding from varices decreased, and minimize the incidence of encephalopathy.

### Selective Shunts

To diminish the encephalopathy that followed portacaval shunting, Warren and Zeppa[116] described a shunt between the portal end of the splenic vein and the side of the renal vein (Fig. 108-6). The splenic confluence with the portal vein was ligated, and the coronary vein was also interrupted. In this manner, the gastroesophageal varices were decompressed across the short gastric vessels and the spleen was decompressed into the renal vein. Long-term studies have shown

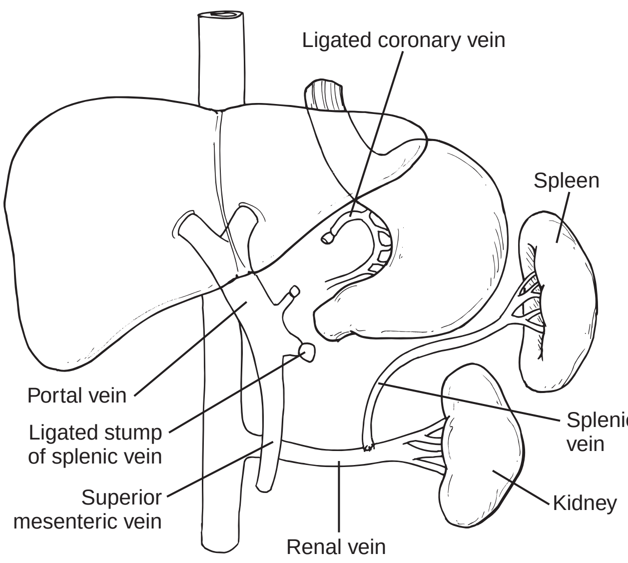


**FIGURE 108-6** Schematic drawing of the distal Warren shunt. Note that the coronary vein has been ligated. The varices are both decompressed by allowing them to drain via the short gastric vessels and splenic vein into the left renal vein and by decreasing blood flow to the varices by tying off the blood that reaches them through reverse flow in the coronary vein.

that the disconnection between the lower-pressure splenic circulation and the higher-pressure hepatic one is not always maintained, and the connection may re-form over time. Hepatopetal flow may decrease and be redirected to the coronary circulation around the stomach; as a result, the hepatic flow decreases, just as in more central shunts.[117,118] In this case, there would be both angiographic and endoscopic evidence of gradual conversion of a selective shunt to a less selective shunt over time. A more complete pancreaticosplenic disconnection may avoid the reestablishment of communication between the splenic and hepatic circulations. Long-term mortality and rebleeding rates in adults are equivalent with selective and nonselective shunts,[119] but the rate of encephalopathy is reduced with selective shunts.[120,121]

In children, the selective shunt as described by Warren or with minor modifications has been used successfully for the treatment of bleeding varices, as well as for the treatment of hypersplenism.[122] Long-term patency rates exceeding 90% have been reported in most series.

Distal splenorenal shunting is used primarily in children with extrahepatic portal vein thrombosis, stable Child-Pugh classification A or B cirrhosis, or less common forms of intrahepatic portal hypertension such as congenital hepatic fibrosis with well-preserved liver function but symptomatic variceal bleeding.

The preservation of neurocognitive function is particularly important in children; thus all forms of nonselective shunting should be avoided whenever possible. Encephalopathy in children may manifest as learning disorders or behavioral abnormalities that are not usually attributed to portosystemic shunting.[123]

Hypersplenism may be particularly problematic in children and has led to splenectomy or splenic embolization in some children[100,124–132] with or without a central splenorenal shunt.

The distal splenorenal shunt has been beneficial in children with advanced hypersplenism as a more physiologic alternative to the splenectomy.[133] Spleen size regresses, and the platelet and leukocyte counts return toward normal. Following splenic decompression by shunting, hematologic indices may continue to improve for years after the procedure.

Splenectomy and splenic embolization were advocated in the past for hypersplenism. However, these procedures are not without complications and may, in the long run, exacerbate bleeding from gastroesophageal varices and leave the child prone to postsplenectomy sepsis. In addition, splenectomy removes the possibility of later distal splenorenal shunting if the child continues to suffer from variceal bleeding. Pediatric surgeons should preserve the spleen whenever possible, leaving splenectomy as the last resort in children who have no other options.

## MESENTERIC-TO-LEFT PORTAL VEIN BYPASS

The treatment of extrahepatic portal vein thrombosis has been evolving since the advent of mesenteric vein-to-left portal vein bypass in 1992. The operation was originally described as a way to revascularize liver transplant grafts after post-transplant portal vein thrombosis,[134,135] but the indications were later expanded to treat children with idiopathic portal vein thrombosis.[136] A growing number of children have been reported in the literature from a small group of institutions worldwide.[11,47,137,138]

Essentially, the operation relieves portal hypertension by redirecting blood from the obstructed mesenteric system to the still patent intrahepatic portal vein. The prerequisites for a successful bypass operation are threefold: (1) no intrinsic liver disease, (2) a patent intrahepatic portal tree, and (3) a suitable vein in the mesenteric circulation to function as a suitable inflow tract for mesenteric blood.

In portal vein thrombosis, the extrahepatic portal vein is replaced by a network of small collaterals that supply the liver with a small amount of mesenteric blood and keep the intrahepatic portal circulation patent. The intrahepatic portal tree in these children is patent but hypoplastic.

The preoperative workup includes CT-angiography to assess the caliber and patency of the intrahepatic portal vein, a liver biopsy to rule out intrinsic liver disease, and a coagulation workup to rule out a hereditary hypercoagulable state.[139] It was once thought that hereditary hypercoagulable states, particularly protein C deficiency, often may have caused the thrombosis of the portal vein.[140–142] However, it has been reported that deficiencies not only in the plasminolytic pathway but also the procoagulant pathway may be secondary to the hepatic deprivation of portal blood and are reversible after the successful restoration of portal flow.[51]

The operation starts by dissecting out the intrahepatic portal vein in the recessus of Rex, where the round ligament inserts between segments III and IV of the liver. Portions of segments III and IV are removed. All the branches to segments II, III, and IV are controlled. If it is suitable, the superior mesenteric vein is dissected out at the root of the mesentery. Alternative sources of blood for the bypass including the splenic, inferior mesenteric, and coronary veins have been described.[143]

Once the inflow vein has been isolated, the jugular vein (either right or left) is removed and sewn first to the intrahepatic portal vein and then to the superior mesenteric vein. The vein graft usually goes through the mesocolon and the

lesser sac, up behind the stomach, through the lesser omentum, and up to the liver. In children with malrotation or other congenital disorders, the route of the graft may vary, depending on the child's individual anatomy. CT or MR scanning in the postoperative period demonstrates the patent shunt (Fig. 108-7).

Unlike portosystemic shunting, the mesenteric-to-left portal vein bypass, or Rex shunt, is restorative rather than palliative. It restores portal flow to the liver and relieves the symptoms of portal hypertension. With proper patient selection, patency rates have been in excess of 90%.[11] Patency depends primarily on the quality of the intrahepatic portal vein and the number of branches that allow for sufficient runoff to permit blood flow to be sustained. The intrahepatic portal vein may be difficult to visualize by preoperative imaging, and a final assessment may be possible only at the time of surgery.

### NONSHUNT OPERATIONS

Nonshunt operations for portal hypertension are generally limited to a direct attack on the varices by operative interruption and ligation, as well as esophageal transection to interrupt the intramural varices within the esophagus.[144–147] In the absence of suitable shunt options, these procedures are useful alternatives.

Sugiura and colleagues[147] described an operation in which all perigastric and periesophageal vessels were separated from the incisura of the stomach to the midesophagus at the level of the inferior pulmonary vein. In addition, the esophagus was divided and reattached. This radical approach to portal hypertension presented an alternative to shunting procedures, but it may have additional morbidity. A modified Sugiura operation in which the esophagus is transected and reanastomosed by a stapling device and in which the spleen is preserved has been described in children. As experience with shunting and other vascular surgery in children has increased, the use of these effective but palliative and unphysiologic operations has decreased.

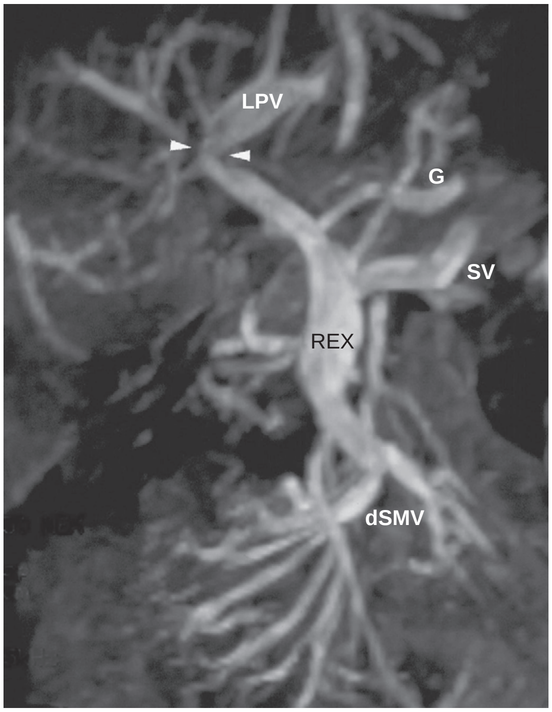


**FIGURE 108-7** The postoperative appearance of a meso-Rex bypass. The blood flows from the superior mesenteric vein (*dSMV*) and recruits blood from the splenic vein (*SV*), the coronary vein (*G*). The vein graft (*Rex*) flows cephalad into the left portal vein (*LPV*). The *white arrows* indicate a mild narrowing near the anastomosis between the jugular vein graft and the intrahepatic portion of the left portal vein.

## Complications of Surgery

### SHUNT THROMBOSIS

Any vascular operation, especially on the venous system, has the potential for thrombosis. Prophylaxis against thrombosis may be instituted in the immediate postoperative period with low-dose heparin and antiplatelet agents such as aspirin or dipyridamole and continued for 3 to 6 months. Once a shunt is thrombosed, it may not be salvageable, and other solutions such as devascularization must be sought if bleeding recurs. Careful follow-up, antithrombotic prophylaxis, and good operative technique to begin with should result in a long-term patency rate of greater than 90%.

### ANASTOMOTIC STENOSIS

Anastomoses can develop narrowing that can cause sluggish flow in the vessels, possibly thrombosis, and recurrence of the original signs and symptoms. Stenoses have characteristic appearances on Doppler ultrasound examinations that include a narrow area at the anastomosis, poststenotic dilatation of the vessel secondary to turbulent flow, and acceleration of the velocity of blood flow through the stenotic area. If the stenosis is believed to be of hemodynamic significance, then it must be dilated either by radiologic or surgical means. Interventional radiologic techniques can study the vessel and the stenotic area, assess the hydrostatic gradient on either side of the anastomosis, and dilate the narrow area by balloon dilatation. The effect of the ballooning can also be assessed by remeasurement of the pressure gradient. Placement of an endovascular stent is also a possibility in recalcitrant strictures (Fig. 108-8). We prefer to avoid stents in smaller children because, once placed, a stent may act as a fixed stenosis as the child grows and cannot be removed.

### ASCITES

Ascites is common after shunt operations because of disruption of the retroperitoneal lymphatic channels. In most cases this resolves spontaneously. Oral diuretics may be necessary for a short time. A reduced-fat diet may also be helpful because all the ascites is chylous in nature. Rarely, paracentesis may be necessary if the ascites is tense and persistent. If so, parenteral nutrition may be used to eliminate any chylous flow for a short time until the lymphatic leak seals. If ascites does not resolve with these measures, it may indicate that the hepatic reserve is small and transplantation may be necessary.

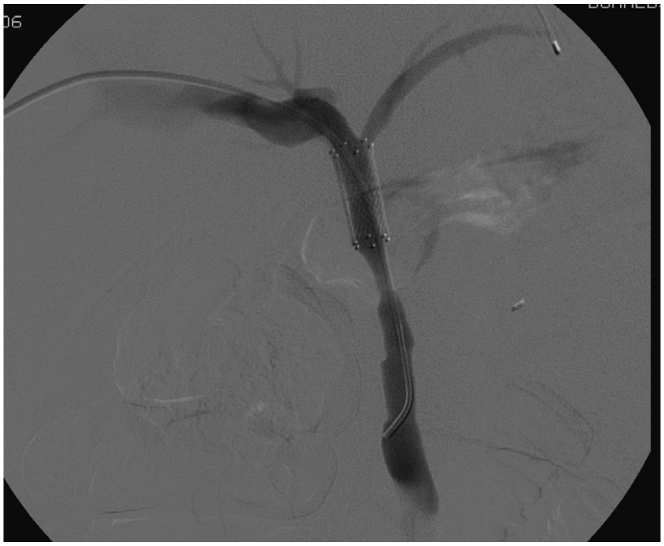

FIGURE 108-8 A transhepatic catheter is entering the liver from the right side of the patient. It has deployed a clearly visible endovascular stent used to treat a stricture in the vein graft or at the anastomotic suture line that was resistant to simple balloon dilatation.

### ESOPHAGEAL STRICTURES

After devascularization procedures accompanied by esophageal transection, it is not uncommon for the esophagus to narrow at the site of transection. Overt leaks are an uncommon but serious complication that requires thoracostomy drainage, prolonged antibiotics, and possibly reoperation. Fortunately, most strictures are manageable by esophageal dilatation, although some may require repeated sessions to achieve satisfactory patency.

## Outcome

The outcome of treatment in a child with portal hypertension depends on the cause of the hypertension and the underlying state of the liver. In the past decade, the care of these patients has improved considerably because of better medical and surgical options and the availability of liver transplantation in children with poor hepatic reserve.

### EMERGENCY BLEEDING FROM VARICES

Medical control of portal hypertension has improved to the point that emergency shunts in children are the exception rather than the rule. Medical therapy and endoscopic control of esophageal varices by ligation is excellent. Emergency shunts, when necessary, are effective in controlling hemorrhage, with good long-term patency rates reported. However, the patency rate of emergency shunts is lower than the 90% or greater patency rate reported for elective operations. Emergency mesocaval shunting is seldom reported today, owing to the availability of medical and endoscopic means of controlling acute variceal hemorrhage.

### INTERMITTENT BLEEDING FROM ESOPHAGEAL OR GASTRIC VARICES

Today, because of the effectiveness of endoscopy and medications, few patients with extrahepatic portal vein thrombosis present with acute, poorly controlled variceal bleeding requiring surgery. Patients are presenting with greater frequency with advanced hypersplenism and well-controlled varices. Controlling variceal bleeding does, however, require numerous endoscopies, occasional transfusions, and treatment with beta blockers and vasodilators.

As surgical options have become more effective and the results more predictable, definitive surgery for extrahepatic portal hypertension should be offered at an earlier point in the disease process rather than waiting until all other therapy has failed.[148] This is especially relevant with the advent of the meso-Rex bypass because this operation restores normal portal pressure and relieves hypersplenism by redirecting mesenteric blood back to the liver. The portal vein delivers 50% of the oxygen and 80% of the total blood supply to the liver. After a successful meso-Rex bypass, the flow in the vein graft increases over time as evidenced by the rapid expansion in portal vein branches inside the liver (Fig. 108-9, *A* and *B*). The effects of restoring portal blood to the liver are not yet apparent and may have far-reaching metabolic consequences during the child's early development. The correction of coagulation parameters back to normal after portal flow restoration may be only one of many ameliorations in hepatic function that take place. The common belief that a child with portal vein thrombosis and portal hypertension has "normal" hepatic function may not be correct.

As experience with the meso-Rex bypass increases, more evidence of the metabolic sequelae of the restoration of portal flow to the liver has become apparent. Both clinical and experimental data point to improved growth, protein synthesis, and neurocognitive function following a meso-Rex bypass.[49,51,149–151] The long-term consequences of portal vein thrombosis on bile and bile ducts are also not well understood, but evidence suggests there is an increased incidence of cholelithiasis and biliary cirrhosis from uncorrected portal vein thrombosis.[152,153]

Recently, the conclusions of a consensus conference held to formulate surgical guidelines in the treatment of children with portal vein thrombosis were published. These take into account both the developing comfort in doing this procedure, as well as the new data that indicate the meso-Rex bypass not only relieves the symptoms of portal hypertension as well as other procedures but also restores to normal many of the metabolic parameters of the liver that have been affected by the long-standing deprivation of portal blood flow.[148]

Selective shunting, through either a distal splenorenal shunt or a coronary-to-vena cava graft, to correct portal hypertension from portal vein thrombosis has been established as a procedure with minimal morbidity and no mortality when done by experienced surgeons. Patency rates exceed 95%, and hospital stays of less than a week are common. In the long run, selective shunting may be better for children than repeated hospital admissions for banding and long-term medication use to control bleeding. In addition, advanced hypersplenism occurs in many of these children when definitive surgical therapy is delayed. Even when variceal banding is instituted prophylactically, bleeding may shift away from the

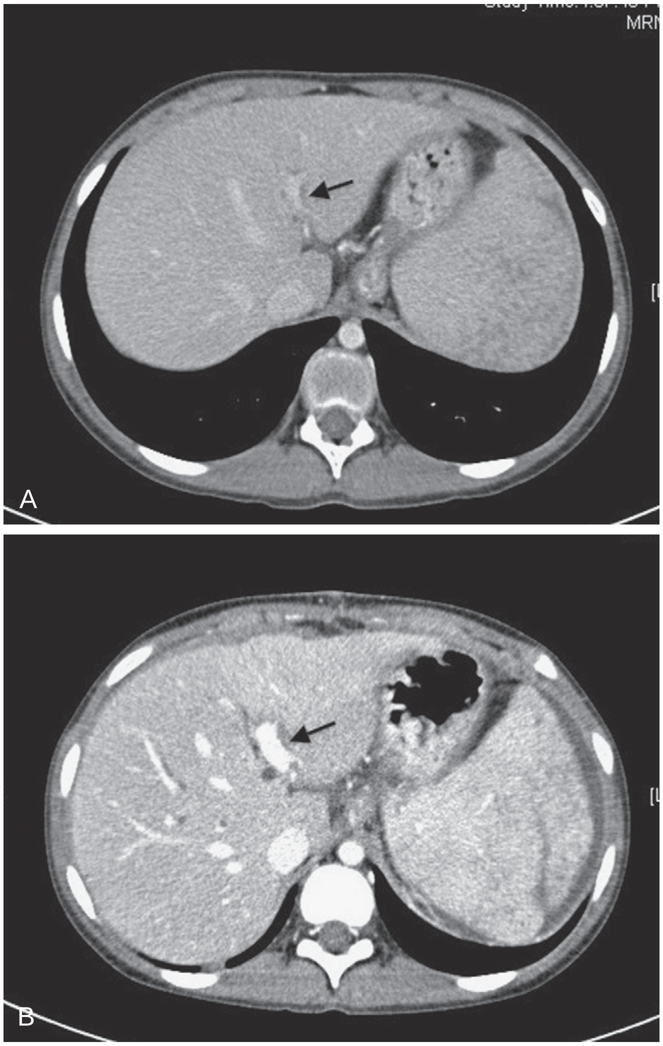


**FIGURE 108-9** These two images of the liver from the same patient before **(A)** and after **(B)** the meso-Rex bypass illustrate the expansion in the intrahepatic portal vein size that occurs quickly after restoration in mesenteric venous flow (*arrows* in both images point to the portal vein in the equivalent area). The change in portal vein size is indicative of an increase in the volume of blood flowing through the liver.

esophagus and into the stomach in many children over time. Surgical therapy (Rex shunt or distal splenorenal shunt) controls bleeding, reduces hospital admissions, decreases the need for medications, and relieves hypersplenism in a physiologic way that does not expose the child to the lifelong risk of overwhelming sepsis after splenectomy.

Shunting for portal hypertension caused by intrinsic liver disease is a more complex proposition because it has to take into account the health of the liver. Selective shunting is excellent at decompressing the child's portal system, with minimal morbidity in patients with low Child-Pugh or PELD scores. Although the theory behind the distal splenorenal shunt is that it separates the splenic and gastric venous drainage from the intestinal and mesenteric venous flow, careful studies have shown that separation between the two systems is not always complete and may disappear over time as the body forms collateral veins to replace the ones that were interrupted. Nevertheless, selective shunts that attempt to preserve hepatopetal flow result in less encephalopathy and better hepatic function than do nonselective shunts in both children and adults.

If a child with well-preserved liver function and portal hypertension cannot have a selective shunt because of a previous failed shunt or because of unfavorable anatomy, it may be better to consider a devascularization procedure to minimize the potential for encephalopathy.[154,155] The only role for nonselective shunts in children may be the rare child with well-preserved liver function and obstructive venopathy that cannot be stented or opened by an interventional radiologic approach. In this case the risk of minimal encephalopathy may be outweighed by the dangers of recurrent bleeding.[156]

### GASTROPATHY

The treatment includes all measures generally applied to bleeding from esophageal varices except that endoscopic treatment is not possible. Measures include drug therapy with somatostatin analogues, acid suppression, antibiotics,[62] and treatment with beta blockers. Long treatment may also include surgical relief of the portal hypertension. This has been shown to reverse the gastropathy.[157] The choice of operation of course depends on the cause of the portal hypertension and the venous anatomy.

### HYPERSPLENISM

As the treatment for esophageal variceal bleeding has improved, more children are presenting with bleeding from gastric varices, portal hypertensive gastropathy, or complications of advanced and debilitating hypersplenism. There is no medical therapy for hypersplenism other than stimulating the bone marrow with granulocyte colony-stimulating factor (GCSF).[158,159] In fact, GCSF may transiently lower the platelet count while it helps with the leucocytes.[160] Surgery is the only alternative.

Almost all shunts have been shown to decrease the severity of hypersplenism when done primarily for the indication of bleeding from symptomatic varices. The same two principles should govern the choice of surgery done primarily for hypersplenism: splenic preservation and the avoidance of encephalopathy. The distal splenorenal shunt has been shown to ameliorate hypersplenism in children. In children with extrahepatic portal vein thrombosis, the Rex shunt has had excellent results in terms of resolving hypersplenism and also improving the neurocognitive parameters associated with portosystemic shunting.

## Summary

A child with portal hypertension presents a unique challenge to the surgeon. The number of treatment options has increased over the past 2 decades and includes a wider variety of effective medications that reduce the pressure in the mesenteric tree and diminish the blood flow in the portal circulation. These options have greatly decreased the need for emergency surgery in children with portal hypertension. Figure 108-10 summarizes the treatment options discussed in this chapter on the basis of the underlying cause of portal hypertension.

Ancillary interventions such as endoscopic ligation of varices and radiologically guided placement of intrahepatic stents have also reduced the reliance on operative control of bleeding

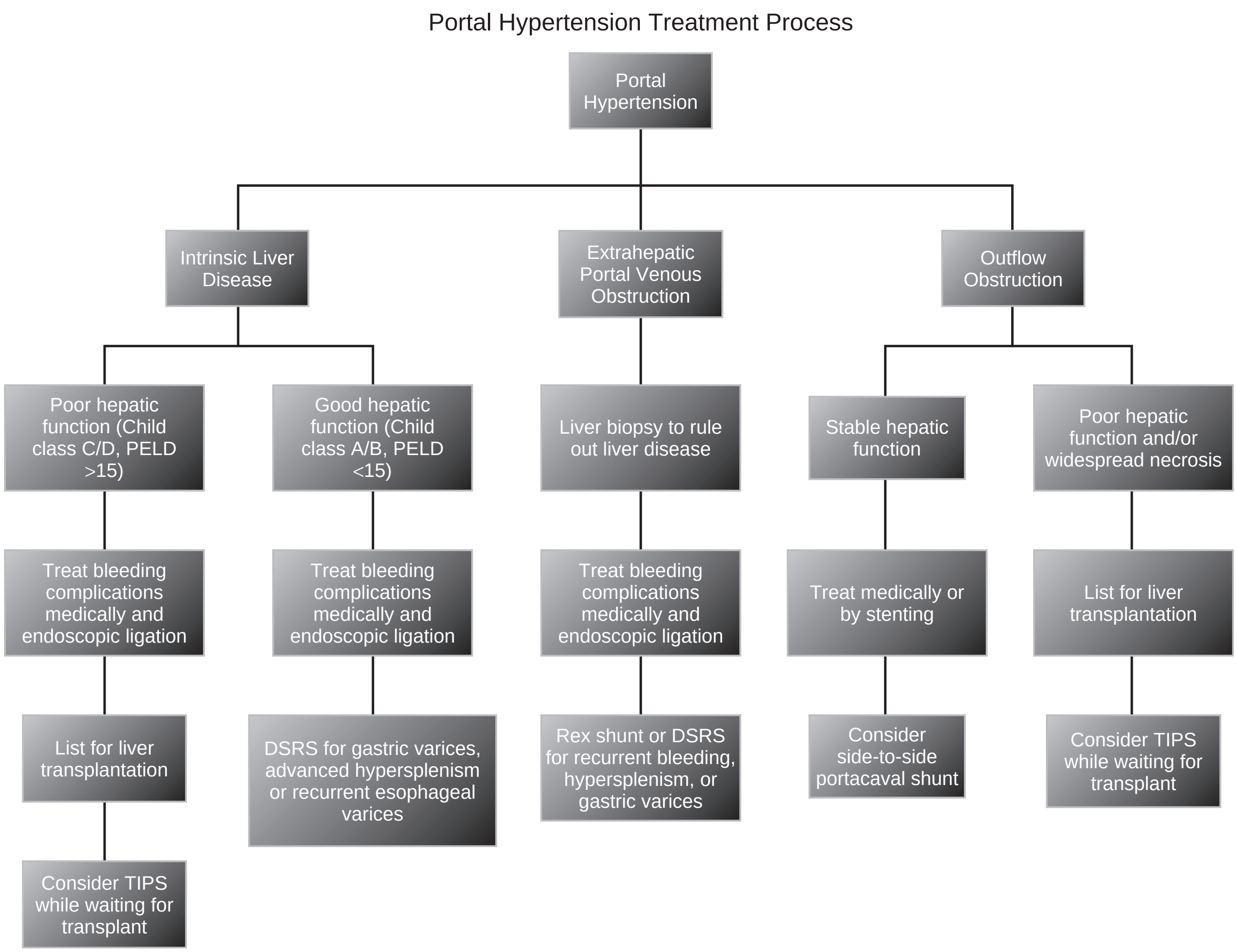


**FIGURE 108-10** Treatment algorithm according to the underlying cause of portal hypertension. Portal hypertension accompanied by advanced liver dysfunction from either venous outflow obstruction or intrinsic liver disease is ultimately treated by transplantation, with or without a transjugular intrahepatic portosystemic shunt (*TIPS*) procedure. If the liver dysfunction is acceptable and not rapidly progressive, an appropriate shunt may be a good long-term solution. For symptomatic portal hypertension from extrahepatic portal hypertension, mesenteric-to-left portal vein bypass is the procedure of choice, followed by distal splenorenal shunt (*DSRS*). PELD, Pediatric end-stage liver disease.

in patients with advanced liver disease. Such interventions increase the chance that these patients will survive to receive a liver transplant.

Although the need for surgical procedures has been reduced, surgical results have improved so that both shunt and nonshunt procedures offer a more permanent solution to bleeding and hypersplenism in patients with prehepatic and posthepatic portal hypertension and in those with well-compensated cirrhosis. With the decreased morbidity associated with portal hypertension surgery, the excellent long-term patency rates reported even in infants and small children after shunt surgery, and the increased number of surgical options available for children, surgery for portal hypertension offers a good alternative to medical treatment, even early in the course of treatment.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 109

# The Pancreas

N. Scott Adzick

## Embryology

The pancreas originates from two endodermal buds that arise from the caudal part of the foregut. One is the ventral bud, which arises from the base of the hepatic diverticulum and is closely related to the bile duct; the other arises from the dorsal surface of the duodenum immediately opposite and in a slightly rostral direction to the liver diverticulum. Both fuse at approximately the sixth or seventh week of gestation. The dorsal bud appears before the ventral bud, grows faster, and becomes larger.[1,2] An axial duct is formed and opens into the gut tube by the beginning of the sixth week of gestation, and short branches appear soon thereafter.[3]

The ventral bud of the pancreas transiently consists of two lobules[4]; small ducts form within these lobules and open into the hepatic diverticulum close to the gallbladder. The ventral bud is carried away from the duodenum by elongation of the proximal part of the hepatic diverticulum from which it arises. This proximal part is called the *common bile duct*. The left ventral bud lobule later regresses completely. Because of rapid growth of the duodenum, which is limited to the left half of its circumference,[5] the right ventral bud and the developing common bile duct rotate backward and become situated close to the posterior and inferior surface of the dorsal pancreatic bud. The outcome of this rotation is to bring the opening of the common bile duct to the same side as the dorsal bud so that the duct lies ventral to and below the opening of its duct. The tip of the right ventral bud lobule eventually rests behind the superior mesenteric artery. During the seventh week of gestation, the smaller ventral bud fuses with the proximal part of the dorsal pancreas.

Secretory acini appear during the third month as clusters of cells around the ends of the ducts from which they are derived.[6] Pancreatic development involves a process in which two morphologically distinct tissue types must derive from one simple epithelium. These two tissue types, exocrine (including acinar cells, centro-acinar cells, and ducts) and endocrine cells, serve disparate functions and have entirely different morphology. In addition, the endocrine tissue must become disconnected from the epithelial lining during its development.[7,8]

### PANCREATIC ANOMALIES

Pancreatic anomalies are numerous and are listed in Table 109-1.

### ANNULAR PANCREAS

During the sixth week of gestation, the common duct and the right ventral bud lobule are carried in a dorsal direction around the circumference of the duodenum. The longer duct of the dorsal pancreas anastomoses with that of the ventral pancreas to establish the main pancreatic duct. Developmental errors at this stage are believed to cause annular pancreas. This anomaly occurs in 1 in 20,000 births and is more frequent in males than females with a ratio of 2:1. The appearance of an annular pancreas in a woman and her child,[9] in siblings, and in members of two successive generations[10] suggests a possible hereditary link, but this has yet to be delineated. Annular pancreas can cause duodenal stenosis or obstructive symptoms in the first days of life.[11]

### PANCREAS DIVISUM

The adult pancreas is derived from ventral and dorsal pancreatic buds that fuse by the end of the eighth week of gestation. Most of the gland is derived from the dorsal bud and includes the superior anterior part of the head, body, and tail; it is drained by the duct of Santorini through the minor papilla. The ventral bud becomes the posterior and inferior part of the head. The ventral pancreatic bud is drained by the duct of Wirsung into the major papilla of Vater. With fusion of the ventral and dorsal pancreas and their duct system, the duct of Wirsung becomes the major duct, and the duct of Santorini usually regresses with the minor papilla in approximately 90% of people. Failure of the two ductal systems to unite results in the anatomic variant known as *pancreas divisum*. In this disorder the duct of Wirsung is small, and the duct of Santorini becomes the major ductal system and maintains communication with the duodenum through the minor papilla. This configuration is found in 4% to 11% of cadavers and in 3.25% of patients undergoing endoscopic retrograde cholangiopancreatography (ERCP).

### CONGENITAL SHORT PANCREAS

Congenital shortening of the pancreas is an unusual anomaly that has been described in individuals with polysplenia syndrome,[12] as well as being an isolated anomaly.[13] It has also

**TABLE 109-1**
**Errors in Pancreatic Development**

| |
|---|
| Aplasia and hypoplasia |
| Hyperplasia and hypertrophy |
| Dysplasia |
| Ductal anomalies |
| Pancreas divisum |
| Annular pancreas |
| Rotational anomalies |
| Heterotopic pancreas |
| Cysts |
| Arterial, vascular, and lymphatic anomalies |
| Neoplasm |
| Cystic fibrosis |

been seen in conjoined twins with a shared duodenum. In this condition the pancreas appears blunted and lacks tissue in the region of the body and tail, which is believed to be caused by agenesis of the dorsal pancreatic bud. Pancreatic function generally remains normal despite partial absence of the pancreatic parenchyma.[14]

# Surgical Anatomy

The pancreas is composed of a head, body, and tail, although these areas have no distinct anatomic borders. The head sits to the right on L2, the body covers L1, and the tail rises to T12 on the left. The abdominal aorta and vena cava provide some cushioning effect against the vertebrae; however, certain forces (such as seat-belt and steering wheel injuries) can cause blunt trauma to the body of the pancreas.

The pancreas is retroperitoneal. Peritoneal reflections from the transverse mesocolon, small intestinal mesentery, and the splenorenal and phrenocolic ligaments are present and establish mesenteric planes for the direct spread of extravasated pancreatic enzymes.[15] These anatomic relationships are important for understanding the pathophysiology of the various radiographic signs seen in patients with acute pancreatitis.

The splenic artery provides most of the blood supply to the pancreas and lies along its superior border with the splenic vein. It seems that the blood supply is generally greatest to the head of the pancreas. The head of the pancreas shares its blood supply with the duodenum through the gastroduodenal artery and superior and inferior pancreaticoduodenal arteries, which may complicate surgery on the head of the pancreas. Blood from the pancreas drains in a posterior direction into the superior mesenteric vein and splenic vein via small, delicate branches.

Several anomalies of the pancreatic (third) part of the common bile duct have been noted: (1) The bile duct may be partly covered by a tongue of pancreas (44%), (2) the bile duct may be completely covered by the pancreas (30%), (3) the posterior surface of the bile duct may be uncovered (17%), and (4) the bile duct may be covered by two tongues of the pancreas (9%).[16] Surgeons must be aware of these variants during surgery involving the head of the pancreas.

# Pancreatitis

Although pancreatitis is uncommon during childhood, it must be considered in every child with unexplained acute or recurrent abdominal pain. The prognosis in children is generally good, with the exception of pancreatitis occurring with multiorgan failure. Regardless of the cause, certain common features are found in all types of pancreatitis. Patient management must be highly individualized because numerous disease entities can cause pancreatitis.

## ACUTE PANCREATITIS

Clinically, acute pancreatitis is defined as a single episode or recurrent episodes of abdominal pain associated with elevated serum pancreatic enzyme levels. The morphologic correlate is acute focal or diffuse swelling and inflammation of the pancreas. Resolution of symptoms and normalization of blood biochemistry and anatomic abnormalities follow an acute episode. A continuum exists between acute and chronic pancreatitis; as a result, recurrent episodes of acute pancreatitis may evolve into the typical clinical and morphologic features of chronic pancreatitis.

### Etiology

Although pancreatitis in adults is usually related to alcohol abuse or biliary tract disease, in children the causes are more diverse.[17–19] Most cases of acute pancreatitis in children result from systemic infection, trauma, choledocholithiasis, anomalies of the pancreaticobiliary duct system, and drugs (Table 109-2). Less common causes include idiopathic

**TABLE 109-2**
**Causes of Acute Pancreatitis in Children**

| |
|---|
| Systemic infection |
| Mumps |
| Rubella |
| Coxsackie B virus |
| Trauma |
| Blunt abdominal trauma |
| Iatrogenic (e.g., surgery, ERCP) |
| Anomalies of the pancreaticobiliary duct system |
| Pancreaticobiliary malunion |
| Pancreas divisum |
| Hypertensive sphincter of Oddi |
| Choledochal cyst |
| Choledocholithiasis |
| Drugs |
| Azathioprine |
| Tetracycline |
| L-Asparaginase |
| Immunosuppressants |
| Valproic acid |
| Metabolic abnormalities |
| Hypertriglyceridemia |
| Hypercalcemia |
| Cystic fibrosis |
| Liver transplantation |
| Miscellaneous |
| Idiopathic |

ERCP, Endoscopic retrograde cholangiopancreatography.

disease, metabolic disorders, and miscellaneous conditions such as familial pancreatitis and Crohn disease.

Six percent to 33% of cases of pancreatitis are related to disorders of the biliary or pancreatic duct,[20] with choledochal cyst and cholelithiasis being the most common. A choledochal cyst is often associated with malunion of the pancreatic and biliary ducts (pancreaticobiliary malunion), and a long common channel may form and permit reflux of bile into the pancreatic duct.[21] The common channel is seen easily on ERCP; this channel is often dilated and contains protein plugs or stones, which may cause obstructive pancreatitis or jaundice.

Cholelithiasis in children is frequently associated with various hemolytic disorders including spherocytosis, alpha-thalassemia, and sickle cell disease. It may also be caused by obesity and the use of total parenteral nutrition.[22] The role of pancreatic duct anomalies such as pancreatic divisum and stenosis of the ampulla of Vater has only recently been appreciated.[23–26] Pancreaticobiliary malunion not associated with a choledochal cyst is drawing clinical attention because it tends to be overlooked on ultrasonography; most patients with the disorder have recurrent abdominal pain as a result of pancreatitis.[24,26–28] Tagge and colleagues[26] found ductal anomalies in 6 of 61 (10%) patients with pancreatitis. They noted that patients with ductal abnormalities usually had recurrent episodes and that relapsing or chronic pancreatitis was also associated with ductal anomalies.

Severe abdominal trauma may cause immediate acute symptoms.[29] However, less severe trauma may result in a delayed onset and subacute manifestation. Child abuse should be considered in all children with acute pancreatitis who have a vague history.[19] Finally, trauma may also be iatrogenically induced during the course of abdominal surgery or ERCP.[30]

Drugs cause 8% to 25% of the cases of pancreatitis. Drugs that cause pancreatitis most frequently include didanosine, azathioprine, mercaptopurine, L-asparaginase, and valproic acid.[20,31,32] Recently, liver transplantation has been reported as a possible cause of acute pancreatitis. The incidence of this complication and the mortality rate in children were 1.9% and 43%, respectively.[33] A strong association between the development of acute pancreatitis after liver transplantation and several risk factors such as the diagnosis of fulminant hepatic failure, retransplantation, extensive dissection at the time of liver transplantation, and the use of infrarenal arterial grafts has been reported.[34]

Certain variants of the trypsinogen gene and cystic fibrosis transmembrane regulation (CFTR) gene may cause acute recurrent pancreatitis. Many patients with the diagnosis of idiopathic pancreatitis have compound heterozygote genotypes in which both alleles of the CFTR gene are abnormal, thus constituting a variant of cystic fibrosis. There are also numerous reports of an association between chronic pancreatitis and a number of CFTR mutations both in patients with cystic fibrosis and in carriers with a single mutation.[35]

In certain conditions, destruction of the pancreas begins antenatally. Infants with Shwachman-Diamond syndrome, an autosomal recessive disorder mapped to the centromeric region of chromosome 7,[36] have pancreatic insufficiency at birth, generally with low serum trypsinogen levels, indicative of nearly total exocrine pancreatic atrophy by birth.

## Diagnosis

The diagnosis of acute pancreatitis is based on the clinical history, physical examination, laboratory test results, and findings of diagnostic imaging investigations. Determination of amylase isoenzymes has also been used to increase diagnostic accuracy by identifying the tissue from which the amylase originates. Serum lipase levels may also complement pancreatitis testing and increase the yield of positive diagnoses.[37] A new scoring system for acute pancreatitis in children has been proposed that has better sensitivity than the Ranson and Glasgow scores.[22] The parameters are age (<7 years), weight (<23 kg), admission white blood cell count (>18,500), admission lactate dehydrogenase level (>2000), 48-hour trough $Ca^{2+}$ level (<8.3 mg/dL), 48-hour trough albumin level (<2.6 g/dL), 48-hour fluid sequestration (>75 mL/kg/48 hr), and 48-hour rise in blood urea nitrogen (>5 mg/dL).

Plain radiographs of the chest and abdomen are obtained to exclude intestinal perforation. Occasionally radiopaque gallstones, a gas-filled right colon, or a distended loop of small intestine (sentinel loop) may be seen. Left basal pleural effusion is relatively common, and mottling of the lung fields is a sign of systemic cytokine release. Radiographic studies enhanced by water-soluble contrast of the upper gastrointestinal tract are occasionally useful, particularly in cases of trauma when injury to the duodenum or small intestine is suspected. Ultrasonography (US) and computed tomography (CT) are useful for detecting pancreatic abnormalities. Trauma-induced injuries to abdominal organs, particularly the pancreas, are readily detected on CT.

ERCP is rarely indicated for acute pancreatitis, but it eventually becomes essential in any child who has pancreatitis with an unclear cause.[23,26] This technique is useful in cases of relapsing pancreatitis associated with pancreaticobiliary malunion.[21,24] ERCP is an invasive method that can aggravate pancreatitis and is often not an option during the acute phase of pancreatitis. Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive method of obtaining images of the pancreaticobiliary tract. MRCP images the common bile duct in more than 96% of patients and detects common bile duct stones with a sensitivity of 71% to 100%, thus exceeding the sensitivity of US (20% to 65%) and CT (45% to 85%). Visualization of the smaller pancreatic duct is successful in more than 80% of patients.[37] Miyano and colleagues[38] have previously evaluated the efficacy of MRCP in pediatric patients with acute pancreatitis. Patients were divided into two groups. Group 1 consisted of seven patients in whom choledochal cysts were sonographically diagnosed, and group 2 consisted of nine patients with no obvious cause of acute pancreatitis. Pancreaticobiliary malunion was detected in six of seven in group 1 and in one of nine in group 2. Pancreatic divisum was detected in one patient in group 1 but could not be confirmed in any of the group 2 patients. Dilatation of the main pancreatic duct was detected in one in group 1 and in three in group 2. These findings indicate that MRCP is a potentially useful method for identifying and ruling out structural abnormalities of the pancreaticobiliary tract in children.

## Treatment

Treatment of acute pancreatitis has two primary goals: (1) to minimize any causative factors and (2) to provide meticulous supportive care including liberal use of analgesics,

administration of parenteral fluids, maintenance of nutrition, prevention of infection, and inhibition of endocrine and exocrine activity.

Parenteral analgesia with narcotics or nonsteroidal antiinflammatory agents is generally required, even in mild cases of pancreatitis, because the pain can be extreme. It is traditional to administer meperidine rather than morphine because the latter produces ampullary spasm. Although nasogastric suction is usually initiated to reduce vomiting and abdominal distention, the value of nasogastric decompression is questionable, unless the patient is vomiting. Aspiration of gastric acid may reduce pancreatic exocrine secretion by limiting the release of secretin. Oral feeding must be withheld to reduce pancreatic stimulation. Total parenteral nutrition should be initiated early to avoid malnutrition.[39] In addition, early placement of a central venous catheter in patients with severe disease will provide access for aggressive intravascular volume support and nutrition. The hematocrit and serum levels of glucose and calcium should be measured, and hourly urine output should be monitored carefully.

Although the advantages of prophylactic antibiotics have not been proved, patients with necrotizing pancreatitis may benefit.[40] Other treatment strategies involving somatostatin, glucagon, anticholinergics, histamine blockers, and protease inhibitors have been recommended, but to date they have not shown conclusive benefit.

Standard medical treatment must be used in patients with acute pancreatitis in an attempt to control the disorder before surgical intervention, which is rarely required in children but is occasionally performed if the diagnosis is uncertain or a complication develops after an acute episode such as a pseudocyst or an abscess. Patients with acute pancreatitis associated with underlying pancreaticobiliary disease generally require surgical correction of the underlying condition before cure can be expected.

In the management of severe acute pancreatitis, a major decision is whether and when surgery for pancreatic necrosis or infection is necessary. Infection of necrotic pancreatic tissue is the major risk factor for mortality in severe acute pancreatitis and is an indication for surgery. On the other hand, there is support for nonsurgical conservative management of sterile pancreatic necrosis including antibiotic treatment. The reported death rate is 1.8% with sterile pancreatic necrosis and 24% with infected necrosis.[41] Early surgery has been associated with increased mortality and should be delayed, if not avoided.[42]

## CHRONIC RELAPSING PANCREATITIS

Chronic relapsing pancreatitis is characterized by recurrent episodes of upper abdominal pain associated with varying degrees of pancreatic exocrine and endocrine dysfunction. Relatively few case series of chronic relapsing pancreatitis in childhood exist, although it is more frequently being suspected in children with recurrent episodes of abdominal pain.[43–45] The disease produces a wide variation of progressive and irreversible structural changes in the pancreas.[44] At present, the most controversial aspect of treatment of this disorder is the choice of an appropriate surgical procedure.

### Causes and Pathophysiology

In children the most common causes of chronic relapsing pancreatitis are trauma, heredity, systemic disease, and malformations of the pancreaticobiliary duct such as pancreas divisum, annular pancreas, and choledocholithiasis. In addition, various unusual conditions including metabolic disease, endocrine disorders, and inflammatory bowel disease[13] may cause the disorder. Causes of chronic relapsing pancreatitis are listed in Table 109-3.

Certain congenital anomalies affect the pancreas and surrounding tissue, several of which are associated with chronic relapsing pancreatitis. Obstruction of pancreatic flow caused by a stenotic papilla of Vater and bile reflux resulting from a common channel are believed to be responsible for the resultant inflammation, which may be reversible if the obstruction is relieved. A relatively common cause of relapsing pancreatitis is pancreas divisum,[46] in which most of the pancreatic fluid flows through the minor duct of Santorini, with the possibility of a relative obstruction to flow because of anatomy and flow dynamics. Some series have reported an increased incidence of pancreas divisum in patients with idiopathic chronic pancreatitis.[46] Annular pancreas, which results from an error of rotation or fixation of the embryologic pancreatic primordium, has also been associated with chronic pancreatitis (Fig. 109-1).[63] Pancreaticobiliary malunion with or without choledocholithiasis may likewise result in relapsing chronic pancreatitis.[24,27]

In the past few years, several genes have been identified as being associated with hereditary and idiopathic chronic pancreatitis: PRSS1, CFTR, and SPINK1. SPINK1 mutations were found predominantly in patients without a family history. These mutations were most common in those with idiopathic chronic pancreatitis, whereas patients with hereditary chronic pancreatitis predominantly had PRSS1 mutations.[47]

**TABLE 109-3**

| Causes of Chronic Relapsing Pancreatitis in Children |
|---|
| Congenital anomalies of the pancreatic duct |
| Pancreaticobiliary malunion |
| Pancreas divisum |
| Annular pancreas |
| Biliary tract disorders |
| Choledocholithiasis |
| Cholelithiasis |
| Trauma |
| Systemic infection |
| Hereditary pancreatitis |
| Hyperlipoproteinemia |
| Hyperparathyroidism and hypercalcemia |
| Cystic fibrosis |
| Inborn errors of metabolism |
| Chronic inflammatory conditions |
| Crohn disease |
| Ulcerative colitis |
| Systemic lupus erythematosus |
| Chronic fibrosing pancreatitis |
| Juvenile tropical pancreatitis |
| Idiopathic chronic pancreatitis |

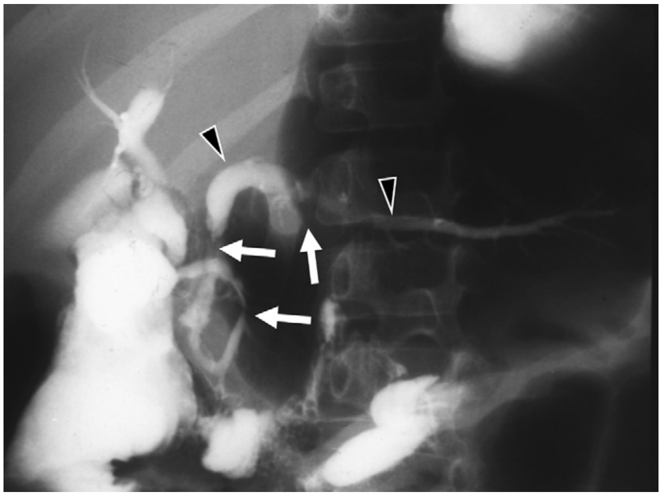

**FIGURE 109-1** Preoperative endoscopic retrograde cholangiopancreatography in a patient with an annular pancreas. A complex anomaly of the pancreatic duct with dilatation (*arrowheads*) and stenosis (*arrows*) is shown. The patient underwent a longitudinal pancreaticojejunostomy (Puestow) procedure.

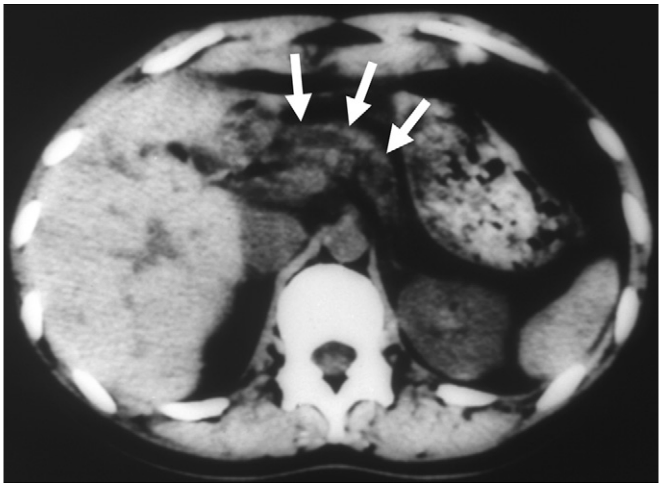

**FIGURE 109-2** Computed tomographic scan of a patient with an irregularly dilated pancreatic duct (*arrows*). The patient underwent a longitudinal pancreaticojejunostomy (Puestow) procedure.

### Diagnosis

The degree of permanent damage to the pancreas may be assessed by blood tests (pancreatic enzymes), stool tests (pancreatic enzymes, fecal fat), and noninvasive tests of pancreatic function such as the pancreatic stimulation (secretin) test. In 30% to 50% of adolescents and adults with chronic pancreatitis, plain radiographs of the abdomen reveal pancreatic calcification. Calcification is diagnostic of chronic pancreatitis, even if clinical evidence of pancreatic disease is absent. However, the incidence of calcification in children with chronic relapsing pancreatitis is low, except in younger children with hereditary pancreatitis, in whom the incidence is high.

US is ideal for examining the pancreas in children. Dilatation of the pancreatic or biliary tracts may be noted, and calcification and complications such as pseudocysts, abscesses, calculi, and ascites can be seen. CT is useful for visualizing the size of the pancreas and its ducts (Fig. 109-2) and for detecting small calculi that may be missed on plain radiographs and US. ERCP is an important tool in the diagnosis and management of chronic relapsing pancreatitis in adults and children.[23] Pancreaticobiliary malunion with or without dilatation of the bile duct may be detected.[24] ERCP is up to 90% accurate in diagnosing ductal abnormalities. However, as described earlier, MRCP has been greatly refined in the past decade. MRCP is considered to be equivalent to ERCP for the diagnosis of many pancreatic and biliary conditions and is preferable because it is noninvasive and safer.[38]

### Surgical Treatment

Surgery for chronic relapsing pancreatitis is done to relieve pain, treat complications, or both. Surgery on the pancreas is generally of three types: (1) sphincteroplasty[45]; (2) pancreatic drainage via longitudinal pancreaticojejunostomy (Puestow),[48] end-to-end pancreaticojejunostomy (Duval),[49] or the Frey procedure[50,51]; or (3) partial or total pancreatectomy. Several groups of investigators have attested to the success of sphincteroplasty in controlling the symptoms of chronic pancreatitis in carefully selected patients. Correct use of this procedure, however, demands that intrapancreatic ductal obstruction be ruled out by pancreatography. O'Neill and colleagues[45] reported good results in six of seven children who underwent sphincteroplasty for chronic pancreatitis.

The general indication for the use of a direct ductal decompression procedure is evidence of pancreatic ductal ectasia with multiple intrapancreatic duct strictures. An important secondary feature of drainage procedures is preservation of existing endocrine function by avoiding major pancreatic resection. Longitudinal pancreaticojejunostomy (Puestow technique) in adults has been successful in eliminating or ameliorating pain from chronic pancreatitis in 70% to 97% of patients in series reported 3 decades ago.[52,53] In children, several authors have shown that either the Puestow procedure[43,54–56] or the Frey procedure[51] improves pancreatic function, decreases hospitalization, and increases body weight toward ideal. Others have reported that distal pancreatectomy and pancreaticojejunostomy are effective.[57] Tailored organ-preserving resective pancreatectomy can also be performed with low morbidity and mortality in pediatric patients with chronic pancreatitis and not responding to medical management. Total pancreatectomy is not generally indicated in children.[58] The individual procedure for chronic pancreatitis should be tailored to the pancreatic ductal anatomy.

## PANCREAS DIVISUM

The embryology of this entity was described in the first section of this chapter. Pancreas divisum is suspected on MRCP or ERCP when the duct of Wirsung fails to be visualized after injection of the major papilla or when it is attenuated and rudimentary. MRCP is a useful and noninvasive diagnostic tool for pancreas divisum (Fig. 109-3), but ERCP can provide detailed information on the pancreatic duct. If pancreas divisum is suspected after injection of the papilla of Vater, an attempt should be made to find and cannulate the minor papilla, but this is possible in less than half the cases because of its small size and the angle at which it meets the duodenum. If the minor papilla can be entered, ERCP will demonstrate that the duct

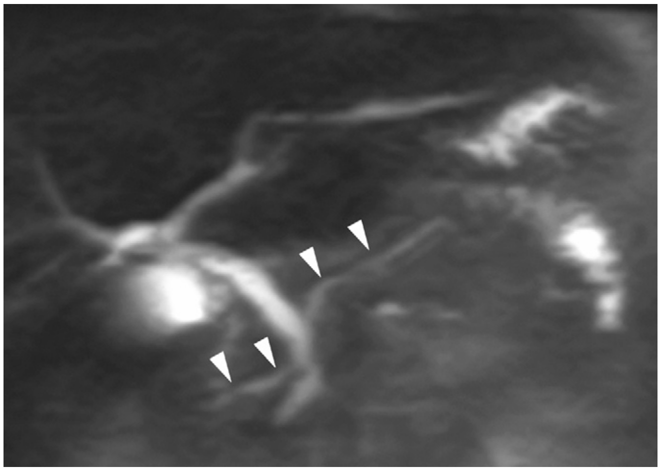

FIGURE 109-3 Magnetic resonance cholangiopancreatography in a patient with recurrent pancreatitis. The duct of Santorini is the dominant duct, and it extends the entire length of the body and tail of the pancreas (*arrowheads*).

of Santorini is the dominant duct and that it extends the entire length of the body and tail of the pancreas. Imaging of the duct of Santorini occasionally demonstrates dilatation, irregularity, or stricture suggestive of chronic pancreatitis.

Autopsy studies have suggested that pancreas divisum, which is found in 4% to 11% of patients, is the most common congenital anomaly of the pancreas. When absence of the duct of Wirsung is associated with pancreas divisum, approximately 10% of affected patients have anomalous anatomy resulting in most or all of the pancreatic secretions draining by means of the accessory papilla.[59,60]

Pancreas divisum should not be regarded as a disease. However, if the orifice of the accessory papilla is stenotic, pancreatitis can result. Stenosis of the minor papilla is probably developmental because the orifice is usually small with no evidence of inflammation. The incidence of pancreas divisum may be significantly higher in patients with unexplained recurrent pancreatitis, and it was detected in up to 25% of patients. Neblett and O'Neill reported that pancreas divisum was identified in 7.4% of all children with pancreatitis and 19.2% of children with relapsing or chronic pancreatitis. In 10 patients with pancreas divisum, 8 had complete pancreas divisum and 2 had incomplete variants.[61]

The primary goal of treatment of pancreas divisum associated with pancreatitis is to establish adequate drainage of the duct of Santorini. The progression of disease to pancreatic insufficiency can be arrested when the obstruction is relieved early. Correction may not only preserve pancreatic function but may also help ensure that normal growth and development occur.

Several reports have shown that adequate drainage of the duct of Santorini can be achieved with accessory papilla sphincteroplasty.[46,59–61] A report by Adzick and colleagues delineated the technical details of the operative procedure.[46] Endoscopic sphincterotomy has been performed, but restenosis and recurrence of symptoms have been reported. If chronic pancreatitis has developed in the presence of a dilated duct, longitudinal pancreaticojejunostomy should be considered. Neblett and O'Neill[61] reported that 8 of 10 patients with pancreas divisum underwent surgery: 7 underwent transduodenal sphincteroplasty of the accessory papilla, along with sphincteroplasty of the major papilla in 2 (plus septoplasty in 1). Three patients underwent longitudinal pancreaticojejunostomy, as a primary procedure in one patient with mid-ductal stenosis and in two because of recurring pancreatitis after sphincteroplasty without endocrine and exocrine pancreatic insufficiency. Surgical intervention is directed toward relief of ductal obstruction and may involve accessory duct sphincteroplasty alone or in conjunction with major sphincteroplasty and septoplasty. Patients with more distal ductal obstruction or ductal ectasia may benefit from pancreaticojejunostomy. In an extremely rare case, Miyano and colleagues treated a patient with coexistence of pancreas divisum, choledochal cyst, and pancreaticobiliary malunion. Figure 109-4 shows the preoperative ERCP and intraoperative cholangiogram. This patient underwent complete excision of the choledochal cyst with a Roux-en-Y hepaticojejunostomy, followed by transduodenal papilloplasty to allow complete drainage of the common channel.[62]

# Cysts and Pseudocysts

Pancreatic cysts are relatively unusual in children. The causes of these cysts tend to be diverse and include both congenital and acquired conditions. Pancreatic cysts can be classified as congenital and developmental, retention, enteric duplication, and pseudocysts.

## CONGENITAL AND DEVELOPMENTAL FORMS

Congenital and developmental cysts of the pancreas are rare and may be encountered in a fetus, infant, child, or adult. Only 25 cases have been reported in the pediatric literature to date.[64–67] These cysts have a female preponderance. They are most common in the body and tail of the pancreas, are more often unilocular than multilocular, and are lined with epithelium. The cysts are usually filled with a cloudy, yellow sterile fluid that has no enzyme activity, and they are remarkably free of adhesions and infection. They have been reported to occur simultaneously in other organs; for example, von Hippel-Lindau disease is characterized by hereditary cerebellar cysts, retinal hemangiomas, and cysts of the pancreas and other organs.[68] The cysts that occur with cystic fibrosis are not considered pancreatic pseudocysts and are not discussed in this chapter.

Clinically, congenital and developmental cysts are detected in the prenatal period as an incidental sonographic finding or as a cause of polyhydramnios. After birth, they may be manifested as asymptomatic abdominal distention, as vomiting or jaundice caused by extrinsic pressure on neighboring organs, or as an asymptomatic mass. Surgical treatment consists of total excision of cysts located in the pancreatic body or tail and either internal drainage or complete resection of those in the pancreatic head.

## RETENTION CYSTS

Retention cysts of the pancreas are rare and believed to result from chronic obstruction of the gland. They contain cloudy fluid composed of pancreatic exocrine secretions and a high concentration of pancreatic enzymes. Such cysts are lined with ductal epithelium unless it has been destroyed by chronic dilatation or inflammation from enzyme exposure.

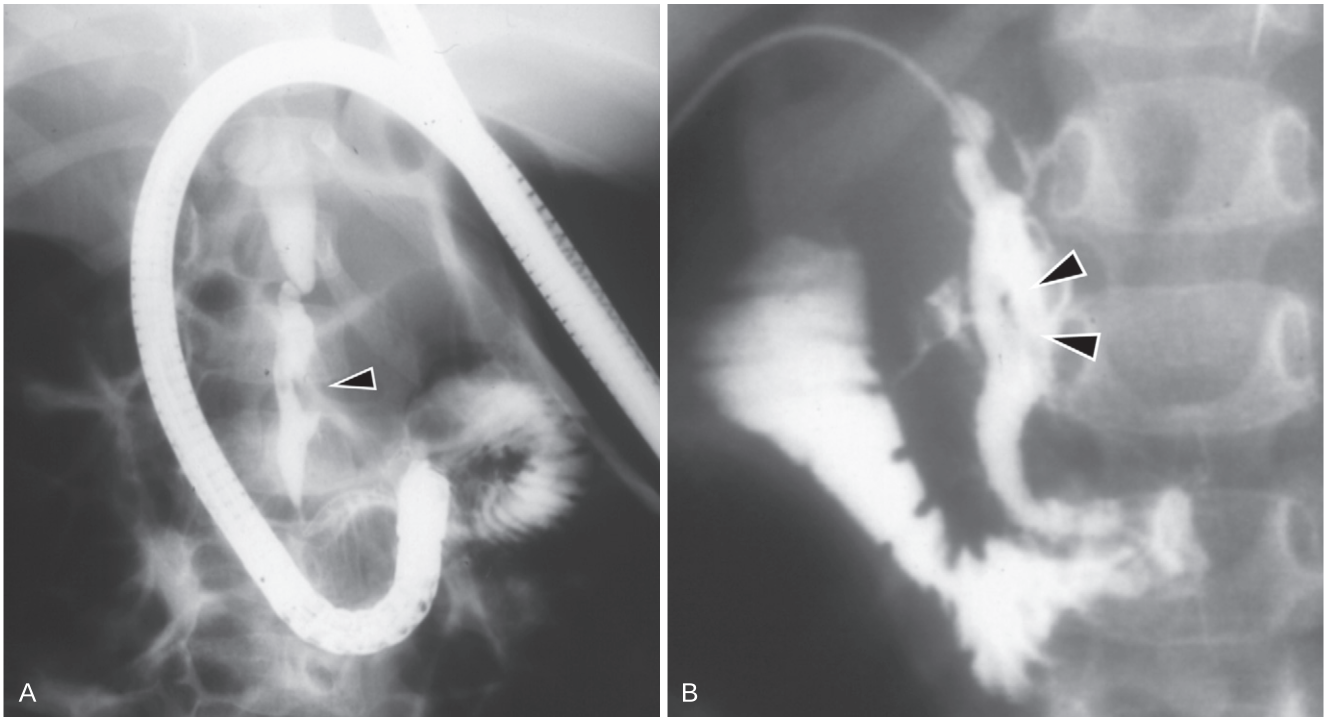


FIGURE 109-4 **A,** Preoperative endoscopic retrograde cholangiopancreatography. **B,** Intraoperative cholangiogram in a patient with a choledochal cyst associated with pancreas divisum. The septum (*arrowheads*) in the intrapancreatic bile duct is also seen.

## ENTERIC DUPLICATIONS

Enteric duplication involving the pancreas is rare and usually associated with gastric duplication.[69] This duplication is most likely to result from failure of regression of an enteric diverticulum formed from the pancreatic duct. Many of the reported cases of enteric duplication involving the pancreas communicate with the pancreatic duct, are lined with gastric-type epithelium, and contain ectopic pancreatic tissue in their walls. Pancreatic duplication cysts have been noted on fetal US.[70]

The most common symptom in these patients is recurrent abdominal pain, often postprandial. Pancreatitis associated with enteric duplication cysts is believed to be caused by obstruction of the pancreatic ducts by viscous secretions from the cyst or by blood and debris from peptic ulceration within the cyst. In patients without pancreatitis, pain may be caused by tension on the wall of the cyst as a result of accumulation of secretions and muscular contraction.[71] CT may help identify the location and size of duplication cysts, as well as any edema of the pancreatic head. ERCP or MRCP is useful to outline ductal anatomy and demonstrate any communication between the duplication cyst and the pancreatic duct to aid in planning the surgical approach. To date, virtually all duplication cysts reported in the literature have been treated by extirpation, and some have required pancreaticoduodenectomy.[69,72]

## PSEUDOCYSTS

### Clinical Features

Pancreatic pseudocysts are localized collections of pancreatic secretions that do not have an epithelial lining and develop after pancreatic injury, inflammation, or duct obstruction. The most common causes of pseudocysts in children are trauma and infection.[73] Drug-induced acute pancreatitis such as with valproic acid is also a rare cause of pancreatic pseudocyst.[74] These cysts typically lie in the lesser sac behind the stomach and are composed of a fibrous capsule surrounded by inflamed connective tissue. The capsule of the cyst may also be formed by neighboring tissue such as the stomach, duodenum, colon, small intestine, or omentum. Pseudocyst fluid is clear or straw colored in most cases and may contain toothpaste-like debris. The amylase level of cyst fluid is typically higher than 50,000 Somogyi U/mL.

### Diagnosis

The presence of a pancreatic pseudocyst is suggested by a history of blunt abdominal trauma; an illness resembling pancreatitis, possibly followed by a symptom-free interval of weeks to months; or palpation of a mass in the epigastrium or left upper quadrant. Abdominal pain is the most common symptom, with jaundice, chest pain, signs of gastric obstruction, vomiting, gastrointestinal hemorrhage, weight loss, fever, and ascites also being features.

US, CT, and magnetic resonance imaging (MRI) are helpful and accurate in diagnosis. These studies are also invaluable for evaluating the thickness of the cyst wall and for observing changes in the cyst during the ensuing period of treatment (Fig. 109-5). ERCP is often useful because it can definitively determine the status of the pancreatic duct and thus guide surgical interventions.[75,76] Rarely, pancreatic pseudocysts can extend into the mediastinum in children.[77]

### Treatment

Optimal management of a pancreatic pseudocyst remains controversial. Treatment options range from conservative medical management to surgical drainage.[78] Conventional

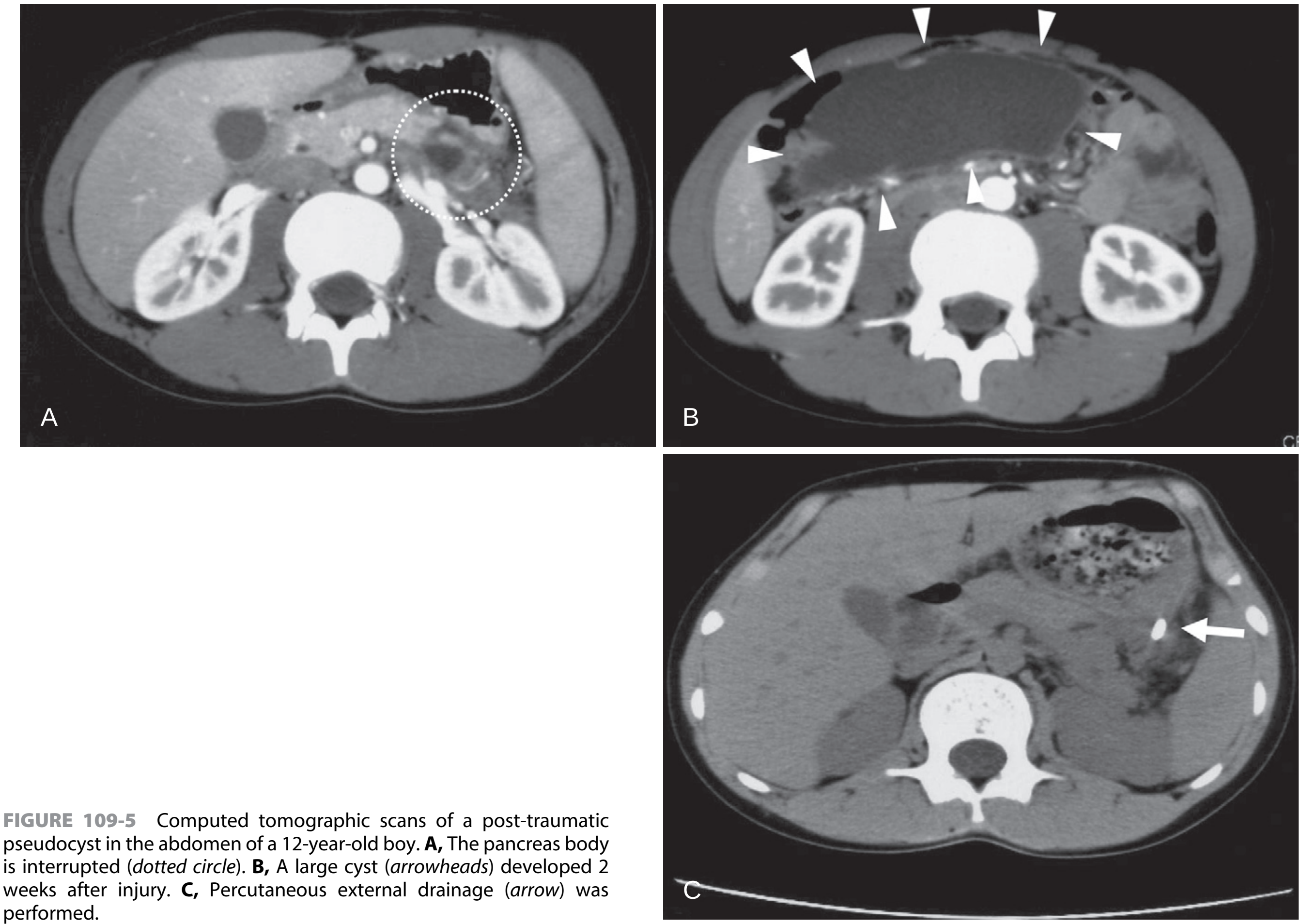


**FIGURE 109-5** Computed tomographic scans of a post-traumatic pseudocyst in the abdomen of a 12-year-old boy. **A,** The pancreas body is interrupted (*dotted circle*). **B,** A large cyst (*arrowheads*) developed 2 weeks after injury. **C,** Percutaneous external drainage (*arrow*) was performed.

management involves supportive therapy over a 6-week waiting period, during which time either the cyst resolves spontaneously or the cyst wall undergoes fibrous maturation, thereby permitting internal surgical drainage to the stomach or jejunum. This 6-week interval is what has traditionally been accepted, but CT may demonstrate thickening of the cyst wall sufficient to hold sutures as early as 3 to 4 weeks. Surgical drainage is usually performed in adults when necessary but is controversial in children because some pancreatic pseudocysts in this group resolve without surgical intervention and have a low risk for recurrence. Pseudocysts from nontraumatic etiologies are more likely to require surgical intervention, whereas traumatic pseudocysts are more amenable to nonoperative treatment.[79] Octreotide acetate, a long-acting analogue of somatostatin, may facilitate medical management of pancreatic pseudocysts.[80]

A significant risk for complications such as infection or major hemorrhage in untreated pseudocysts or persistence of severe symptoms may be an indication for earlier intervention. If the patient cannot withstand major surgery, external drainage is preferred. There is significant evidence indicating that internal drainage, especially transgastric cystogastrostomy or Roux-en-Y cystojejunostomy, is effective in the treatment of pancreatic pseudocyst. Roux-en-Y cystojejunostomy is the most widely used internal drainage procedure for this problem and is associated with the lowest rate of complications and recurrence.[81]

In contrast to this approach, others[82,83] have reported that percutaneous drainage and endoscopic transmural drainage are safe and efficient procedures. However, it is generally recognized that external drainage carries a higher risk for complications such as fistula formation and a higher recurrence rate than internal drainage does. Internal drainage procedures cannot be accomplished until the wall of the pseudocyst has matured. Recent studies have shown that internal drainage should be performed in patients with pseudocysts that are more than 6 weeks old and have a diameter larger than 5 cm because a large proportion of pseudocysts regress during the first 6 weeks after diagnosis and the risks associated with managing the pseudocyst are reduced. Cystogastrostomy has been performed laparoscopically.[84]

Though less commonly used than drainage procedures into the stomach or jejunum, cystoduodenostomy is effective when a cyst is closely adherent to the duodenum. Either pancreaticoduodenectomy or distal pancreatectomy, as indicated by anatomy, is effective in treating patients with pseudocysts under ideal circumstances. Distal pancreatic resection is indicated in patients with a pseudocyst in the body or tail of the pancreas, particularly if associated with multiple small cysts. Pseudocysts involving the head and uncinate process of the pancreas that are not amenable to internal drainage are rare and may require proximal pancreatic resection, but such resection should be done only as a last resort.

## Hyperinsulinism

Congenital hyperinsulinism (HI) is a rare derangement of glucose metabolism, which carries an estimated incidence of 1 to 1.4 in 50,000 live births, leading to about 80 to 120 new cases in the United States each year. Higher rates of 1 in 2500 live births have been reported in areas of high consanguinity such as the Arabian Peninsula. Pancreatectomy for management of persistent infantile hypoglycemia was first performed at the Children's Hospital of Philadelphia (CHOP) in 1950. Inappropriate oversecretion of insulin is the hallmark of HI. The old term "nesidioblastosis" should be discarded. HI is the most common cause of persistent hypoglycemia in neonates and can lead to seizures and irreversible brain damage.[85]

### DIAGNOSTIC APPROACH

#### Genetics

Molecular biologic studies have shown that abnormalities of the $K_{ATP}$ channel, which are encoded by the sulfonylurea receptor 1 *(SUR1)* and *Kir6.2* genes, are responsible for altered control of insulin secretion.[85] In response to elevated glucose levels, the $K_{ATP}$ channel closes, depolarizing the beta-cell membrane and initiating calcium-dependent release of insulin from the beta-cell storage granules. Uncontrolled insulin secretion may occur if either the *SUR1* or *Kir6.2* proteins are defective. The *SUR1*/*Kir6.2* form of HI may not be controlled with medical therapy such as diazoxide, which acts on *SUR1* to suppress insulin secretion, and pancreatectomy is often necessary.[86] In contrast, surgery is not usually necessary in other genetic forms of HI that result from mutations of glucokinase or glutamate dehydrogenase genes that are responsive to diazoxide treatment.

Neonates with HI may have either diffuse involvement of the pancreatic beta-cells or focal adenomatous islet cell hyperplasia. Mutations of the *SUR1*/*Kir6.2* complex are involved in both of these types. Recessive mutations cause diffuse HI, whereas loss of heterozygosity together with inheritance of a paternal mutation causes focal adenomatous HI. Patients with diffuse disease have recessively inherited mutations of the *SUR1*/*Kir6.2* complex, whereas patients with focal disease have normal beta cells, as well as a focal clone of abnormal beta cells that are homozygous for the *SUR1*/*Kir6.2* mutation. The focal lesions arise by a two-hit loss-of-heterozygosity mechanism.[87] First, there is a specific loss of maternal alleles of the imprinted chromosome region 11p15 in cells from the focal lesion but not in the surrounding normal pancreatic cells. Second, there is a transmission of a mutation of *SUR1*/*Kir6.2* in the paternal chromosome 11p; focal lesions have been linked to non-Mendelian expression of paternally transmitted *SUR1* mutation in which there is duplication and reduction to homozygosity of the mutant paternal allele. In the future, molecular biology testing of peripheral leukocytes may help differentiate focal from diffuse disease. However, the search for mutations is currently of limited use in clinical practice because the process takes many weeks and not all mutations are known.

One of the big challenges in diagnosis has been that the diffuse and focal forms of HI are clinically identical. Patients with either focal or diffuse disease are usually large for gestational age, reflecting the effects of HI on fetal growth. We have found that approximately 55% of our patients have focal disease, and about 45% have diffuse disease. Distinguishing focal from diffuse disease is of importance in guiding the extent of surgical resection. Patients with diffuse disease often require near-total pancreatectomy, which has the long-term risk of diabetes mellitus. Conversely, babies with focal disease can be cured with a selective partial pancreatectomy with little risk of subsequent diabetes.

At the Congenital Hyperinsulinism Center at CHOP, we use a multidisciplinary approach (pediatric endocrinology, radiology, pathology, and surgery) for patients with HI to distinguish focal from diffuse disease, localize focal lesions, treat focal disease with partial pancreatectomy, and treat medically refractory diffuse disease with near-total pancreatectomy. During the past 12 years, more than 250 patients (median age 10 weeks) with HI have been treated with pancreatectomy at CHOP. This section on hyperinsulinism will be based largely on the clinical experience at CHOP. We have also crafted an educational DVD regarding the management of congenital hyperinsulinism that is available at the CHOP website (www.chop.edu).

#### Diagnosis and Medical Management by Pediatric Endocrinology

Babies with HI present with severe and persistent hypoglycemia manifested by seizures, lethargy, apnea, and other symptoms resulting from neuroglucopenia.[85] The diagnosis of congenital HI is established if fasting hypoglycemia (glucose $< 50$ mg/dL) occurs simultaneously with an inappropriately elevated plasma insulin ($>2$ μU/mL), low plasma beta-hydroxybutyrate ($<2$ mmol/L) and free fatty acids ($<1.5$ mmol/L), and an inappropriate glycemic response to intravenous glucagon ($>30$ mg/dL rise in serum glucose level). Medical therapy to maintain euglycemia is standardized and involves high continuous intravenous infusions of glucose as measured by the Glucose Infusion Rate (which is the amount of glucose infused in mg/kg/min), frequent oral feedings, and administration of diazoxide, glucagon, and octreotide. Early efforts to distinguish focal from diffuse disease involved the injection of intravenous calcium and tolbutamide (a sulfonylurea) to elicit different types of insulin responses by focal and diffuse disease, but the results were not predictive enough to be clinically useful.

Preoperative assessment of babies with HI reveals that they are large, are often fluid overloaded due to high intravenous glucose requirements, have hepatic enlargement due to steatosis, may be anemic due to frequent blood sampling, and have oral aversion. They are predisposed to central venous line sepsis both preoperatively and postoperatively. Octreotide is the mainstay of medical therapy for HI but can rarely lead to necrotizing enterocolitis because octreotide reduces splanchnic blood flow in a dose-dependent manner.[88]

#### Localization Procedures Performed by Radiology

Diagnostic radiology tests such as US (both preoperative and intraoperative), MRI, CT, contrast angiography, and radiolabeled octreotide scans have all been unsuccessful in identifying focal lesions. For insulinoma localization in adults, intraoperative saline injection into the pancreas followed by tissue aspiration with rapid insulin measurements has been helpful, but this localization technique is untenable in the fragile neonatal pancreas.

Two interventional radiology tests have been used in an attempt to differentiate focal from diffuse disease. The Arterial Stimulation with Venous Sampling (ASVS) technique involves selective pancreatic angiographic stimulation and venous sampling using intra-arterial calcium, which stimulates abnormal islet cells to release insulin. An immediate rise in insulin from stimulation in only one artery suggests focal HI in the corresponding area of the pancreas (gastroduodenal artery—pancreatic head; superior mesenteric artery—uncinate process and neck; splenic artery—pancreatic body or tail), whereas an insulin rise in all three areas suggests diffuse HI. We and others have also used transhepatic portal venous catheterization and selective sampling of the pancreatic veins (THPVS). Both techniques require that the patient be off all glycemic medications (5 days for diazoxide, 1 to 2 days for octreotide) before catheterization under general anesthesia. THPVS requires that glucose levels be maintained at 50 mg/dL during the procedure as compared with 60 to 80 mg/dL for ASVS. For THPVS, the pancreatic venous insulin levels are compared with simultaneously drawn plasma levels of insulin and glucose. Both ASVS and THPVS are technically demanding and have limited specificity and sensitivity for distinguishing between focal and diffuse disease. These techniques are being replaced by a new PET-CT scan technique using 18-Fluoro-L-DOPA.

Neuroendocrine cells have an affinity for taking up and decarboxylating amino acid precursors such as L-dihydroxyphenylalanine (L-DOPA). Decarboxylation of the L-DOPA to dopamine in islet cells allows meaningful localization by means of PET scanning, using the radioactive isomer 18-Fluoro-L-DOPA. The isotope is manufactured by the Cyclotron Facility at the University of Pennsylvania on the day of the PET scan because of the isotope's short half-life, and it is administered to patients under an Investigational New Drug (IND) program approved by the U.S. Food and Drug Administration. Hopefully, 18-Fluoro-L-DOPA will become commercially available in the future so that it can be used in other medical centers. The PET results are dramatic and visually spectacular for preoperative localization of a focal lesion (Fig. 109-6).[89] In more than 140 PET scans for HI, we have found that PET-CT scans read as showing a focal lesion have been 100% accurate in localizing a lesion. However, in about 20% of PET scans that were interpreted as showing diffuse disease, the patient at operative exploration will prove to have a focal lesion that was usually small. This false-negative rate should decrease with greater clinical experience.

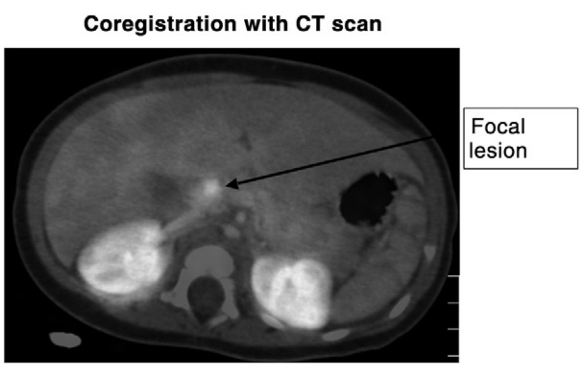


**FIGURE 109-6** Positron emission tomography scan is coregistered with a computed tomography scan that shows a focal lesion (*arrow*) in the head of the pancreas. The kidneys excrete the 18-FluoroDOPA and also light up.

## Histopathology

A focal lesion is characterized by a tumor-like proliferation of islet cells that push exocrine elements aside or haphazardly incorporate them (Fig. 109-7). Unlike insulinomas, the focal lesion retains the lobular architecture of the normal pancreas, and exocrine elements usually remain within the lesion. The lesions often have irregular borders, and the endocrine cells frequently have enlarged nuclei. Islets outside the lesion appear normal. Patients with diffuse disease have abnormal islets containing 5% to 10% of cells with enlarged nuclei present throughout the pancreas. After the surgery, all frozen samples are processed for routine histology and confirmation of findings on the basis of paraffin-embedded sections and insulin immunohistochemistry.

## Surgery

Open operations are approached in a similar manner using a transverse supraumbilical laparotomy.[90–92] The pancreas is exposed by an extended Kocher maneuver, entry into the lesser sac, and mobilization of the inferior border of the pancreas. It is not necessary to mobilize the spleen. The pancreas is inspected under 3.5× loupe magnification in an attempt to visualize a focal lesion, and the pancreas is palpated. If no focal lesion is seen, then 2- to 3-mm-diameter biopsies are taken each from the pancreatic head, body, and tail. Patients with suspected diffuse HI have intraoperative biopsies to confirm the diagnosis and then undergo near-total pancreatectomy. Near-total pancreatectomy (95% to 98%) involves resection of the entire pancreas leaving only a tiny residual piece of the pancreas between the common bile duct and the duodenum. The intrapancreatic course of the common bile duct should be completely dissected for an adequate near-total pancreatectomy to be performed.[90] For children with diffuse disease treated by near-total pancreatectomy, a gastrostomy tube is also placed to make it easier to administer supplemental glucose or night-time feedings if necessary.

When the biopsies demonstrate normal pancreatic histology, a further search for the focal lesion using the preoperative localization data is conducted. Additional biopsies of suspicious areas are obtained until the focal lesion is diagnosed by frozen section. Expert pediatric pathologic interpretation is vitally important. Focal lesions tend to be less than 10 mm in size (although they can be much larger) and are frequently irregularly shaped. Some lesions have octopus-like tentacles that make imperative the intraoperative confirmation of clear margins by frozen section analysis. Although focal lesions may maintain a lobular structure similar to that of the normal pancreas, subtle visual clues (ranging from a slightly reddish color to a marble-like appearance) may permit visual detection of the lesion intraoperatively and accurate preoperative localization studies greatly facilitate the visual search for a focal lesion. In some cases the lesion will feel firmer than the surrounding normal pancreas. However, a tiny focal lesion can be buried within the pancreas and be impossible to see or feel. Greater operative experience has led to more frequent intraoperative visualization or palpation of a focal lesion. Insulinomas differ from focal lesions because they are usually straightforward to identify intraoperatively and occur in older children.

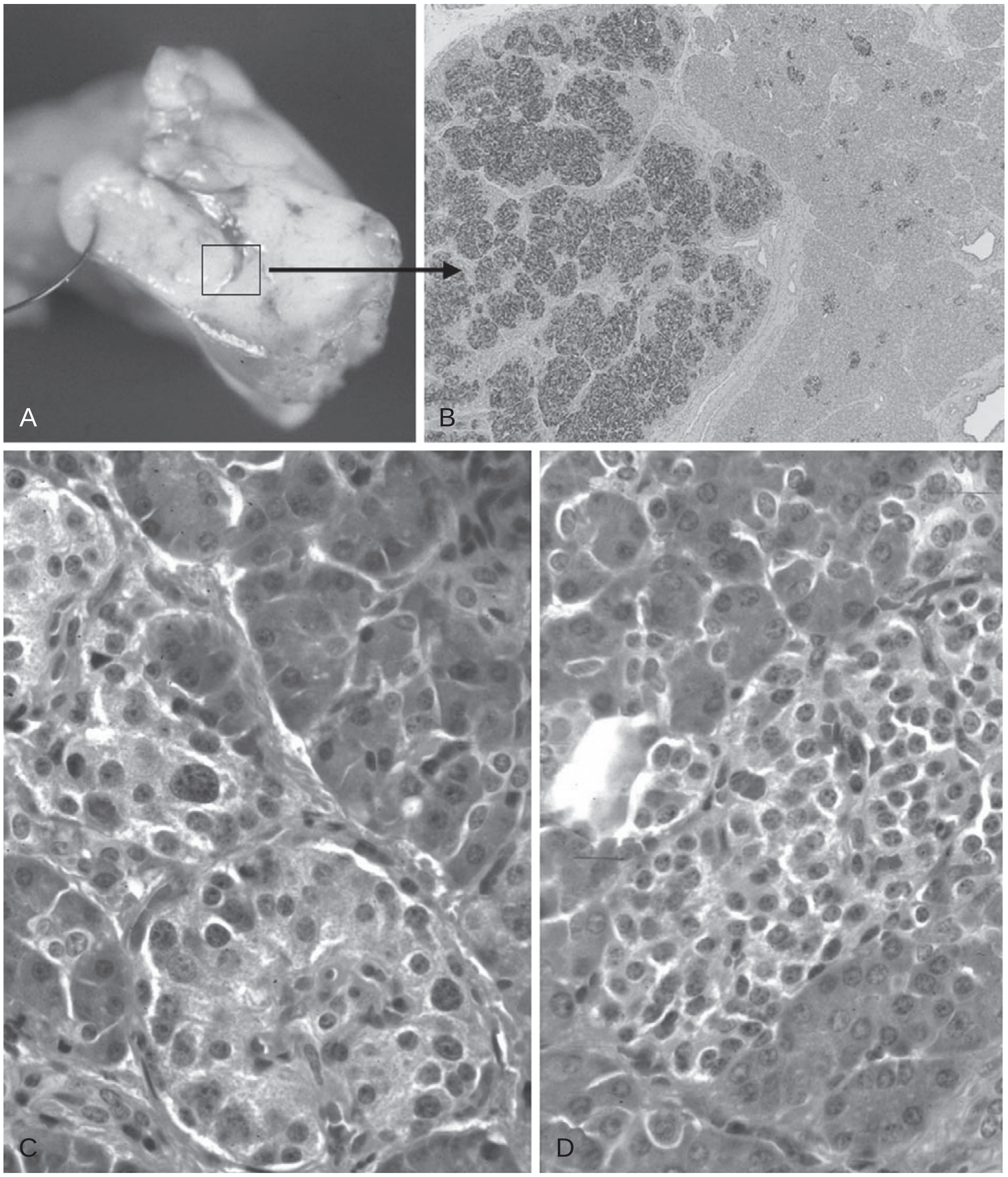


**FIGURE 109-7** **A,** Cut surface of pancreatectomy specimen through a focal lesion (marked by suture). **B,** Chromogranin A immunolabeling highlights the architecture of the focal lesion *(left)* and adjacent normal pancreas *(right)*. Comparison of cytologic features of the endocrine tissue in the focal lesion **(C)** and normal pancreas **(D).** Note enlarged islet cell nuclei in **C.**

Once the focal lesion is identified, a partial pancreatectomy is performed using frozen sections of margins to ensure a complete resection. For periductal lesions in the body and tail, a distal pancreatectomy is performed. With pancreatic head lesions close to the common bile duct or pancreatic duct, it can be tricky to excise all of the lesion, particularly if there are tentacles of diseased tissue that emanate from the lesion. To ensure complete lesion resection in these challenging cases, the surgeon should remove most or all of the pancreatic head followed by Roux-en-Y pancreaticojejunostomy to drain the remaining pancreatic body and tail. In this way, the endocrine and exocrine function of the remaining normal pancreas is saved. In babies the pancreatic duct on the cut surface of the transected pancreatic body is not visible, so the end of the Roux-en-Y jejunal limb is meticulously anastomosed to the capsule of the pancreatic body with fine interrupted monofilament suture to effectively dunk the cut end of the pancreas into the small bowel lumen. Rarely, a focal lesion in the head will extend into the duodenal wall in which case a Whipple procedure may be necessary. Because PET scan localization of focal lesions has proven to be so accurate, focal lesions in the body and tail are now resected using laparoscopic techniques. The drawback to the laparoscopic approach is that there is little tactile feedback to help locate a nonvisible focal lesion.

Because more than 50% of focal lesions involve the pancreatic head, subtotal (50% to 75%) distal pancreatectomy is inadequate therapy in many of these cases. Our experience with several referrals who underwent subtotal pancreatectomy elsewhere with the focal lesion remaining within the residual pancreas are good examples of this potential pitfall.

### Postoperative Care and Follow-up

Postoperative management has been standardized by a clinical care pathway including the use of the Glucose Infusion Rate to quantitate the patient's glucose requirement.[85] Glucose Infusion Rate (GIR) is calculated as % dextrose × IV rate × 0.169/Wt in kilograms. For the initial postoperative period, blood glucose values are determined hourly. The GIR begins at 2 mg/kg/min immediately postoperatively, is increased to a GIR of 5 on the morning of postoperative day 1, and then usually advances to a GIR of 8 by the evening of the first postoperative day. It is not unusual for an intravenous insulin infusion to be necessary for the first few postoperative days. After hospital discharge, a complete response at follow-up is defined as no requirement for glycemic medications, no continuous tube feedings, no diabetes mellitus, and the ability to tolerate an 18-hour fast without hypoglycemia.

In our entire experience, 95% of babies with the focal form of HI are cured after limited pancreatectomy. The vast majority had a less than 50% pancreatectomy. For babies with diffuse HI treated with near-total pancreatectomy (95% to 98%), about one third require no glycemic medications, one third require insulin to treat diabetes, and one third require a glycemic medication (usually octreotide). Long-term follow-up is necessary for all of these children, particularly with regard to neurodevelopmental issues.

# Neoplasms

Pancreatic neoplasms are relatively rare in infants and children. They can be cystic, solid, and benign or malignant and may or may not be hormonally active. In 1990 Grosfeld[93] reported 13 cases of pancreatic tumor in children including 5 insulinomas, 2 mucinous cystadenomas, 2 rhabdomyosarcomas, and 4 carcinomas. In 1992 Jaksic reported 6 cases of pediatric pancreatic tumors,[94] and now more than 200 cases have been reported in the English literature. More recently, pancreatic tumor series have been reported by Shorter (17 cases),[95] Perez (58 cases),[96] and Yu (18 cases).[97] Unlike malignant pancreatic tumors in adults, tumors in children and adolescents are usually resectable and long-term survival is likely.

## CYSTIC NEOPLASMS

Cystic neoplasms of the pancreas are relatively rare.[98,99] Howard[100] classified these lesions into (1) cystadenoma and cystadenocarcinoma, which include benign (microcystic) cystadenoma, benign and malignant mucinous (macrocystic) cystadenoma and cystadenocarcinoma, papillary-cystic epithelial neoplasm, and acinar cell cystadenocarcinoma (not reported in children) and (2) teratomatous cysts.

### Cystadenoma and Cystadenocarcinoma

Cystadenoma of the pancreas is rare in children and adults. Only six cases including one in a newborn have been reported in the pediatric population to date.[93,101,102] Cystadenoma and cystadenocarcinoma should be divided into two groups. Because large mucinous cystic adenomas have considerable malignant potential, these tumors should be distinguished from serous cystadenomas, which are benign; the latter tumors are rich in glycogen and contain little or no mucin.[103]

***Serous Cystadenoma and Cystadenocarcinoma*** Serous cystic neoplasms of the pancreas are rare in children and adults, are more often observed in females, and are found mainly in the body and tail of the pancreas. These tumors consist predominantly of small cysts (microcystic adenomas).[104] Calcification is often demonstrated on CT and US. Serous cysts do not need to be excised unless they create a mechanical obstruction because nearly all of them are benign with no malignant potential.[105] Biopsy is required. Serous cystadenocarcinoma is virtually nonexistent in children, and only a few cases have been reported in adults.

***Mucinous Cystadenoma and Cystadenocarcinoma*** Mucinous cystic neoplasms of the pancreas are usually large and often multilocular. They form papilla lined with columnar, mucin-producing epithelium; are more often observed in females; and are found mainly in the body and tail of the pancreas.[106] Other features are the association of large blood vessels within the capsule and the presence of subepithelial hemorrhage. A common differential diagnosis is pancreatitis with pseudocyst formation. Mucinous cystadenocarcinoma of the pancreas represents 1% of all malignant conditions of the pancreas, occurs at an earlier age than conventional solid pancreatic tumors do, and seems to be approximately half as common as cystadenoma. The clinical and radiologic manifestations of mucinous cystadenocarcinoma are similar to those of mucinous cystadenoma. It is not always possible to differentiate mucinous cystadenoma from cystadenocarcinoma pathologically. It is also common to find apparently benign epithelium[103] in the same tumors as malignant epithelium, thus suggesting that a malignant focus may develop within a mucinous cystadenoma. Therefore mucinous cystadenoma should be considered a premalignant lesion that should be completely excised after incomplete excision or marsupialization.[98,103] However, the prognosis for this form of pancreatic malignancy is significantly better than that for the common typical solid ductal adenocarcinoma because of its slow growth and lack of metastatic potential.

### Papillary-Cystic Epithelial Neoplasm

The first cases of papillary-cystic endothelial tumors of the pancreas were reported by Franz in 1959.[107] Since these tumors were described as solid and cystic acinar cell tumors of the pancreas by Kloppel and colleagues,[108] increasing numbers have been reported in children. They occur predominantly in girls and young women and are manifested as large, encapsulated masses, usually with extensive necrosis and varying amounts of cystic change. Histologically, they are composed of solid areas of rather small cells with pseudorosette formation reminiscent of endocrine tumors and cystic areas with papillary structures.[109] Immunohistochemically, the tumor cells of solid and cystic pancreatic neoplasms contain periodic acid-Schiff-positive granules and often have progesterone receptors. Immunologic hallmarks are immunoreactivity with alpha-antitrypsin, alpha-antichymotrypsin, phospholipase $A_2$, and neuroendocrine markers such as neuron-specific enolase and synaptophysin. However, they are generally free of the usual markers of pancreatic carcinoma

such as carcinoembryonic antigen, CA19-9, and tissue peptide antigen.[110] These tumors seem to be associated with a much better prognosis than the usual type of pancreatic carcinoma but still have malignant potential.[111] The tumor follows a benign course after resection in most cases. Metastasis or recurrence has occurred in 5% of cases in Japan.[112] Thus complete extirpation is necessary because of the slow tumor progression associated with metastatic disease.[113] Liver metastases have been treated with resection and liver transplantation.[114]

### Other Cystic Neoplasms in Children

In 1992 Flaherty and Benjamin[115] reported a case of multicystic pancreatic hamartoma in a 20-month-old girl. In 1990 Mester and colleagues[116] reviewed 10 cases of cystic teratoma of the pancreas including one of their own. Cystic teratomas were usually seen as benign extragonadal germ cell tumors in younger patients; 5 of 10 patients were younger than 11 years.

## HORMONALLY ACTIVE TUMORS

Endocrinologically active tumors are usually identified by their symptoms, and most of them originate in the islet cells. Beta-cell tumors secrete insulin; alpha cell tumors, glucagon; gamma cell tumors, gastrin; delta cell tumors, somatostatin; and delta$_1$ cell tumors, vasoactive intestinal polypeptide (VIP) and possibly substance P and secretin. Glucagonomas and somatostatinomas have not been identified in children.

### Insulinoma

Insulinomas are the most common tumor arising from islet cells and are usually benign (>90%), solitary (80%) lesions that occur in children older than 4 years. A plasma insulin-to-glucose ratio greater than 1 is diagnostic (<0.4 is normal),[117] and the ratio increases with fasting. Concomitant measurement of C peptide levels may be used to exclude factitious hypoglycemia. CT, US, arteriography, and transhepatic portal venous sampling can be used to localize an insulinoma. The tumor is usually discrete and well encapsulated, and most can be enucleated. The introduction of endoscopic and intraoperative US has allowed obscure lesions to be identified. If all methods of tumor localization are unsuccessful, distal pancreatectomy with careful sectioning of the gland is advisable. In that circumstance, measurement of intraoperative insulin levels is recommended to avoid missing lesions. Virtually all infants and children with insulinoma can be cured.

Multiple endocrine neoplasia type I (MEN-I) is characterized by endocrine tissues in the gut and pancreas including insulin-secreting tumors, but expression is usually delayed beyond the first decade of life. MEN-I is rare, with a frequency not exceeding approximately 1 in 10,000. The gene for MEN-I has been localized to the long arm of chromosome 11 and functions as a tumor suppressor gene, unrelated to the functional alterations in the SUR1/Kir6.2 components of $K_{ATP}$ on the short arm of chromosome 11.[118]

### Gastrinoma

The second most commonly reported pancreatic hormonal tumor is the gamma cell tumor. The clinical syndrome related to gastrinoma is often referred to as *Zollinger-Ellison syndrome,* a condition characterized by hypergastrinemia with severe peptic ulcer disease. This syndrome is rare in children. Gastrinoma is part of the MEN-I syndrome and is commonly malignant, multicentric, and metastatic at discovery.[93] The diagnosis is usually made after recurrent episodes of peptic ulceration associated with an elevated gastrin level (>500 pg/mL). Calcium infusion and secretin simulation tests are used for diagnosis. CT, percutaneous transhepatic venous sampling, and gastrin assay have been useful for localization. Although total gastrectomy was originally the most common method of treatment, the development of inhibitors of gastric acid secretion such as $H_2$ blockers and omeprazole has changed the direction of treatment of gastrinoma substantially. Children with gastrinoma generally require lifelong medical treatment, and somatostatin, although beneficial because it decreases gastric acid secretion, also inhibits growth hormone secretion, so it cannot be used long-term. Surgical treatment should thus be aggressive, especially if a solitary tumor is found with no evidence of metastasis at the time of laparotomy. However, total gastrectomy may still be required for patients in whom medical treatment has failed or those with residual tumor or metastatic disease.[93]

### VIPoma

VIPoma in children is far more commonly related to other neurogenic neoplasms such as neuroblastoma or ganglioneuroma than to tumors of primary pancreatic origin. Only a few cases of VIPoma in children have been reported. The VIP that is produced by a pancreatic VIPoma probably originates from neural cells in the islets.[117] Patients have profuse, watery diarrhea associated with hypokalemia and hypochlorhydria (WDHA syndrome), and metabolic acidosis and prerenal azotemia secondary to dehydration are often present. Although medical therapy includes the use of streptozotocin and somatostatin, long-term use of somatostatin is undesirable. Surgical extirpation of the tumor-bearing gland is recommended whenever possible because 50% of pancreatic VIPomas are malignant.[93]

## CARCINOMA

Carcinoma of the pancreas is common in adults but rare in children. The clinical features are different in that obstructive jaundice is the primary finding in adults, whereas an abdominal mass is usually the initial feature in children. Pancreatic carcinoma in children can be divided into four groups: islet cell carcinoma, adenocarcinoma, pancreatoblastoma, and miscellaneous lesions.

### Islet Cell Carcinoma

Islet cell carcinoma in children may or may not be functional. Functioning beta-cell and non–beta-cell islet cell carcinoma occurs in infants and children with hypoglycemia in conjunction with Zollinger-Ellison syndrome, but it is not associated with a palpable mass. A beta-cell carcinoma is usually discovered during laparotomy for insulinoma. Four functional islet cell carcinomas have been described in children; all were treated by surgical extirpation, with good long-term survival.[119–121] Seven of the eight children with Zollinger-Ellison syndrome described by Wilson had non–beta-cell carcinoma with metastatic disease.[122]

Nonfunctioning islet cell carcinomas are more common in children than adults. Because these tumors are usually discovered by palpation of an abdominal mass, they are often

diagnosed late, and many affected infants and children have distant metastatic disease at the time of diagnosis. Most nonfunctional tumors are large, solitary lesions that can appear in any location within the gland. In general, although most of these tumors grow slowly, aggressive surgical therapy is warranted because of their malignant potential.[123]

## Adenocarcinoma

Adenocarcinoma of the pancreas is rare in children. Vejcho[124] reviewed 37 cases of adenocarcinoma in 1993. The clinical manifestations differ from those of adults in that the incidence of pain with jaundice is lower.[121] Abdominal pain and a palpable epigastric mass are the primary findings in children. Classification is still controversial and is based on tumor activity and histopathologic and immunohistochemical findings. Kloppel classified adenocarcinoma into three types: acinar cell carcinoma, solid and cystic tumor (papillary cystic tumor), and pancreatoblastoma.[108] Acinar cell tumors are proportionately more common in children.[111] It seems that children with an acinar cell tumor have a somewhat better prognosis than do those with an adenocarcinoma of the duct cell type. The prognosis for children with adenocarcinoma of the duct cell type is discouraging and similar to that for adults. CT and sonography are useful for diagnosis. For localized lesions, pancreaticoduodenectomy seems to be associated with a favorable prognosis. Infants and children tolerate radical resection of the pancreas somewhat better than adults do and have a lower mortality rate and better long-term survival.

## Pancreatoblastoma

In 1977 Horie[125] reported two cases of pancreatic carcinoma, which they termed pancreatoblastoma, an infantile type of pancreatic carcinoma. In 1984 Buchino[126] reviewed eight patients with pancreatoblastoma, six of whom survived after surgical extirpation. Pancreatoblastoma is the most common pancreatic neoplasm in young children. Pancreatoblastomas have a better prognosis than adenocarcinoma because they have an encapsulated organoid structure that does not directly interfere with the main duct system. The criteria for diagnosing pancreatoblastoma have been described.[126–128] Although there is no agreement on the pathology of these rare lesions, terminology based on recognizable lines of differentiation seems preferable (e.g., islet cell, duct cell, acinar cell, undifferentiated lesions).[111] The recurrence risk after resection is high. These tumors can be responsive to chemotherapy and radiation, but the appropriate role for these modalities is unknown.

## Miscellaneous Carcinomas

The following miscellaneous carcinomas in children have been reported in the literature: one case of carcinoma simplex; one case of medullary carcinoma[129]; six cases of sarcoma (two lymphosarcomas,[129] two with sarcomatous degeneration from cystadenoma,[93,130] and two rhabdomyosarcomas[93]); four cases of undifferentiated carcinoma[121,126]; and two cases of cylindrical cell adenocarcinoma.[131]

## *Acknowledgments*

This revised chapter based on the version written by Takeshi Miyano that appears in the sixth edition.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 110

# The Spleen

Katherine A. Barsness and Marleta Reynolds

Splenic physiology can be broadly categorized into red blood cell maintenance and reservoir and immunologic functions. Children frequently require splenectomy for disease processes involving abnormalities in red cell deformability or the presence of antiplatelet antibodies resulting in excessive splenic red cell destruction or platelet sequestration. The vital role of the spleen as an immunologic organ has not only led to nonoperative management of splenic trauma but also affected the timing of elective splenectomy and renewed interest in partial splenectomy for certain disorders. The technique of splenectomy has changed significantly with the advent of advanced laparoscopy. The technique of laparoscopic splenectomy and the available evidence comparing it with open splenectomy are discussed in the latter part of this chapter.

## History

The role of the spleen has been the subject of debate for more than 300 years. Billroth is credited with developing the open circulation theory of the splenic microcirculation, and the endothelial cords of the red pulp bear his name. The recognition of the spleen as a functional organ in health and disease has been well documented in the twentieth century. One of the more important observations was that of King and Shumaker in 1952, who noted the susceptibility of infants to infection after splenectomy.[1] The protective role of the spleen in bacterial infections prompted pediatric surgeons to study the role of nonoperative management of splenic injuries,[2] a development that evolved into the preferred method for treating both childhood and adult splenic injuries. Another significant development in the surgical management of splenic disorders was the initial report of laparoscopic splenectomy in 1991 by Delaitre and Maignien.[3] This technique has quickly become the preferred technique for splenectomy in children.

## Embryology and Anatomy

The splenic primordium is first recognized at the 8- to 10-mm stage as a mesenchymal bulge in the left dorsal mesogastrium between the stomach and pancreas. By the 10- to 12-mm stage a true epithelium is noted, and sinusoids are present with communication to capillaries. By 4 months of fetal life, the spleen produces red and white cells; however, this function ceases later in gestation, and the spleen is rarely the site of clinically significant hematopoiesis in childhood. The anatomic arrangement of the spleen is consistent with the various functions of the spleen. Blood enters the spleen through splenic artery segmental vessels that branch into trabecular arteries; and, after further bifurcations, small arteries enter the white pulp. The white pulp consists of lymphocytes and macrophages arranged as a germinal center around the central artery. Branches off of the central artery deliver suspended particulate material into the white pulp, an arrangement that may facilitate antibody formation in response to particulate antigens.[4–7] Approximately 20% of the volume of the spleen is white pulp, and the remainder is the red pulp, consisting of the endothelial cords of Billroth.[8] Blood passing through the spleen traverses in either an “open” or “closed” fashion. Ten to 20 percent of blood passes through the closed system directly from capillaries into venous sinusoids. The remainder passes directly into the red pulp. These cells and other particulate material must pass through in an open fashion within the cords of Billroth and then migrate into the sinusoids, which enter into trabecular veins.

## Function

The function of the spleen is closely related to the anatomic arrangements and can be divided into red cell maintenance, immune function, and reservoir. Derangements in the substrate entering the spleen often lead to excessive function of one of the splenic roles, thus leading to the need for splenectomy. The spleen destroys red cells at the end of their life span and repairs other damaged red cells. Because the spleen selectively removes abnormal cells such as spherocytes, removal of the spleen increases the life span of these cells. As blood passes through the spleen, Howell-Jolly bodies (nuclear remnants), Heinz bodies (denatured hemoglobin), and Pappenheimer bodies (iron granules) are removed, and after splenectomy they are noted in red cells on a peripheral smear.

The immune function of the spleen is characterized by specific and nonspecific responses. The specific immune function of the spleen is primarily related to antigen processing. Antigens come into contact with macrophages and helper T cells in the area of the arterioles of the white pulp. T-cell populations

respond with synthesis of cytokines as part of the cellular response, and activated T cells then circulate to modulate the response. A humoral response can occur as antigens come in contact with macrophages and helper T cells and are then transmitted to antibody synthesizing cells.[9]

The nonspecific function involves removal of the particulate matter from the blood primarily by macrophages. The spleen is also the principal source of nonspecific opsonins, which further activate the complement system, facilitating the destruction of organisms.

The spleen provides another aspect of the immune function, by simply serving as a biologic filter. If little antibody is available for opsonization of bacteria, the spleen assumes a greater role in clearance of bacteria. This may be the basis for the age-related differences in postsplenectomy infections because young children lack adequate antibody response.[5] The spleen also serves as a reservoir, which in humans is primarily limited to platelets. The proportion of platelets in the spleen is increased in cases of splenomegaly, occasionally leading to thrombocytopenia. The spleen also serves as a reservoir for factor VIII.

FIGURE 110-1 Computed tomography scan of a wandering spleen in a 7-year-old boy with intermittent abdominal pain and an abdominal mass. A laparoscopic splenopexy was used to secure a left upper quadrant fixation.

# Anatomic Abnormalities

## ACCESSORY SPLEENS

Accessory spleens represent the most common anatomic abnormality and are present in 15% to 30% of children. They most likely originate from mesenchymal remnants that do not fuse with the main splenic mass. The majority (75%) are located near the splenic hilum or adjacent to the tail of the pancreas; a few are found along the splenic artery, in the omentum, mesentery, and retroperitoneum and have even been noted in the scrotum.[10] Of those with accessory spleens, 86% have one, 11% have two, and 3% have three or more,[11,12] with the hilum the most common site of multiple accessory spleens. Surgeons must be cognizant of these locations and routinely check for their presence because a missed accessory spleen can be a cause of recurrence of immune thrombocytopenic purpura (ITP) or hereditary spherocytosis. Recurrence with ITP is frequently early,[13,14] whereas recurrence with hereditary spherocytosis has been reported as long as 31 years later.[15]

## WANDERING SPLEEN

Wandering spleen is characterized by lack of ligamentous attachments to the diaphragm, colon, and retroperitoneum. The embryologic basis of this is probably related to failure of development of the splenic ligaments from the dorsal mesentery.[16] Children with this condition most often present with diffuse abdominal pain secondary to torsion and infarction, although they may also present with episodic pain and an abdominal mass (Fig. 110-1).[17–22] Although splenectomy is required for infarction, splenopexy is preferred in nonischemic and incidentally detected cases. Splenopexy has been performed with various techniques including placement in an extraperitoneal pocket,[21] use of Dexon mesh basket,[22,23] suture splenopexy,[22,24] and colonic displacement with gastropexy.[22,25] Laparoscopic detorsion and splenopexy can be performed with the use of an absorbable mesh bag that is closed around the splenic hilum and then tacked to the diaphragm and posterolateral abdominal wall.

## SPLENIC CYSTS

Primary splenic cysts have an epithelial lining, frequently with a trabeculated internal appearance. They most likely originate from inclusion of the surface mesothelium into the splenic parenchyma. They may be asymptomatic or may present as pain,[26] rupture,[27] abscess,[28] or symptoms due to gastric compression. Symptomatic cysts are usually greater than 8 cm.[26] Small (<5 cm) simple cysts can be observed; however, larger, enlarging, or symptomatic cysts require definitive treatment. Percutaneous aspiration and sclerosis have been used, but recurrence is common and partial splenectomy has been required.[29] Alcohol sclerosis of a congenital cyst has been reported with success, although the length of follow-up was not specified.[30] Marsupialization can be associated with recurrence if an adequate segment of cyst is not removed.[31,32] Laparoscopic partial cyst excision and cyst resection with partial splenectomy[33–40] have been reported but are accompanied with a 64% to 88% recurrence rate. Partial splenectomy with excision of the cyst at the margin with the spleen can be performed with an electrosurgical device[41–43] or with the use of stapling devices in an open[40,44] or laparoscopic approach.[40,45,46] Use of cautery,[46] sutures, and omental packing of the defect may also be useful.[43] Splenic pseudocysts lack an epithelial lining and most frequently occur after trauma. Enlarging cysts and symptomatic cysts should be excised.[47]

## ASPLENIA AND POLYSPLENIA

Asplenia and polysplenia syndromes have many similar features. Congenital asplenia is usually noted with complex congenital heart disease, as well as bilateral "right-sidedness" including bilateral three-lobed lungs, right-sided stomach, and a central liver.[5] Intestinal malrotation has also been observed.[48] Howell-Jolly bodies are noted on peripheral smear, and infants have the risk of overwhelming infection.

Polysplenia in which the spleen is divided into multiple splenic masses is often associated with biliary atresia. Other associated features included preduodenal portal vein, situs inversus, malrotation, and cardiac defects.[49] These children have adequate splenic immune function.

### SPLENIC GONADAL FUSION

Splenogonadal fusion occurs as a result of early fusion between the spleen and left gonad.[50] The remnant may be continuous with a fibrous band or discontinuous with splenic tissue attached to the gonad. Another abnormality identified has been ectopic splenic tissue in the scrotum apart from a gonadal fusion.

## Indications for Splenectomy

### HEREDITARY SPHEROCYTOSIS

Hereditary spherocytosis is the most common inherited red cell disorder among northern European descendants. Approximately 75% of affected children have an autosomal dominant inheritance pattern; the remainder are new mutations or autosomal recessive. The attendant membrane defects in ankyrin or spectrin proteins result in poorly deformable spherocytes. The degree of splenic hemolysis can range from mild to severe. Most children are noted to have anemia, an elevated reticulocyte count, and a mild elevation of bilirubin. The presence of spherocytes along with a positive osmotic fragility test confirms the diagnosis. In affected children, an aplastic crisis can occur secondary to parvovirus B19 infection, with suppression of red cell production and a resultant low hematocrit due to ongoing destruction.[51] Splenectomy is usually required for moderate to severe anemia. Gallstones are common, increasing in frequency with the age of the child and degree of hemolysis,[52] and thus a gallbladder ultrasound is required before splenectomy. Hereditary elliptocytosis is a similar disorder associated with spectrin defects, but most patients are asymptomatic and without significant hemolysis.

### IMMUNE THROMBOCYTOPENIC PURPURA

ITP occurs when antiplatelet autoantibodies, usually IgG, bind with platelets, leading to destruction in the reticuloendothelial system. The thrombocytopenia can be transient or can persist in a chronic phase. The decision to treat a patient with ITP is based primarily on bleeding complications, not on an absolute platelet count. Childhood ITP is usually a self-limited, acute disorder, and splenectomy is only required in chronic cases. First-line therapies include short-course corticosteroids, which may function by inhibiting the reticuloendothelial binding of platelet-antibody complexes; intravenous immunoglobulin (IVIG), which competitively inhibits the Fc receptor binding of platelets by macrophages; and Rho (D) immunoglobulin in Rh-positive children, which binds to red cells that then saturate the splenic capacity and spares the antibody-coated platelets. Second-line therapies include rituximab, which binds the CD20 antigen on B lymphocytes and is presumed to decrease autoantibody production, and splenectomy. With poor long-term response and concerning drug toxicities associated with rituximab,[53,54] children with chronic ITP (with bleeding complications) resistant to first-line therapies are often referred for splenectomy.[55] Unfortunately, predicting a response to splenectomy has been difficult. In one study, response to corticosteroids, IVIG, or both predicted a 97% response to splenectomy, whereas failure to respond to either predicted a 70% failure rate to splenectomy.[56] Another study noted the response to IVIG to be a better predictor of response to splenectomy than corticosteroids.[57] The most recent study directly challenged these findings with a 100% response rate among children who were nonresponsive to corticosteroids, with postsplenectomy platelet counts inversely related to peak platelet response to steroids.[58] Despite the widely disparate literature, there is a sustained response rate as high as 80% for children with chronic ITP treated with splenectomy.[59]

### SICKLE CELL DISEASE

Sickle cell disease occurs as the result of a substitution of valine for glutamic acid in the β chain of normal hemoglobin A, resulting in hemoglobin S. These red cells become rigid when oxygen saturation decreases, with subsequent capillary occlusion and shortened red cell life. Children with homozygous sickle cell anemia and with hemoglobin sickle cell disease have significant rates of painful crisis and acute chest syndrome. Splenic sequestration with rapid drop in hemoglobin and platelet counts can occur and, if severe or recurrent, merit splenectomy to reduce the chance of further episodes. Postoperatively, children with sickle cell disease are at risk for acute chest syndrome (ACS). ACS is characterized by basilar pulmonary infiltrates and is thought to be secondary to polymerized deoxygenated sickle hemoglobin, causing local tissue infarction in the lung. Treatment is supportive.

### THALASSEMIA

The thalassemias are a group of disorders characterized by abnormal production of α or β chains of hemoglobin. Thalassemia major (Cooley anemia; β-thalassemia) results in the most severe clinical anemia among this group of disorders. Some children develop significant splenomegaly with sequestration. Splenectomy has been used to decrease the need for transfusions in children with severe anemia and those with significant splenomegaly and platelet or white cell sequestration.

### GAUCHER DISEASE

Gaucher disease is a metabolic disorder characterized by deficiency of the enzyme β-glucocerebrosidase, which results in excessive glucocerebroside in macrophages of the spleen, liver, bone marrow, and lungs. It is an autosomal recessive disorder found most commonly in Ashkenazi Jews. Splenomegaly can be severe, and both partial and total splenectomy have been used to alleviate the hypersplenism and increase the red cell, leukocyte, and platelet counts.[60] However, recurrence has been reported after partial splenectomy.

### ABSCESS

Splenic abscesses are rare but have been noted with increasing frequency with the increase in the number of immunocompromised children. Organisms are frequently fungal or

mycobacterial.[61] Children present with fever, pain, and positive blood cultures. An isolated splenic abscess may be treated with percutaneous drainage and intravenous antibiotics.[62] However, diffuse or multifocal abscesses may be better served by splenectomy.

# Splenectomy

## PREOPERATIVE IMMUNIZATION

The risk of postsplenectomy sepsis remains a concern for any asplenic individual. Preoperative immunization has become the standard of care for all patients being considered for elective splenectomy. In case of emergent splenectomy, postoperative immunization is still strongly encouraged. Current recommendations include polysaccharide pneumococcal, conjugate *Haemophilus influenzae* type b, and polysaccharide meningococcal vaccinations.[63] All vaccinations should be completed at least 2 weeks before planned splenectomy. In addition, yearly influenza vaccination is strongly recommended to reduce the incidence of secondary bacterial pneumonia.

## OPEN SPLENECTOMY

A left upper quadrant subcostal incision provides excellent exposure for most spleens even in cases of splenomegaly. The spleen is retracted medially, and the splenorenal, splenophrenic, and splenocolic ligaments are divided. This can usually be accomplished with a relatively small incision, and the spleen is removed from the abdominal cavity by delivering the lower pole first, taking advantage of the concave medial surface of the spleen. The gastrosplenic ligament and short gastric vessels are divided, followed by the hilar vessels. If the pancreas is close to the hilum, it may be necessary to divide the segmental vessels. A careful search is made for accessory spleens, and, if present, they are removed. An alternative open approach uses a lateral muscle-splitting incision,[64] which has been associated with a 2.7-day length of stay, comparable with some laparoscopic series.[65–67]

## LAPAROSCOPIC SPLENECTOMY

### Technique

The laparoscopic technique for splenectomy was initially reported in 1991 [3] and over the subsequent 5 years has become the preferred method at most institutions. Less pain, as reflected in lower pain medication use; shorter length of stay; and improved cosmesis are the main benefits compared with open splenectomy. The laparoscopic procedure has a steep learning curve for those unfamiliar with advanced laparoscopic techniques, can be difficult in cases of splenomegaly, and is associated with longer operative times than the open procedure. The efficacy of accessory spleen detection has been questioned in adult studies,[13,14] although comparison of open and laparoscopic pediatric series has found similar detection rates.[65–70]

The technique of laparoscopic splenectomy has evolved with the development of smaller instruments and advanced technology such as the Harmonic scalpel and the Ligasure. Although preoperative splenic artery embolization was reported in many initial adult series,[71] complications such as pain, abscess, and retroperitoneal necrosis[72,73] have occurred. Some authors have noted no difference in the risk of bleeding or transfusion requirement. Embolization for spleens between 20 and 30 cm in length and open splenectomy if the organ is larger than 30 cm have been recommended, but most childhood spleens in cases of splenomegaly are smaller, so this appears less relevant in children.[73] Hand-assisted procedures have also been described in adults[74] for large spleens, but the accessory incision prolongs the stay[75] and also appears to have no role in children.

Although some initial reports used an anterior approach, most surgeons currently use a lateral approach, as depicted in Figure 110-2. The patient is placed approximately 45 degrees left side up with slight elevation of the right flank to increase access on the left side. The table is rotated to the patient's left side for trocar placement and then to the right to achieve a right lateral decubitus position for the procedure. The general principle is for the assistant to use two grasping instruments through the upper abdominal midline sites (see *A* and *B* in Figure 110-2) to elevate the spleen and provide traction on surrounding tissues. In young children and older patients with small spleens, 3-mm instruments are used at those sites and placed directly into the abdominal cavity through small stab incisions without the use of trocars. If the spleen is large, at least one of the upper midline trocars must accommodate 5-mm instruments. For most of the procedure the surgeon uses the Harmonic scalpel or Ligasure through the left lower quadrant incision. The umbilical port is most commonly a 15-mm port to accommodate the 15-mm diameter endosurgical bag and the endovascular stapling devices. Use of the 5-mm 30-degree telescope allows its use through the left lower quadrant site, which is necessary

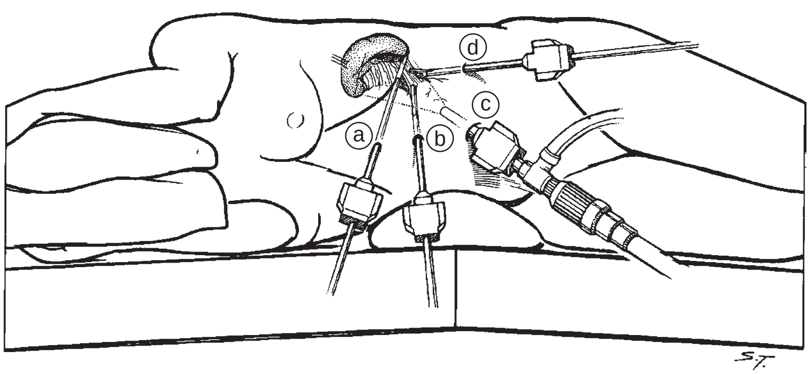


**FIGURE 110-2** Patient position and port size and location for lateral approach: *a* and *b,* 3 or 5 mm midline; *c,* umbilical 12 or 15 mm; *d,* 5 mm left lower quadrant.

when stapling and for placement of the endosurgical bag through the umbilical site.

The splenocolic ligament is divided, allowing the splenic flexure to fall away from the spleen (Fig. 110-3, *A*). The gastrosplenic ligament is then divided (see Fig. 110-3, *B*). The division of the most superior aspect is difficult, owing to the close proximity of the spleen and stomach, and care must also be taken to avoid injury to the diaphragm. Accessory spleens identified at the hilum can often be removed en bloc with the spleen and others from the lesser sac or omentum removed separately, usually through the umbilical trocar.

The spleen is then held up from the superior and inferior poles and the hilum approached, often dividing the inferior set of segmental vessels with either an electrosurgical device or with clips and scissors. The surgeon must decide between the use of clips or an endovascular stapler for the remaining segmental or polar vessels. If the vessels are individually divided, the surgeon must be prepared, should bleeding occur, to control the vessel proximally with a grasper and either clip the vessel or staple the remainder of the hilum. If the stapler is used, the splenorenal ligament can be divided so that the posterior arm of the stapler can easily pass posterior to the hilum. Care must be taken at this step to avoid injury to the tail of the pancreas (see Fig. 110-3, *C*).

The endosurgical bag is placed through the umbilical port; the spleen is then placed in the retrieval bag, and the neck of the bag delivered out the umbilicus. A finger and ring forceps are placed through the external opening and used to fracture the splenic capsule and remove splenic fragments (see Fig. 110-3, *D*). The use of an ultrasonic morcellator and liposuction device[76] to fragment the spleen has been described. Transvaginal removal of the bag has been described.[77] In some cases of splenomegaly it may be difficult to place the spleen in the bag. Hebra and colleagues[78] used a coring device to

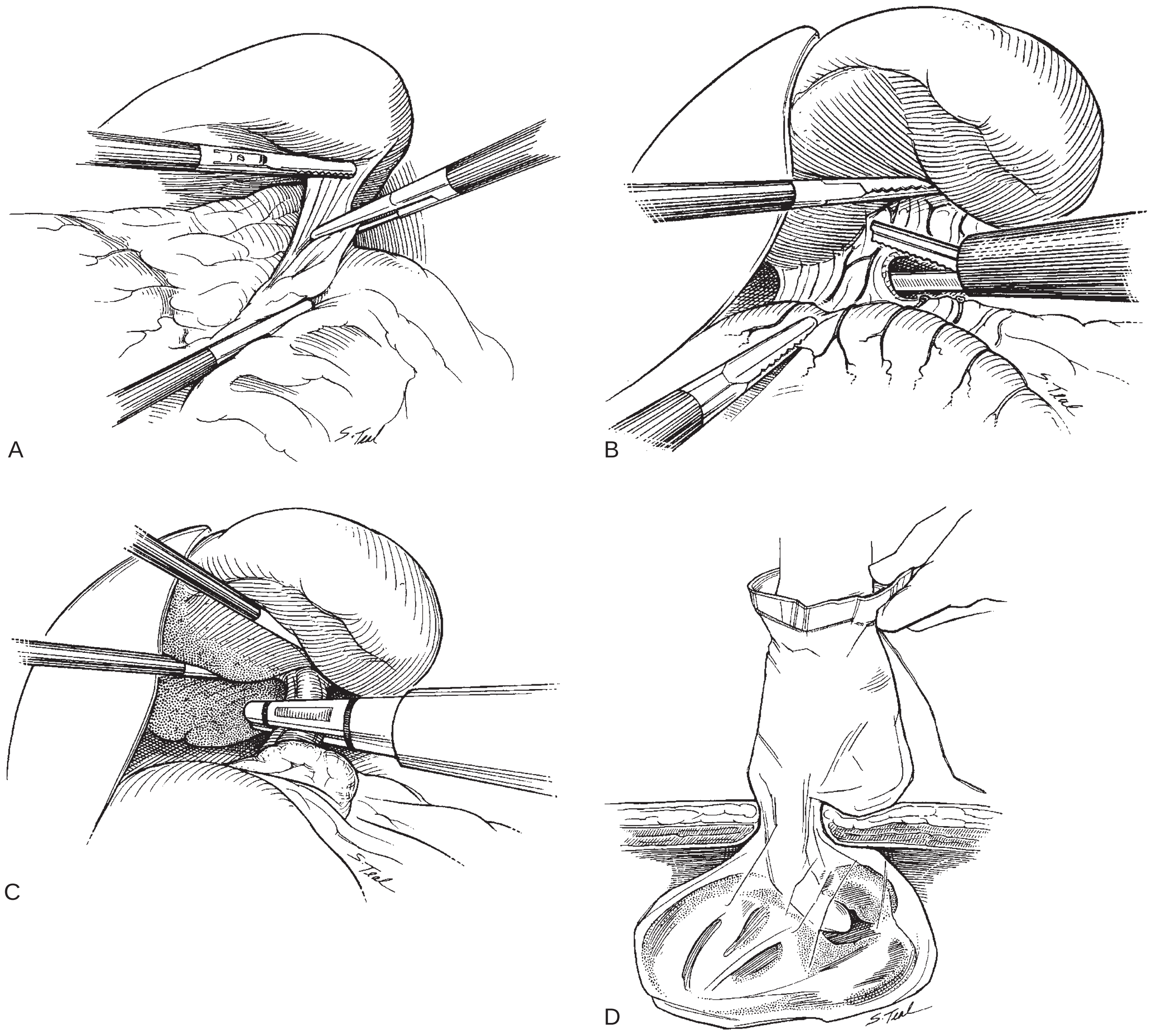


**FIGURE 110-3** Division of the splenocolic **(A)** and gastrosplenic **(B)** ligaments with the Harmonic scalpel. The endovascular stapler is used to divide the splenic hilum **(C)** and, after placement in the retrieval bag, delivered out the umbilical port **(D).** Finger fracture and forceps are used to remove splenic fragments.

remove portions of the spleen before its placement in a bag. This is not recommended in cases of hereditary spherocytosis or ITP in which splenosis could potentially lead to recurrent anemia or thrombocytopenia.

At completion, the fascia at the umbilical site and, if convenient, the anterior fascia layers at the 5-mm sites are closed. The orogastric tube and Foley catheter used intraoperatively are removed at the end of the procedure. Diet is advanced as tolerated the day of surgery, and pain control is achieved with intravenous morphine and nonsteroidal antiinflammatory agents, followed by oral pain medications when the patient is tolerating liquids. The techniques of laparoscopic splenectomy are applicable to other procedures including partial splenectomy for disease or lesions such as cysts, splenopexy for wandering spleen, and treatment of traumatic splenic injuries.[79,80] Single incision or single port techniques are being developed.

### Conversion

Conversion to open splenectomy is most frequently due to splenomegaly or bleeding and is reported in 1.3% to 2.8% in several large series.[68,81–84] Giant spleens with malignancy are more difficult situations, and one author noted a 41% conversion rate in adults with malignancy compared with a 3% conversion rate for benign conditions.[85] In another adult series, Mahon and Rhodes noted that their conversion rate was 0% for spleens weighing less than 1 kg and 60% for those weighing more than 1 kg.[86] A lower conversion rate with increasing surgeon experience has been observed in some series.[72,87]

### Operative Time

Comparative series have uniformly observed longer operative time with the laparoscopic technique,[65–70] and several have noted shorter times with increased surgeon experience.[82,88] In a review of 112 laparoscopic splenectomies, a longer operative time (115 vs. 98 minutes) was noted in the first 50 procedures compared with the next 62 procedures but the differences were not significant.[82]

### Pain

The pediatric reports do not use pain scores but rely on pain medication usage as a reflection of pain. All available comparative studies report lower morphine equivalent dose usage for pain control for laparoscopic compared with open splenectomy, but the difference did not reach statistical significance in two of the five studies.[66,69,70,89,90] This is consistent with an adult study that noted equal quality of life and control of the hematologic disease with less pain in the laparoscopic group.[91]

### Length of Stay

Length of stay ranges from 1.3 to 3.6 days, with more studies reporting 1.7 to 1.8 days.[68–70] All pediatric comparative studies have noted a shorter length of stay with the laparoscopic technique (laparoscopic, 1.3 to 3.6 days; open, 2.5 to 4.9 days), with the reduction ranging from 18% to 56%.[65–70] The underlying disorder can affect length of stay because infants and children with sickle cell disease have been noted to require a longer stay than those with ITP and hereditary spherocytosis (2.5 vs. 1.4 days).[70] This has been due to the occurrence of postoperative acute chest syndrome.

Splenomegaly alone, in children, does not appear to adversely affect length of stay because splenomegaly with hereditary spherocytosis is the most frequent indication for splenectomy and is associated with a short length of stay (1.4 days). A meta-analysis of primarily adult reports (2940 patients; 2119 laparoscopic procedures, 821 open procedures) noted longer mean operative time (laparoscopic, 180 minutes; open, 114 minutes; $P < 0.0001$) but a shorter hospital stay (laparoscopic, 3.6 days; open, 7.2 days; $P < 0.001$) with laparoscopic splenectomy.[92] Unproven benefits of the laparoscopic approach concern the child's return to full activity and the effect of return to school on the parent's return to work. Children undergoing laparoscopic splenectomy have been observed to return to full activity 1 to 5 weeks earlier than with the open procedure.[67] In addition, parents who had themselves undergone splenectomy view the laparoscopic technique better than the open technique.

### Cost

The presumption of most authors is that the shorter length of stay with laparoscopy will offset the higher operative charges related to the longer operative time and the use of disposable materials. Data from comparative studies note three studies with higher[67,90,93] and three with lower[65,69,70] hospital charges with laparoscopy. The method by which individual hospitals determine charges or cost for supplies, operating room time, and inpatient days makes comparison difficult. The available cost data do not appear to confer an advantage to either procedure.

### Complications

A meta-analysis of 26 comparison studies (adult and pediatric) noted a total complication rate of 15.5% for laparoscopic and 26.6% for open splenectomy ($P < 0.0001$).[92] The laparoscopic group had fewer pulmonary, wound, and infectious complications ($P < 0.0001$) but had more hemorrhagic complications when conversions for bleeding were included.

## PARTIAL SPLENECTOMY

Total splenectomy with removal of accessory spleens eliminates splenic hemolysis and sequestration for congenital hemolytic anemias. However, concerns of overwhelming postsplenectomy sepsis, particularly in children younger than 5 years of age, have led to the exploration of partial splenectomy. This has primarily been used for hemolytic anemias such as hereditary spherocytosis but has also been used for Gaucher disease,[60] Hodgkin disease staging,[94] trauma,[95] hypersplenism with cystic fibrosis,[96] as well as excision of splenic cysts,[46] hamartomas,[97] and hemangiomas.[98] When this technique is used for splenic volume reduction, 85% to 95% of the disease-affected splenic mass is removed, leaving approximately 10% to 25% of a normal splenic remnant. Anatomic studies of the splenic blood supply indicate that 86% of spleens have two lobar vessels and 12% have three lobar arteries.[99] In addition, 77% have either four or five segmental vessels, thus allowing preservation of either an upper or lower pole segmental vessel supplying 20% to 25% of the spleen. The spleen is divided with either a stapling device, cautery, or the Harmonic scalpel, and hemostasis is achieved with cautery, argon beam coagulation, or topical agents as needed. If the spleen is totally mobilized, the remnant can be fixed to

the retroperitoneum to prevent torsion. This procedure can be performed laparoscopically using the Harmonic scalpel to both divide the spleen and provide hemostasis (Fig. 110-4).

Long-term follow-up has noted increased red blood cell half-life, higher hemoglobin level, and lower transfusion requirement, reticulocyte count, and bilirubin levels.[100–103] Preservation of splenic phagocytic function has been demonstrated by elimination of Howell-Jolly bodies on peripheral smear and decreased numbers of pitted red cells.[101] Other parameters have included normal IgM and IgG levels of specific antibody titers to *Streptococcus pneumoniae*. Splenic regrowth occurs in all patients with hemolytic anemias, although the degree of regrowth does not correlate with hemolysis. Laparoscopic *partial* splenectomy has higher intraoperative blood loss, morphine use, and longer times to full oral intake, with longer hospital stays when compared with laparoscopic *total* splenectomy in the same institution.[104] Complications of postpartial splenectomy hemolysis can include ongoing development of cholelithiasis (7% to 22%), recurrent anemia with need for transfusion, or subsequent total splenectomy.[101–103,105] Caution must be exercised in the assumption of normal splenic function because one patient with evidence of residual splenic function by scan after partial splenectomy for trauma died of an *S. pneumoniae* infection 13 years later.[106] This patient had not received pneumococcal vaccine. Preoperative immunization is recommended for all partial splenectomy candidates, and postoperative antibiotics are administered at least until splenic immunologic competence is noted.

# Postoperative Considerations

Complications are relatively rare after splenectomy. Thrombosis of the splenic, portal, and mesenteric veins has occurred after splenectomy, with a reported incidence of 1.6% to 11%.[107–110] Symptoms include fever, vomiting, and/or abdominal pain as early as 2 days postoperatively. The diagnosis can be made by Doppler ultrasonography or contrast-enhanced CT of the abdomen. Treatment consists of antiplatelet and antithrombotic therapy. Recannulization of the portal vein can occur with prompt diagnosis and treatment of the thrombus, but long-term complications of portal hypertension have also been described.[110]

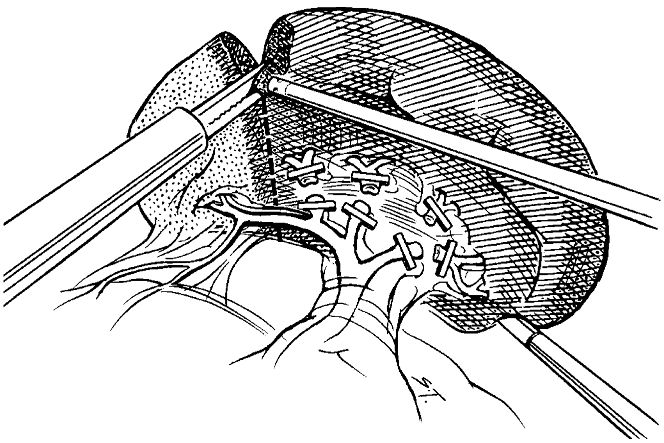

**FIGURE 110-4** Laparoscopic partial splenectomy using the ultrasonic dissector.

Antibiotic prophylaxis is recommended for all asplenic individuals in the immediate postoperative period. Penicillin prophylaxis is given to all children, except for those who are penicillin allergic. In penicillin-allergic children, options are limited. Trimethoprim-sulfamethoxazole can be used, recognizing higher pneumococcal resistance with this antibiotic. There are no universal recommendations on the duration of antibiotic prophylaxis, but most recommend prophylaxis for at least 2 years after splenectomy.[63]

## POSTSPLENECTOMY SEPSIS

The occurrence of overwhelming postsplenectomy infection (OPSI) was first reported by King and Shumacker in 1951 in a series of five infants younger than 6 months of age undergoing splenectomy for hereditary spherocytosis.[1] All five developed serious infections, and two died. Since then numerous reports have documented this risk and the increased risk (60- to 100-fold) in children younger than 5 years of age, as well as during the first few years after splenectomy. The etiology is probably related to decreased clearance of encapsulated bacteria[111] and decreased immunoglobulin levels.[112] The spleen is particularly important in infancy and childhood because the phagocytic function in infection occurs almost exclusively in the spleen.[113]

A cumulative review of the literature reported in the 1970s[114] identified the incidence of OPSI at 3.75%, with a mortality of 1.7%. The rate in pediatric cases was 4.1% compared with 1.9% in adults and a mortality rate of 1.8% in children compared with 1.1% identified in adults. Other studies in the 1980s and 1990s had a wide range of OPSI, and as of the mid-1990s the overall incidence of OPSI ranged from 0.13% to 8.1% in children younger than 15 years of age compared with 0.28% to 1.9% in adults.[115] *S. pneumoniae* was causative in 50% to 90% of all infections and is responsible for 60% of all fatal infections.[114,116–118] *H. influenzae* accounted for 32% of mortality,[119] and the meningococcus and group A *Streptococcus* were also significant pathogens.

The risk of late infectious mortality also varied with the disease state with a rate of 0.51% for spherocytosis and 2.67% for ITP.[120] Others also noted a higher mortality in children younger than 4 years of age (mortality: 8.1% in those younger than 4 years of age, 3.3% in older patients) with most deaths within 4 years of splenectomy.[121,122] In view of this, penicillin prophylaxis was advocated. The increased risk in children relative to adults was documented with an incidence of fatal OPSI of 3.77% in children compared with 0.39% in adults.[123] Many of these early reports were performed before widespread vaccination and use of prophylactic antibiotics, and more recent studies have somewhat lower rates of OPSI of 3.5% to 3.8%.[124,125] Vaccination has been shown to decrease the risk of bacteremia.[126]

A more recent population-based study out of Denmark determined that among all patients undergoing splenectomy (adults and children), excess risk of bacteremia was greatest in the first 90 days after splenectomy, occurring in 10% of all patients.[127] The risk remained higher than the general population for the first year. Different than previous studies, the Denmark study found enteric rods to be the predominant organism isolated from the blood in early and late postsplenectomy infections.

A comparison study of an early era of splenectomy with no immunizations or prophylactic antibiotics compared with a later era with a 70% immunization and a 100% prophylaxis rate noted a decrease in the infection rate (6% to 3.8%) and mortality (3.9% to 0.9%).[124] Even in this more recent study the rate of infection was related to age at splenectomy (birth to 5 years, 13.8%; >5 years, 0.5%). The historical mortality associated with OPSI has been 50% to 70%,[115,118,128,129] but more recently a mortality of around 10% has been observed.[124,130]

*The complete reference list is available online at www.expertconsult.com.*

Part VIII

# GENITOURINARY DISORDERS

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CHAPTER 111

# Renal Agenesis, Dysplasia, and Cystic Disease

Kenneth I. Glassberg and Grace Hyun

## Renal Development

More than 400 genes have been identified as playing a role in renal development. A defect in any of the more important genes can lead to specific abnormalities of development such as renal dysplasia, hypoplasia, or cystic disease. The kidney develops as a result of cross-talk between the wolffian duct (later, the ureteric bud) and the future metanephric blastema; each sends messages to the other, sometimes simultaneously and sometimes in response to the message received. Each step of renal development is dependent on the expression of different genes and their protein products. For example, the mesenchymal cells of the metanephric blastema persist and proliferate in response to insulin-like growth factor-2 (IGF-2). Expression of the Wilms' tumor 1 gene *(WT1)* suppresses IGF-2 and allows a cascade of events to occur including development of the ureteric bud from the wolffian duct and conversion of mesenchymal cells into epithelial cells. This latter conversion is initiated by the *PAX2* gene.

Ureteric bud formation from the wolffian duct occurs in response to a protein produced by the mesenchymal cells called *glial cell line–derived neurotrophic factor* (GDNF). This protein binds to a tyrosine kinase c-ret receptor on the caudal wolffian duct, inducing the formation of the ureteric bud. The ureteric bud elongates and penetrates the nearby mesenchymal blastema, where it undergoes multiple generations of bud divisions. Mesenchymal (blastemal) cells cluster around the tip of each terminal branch and differentiate into epithelial, stromal, and endothelial cells, the building blocks of the metanephric kidney. The epithelial cells first form into a hollow ball (renal vesicle), which elongates into a prenephron tubular structure that eventually attaches to the terminal branches of the ureteric bud, the future collecting ducts.[1]

Decreased ureteric bud branching will be associated with fewer clusters of mesenchymal cells and therefore fewer nephrons (i.e., hypoplasia). Poor communication between the branching bud tips and the clusters of mesenchymal cells or absence of continuity between the collecting ducts and developing nephrons can lead to persistence of immature structures (i.e., dysplasia). Overexpression or lack of expression of specific growth factors can lead to hyperproliferative renal disorders such as Wilms' tumor and renal cystic disease. For example, the aforementioned gene *IGF2* is overexpressed in most sporadic Wilms' tumor and *WT1,* a tumor suppressor gene, is mutated in many syndromal Wilms' tumors.

## Renal Dysgenesis

Maldevelopment of the kidney that affects its size, shape, or structure is referred to as *renal dysgenesis.* There are three principal forms: hypoplasia, dysplasia, and cystic dysplasia (as well as various other forms of renal cystic disease). Hypoplasia refers to a kidney or a segment of a kidney with a decreased number of nephrons. The hallmark of dysplasia is the presence of primitive ducts, structures thought to represent earlier stages of development and characterized by a surrounding collar of smooth muscle and collagen but lacking elastin.[2] Sometimes cysts appear in dysplastic kidneys or in areas of dysplasia. The cysts may be microscopic or macroscopic, focal or diffuse. When the entire kidney is involved with both dysplasia and cysts, it is referred to as a *multicystic dysplastic kidney.* Multicystic dysplastic kidneys may involute with time to become a "nubbin" of tissue; this is referred to as *renal aplasia.* The latter represents a tiny cluster of cells with no reniform shape. Kidneys that are severely dysplastic have either immature or absent collecting systems.

## Renal Agenesis

A defect of the wolffian ducts, the ureteric bud, or the metanephric blastema can lead to absence of kidney development, or renal agenesis. Renal agenesis occurs bilaterally in 1 of every 4000 births, with a predominance in males.[3] Because of the lack of urine production, oligohydramnios develops. Affected infants are born with immature lungs, pneumothorax, and Potter facies (hypertelorism, prominent inner canthal folds, and recessive chin). Bilateral renal agenesis can also appear as part branchio-oto-renal syndrome.[4] It is universally fatal. Unilateral renal agenesis is compatible with life; its incidence is 1 in 450 to 1000 births.[5] It is difficult to accurately determine

the true incidence of unilateral renal agenesis because in some conditions, such as a multicystic kidney, the organ can regress into a nubbin of tissue that does not appear on imaging studies.

Unilateral renal agenesis is associated with other urologic abnormalities including primary vesicoureteral reflux (28%), obstructive megaureter (11%), and ureteropelvic junction obstruction (3%).[6] Either unilateral renal agenesis or renal ectopia can be associated with ipsilateral müllerian defects and vaginal agenesis; this association is referred to as *Mayer-Rokitansky-Küster-Hauser syndrome.*

# Hypoplasia and Hypodysplasia

With hypoplasia, an entire kidney or a segment of one has a decreased number of nephrons. A hypodysplastic kidney also has a decreased number of nephrons; it may have a reniform shape but contains areas of dysplasia. Kidneys associated with ectopic orifices may be totally dysplastic, hypoplastic, or hypodysplastic. Ectopic orifices may be secondary to an abnormal ureteric bud site on the wolffian duct and are associated with abnormal renal development.

# Renal Cystic Disease

Renal cysts may be congenital, sporadic, or acquired; single or multiple; unilateral or bilateral. The majority arise from nephrons and collecting ducts. Multicystic dysplastic kidneys contain cysts that form from tubular structures before the nephrons develop. Benign multilocular cysts are a form of neoplasia and must be differentiated from possible malignant tumors. The origin of simple cysts is not clear. Most develop in kidneys that are otherwise normal.

Renal cysts vary in size from microscopic to macroscopic. All cysts are lined by epithelial cells. Some actually represent ectatic tubules or collecting ducts and remain continuous with the nephron. Others may pinch off from the nephron and become isolated structures. According to Gardner,[7] any duct that is dilated to four times the normal diameter is considered a cyst.

The classification system used in this chapter is based on that proposed by the Committee on Terminology, Nomenclature, and Classification of the Section on Urology of the American Academy of Pediatrics, which divides the various conditions into genetic and nongenetic disease.[8] Some modifications based on more recent findings have been added (Table 111-1).[1]

**TABLE 111-1**
**Classification of Cystic Disease of the Kidney**

| |
|---|
| Genetic |
| Autosomal dominant (adult) polycystic kidney disease |
| Autosomal recessive (infantile) polycystic kidney disease |
| Juvenile nephronophthisis–medullary cystic disease complex |
| Juvenile nephronophthisis (autosomal recessive) |
| Medullary cystic disease (autosomal dominant) |
| Congenital nephrosis (familial nephritic syndrome; autosomal recessive) |
| Familial hypoplastic glomerulocystic disease (autosomal dominant) |
| Multiple malformation syndromes with renal cysts (e.g., tuberous sclerosis, von Hippel-Lindau disease) |
| Nongenetic |
| Multicystic kidney (multicystic dysplastic kidney) |
| Benign multilocular cyst (cystic nephroma) |
| Simple cyst |
| Medullary sponge kidney |
| Sporadic glomerulocystic kidney disease |
| Acquired renal cystic disease |
| Caliceal diverticulum (pyelogenic cyst) |

From the outset, it must be clarified that although the terms *multicystic* and *polycystic* both mean "many cysts," they describe different conditions. The former refers to a dysplastic entity, and the latter refers to a number of separate entities, most of which are inherited, most of which are associated at some point in life with cysts in communication with nephrons or collecting ducts, but not all of which are associated with dysplasia. The most common conditions associated with the term *polycystic kidney disease* are autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD). These conditions may progress to renal failure.

The entities with more important surgical implications include the various forms of multilocular cysts and the neoplasms associated with von Hippel-Lindau disease and tuberous sclerosis (TS) . Although multicystic kidneys often present as an abdominal mass, they are rarely removed. The large cysts in ADPKD have been treated with laparoscopic unroofing, but this author is unaware of any unroofing procedures performed in children.

# Autosomal Dominant (Adult) Polycystic Kidney Disease

ADPKD was formerly referred to as *adult polycystic kidney disease* because it is seen predominantly in adults; however, it may manifest in childhood or even in utero. ADPKD is the most common cause of renal failure, accounting for 10% to 15% of patients requiring kidney dialysis and transplantation.[9] Its incidence ranges from 1 in 500 to 1 in 1000 individuals. The condition affects both kidneys, although it may present predominantly on one side before it manifests on the contralateral side.

## GENETICS

ADPKD has been associated with three different mutations: *PKD1* on chromosome 16 accounts for approximately 90% of cases,[10,11] *PKD2* on chromosome 4 accounts for 5% to 10% of cases,[12,13] and *PKD3* has not yet been characterized. Penetrance is thought to be 100%, and 50% of the offspring of affected individuals have the potential of developing the disease. ADPKD will manifest in 96% of affected individuals by age 90 years.[12,14]

## CLINICAL FEATURES

Because 50% of them will eventually develop the disease, the offspring of patients with ADPKD are screened by ultrasonography. By age 25 years, at least 85% of individuals will have cysts, but most will be asymptomatic.[15] Family members of individuals with ADPKD are unable to obtain life insurance

before age 25 years because of the possibility of developing the disease. The majority of individuals present between 30 and 70 years of age with findings that include microscopic and gross hematuria, flank pain, hypertension, and renal colic secondary to either clots or stones. In adults, the disease is associated with colonic diverticula, hepatic cysts, and berry aneurysms. Hepatic cysts appear much more frequently in adults than in children and are more common in females. ADPKD occasionally presents in utero or in infancy; when it does, 50% of the kidneys are large and usually contain macrocysts. Sometimes the large cysts are not apparent, and the kidneys are hyperechogenic due to the reverberation of ultrasound waves caused by the multiple interfaces between dilated ducts and tubules; the latter presentation is more typical for ARPKD (Fig. 111-1). Eventually, the cysts enlarge to macroscopic size. When prenatal ultrasonography identifies a patient suspected of having ADPKD or ARPKD, genetic or ultrasound studies of the parents must be obtained. It is important to monitor these children for hypertension because control of blood pressure delays the onset of renal failure. Those with elevated serum creatinine levels, increased urinary protein excretion, and high blood pressure at a young age tend to decline faster and go on to renal failure. Almost all patients who present in utero or in the first year of life eventually develop renal failure, but with close monitoring, the onset can be delayed.

# Autosomal Recessive (Infantile) Polycystic Kidney Disease

This entity is no longer referred to as *infantile polycystic kidney disease* because it is now realized that some patients can present as adolescents or in their early 20s. ARPKD is a relatively rare disease occurring in approximately 1 of every 40,000 live births.[16] All patients have some degree of congenital hepatic fibrosis. In general, younger patients with severely affected kidneys have the mildest congenital hepatic fibrosis.

## GENETICS

The disease is transmitted by *PKHD1,* a gene located on chromosome 6, with possible involvement of the mTOR pathway, as recently described.[17,18] Both the severe and mild forms of ARPKD are associated with this mutation. Because it is an autosomal recessive trait, one of four offspring is affected and neither parent shows evidence of the disease.

## CLINICAL FEATURES

For infants with ARPKD identifiable in utero or at birth, death in the first 2 months of life from uremia or respiratory failure is not unusual. If they survive the first month of life, their chances of living for a year with proper supportive therapy are improved. Eventually, all infants with ARPKD develop renal failure (Fig. 111-2). In children who present later in life, hypertension presents later and is more controllable and progression to renal failure is slow.

Newborns with ARPKD may have significant nephromegaly. The kidneys can be so large that they compromise breathing or cause a difficult delivery. When severe, oligohydramnios may be present, as well as Potter facies and deformities of the limbs. Rarely, the kidneys are so enlarged that the diaphragm is significantly elevated, resulting in respiratory compromise; in these cases, nephrectomy may be required. Respiratory care helps extend the child's life.

Those with advanced congenital hepatic fibrosis may have portal hypertension, esophageal varices, and hepatosplenomegaly. Variceal bleeding due to portal hypertension may require a splenorenal shunt. The kidneys in utero are typically large and hyperechogenic on ultrasound examination. Hyperechogenicity is due to the presence of numerous small microscopic cysts and dilated ducts and tubules within the kidney, creating reverberations of the sound waves. With time, macrocysts develop. As these patients get older, their kidneys get smaller, contrary to the sequence of events in ADPKD. On histologic examination, the collecting ducts are elongated and very dilated. There is no cure for the condition.

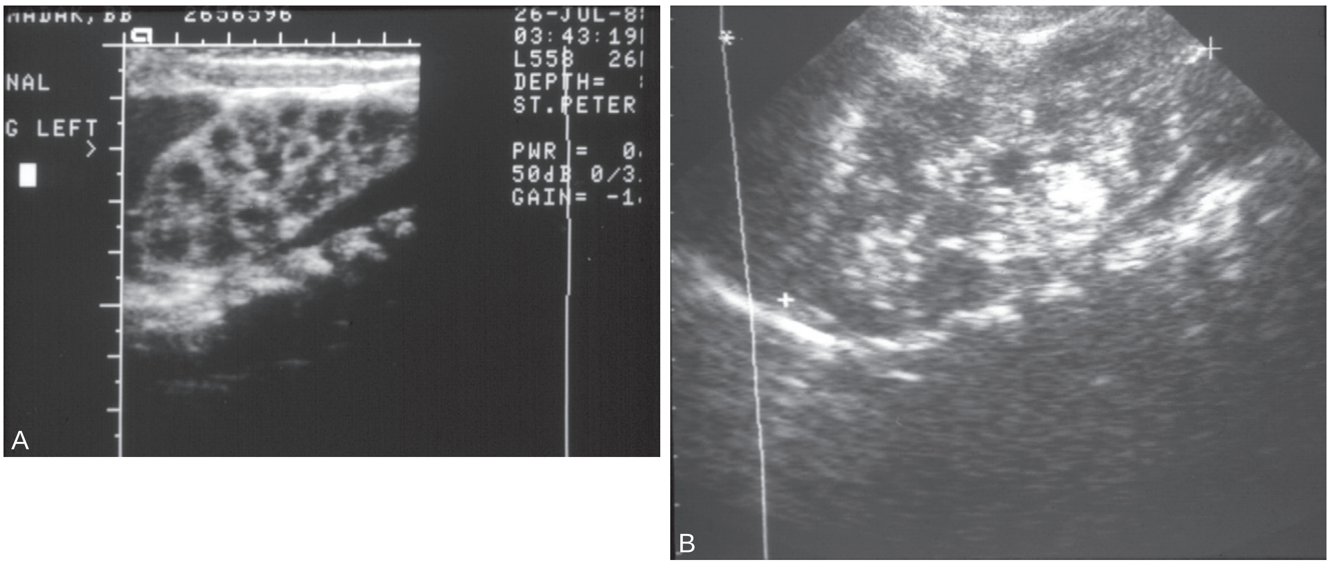


**FIGURE 111-1** **A,** Multiple cysts are seen throughout the left kidney on this ultrasound study in a newborn with autosomal dominant polycystic kidney disease. **B,** Newborn with autosomal recessive polycystic kidney disease. Note the increased echogenicity and the small cysts. (Courtesy Walter Berdon, MD.)

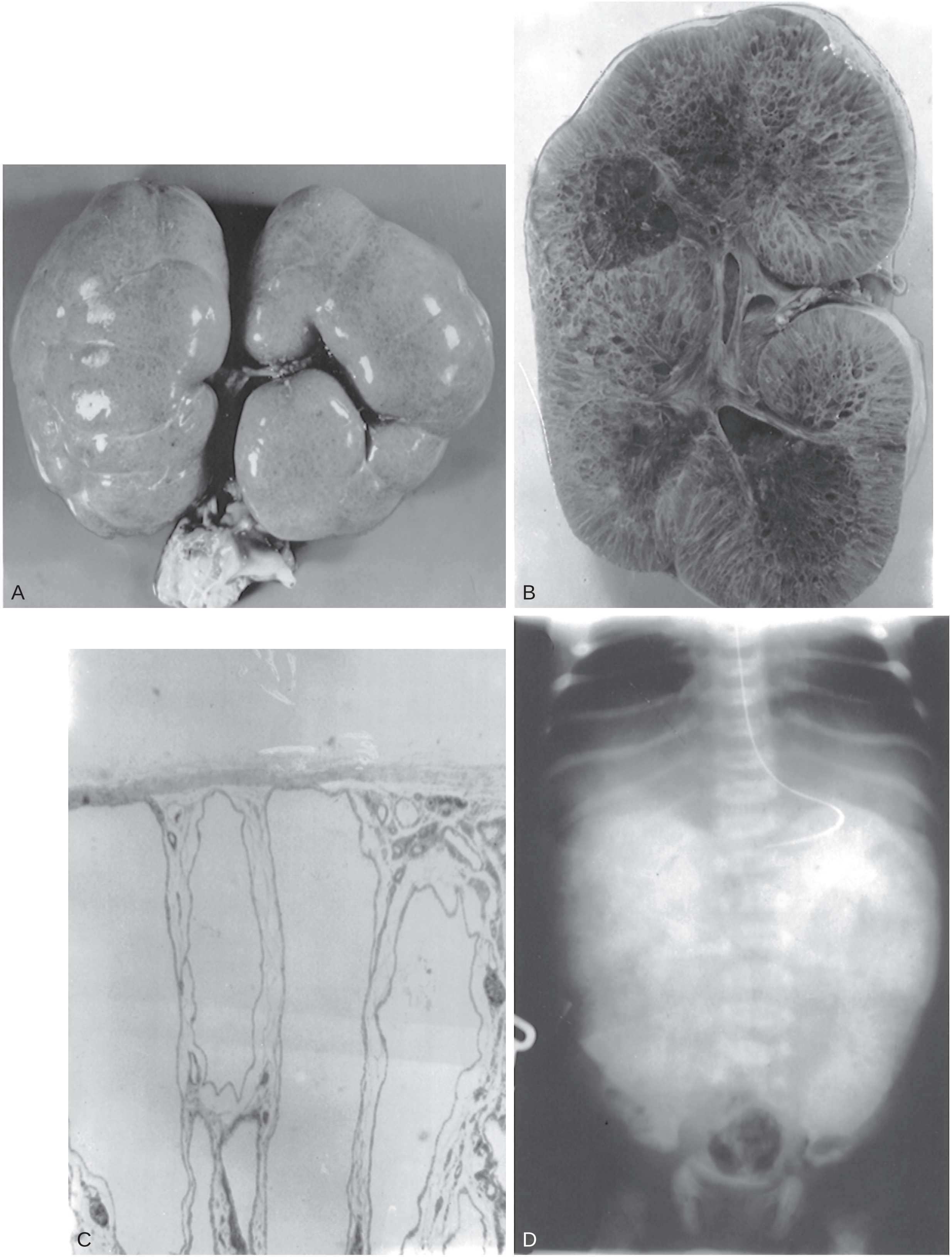


FIGURE 111-2 Autosomal recessive polycystic kidney disease. **A,** Gross specimen with diffuse, small subcapsular cysts. **B,** Radially arranged, elongated, “cystic,” dilated collecting ducts. **C,** On low-power microscopic view, dilated collecting ducts are seen. **D,** On intravenous urography, the characteristic delayed “sunburst” pattern is identified, secondary to contrast pooling in the dilated collecting ducts.

# Multiple Malformation Syndromes with Renal Cysts

A number of multiple malformation syndromes are characterized by renal cysts. Two that are of particular interest to surgeons are TS and von Hippel-Lindau disease.

## TUBEROUS SCLEROSIS

TS is associated with the classic triad of epilepsy (80% of cases), adenoma sebaceum (75% of cases), and mental retardation (60% of cases).[19] Adenoma sebaceum consists of flesh-colored papules of fibroma located on the malar area of the face. The hallmark lesion is a superficial cortical hamartoma of the cerebrum, which looks like a hardened gyrus, suggesting the appearance of a tuber (root). Hamartomas affect other areas of the body as well, especially the kidneys and eyes. Other kidney lesions include angiomyolipomas and cysts.

### Genetics

The trait is transmitted in 25% to 60% of cases and occurs either sporadically or as a genetic condition with variable or incomplete penetrance. Two genes have been identified as being responsible for the autosomal dominant transmission of TS.[20,21] *TSC1* is located on chromosome 9, and *TSC2* on chromosome 16. The latter gene defect is located at a site contiguous with *PKD1*, the mutation most commonly associated with ADPKD.[50] The fact that both TSC gene mutations result in similar clinical manifestations suggests that both genes are involved in a common developmental pathway. When either gene does not produce its normal protein product, similar results occur. Both are considered tumor suppressor genes because a mutation of either can result in tumor development.

### Clinical Features

Twenty percent of patients develop renal cysts, and these usually manifest before 3 years of age. One third of children who present with cysts are younger than 1 year. The disease may be detected on prenatal ultrasonography because of the presence of cysts. When it does present in utero, there is a greater likelihood that it is secondary to a mutation of the *TSC2* gene on chromosome 16. In such cases, defects of the adjacent *PKD1* gene responsible for ADPKD may also be present. The renal cysts rarely cause a problem. In the past, many of these patients died early of central nervous system lesions; however, they are now living longer, and in the future, it may be discovered that renal cysts cause compromised kidney function. On histologic examination, the cysts have a unique appearance and are lined by hypertrophic, hyperplastic eosinophilic cells. In theory, these hyperplastic cells may account for the 2% incidence of renal cell carcinoma in patients with TS. Patients as young as 7 years have been reported with this tumor.

## ANGIOMYOLIPOMA

Renal angiomyolipoma (AML) is a benign hamartomatous neoplasm consisting of varying amounts of mature adipose tissue, smooth muscle, and thick-walled vessels and occurs in 40% to 60% of patients with TS.[22–24] These lesions are rarely seen before 6 years of age and are common after age 10.[25] Fortunately, AMLs can be diagnosed via computed tomography (CT) scan. The presence of fat, −20 HU or lower, within a renal lesion on a CT scan is pathognomonic for an AML, excluding the diagnosis of RCC.[26–28] Life-threatening hemorrhage is the most significant complication of AMLs. Risk factors have been identified specifically, tumors larger than 4 cm, pregnancy, multicentricity, and TS. Therefore proactive intervention should be considered in these patients.[29] Furthermore, a nephron-sparing approach, by either selective embolization or partial nephrectomy, is clearly preferred in patients with small AMLs requiring intervention because of symptoms, in patients with TS or multicentric AML, and in patients for whom preservation of renal function is critical.

## VON HIPPEL-LINDAU DISEASE

This autosomal dominant condition is associated with cerebellar hemangioblastomas, retinal angiomas, cysts of the pancreas, epididymis and kidney epididymal cystadenoma, pheochromocytoma, and clear cell renal cell carcinoma. Its incidence is approximately 1 in 35,000.[30,31]

### Genetics

The *VHL* gene is a tumor suppressor gene located on chromosome 3 and has a dominant transmission; 50% of offspring of affected persons can expect to develop the disease. Individuals are born heterozygous for the disease initially. When the second allele of the *VHL* gene mutates in a specific organ, the typical lesions develop in that site. Different mutations of the *VHL* gene have been found in cases of renal cell carcinoma not associated with von Hippel-Lindau disease.

### Clinical Features

The mean age of presentation is 35 to 40 years; rarely, von Hippel-Lindau disease presents in childhood. Renal cysts are the most common renal lesion and are the first manifestation of the disease in 76% of patients.[32] Pheochromocytomas occur in 10% to 17% of affected individuals but seem to be more common in specific families.[33,34] Some patients present with seizures because of hemangioblastomas of the central nervous system. Because the cells lining the cysts are hyperplastic, these patients have a high risk of developing renal cell carcinoma (RCC).[31] In adulthood, the possibility of bilateral renal cell carcinoma should be considered, even if it is not bilateral initially. Annual or biannual examinations of the kidney, usually by CT, are recommended after age 30 years, particularly when small tumors, representing benign adenomas, are present. RCC is responsible for 30% mortality rate for those patients with VHL.[35]

# Multicystic Dysplastic Kidney

This condition represents an extreme form of dysplasia involving the entire kidney (Fig. 111-3). When occurring in one pole of a kidney, it is likely associated with a duplicated system. When patients have the disease bilaterally, it is incompatible with life and is therefore associated with stillbirth, oligohydramnios, and Potter facies. The condition is usually associated with atretic ureters and no renal pelvis. When a renal pelvis is present, the entity is referred to as a *hydronephrotic*

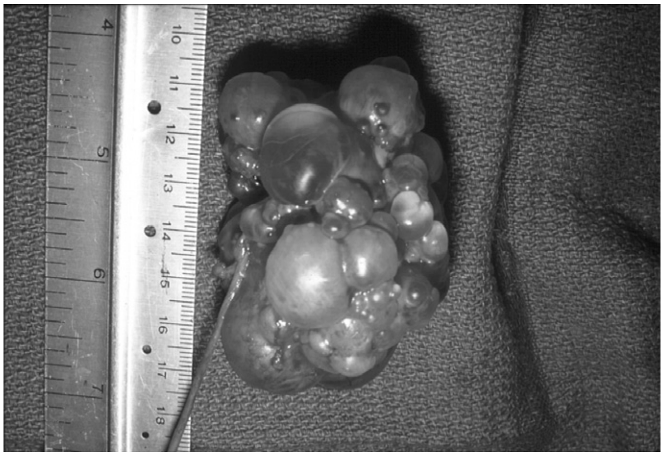

**FIGURE 111-3** Typical multicystic kidney with atretic ureter. Note the "bunch of grapes" appearance. (From Shah SH, Glassberg KI: Multicystic dysplastic kidney disease. In Gearhart JP, Rink RC, Moriquand PDE [eds]: Pediatric Urology. Philadelphia, WB Saunders, 2001, p 279.) *(See color plate.)*

*form of multicystic kidney* (Fig. 111-4). When the kidney appears solid, with fewer cysts, the disease is referred to as *solid cystic dysplasia.* Typically, however, the appearance is that of a bunch of grapes, and on ultrasound studies the kidney has a nonreniform shape; the cysts have a haphazard appearance, with no central or medial cyst, suggesting the presence of a renal pelvis (Fig. 111-5). This form of multicystic kidney must be differentiated from hydronephrosis, in which there is a central or medial cyst—the largest—and there is communication with peripheral cysts, representing dilated calices. In the past, it was thought that the cysts do not communicate; however, injection of contrast into one cyst invariably demonstrates communication between cysts (Fig. 111-6).[15]

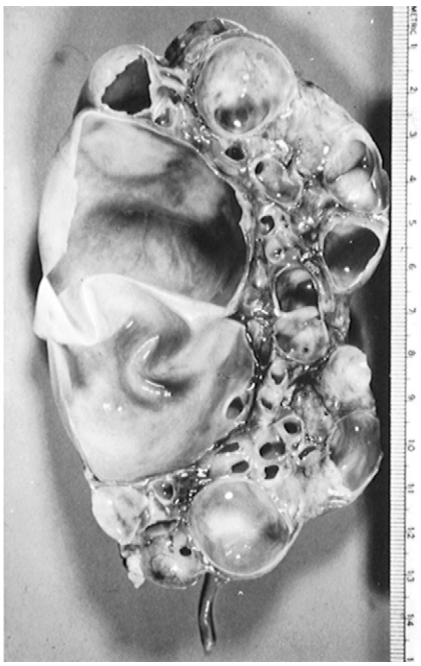

**FIGURE 111-4** Hydronephrotic form of multicystic dysplastic kidney. The largest cyst is located centrally and medially, and the smaller cysts are at the periphery.

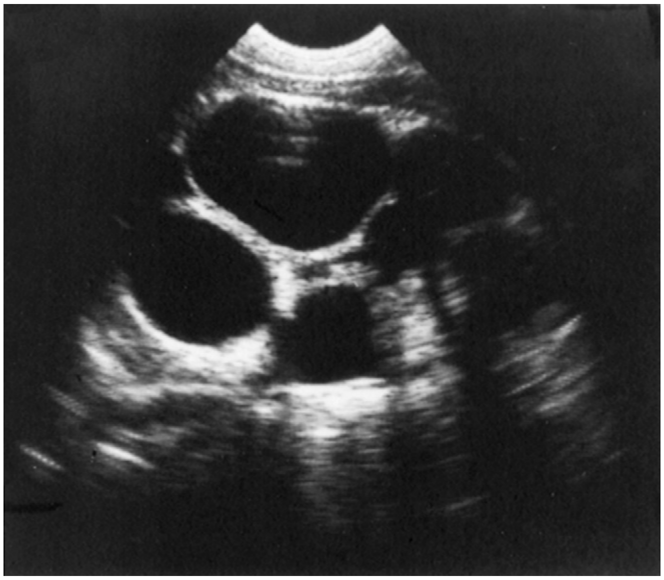

**FIGURE 111-5** Typical ultrasound appearance of a multicystic kidney. Three large cysts are seen, with some smaller cysts in between. Little parenchyma is identified.

## CLINICAL FEATURES

Multicystic dysplasia is the most common form of renal cystic disease, and it along with ureteropelvic junction obstruction are the most common causes of a palpable abdominal mass in an infant. It is important to evaluate the contralateral system because 3% to 12% of infants with multicystic kidney disease have a contralateral ureteropelvic junction obstruction, and 18% to 43% have contralateral vesicoureteral reflux.[11,36–38] Because of the latter finding, voiding cystourethrography should be obtained in all infants diagnosed with the entity. Historically, these kidneys were detected in the first year of life by palpation. Before the use of ultrasonography, most multicystic kidneys were removed because it was hard to confidently differentiate them from renal tumors and because of rare reports of Wilms' tumors being identified in multicystic kidneys. To help differentiate a multicystic kidney from a

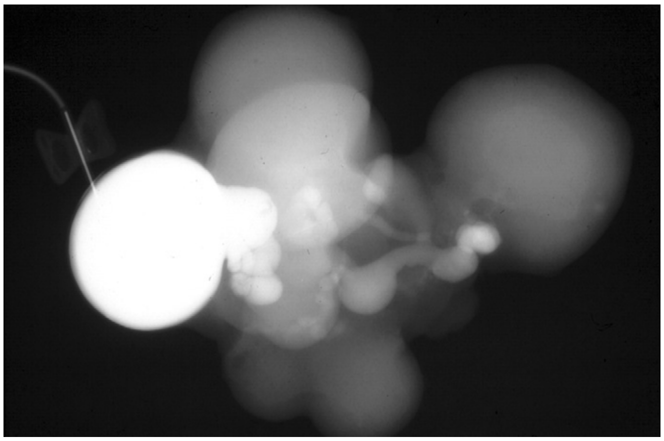

**FIGURE 111-6** Multicystic dysplastic kidney. Contrast material injected into one cyst is identified moments later in all cysts, demonstrating a duct-like communication between them. Although the cysts do not appear to communicate on ultrasonography, they are invariably found to communicate when contrast material is injected into excised specimens.

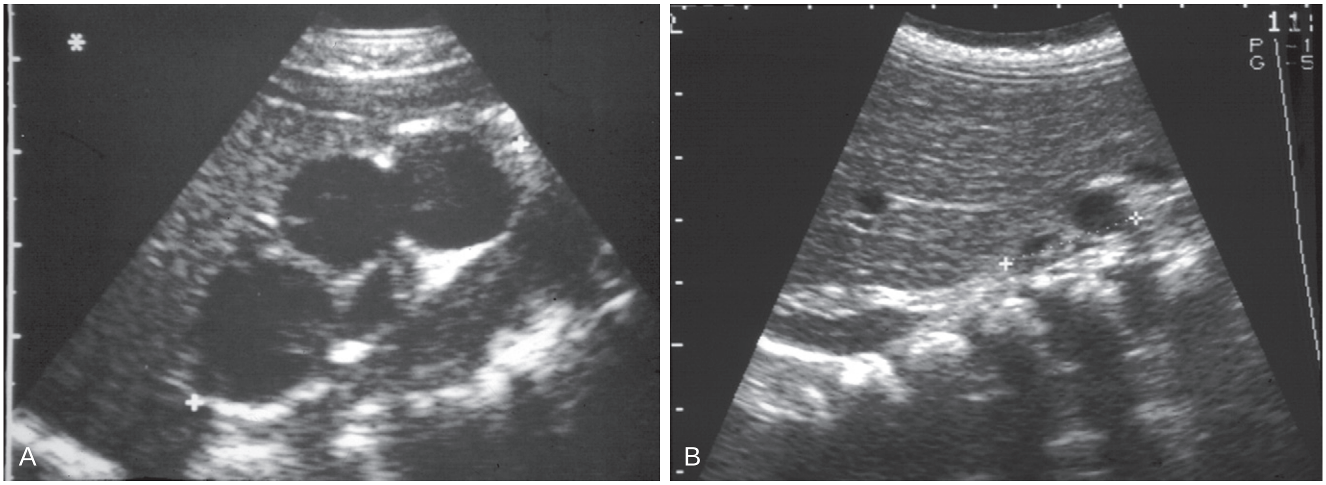


**FIGURE 111-7** **A,** Multicystic kidney identified on ultrasonography in a newborn. **B,** At age 9 months, the cysts have shrunken, and the kidney is barely visible. (From Shah SM, Glassberg KI: Multicystic dysplastic kidney disease. In Gearhart JP, Rink RC, Moriquand PDE [eds]: Pediatric Urology. Philadelphia, WB Saunders, 2001, p 284.)

hydronephrotic kidney, a dimercaptosuccinic acid (DMSA) scan is obtained. Little, if any, function exists in a multicystic kidney, whereas a hydronephrotic kidney rarely has no function. The decision must be made whether a multicystic dysplastic kidney requires removal. With ultrasonography and other imaging studies providing a more definitive evaluation, the incidence of nephrectomy for an inconclusive diagnosis has fallen dramatically. Most cases of Wilms' tumor in multicystic dysplastic kidneys have occurred in kidneys that were not previously known to be multicystic. Thus it is unclear whether the multicystic dysplastic kidney led to the development of the Wilms' tumor. Two reports in the literature that imply that these kidneys should be removed describe a total of 120 patients, 5 of whom were found to have nephrogenic rests of nodular renal blastoma.[39,49] One had Wilms' tumorlets in the hilar region. However, renal blastomas have been reported to occur in normal kidneys as well, so it is not clear that the presence of these rarely seen tumorlets in multicystic kidneys implies a greater risk of developing Wilms' tumor. According to Beckwith,[40] only 5 of 7500 Wilms' tumor specimens in the Wilms' Tumor Registry occurred in multicystic kidneys. Beckwith calculated that multicystic kidneys have a fourfold increased risk of developing Wilms' tumor, and this low incidence does not justify prophylactic nephrectomy. He pointed out that even if Wilms' tumor did develop, the current survival rate is now greater than 90% with treatment. Zerres and colleagues[17] and Aslam and colleagues[41] suggest conservative therapy for multicystic kidneys as long as there is follow-up ultrasound surveillance every 3 months until 8 years of age. They calculated a $2000 to $5000 cost for such surveillance, in comparison with a simple nephrectomy at $5000 to $7000.

There have been isolated case reports of hypertension developing in association with a multicystic kidney, with removal of the kidney curing the hypertension. In the National Multicystic Kidney Registry of the Section on Urology of the American Academy of Pediatrics, most neonatal cystic kidneys became smaller or stayed the same size over a 5-year period, with a small percentage becoming larger.[16] Therefore many kidneys that become smaller will disappear from view on ultrasonography. This does not mean that the kidney itself has disappeared; it implies that the cysts have disappeared (Fig. 111-7). The cells that lined the cysts persist, however; this amorphous group of cells forms a nubbin of kidney without any function (renal aplasia).

Although it is customary to follow multicystic kidneys with ultrasound studies every 3 to 6 months during the early years of life and at progressively longer intervals until 8 years of age, it is not clear whether it is necessary to follow a patient whose kidney disappears on imaging studies, or even when those findings persist. Because these cells remain without the cyst fluid, their presence, by itself, should not determine whether to obtain ultrasound follow-up.

## Benign Multilocular Cyst (Cystic Nephroma)

A benign multilocular cyst is a neoplasm of the kidney that is not associated with renal dysplasia. The lesions are large and circumscribed by a thick capsule. There is usually normal renal parenchyma adjacent to the lesion. The loculi, which represent cysts within the lesion, can measure a few millimeters to a few centimeters in size and do not intercommunicate. The cysts are lined by cuboidal or low columnar epithelial cells. The septa of a benign multilocular cyst are composed of fibrous tissue, and no poorly differentiated tissues or blastema cells are present.

It is important to note that when a multilocular cystic lesion is identified on an imaging study, particularly ultrasound, it is impossible to determine whether it is a benign multilocular cyst, a multilocular cyst with partially differentiated Wilms' tumor, a benign multilocular cyst with nodules of Wilms' tumor, or a cystic Wilms' tumor. Thus multilocular cystic lesions can be considered a spectrum of entities, and there have been no reports of one entity converting into another (Fig. 111-8). Because imaging studies cannot differentiate them, it is essential that these lesions be removed (Fig. 111-9). If they are located in one pole of the kidney and there is a large remaining portion of normal parenchyma present, a partial nephrectomy should be considered. Even when the lesion is not a typical benign multilocular cyst, there is little chance of the disease being aggressive. None of these conditions involves expansive nodules, and metastasis rarely if ever occurs.[42] The lesion

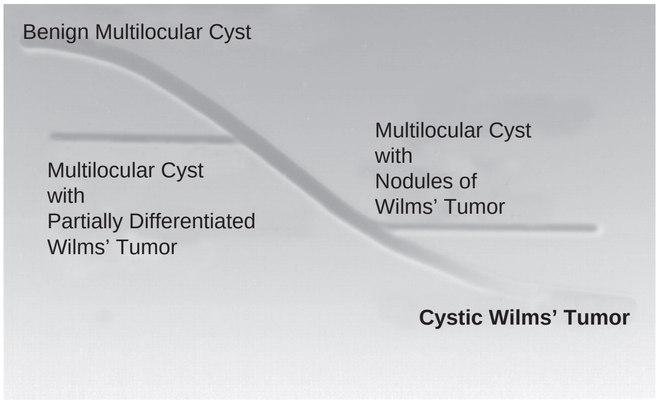


FIGURE 111-8 Spectrum of multilocular cystic lesions in childhood. Because imaging studies cannot differentiate one type of lesion from another, the diagnosis must be made under the microscope.

should not be confused with a Wilms' tumor that contains necrotic areas, which can simulate cysts on ultrasonography; the latter represents a more aggressive tumor.[43] The age distribution is bimodal, occurring primarily in boys during the first 2 to 3 years of life, and again after the fourth decade, usually women.[42] Children tend to present with an asymptomatic abdominal mass detected on routine physical examination, whereas symptomatic presentation is more common in adults.[44]

## Simple Cyst

Simple cysts are discrete findings within the kidney that usually appear oval to round with a smooth border. The cysts usually contain clear or straw-colored fluid, and when they manifest in utero, they usually disappear by birth. When they appear during childhood, they should be evaluated just as in

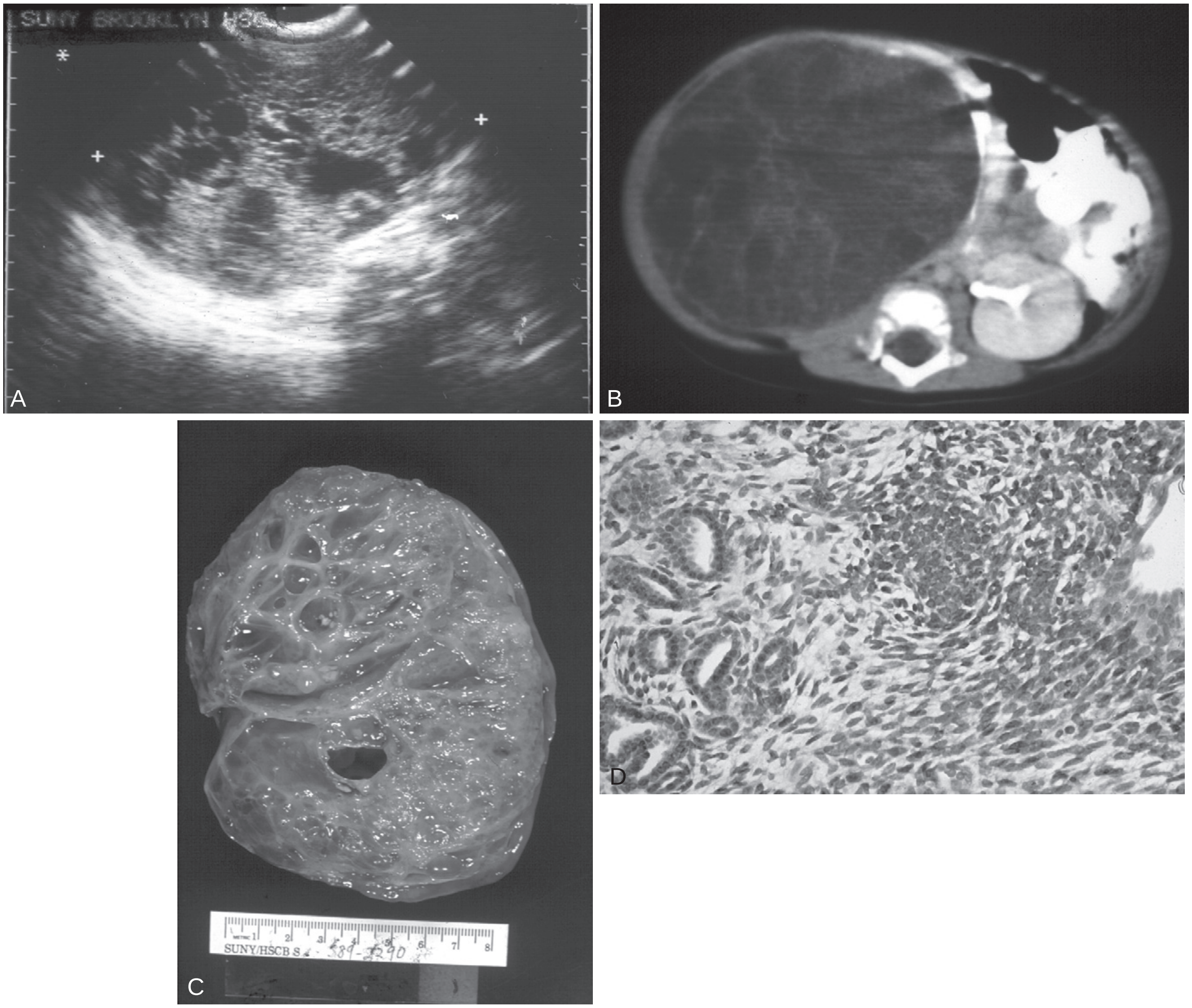


FIGURE 111-9 Multilocular cyst with partially differentiated Wilms' tumor. **A,** Ultrasound image identifies a mass in the kidney with cystlike structures within it. **B,** On contrast-enhanced CT, a large, smoothly outlined renal mass is seen with fine septa within it; note the caliceal system compressed on its edge. **C,** Cross section of the mass reveals noncommunicating loculations. **D,** On microscopy, nests of blastema cells with tubular elements are seen between the loculi, findings typical of multilocular cyst with partially differentiated Wilms' tumor.

adults with simple renal cysts. Because cysts were once considered such an infrequent finding in children, and because the ability to clearly define a cyst was limited, most simple renal cysts were operated on in the past. In children, renal cysts are rarely symptomatic. When more than one simple renal cyst is present in a kidney, the patient should be followed and the contralateral kidney carefully evaluated with imaging studies, because unilateral multiple cysts may represent an initial asymmetric presentation of ADPKD.

The sonographic criteria for a classic benign simple cyst are as follows:

1. Sharply defined, thin, distinct wall with smooth and distinct margin
2. Absence of internal echoes
3. Good transmission of sound waves through the cyst with acoustic
4. Spherical or slightly ovoid shape (Fig. 111-10)

If all these criteria are met, the chance of malignancy is negligible.[44] Sometimes there is a cluster of renal cysts at one pole of a kidney, and this must be differentiated from a multilocular cystic lesion. When the cysts are all simple, the condition may be referred to as *unilateral renal cystic disease,* a variant of simple cysts.[45] Although follow-up recommendations have not been established with evidence-based reports, it seems reasonable to follow these patients with sequential ultrasonography with decreasing frequency, mainly to ensure the stability of the simple cyst and screen for an asymmetric presentation of ADPKD.

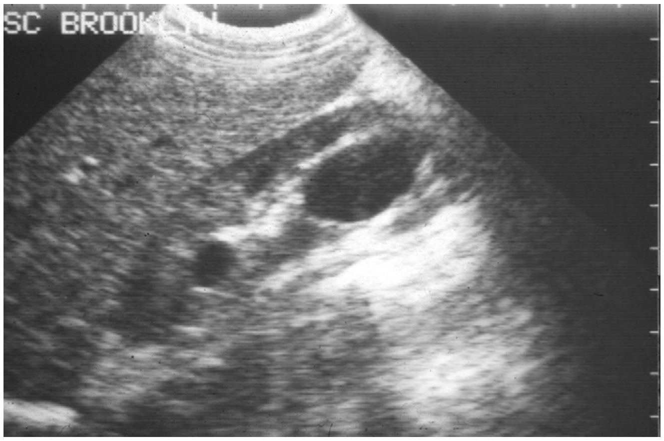

**FIGURE 111-10** Two simple renal cysts in a 7-year-old. Note the whiteness (hyperechogenicity) just outside the kidney on ultrasonography. This is referred to as acoustic enhancement, a finding typical of simple cysts. It occurs secondary to increased sound wave reverberation through the cyst, and it interfaces with the kidney. It is important not to confuse this finding with an atypical, asymmetric presentation of autosomal dominant polycystic kidney disease.

## Acquired Renal Cystic Disease

Acquired renal cystic disease is common in dialysis patients with chronic renal failure. There are few reports on acquired renal cystic disease in children, but as in adults, the incidence increases with the length of time on dialysis.[31] Young patients exposed to dialysis may develop the condition later in childhood. Once renal cysts develop, the kidneys should be followed regularly with imaging studies to rule out tumors. After renal transplantation, the cysts regress in size. New cysts can form in transplanted patients, but they tend to be small.

## Caliceal Diverticulum

A caliceal diverticulum is a cystic, smoothly outlined sac, usually located at one of the poles, most frequently the upper one. It communicates with the pelvicaliceal system by means of a narrow neck. It has also been referred to as a *pyelogenic cyst;* that term, however, is best used when the lesion communicates with the renal pelvis. These diverticula have the same lining as calices, with a smooth layer of transitional epithelium. Caliceal diverticula are benign lesions, and small diverticula are usually asymptomatic and discovered as an incidental finding. The diagnosis is best made by excretory urography or CT with delayed images. Whereas simple cysts do not take up contrast, calyceal diverticula will fill with contrast specifically on the delayed images. Asymptomatic patients do not require treatment. Over time these diverticula tend to progressively distend with trapped urine. Infection, hematuria, flank pain, milk of calcium (crystallization of calcium salts without actual stone formation), and true stone formation are complications of stasis or obstruction that can produce symptoms[46] and are indications for surgical intervention. Percutaneous removal of the stones and ablation of the mucosal surface[47] and ureteroscopic enlargement of the diverticular communication with removal of the stones[48] are the modern treatment options available.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 112

# Renal Fusions and Ectopia

Pierre Mouriquand and Nicoleta Panait

## Embryology

The embryology of congenital anomalies of the kidneys involves two protagonists and three events. The two protagonists are the nephrogenic material (pronephros, mesonephros, metanephros) and the ureteral buds (wolffian structures). The three events are induction of metanephric tissue (renal construction), ascent of the kidneys (cephalad migration), and positioning of the kidneys (partition and rotation). Incidents occurring during these three phases (first 8 weeks of gestation) may affect the presence, number, and location of the kidneys.

The nephrogenic cord is divided into three parts (Fig. 112-1)[1]: The most cranial segments collectively constitute the pronephros; the intermediate segments, the mesonephros; and the most caudal segments, the metanephros or kidney. This classification is purely topographic, and the nephrogenic material arises from the same source and exhibits identical properties throughout its craniocaudal extent.[2] The pronephros (eight-somite–stage embryo) degenerates completely (day 24 to 25); however, its duct contributes to the formation of the mesonephros. In an embryo with 23 somites, the mesonephros produces small quantities of diluted urine and forms mesonephric vesicles and excretory tubules, which also degenerate with a few embryonic remnants left such as the paradidymis in the male and the paroöphoron in the female.[3] The metanephros develops from the portion (metanephric blastema) of the nephrogenic cord caudal to the mesonephros.

The ureteral buds arise from the mesonephric duct near its junction with the cloaca during the fourth to fifth week of gestation. The cranial end of the ureter then ascends to meet the nephrogenic cord, which begins to develop into the metanephros and continues its cephalad migration. The cranial end of the ureteral bud begins a series of branchings to form the renal pelvis, the calices, and a portion of the collecting ducts.[4] The cephalad migration of the kidneys ends at the eighth week of gestation, as well as their axial rotation of 90 degrees medially. During their ascent, the kidneys receive their blood supply from the neighboring vessels. Blood is initially supplied by the middle sacral artery, then the common and inferior mesenteric arteries, and finally the aorta. Renal development is closely related to the location of the origin of the ureteral buds.[5] The ureteral ducts (which in the first phases of development are permeable until the 35th day) subsequently undergo a process of obstruction and recanalization of their lumen until the embryo is 41 days of age.[6,7] The muscular and neurologic construction and maturation of the urinary excretory system are a slow phenomenon (Fig. 112-2) that, when impaired, may affect the entire anatomic organization of the urinary tract. Any delay or mislocation of these complex events may lead to the following renal anomalies[8]: renal agenesis, multicystic dysplastic kidney and other renal cystic diseases, small congenital kidney, supernumerary kidney, and renomegaly. Anomalies related to abnormal ascent and abnormal fusion[9] are discussed in the following sections. Many genes are likely to control all these events, although few are identified.[10] Renal metanephric development results from the expression of many genes in the ureteral bud and metanephric blastema with each sending messages to the other to induce organogenesis.[11] The transcription factor BF2[12] studied in the mouse model seems to play an important role in this embryonic construction.

## Anomalies Related to Abnormal Ascent of the Kidneys (Ectopic Kidneys)[13]

### PELVIC KIDNEY

A pelvic location (sacral or pelvic) below the aortic bifurcation is the most common site of ectopic kidneys.[14] A pelvic kidney (Fig. 112-3) is generally unilateral with a slight predilection for the left side. It is found bilaterally in 10% of cases.[15] In addition to its abnormal location, a pelvic kidney is frequently small, with an irregular shape, variable rotation, and extrarenal collecting system.

### LUMBAR OR ILIAC ECTOPIC KIDNEY

These kidneys are fixed above the crest of the ileum but are below the level of L2 and L3. Such kidneys can be difficult to differentiate from an ptotic kidney, which has a normal ureteral length, is not malrotated, is mobile, and can usually be manipulated into its normal position.[15]

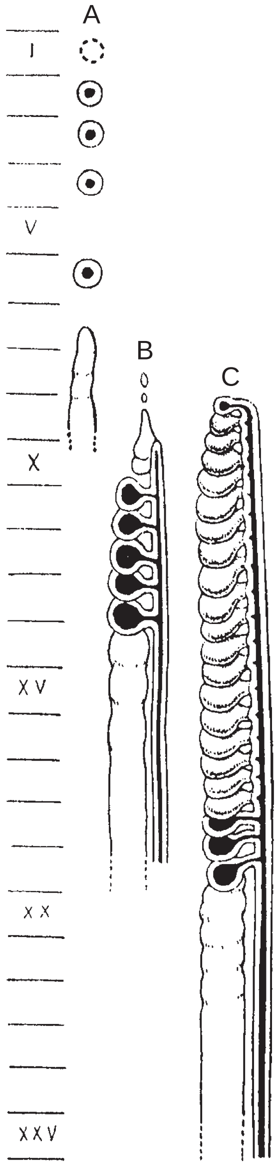



**FIGURE 112-1** Schemes showing early development of the human nephros. **A,** Ten-somite embryo. **B,** Twenty-somite embryo. **C,** Twenty-five-somite embryo. The Roman numerals indicate the level in somites. The circles indicate nephrotomes that do not contribute to the nephros (based on Torrey[85]). (From Hamilton WJ, Boyd JD, Mossman HW [eds]: Human Embryology, 3rd ed. Cambridge, England, Heffer, 1962.)

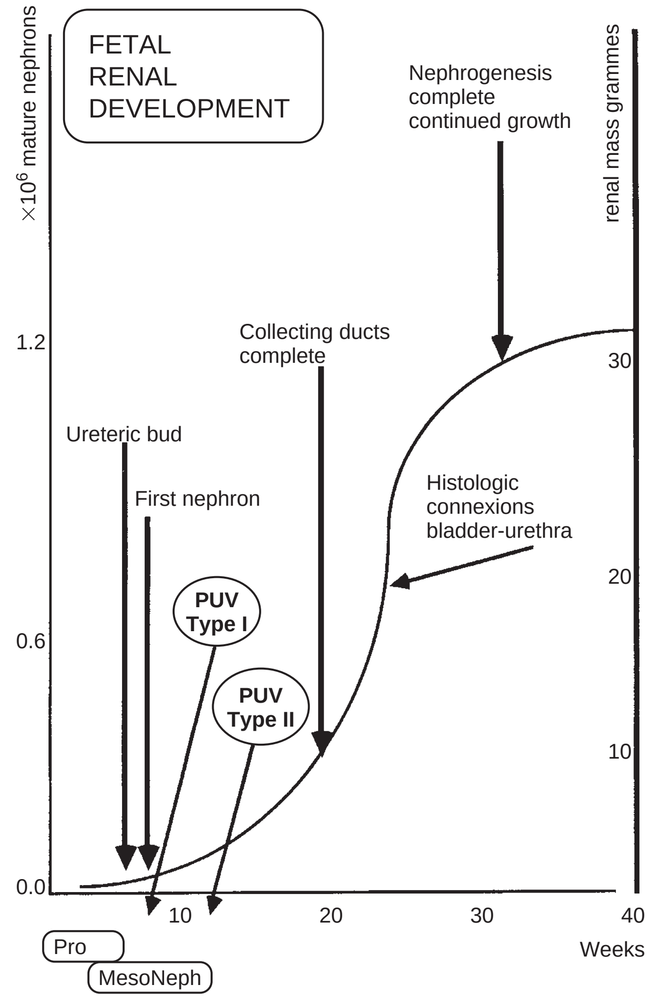



**FIGURE 112-2** Chronology of development of the urinary tract. PUV, posterior urethral valves.

## THORACIC KIDNEY

Thoracic kidneys (Fig. 112-4, *A* and *B*) are rare (1 in 16,000)[16–19] and may be related to delayed mesonephric involution (i.e., persistence of the nephrogenic cord).[20] Thoracic kidneys may be associated with cardiovascular, pulmonary, diaphragmatic,[21,22] and spinal anomalies.[23,24]

## ASSOCIATED ABNORMALITIES

Ectopic kidneys are often associated with genital and contralateral urinary abnormalities such as the absence of a vagina,[25] retrocaval ureter,[26] bicornuate uterus, supernumerary kidney,[27] and contralateral ectopic ureter.[28] An ectopic kidney can be a component of a more complex syndrome such as the Mayer-Rokitansky-Küster-Hauser syndrome,[29–31] Fanconi anemia,[31,32] or conjoined twins.[33] Cephalad kidneys have also been reported in patients with omphaloceles.[34]

## DIAGNOSIS OF ECTOPIC KIDNEYS

Ectopic kidneys may be an incidental finding that requires no surgery or may be associated with impaired drainage or reflux that may require surgical correction. Isotope studies, antenatal and postnatal ultrasonography, magnetic resonance imaging (MRI) (Fig. 112-5), and intravenous urography usually allow identification of the ectopic renal parenchyma. These investigations can be complemented by retrograde contrast studies when required. Computed tomography (CT) has been reported as a possible method for identifying ectopic renal tissue, especially in the thoracic cavity.[17] An ectopic kidney can be suspected antenatally, especially if the abnormality is associated with some degree of dilatation.

# Anomalies Related to Abnormal Fusion of the Kidneys

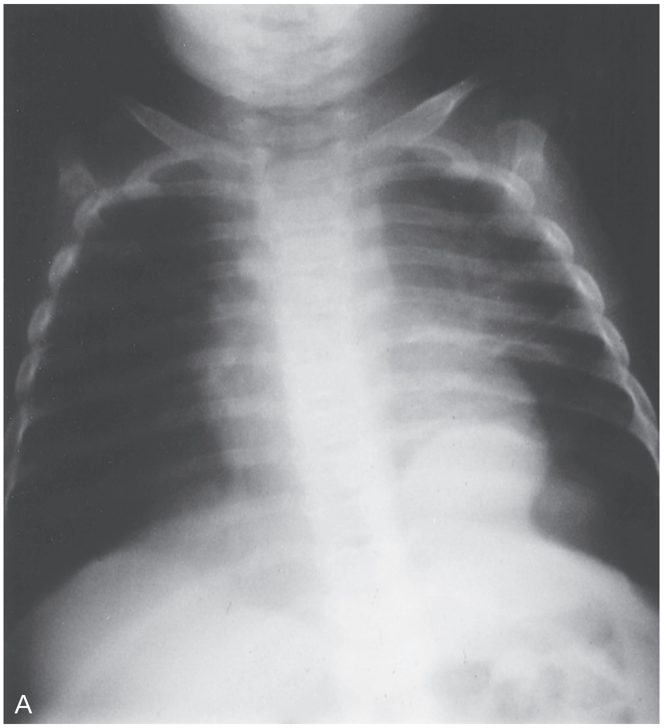
## HORSESHOE KIDNEY

A horseshoe kidney is the most common fusion defect of the kidneys. The incidence of horseshoe kidneys (Figs. 110-6, *A* and *B* and 110-7, *A* and *B*) varies from 1 in 400 [35] to 1 in 1800 [36] autopsies. The condition is more common in male patients. Horseshoe kidney and other renal fusion abnormalities such

FIGURE 112-3 Pelvic kidney. (Courtesy Professor I. Gordon, Department of Radiology, Great Ormond Street Hospital, London.)

as crossed ectopia have been reported to occur in more than one member of a family including apparently identical twins. These findings suggest a genetic influence.[37–39] In 95% of cases, the lower poles of the two kidneys are joined by a bridge of renal tissue that can be either normal renal tissue or dysplastic or fibrous tissue. In approximately 40% of cases, the isthmus lies at the level of L4, just beneath the origin of the inferior mesenteric artery; in 20% of cases, the isthmus is in the pelvis; and in the remaining cases, it lies at the level of the lower poles of normally placed kidneys.[25] Although the isthmus usually passes anterior to the great vessels, it may pass posterior to the aorta or inferior vena cava.[40] It is postulated that the inferior mesenteric artery obstructs the isthmus and prevents further ascent. A few horseshoe kidneys have fusion at their upper poles. Ureters arch anteriorly to pass over the isthmus.[41] The blood supply of horseshoe kidneys varies considerably, a fact that must be borne in mind at the time of surgery: 30% of patients have a renal blood supply that consists of one renal artery for each kidney. However, the supply may be asymmetric, with duplicate or even triplicate vessels. The isthmus may be supplied by the aorta or by the renal, inferior mesenteric, common or external iliac, or sacral arteries. In addition, the entire blood supply may enter through the isthmus.[42] Duplication of the horseshoe kidney and communicating renal duplication have also been mentioned in previous reports.[43,44] One part of the horseshoe kidney may be dysplastic and nonfunctioning.[45]

Associated abnormalities are common and occur in 78% of cases.[46,47] The most common involve the central nervous system, gastrointestinal tract, and skeletal and cardiovascular systems. In children with trisomy 18, the incidence of fused kidneys is 20%.[48,49] More than 60% of patients with Turner syndrome have renal abnormalities[50] including horseshoe kidneys (7%).[51,52] Horseshoe kidneys can be complicated later in life by aortic aneurysms.[53]



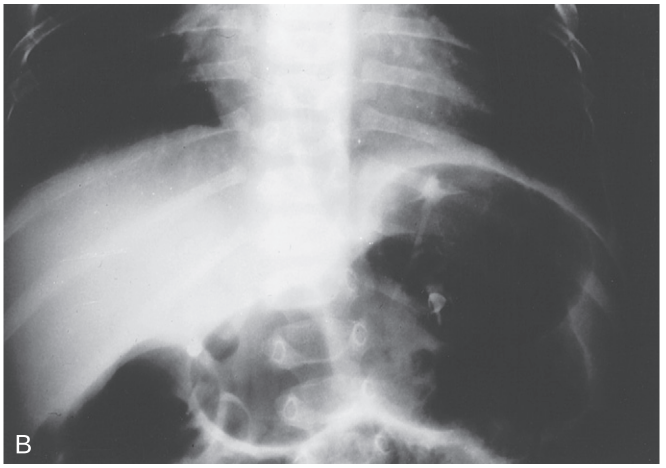




FIGURE 112-4 **A** and **B,** Thoracic kidney (intravenous urography). (Courtesy Professor I. Gordon, Department of Radiology, Great Ormond Street Hospital, London.)

Horseshoe kidneys are diagnosed with the same investigations mentioned earlier; isotopic studies usually give the clearest information. On intravenous urography, the diagnosis is clearly indicated by malrotation of each kidney with a projection of the calices medially to the renal pelvis, a renal axis that is more vertical or shifted outward, and the low position of the excretory cavities. The course of the ureters varies, but their upper segments seem to be laterally displaced by the parenchymal bridge. Association with a dilated renal pelvis is common and due to either anterior projection of the ureter (which can be kinked) or obstruction of the pyeloureteric junction caused by an anomaly of the junction itself or the disposition of the blood vessels around the junction. It is usual in these cases for the horseshoe kidney to be associated with some degree of impaired urine flow, and thus the diagnosis can be suspected antenatally. Vesicoureteric reflux is also commonly associated with horseshoe kidneys (10% to 80% of cases).[43,52,54]

FIGURE 112-5 Magnetic resonance image of a pelvic kidney *(arrow)*. (Courtesy Professor J. P. Pracros, Department of Radiology, Debrousse Hospital, Lyon, France.)

The prognosis of patients with horseshoe kidneys depends on the associated anomalies. Most horseshoe kidneys are asymptomatic throughout life. However, associated hydronephrosis, reflux, lithiasis, or dysplastic tissue may lead to surgical intervention because of recurrent urinary tract infections, pain, or hematuria. A horseshoe kidney carries a conceivably increased risk for nephroblastoma and an approximately threefold to fourfold higher risk for cancer of the renal pelvis.[55,56] Overall, the risk of Wilms tumor in a horseshoe kidney is approximately twice that of the normal population. Tumors that arise, mostly in the bridge of a horseshoe kidney, can mimic the symptoms of an intra-abdominal disease process. A parenchymatous renal isthmus that is the result of an abnormal migration process may be predisposed to the development of renal cell carcinoma.[51] The risk for primary renal carcinoid tumor is even greater, and it might arise from neuroendocrine cells within foci of metaplastic or teratomatous epithelium within the kidney.[57] Association with ganglioneuroblastoma has also been reported.[58] Although these tumors have a higher risk in a horseshoe kidney, the frequency does not justify routine surveillance. An infected caliceal diverticulum can be associated with this malformation.[59] Xanthogranulomatous pyelonephritis in a horseshoe kidney is another possible, though a rare complication that represents a response of the parenchyma to chronic infection.[60]

Robotic, laparoscopic, or open correction[61–63] of ureteropelvic junction obstruction is the most frequent indication for surgical intervention in a patient with a horseshoe kidney. Division of the isthmus is no longer recommended in most cases because the isthmus probably does not contribute to the obstruction.[64] If the position of the kidney is within normal limits and the procedure is unilateral, the traditional

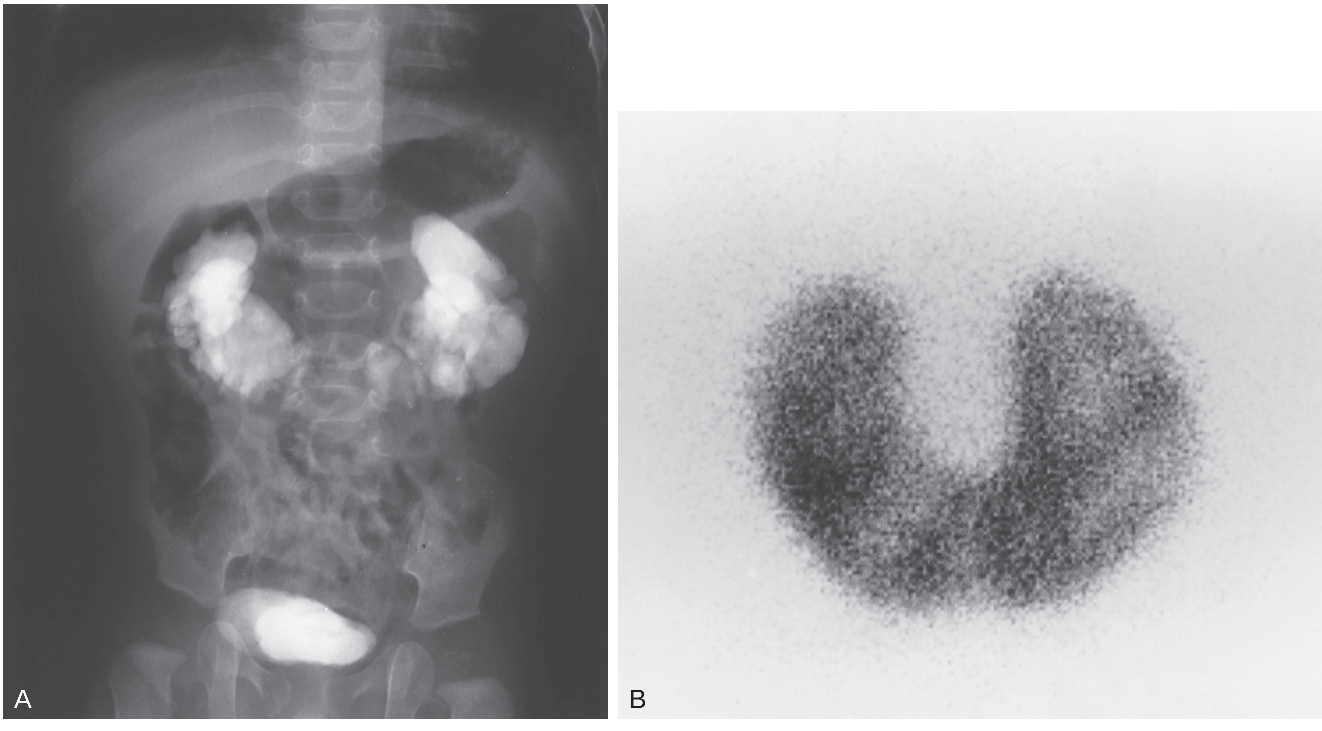



FIGURE 112-6 Horseshoe kidney. **A,** Intravenous urogram. **B,** Dimercaptosuccinic acid [DMSA] scan. (Courtesy Professor I. Gordon, Department of Radiology, Great Ormond Street Hospital, London.)

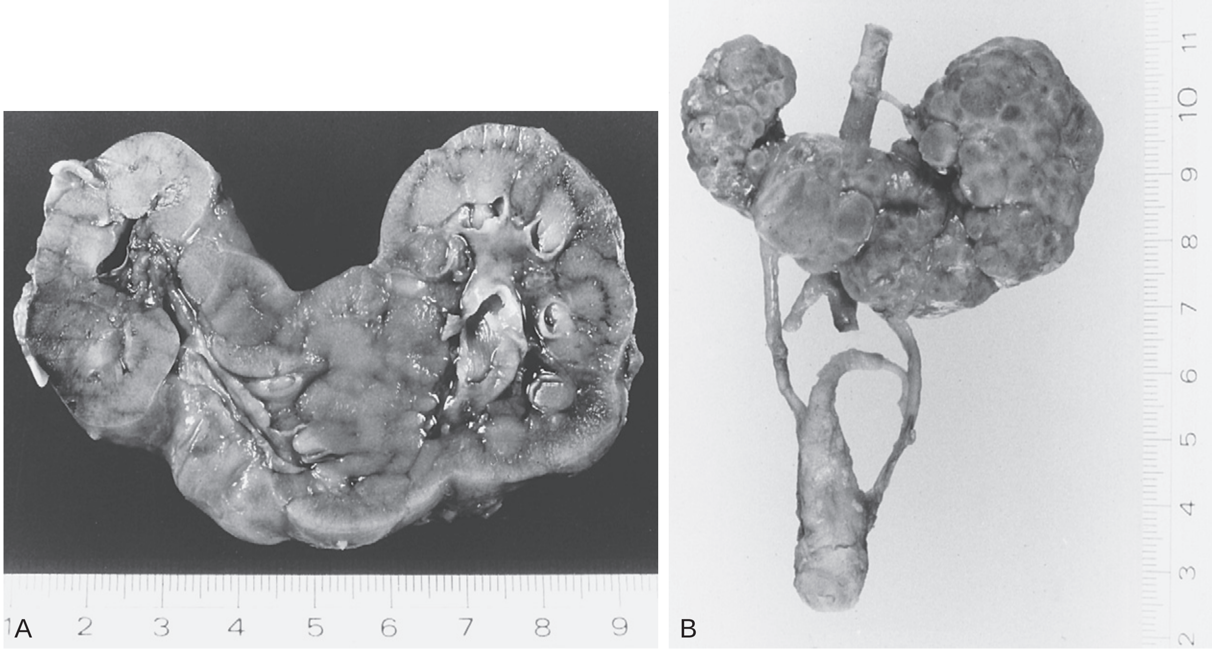



**FIGURE 112-7** **A** and **B,** Horseshoe kidney pathology specimens. (Courtesy Professor A. R. Risdon and Dr. G. Anderson, Department of Histopathology, Great Ormond Street Hospital, London.)

anterolateral extraperitoneal approach is recommended. If the kidney has a more awkward position or if the procedure is bilateral, a transperitoneal approach is preferable. Ureterocalicostomy is an excellent alternative for achieving dependent drainage of the urinary tract.[65] Endopyelotomy is another alternative but is best reserved for older children[66] because the recurrence rate is relatively high. Urolithiasis develops in 20% of patients with a horseshoe kidney[15] and can usually be treated by extracorporeal shock wave lithotripsy or percutaneous surgery. Laparoscopic heminephrectomy for benign disease of a horseshoe kidney is an elegant option for experienced surgeons.[67] Experienced surgeons are required because of the increased incidence of visceral and vascular surgery associated with these anomalies.[61,63]

## CROSSED RENAL ECTOPIA

Crossed renal ectopia (Fig. 112-8, *A* and *B*) is the second most common fusion anomaly after horseshoe kidney.[15] Its incidence is around 1 in 7000 autopsies. There are four varieties of crossed renal ectopia: (1) with renal fusion (85% of cases), (2) without fusion (<10%), (3) solitary, and (4) bilateral.[1,68,69] It has a slight male preponderance, and crossing from left to right occurs more frequently than from right to left. The fusion is usually located between the upper pole of the crossed kidney and the lower pole of the normally positioned kidney (unilateral fused type). The renal pelvises remain in their anterior position with incomplete rotation. In the sigmoid or S-shaped kidney, the fusion is the same but both kidneys have completed their rotation; thus the two renal pelvises face in opposite directions. Various degrees of fusion have also been reported rarely (e.g., lump kidney, L-shaped kidney, and superior ectopic kidney).[15] Pseudo-crossed renal ectopia secondary to ureteropelvic obstruction has likewise been reported.[70] Intravenous urography, isotopic studies, ultrasonography, MRI, and CT allow definition of the anatomic type of ectopia. This process is often difficult, however. The vascular supply varies and may also cross the midline.[71] Most cases of crossed renal ectopia are discovered incidentally and are asymptomatic. When surgery is indicated, laparoscopy may have some targeted indications for crossed fused renal ectopia.[72]

Associated anomalies are common including orthopedic and skeletal abnormalities, imperforate anus, cardiovascular anomalies,[1,73] genital anomalies,[68,74] spina bifida,[86] vesicoureteric reflux, reflux nephropathy,[75] crossed ectopic ureter, multicystic dysplasia,[76] renal tumors,[77,78] incarcerated ureter,[79] retrocaval ureter,[26] and testicular tumor.[80] Renal ectopia may also be a component of more complex syndromes such as vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula and/or esophageal atresia, renal agenesis and dysplasia and limb defects (VACTERL) syndrome[81]; agenesis of the corpus callosum[82,83]; and caudal regression. The complexity of some of these anomalies can explain some of the complications reported such as accidental ureteral ligation during repair of an inguinal hernia in a patient with crossed fused renal ectopia.[84]

*The complete reference list is available online at www.expertconsult.com.*

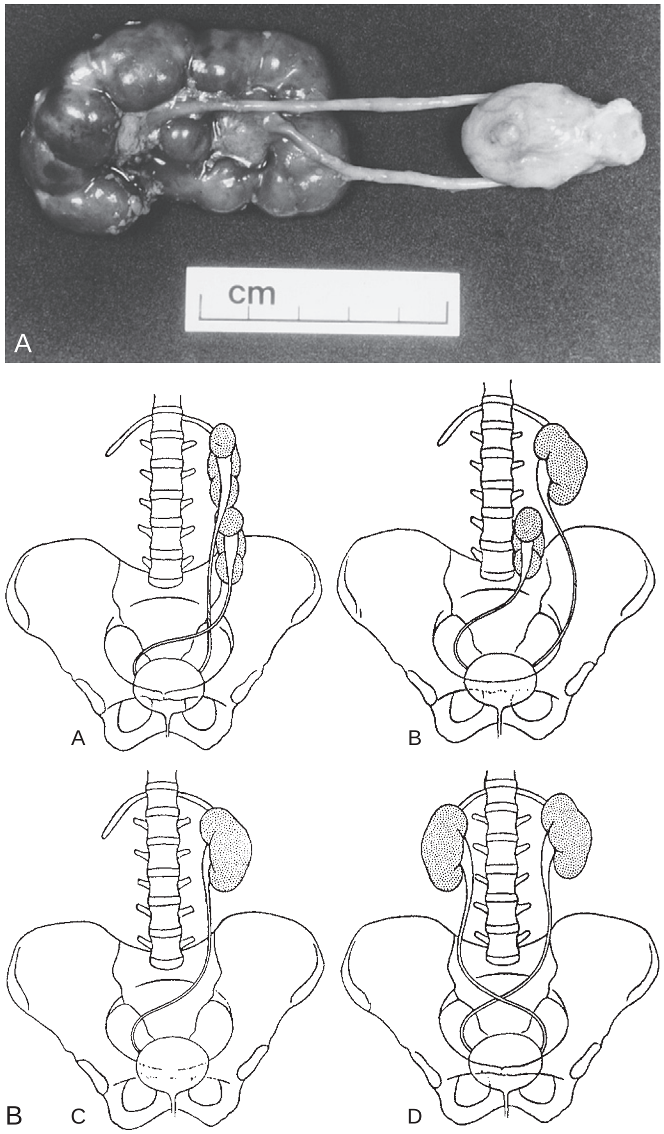



**FIGURE 112-8** **A,** Crossed renal ectopia with renal fusion. (From Professor A. R. Risdon and Dr. G. Anderson, Department of Histopathology, Great Ormond Street Hospital, London.) **B,** The four different types of crossed renal ectopia: with fusion (*A*), without fusion (*B*), solitary (*C*), and bilateral (*D*). (From Ritchey M: Anomalies of the kidney. In Kelalis PP, King LR, Belman AB [eds]: Clinical Pediatric Urology, 3rd ed. Philadelphia, WB Saunders, 1992.)

# CHAPTER 113

# Ureteropelvic Junction Obstruction

Travis W. Groth and Michael E. Mitchell

Hydronephrosis is defined as dilation of the renal collecting system. Clinically, this may result from obstruction or reflux of urine. The physiology of obstruction (hydronephrosis) is complex resulting from interactions between glomerular hemodynamics and alterations in tubular function.[1] In children, hydronephrosis is typically discovered during maternal-fetal ultrasound and accounts for approximately 0.5% to 0.6% of all uropathies seen in the neonatal period. However, one in five neonates with the prenatal diagnosis of hydronephrosis will demonstrate spontaneous resolution of the hydronephrosis.[2] In the neonates with persistent hydronephrosis, ureteropelvic junction (UPJ) obstruction represents 44% of all postnatal causes of hydronephrosis.[3] UPJ obstruction is, therefore, the leading cause of postnatal hydronephrosis.

The natural history of hydronephrosis secondary to UPJ obstruction varies. High-grade UPJ obstruction results in hydrostatic distention, increased intrapelvic pressure, and poor outflow of urine. Chronic increases in intrapelvic pressure can result in irreversible damage to the kidney. However, with low-grade UPJ obstruction, the developing kidney can remain in a homeostatic state and often shows temporal growth and improvement. Between these two extremes there exists a spectrum of pathology—hence the debate regarding the clinical management of kidneys with UPJ obstruction. The inevitable questions remain, “which patient requires surgical intervention, and which can be observed?”

## Etiology/Incidence

The incidence of UPJ obstruction is 1 in 1250 births.[4,5] It occurs more commonly in males (M/F = 2:1). There is a predilection for the left side in children (66%), whereas the reverse is true for UPJ obstruction of adults.[6–8] Bilateral cases of UPJ obstruction occur in 10% to 36% of patients, with the highest percentage occurring in the younger age group.[6,9]

Koff described two types of UPJ obstruction, intrinsic and extrinsic, discovered at the time of surgical exploration (Fig. 113-1).[10] The most common UPJ obstruction is the *intrinsic type*, classically known as the “adynamic” segment. This adynamic segment interferes with the proximal ureteral peristalsis. At surgery, these segments are of variable length and usually narrower than the rest of the ureter. Additionally, these segments are poorly distensible but are typically probe patent. Histologically, they are deficient in circular muscle fibers, which tend to be disorganized and dysmorphic.[11,12]

The second type of UPJ obstruction is the *extrinsic type,* typically related to such mechanical factors as crossing vessels, adhesive bands, arteriovenous malformations, and uretal folds.[13,14] Extrinsic factors create an abrupt angulation by kinking or compressing the UPJ, which leads to obstruction of urine flow and progressive hydronephrosis. Similarly, Östling described pleatlike ureteral folds that occur at the level of the UPJ (Fig. 113-2).[14] Teleologically, these folds are thought to allow the dramatic increase in axial growth that children experience during the first 2 years of life. Östling folds are typically not felt to be obstructive and tend to disappear with patients’ increase in linear growth; however, if persistent, they can result in obstruction.

Aside from the intrinsic and extrinsic types of UPJ obstruction there are *intraluminal* causes of proximal ureteral obstruction, which include ureteral valves and benign fibroepithelial polyps.[15,16] Both lead to partial, intermittent obstruction and typically require surgical intervention (Fig. 113-3).[17]

Another way to characterize types of obstructive processes is by their volume-dependent (extrinsic) and pressure-dependent (intrinsic) characteristics.[10,18] Experimental and clinical observations led Koff to conclude that these parameters, or a combination thereof, may explain the many differences observed in the clinical spectrum of UPJ obstruction.[18]

## Embryology

During human embryogenesis, there are three sequential and interdependent kidney systems: the pronephros, mesonephros, and metanephros or definitive kidney. The earliest and most transient kidney is the pronephros. Sequentially the pronephros is replaced by the mesonephros by the third week of gestation. The mesonephros elongates to form a tubular structure, which eventually forms the caudal end of the mesonephric, or wolffian, duct. At the fifth week of gestation, the

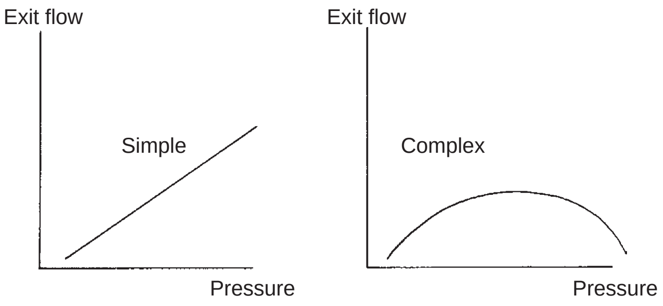



FIGURE 113-1 Diagrammatic representation of simple and complex pressure-flow patterns in human hydronephrosis. (From Koff SA: Pathophysiology of ureteropelvic junction obstruction: Clinical and experimental observations. Urol Clin North Am 1990;17:269.)

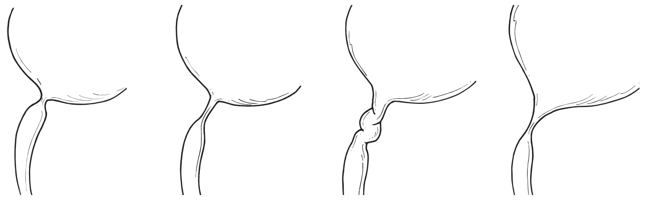


FIGURE 113-3 Ureteropelvic junction obstruction secondary to stenosis: simple, segmented, serpiginous, and shelving. (Courtesy Dr. F. Douglas Stephens.) (From Fung LCT, Lakshmanan Y: Anomalies of the renal collecting system: Ureteropelvic junction obstruction [pyelocalyectasis] and infundibular stenosis. In Belman AB, King LR, Kramer SA [eds]: Clinical Pediatric Urology, 4th ed. London, Martin Dunitz, 2002, p 561.)

dorsomedial wall of this ductal system gives rise to a diverticular outgrowth called the ureteric bud. The "ureteric bud" seems to have an important bidirectional inductive role, which results in differentiation of the mesonephric duct (to form the trigone, posterior bladder neck and proximal urethra) and to initiate the development of the metanephrosis into the kidney. Therefore just as the mesonephric system moves into the bladder to form the trigone, posterior bladder neck, and urethra, the ureteric bud elongates in an ascending fashion toward the primitive metanephric anlagen. On contact, the two structures initiate a cascade of events known collectively as *nephrogenesis*. The ureteric bud ultimately forms the ureter, renal pelvis, and calyceal system.

In this developmental process, mechanical obstruction may occur at three different anatomic sites: the pelvocaliceal, ureteropelvic, and ureterovesical junctions.[19] Each of these sites represents a confluence of two or more embryologic structures (i.e., ureter and bladder and ureter and kidney). The cellular and molecular mechanisms are incompletely understood at this time; however, complex cellular "crosstalk" and induction initiated in a bidirectional manner normally

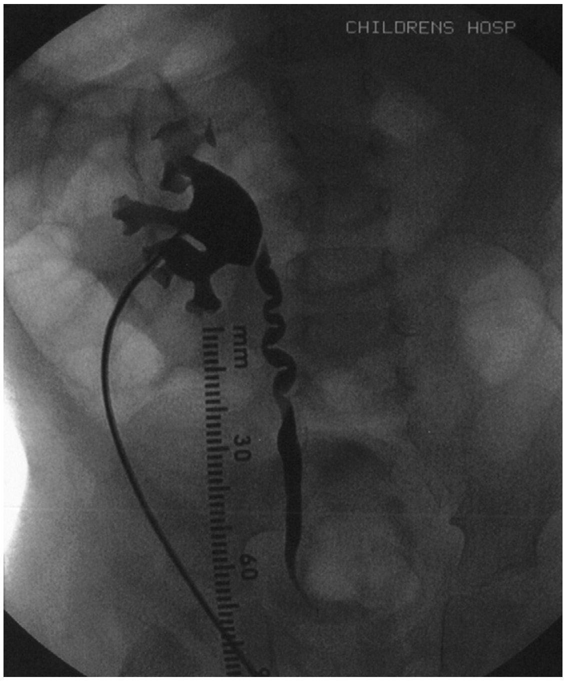



FIGURE 113-2 Percutaneous nephrostogram demonstrating Östling's fetal folds. (Courtesy Children's Hospital and Regional Medical Center, Seattle.)

culminate in appropriate anatomic junctions. However, minor imprecision because of the inherent variables of the process can result in two of the more common pathologic conditions in pediatric urology, namely, vesicoureteral reflux (VUR) and UPJ obstruction.

At one time it was thought that bidirectional recanalization of the ureter explained the frequent obstruction at the last segments to recanalize the UPJ and ureterovesical junction (UVJ).[20] More recently, however, it has been shown that bidirectional recanalization does not occur. Recanalization occurs only at the middle portion of the ureter.[21] None of the current experimental models or theories of ureteral development explain why the UPJ is the most common site of congenital ureteral obstruction. This continues to be an active area of research. For example, a new study using an animal model of obstructive nephropathy has reported a possible genetic component of hydronephrosis.[22] Chang and colleagues[22] describe a mouse model in which the gene encoding the calcineurin B type 1 isoform (Cnb1) has been deleted from the mesenchyme lining the urinary system. Hydronephrosis develops in these animals because of the lack of peristalsis. This study not only points to the renal pelvis as a regulator of peristalsis but may also explain congenital obstruction in which no obvious physical obstruction is identified.

Recently, Wang and colleagues[23] examined the role of bone morphogenic protein 4 (BMP4) signaling by examining a BMP4 murine knock-out mouse model. Antagonism of BMP signaling with Nogin protein inhibited ureteral smooth muscle formation around the ureter and localized antagonism of BMP signaling demonstrated similar histologic findings as intrinsic UPJ obstruction from an adynamic segment.[23] Even though these data support a molecular cause for UPJ obstruction, there has yet to be one molecular theory explaining how and why different UPJ obstructions form.

## Clinical Features

UPJ obstruction can affect infants, adolescents, or adults. The presentation of each differs. Typically, infants are asymptomatic and are now diagnosed by prenatal ultrasonography. Thirty years ago, however, most infants with UPJ obstruction were initially diagnosed with a palpable abdominal mass at initial evaluation or, less often, on workup for urinary tract infection, failure to thrive, feeding difficulties, and nephrolithiasis.[7] With the advent of prenatal fetal ultrasonography, most infants born with UPJ obstruction are detected antenatally. The other population in which UPJ obstruction is detected

consists of children with a variety of symptoms. Accordingly, there seems to be a bimodal age distribution of UPJ obstruction: asymptomatic postnatal infants and symptomatic school-aged children.

## ANTENATAL MANIFESTATIONS

At the eighth week of intrauterine life, fetal urine is produced by the mesonephros. Once this transient kidney regresses, urine is made by the metanephros and continues to be made throughout gestation. Fetal urine production increases from 5 mL/hr at 20 weeks gestation to a rate that may approach 50 mL/hr at 40 weeks of gestation.[24] Thus maternal-fetal sonography should initially be performed between 16 and 20 weeks of gestation when adequate urine production has been established.[25] Most centers performing maternal-fetal ultrasound can detect normal kidneys at 17 to 19 weeks, whereas markedly dilated collecting systems can be identified as early as 12 to 14 weeks.[26]

The first report of antenatally detected urinary tract anomalies was in 1970.[27] Since that time, the American Institute for Ultrasound in Medicine's Bioeffects Committee has concluded that prenatal ultrasound screening is safe. This endorsement has led to the common practice by obstetricians, as well as the expectation by the general population, that screening ultrasound be performed during the second trimester. Despite the fact that protocols for maternal-fetal ultrasonography continue to evolve in this country, they still depend in part on specific conventions and random institutional idiosyncrasies.[4]

Prenatal ultrasound can detect hydronephrosis and abnormal anatomy, but it is not specific for the diagnosis of particular disease processes. Sonographic features suggestive of UPJ obstruction include (1) unilateral or, less frequently, bilateral pelviectasis; (2) normal amniotic fluid volume; (3) no evidence of ipsilateral ureteral dilation; and (4) normal thickness of the bladder wall and normal cycling of the bladder. In cases in which the classic features of hydronephrosis are established, the diagnosis of UPJ is straightforward. Differentiation between true obstructive uropathy and transient hydronephrosis of the neonate is not possible. Additionally, prenatal ultrasound cannot distinguish between UPJ obstruction and multicystic dysplastic kidney (MCDK). Sequential renal ultrasound and other complementary radiographic imaging studies may be required for follow-up.

The Society of Fetal Urology (SFU) organized consensus guidelines for grading different degrees of hydronephrosis (Table 113-1) (Fig. 113-4A to D).[28,29] Once these in utero criteria are established, a prenatal diagnosis of hydronephrosis with a possibility of UPJ obstruction should be entertained by the physician and reported to the parents. In

**TABLE 113-1**
**Society of Fetal Urology (SFU) Grading of Hydronephrosis**

| *SFU Grade* | *Description* |
|---|---|
| 1 | Slight splitting of the central renal complex without calyceal involvement, normal parenchyma |
| 2 | Splitting of the central renal complex with extension to nondilated calyces |
| 3 | Wide splitting of the renal pelvis, dilated outside the renal border, calyces uniformly dilated, normal parenchyma |
| 4 | Large, dilated calyces (may appear convex); thinning of the parenchyma to ≤50% of the ipsilateral (normal) kidney |

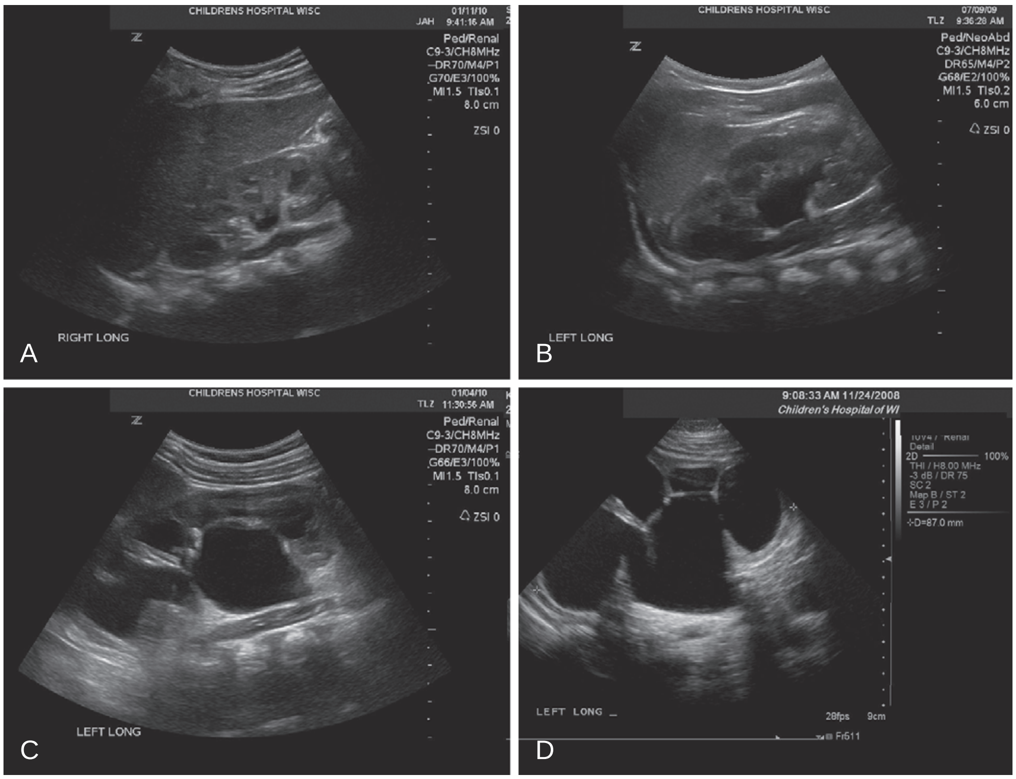



**FIGURE 113-4** Renal ultrasound scans representing the Society for Fetal Urology (SFU) grading schema. **A,** SFU grade 1 hydronephrosis. **B,** SFU grade 2 hydronephrosis. **C,** SFU grade 3 hydronephrosis. **D,** SFU grade 4 hydronephrosis. (Courtesy Children's Hospital of Wisconsin, Milwaukee.)

male fetuses, however, bilateral hydronephrosis should be considered to be a different and more urgent problem relating to bladder outlet obstruction, possibly caused by posterior urethral valves.

### PRENATAL COUNSELING

Parents should be advised of a presumptive diagnosis of hydronephrosis and counseled appropriately. Education and communication are paramount in the process of prenatal counseling. Fortunately, the majority of antenatally detected genitourinary abnormalities are unlikely to require postnatal surgical intervention.[30,31] In fact, only 1% to 25% require surgery at 4 years of follow-up.[32,33] However, referral to a pediatric urologist for prenatal counseling is highly recommended. The survival rate for fetuses found to have unilateral hydronephrosis secondary to obstruction is virtually 100%. Postnatal follow-up is essential to track progression or resolution of hydronephrosis, as well as establish the management principles with the family. For this reason, referral to a pediatric urologist is highly recommended.

### POSTNATAL MANIFESTATIONS

Although often asymptomatic, children with UPJ obstruction may have variable symptoms such as episodic flank, abdominal pain, or less commonly a urinary tract infection. Cyclic abdominal pain, often associated with vomiting, is a classic finding (Dietl crisis*) usually observed in older patients. UPJ obstruction can also be an unsuspected diagnosis made after evaluation for vague and often chronic abdominal symptoms, frequently referred from the pediatric gastroenterologist after an ultrasound had been performed. UPJ obstruction may be associated with renal calculi with an incidence of nephrolithiasis 17 times higher in patients with UPJ obstruction.[34] Hematuria may also be the initial symptom in UPJ obstruction. Trivial trauma can cause friable mucosal vessels in the dilated collecting system to rupture. Left-sided UPJ obstruction can be associated with the insidious manifestation of anorexia and failure to thrive. These children are typically found to have a left UPJ obstruction. The dilated left renal pelvis creates a mass effect on the stomach that results in early satiety, anorexia, and vomiting. Still other children with UPJ obstruction may have profound urosepsis. Snyder and colleagues[6] reported that urinary tract infection is the initial sign in 30% of children with UPJ obstruction beyond the neonatal period (Table 113-2).

**TABLE 113-2**
**Symptoms of Ureteropelvic Junction Obstruction in Children**

| |
|---|
| Episodic flank pain |
| Episodic abdominal pain ± vomiting |
| Cyclic vomiting |
| Urinary tract infections |
| Nephrolithiasis |
| Hematuria |
| Anorexia |
| Asymptomatic |

## Diagnosis

Because hydronephrosis can be caused by multiple etiologies, it is helpful to try and categorize hydronephrosis into obstructive versus nonobstructive causes. Obstructive causes of hydronephrosis include UPJ obstruction (44% incidence); UVJ obstruction (21% incidence); MCDK, ureterocele, and duplicated collecting systems (12% incidence); posterior urethral valves (9% incidence); and ectopic ureter, urethral atresia, sacrococcygeal teratoma, and hydrometrocolpos. Nonobstructive causes of hydronephrosis include VUR (14% incidence), physiologic dilation, prune-belly syndrome, renal cystic diseases, and megacalicosis (Table 113-3).[35,36]

Although it is easy to diagnose hydronephrosis, it is, unfortunately, difficult to prove obstruction. Furthermore, there has yet to be one diagnostic method that has been able to differentiate significant obstruction from insignificant obstruction in an infant. None of the existing imaging modalities can accurately predict which hydronephrotic kidney is at risk for progressive damage and loss of renal function. With this limitation in mind, sequential radiographic studies can be used to define change that may indicate physiologically significant UPJ obstruction that might require surgical intervention.

### INTRAVENOUS UROGRAPHY

Historically, intravenous urography (IVU) was the radiographic modality of choice for noninvasive assessment of the urinary tract. As an imaging study, it combines anatomic accuracy with qualitative information regarding renal function and obstruction. IVU is now infrequently used in the assessment of a pediatric patient with obstructive uropathy and has been replaced by sonography and scintigraphy. Obstruction, on IVU, of the kidney may be inferred from delay in the appearance of contrast material or a negative nephrogram, a delay in drainage, dilution of contrast medium, or uniform cortical loss.

**TABLE 113-3**
**Differential Diagnosis of Hydronephrosis**

| *Obstructive* | *Nonobstructive* |
|---|---|
| Ureteropelvic junction obstruction | Vesicoureteral reflux |
| Ureterovesical junction obstruction | Physiologic dilatation |
| Multicystic dysplastic kidney | Prune-belly syndrome |
| Ureterocele | Renal cystic diseases |
| Duplicated collecting system | Megacalycosis |
| Posterior urethral valves | |
| Ectopic ureter | |
| Urethral atresia | |
| Sacrococcygeal teratoma | |
| Hydrometrocolpos | |

*Jozef Dietl (1804-1878), a Polish physician, described a syndrome characterized by violent paroxysms of colicky flank pain, nausea, chills, tachycardia, oliguria, transient hematuria or proteinuria, and a palpable enlarged tender kidney that was attributed to acute hydronephrosis caused by kinking or vascular obstruction of the ureter of a floating kidney.

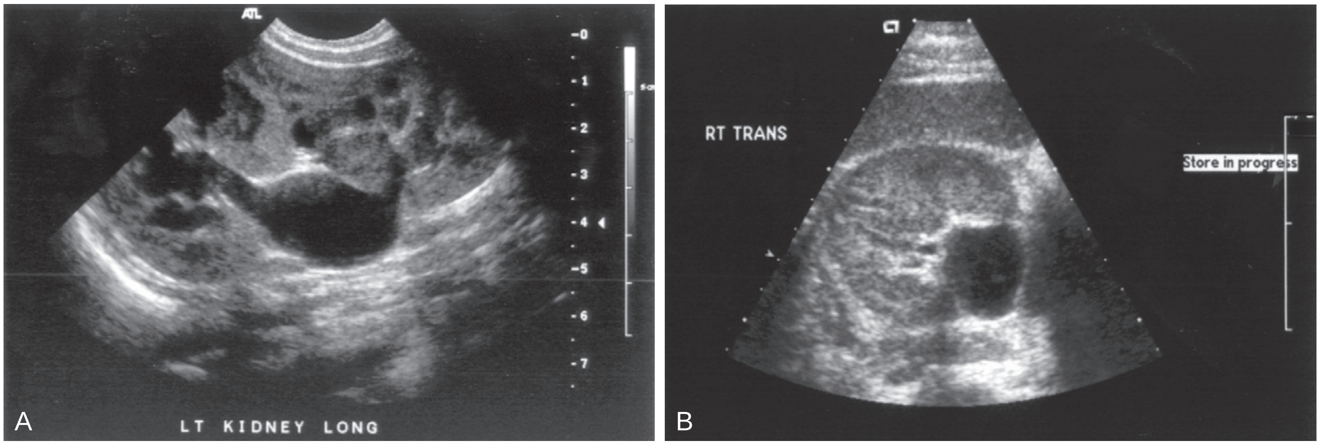



**FIGURE 113-5** **A,** Renal ultrasound representing an obstructed ureteropelvic junction with an intrarenal pelvis. **B,** Renal ultrasound of a nonobstructed extrarenal pelvis. (Courtesy Children's Hospital and Regional Medical Center, Seattle.)

## RENAL ULTRASOUND

Renal ultrasound is a widely available, relatively inexpensive, noninvasive, safe test that provides adequate anatomic visualization without radiation exposure. Given these exceptional qualities, it is widely used both in maternal-fetal sonography and for postnatal imaging. Consequently, renal sonography has resulted in the increased diagnosis of prenatal and postnatal dilation of the upper urinary tract. In fact, renal ultrasound is the most commonly performed initial study for the postnatal evaluation of neonates who have been discovered prenatally to have hydronephrosis. Renal ultrasound is highly accurate in the diagnosis of hydronephrosis. It provides information on findings characteristic of UPJ obstruction including pelviectasis and caliectasis, absence of ureterectasis, normal bladder filling and emptying (cycling), and normal bladder thickness. In unilateral cases of hydronephrosis, ultrasound may delineate parenchymal atrophy on the affected side in comparison with the contralateral side.

Twenty-five years ago, the general consensus among pediatric urologists had been that the amount of hydronephrosis did not correlate with the degree of obstruction. Ransley and colleagues[33] finally established this fact. In their study, progressive hydronephrosis and deterioration in renal function were uncommon in neonates and infants with a maximum anteroposterior renal pelvic diameter of less than 10 mm and no evidence of infundibular or caliceal dilation (SFU grade 1 hydronephrosis). All the patients initially in the nonoperative group who eventually required surgery had a prenatal anteroposterior renal pelvic diameter of greater than 12 mm. However, renal pelvic diameter, alone, was found to be a poor positive predictor of outcome because only 34% of such patients required pyeloplasty. In some of these patients, perhaps, such mild degrees of hydronephrosis are probably physiologic, secondary to the highly compliant nature of the fetal (and neonatal) renal pelvis. An extrarenal pelvis or lucent pyramids of infancy can be mistaken for pathologic hydronephrosis (Fig. 113-5A and B, Fig. 113-6); however, caliceal dilatation is typically *not* present in these patients. An extrarenal pelvis, therefore, is considered to be a variation of normal.

Koff and colleagues[37] proposed the use of serial renal ultrasound to predict progression in unilateral cases of UPJ obstruction. In addition to being able to monitor the temporal behavior of UPJ obstruction, serial renal ultrasound provides


**FIGURE 113-6** Renal ultrasound of normal infant kidney with lucent pyramids, which can be confused with calyceal dilation. (Courtesy Children's Hospital of Wisconsin, Milwaukee.)

the ability to track the axial growth of the kidneys as an indicator of progression of UPJ obstruction. In cases of unilateral UPJ obstruction, the growth rate of the contralateral normal kidney can be used as a comparison standard.[38] With the use of renal growth–function nomograms, compensatory hypertrophy in the contralateral "normal" kidney may be indicative of progressive obstruction in the hydronephrotic kidney. Conversely, a slower than normal growth rate (compensatory hypertrophy) in the normal kidney suggests rapid recovery of function (or even supranormal function) in the unilaterally hydronephrotic kidney and would imply that obstruction is not present. Koff's data, however, have not been corroborated because of operator variability in renal length measurements.

Serial ultrasound studies are important for implementing any protocol for UPJ obstruction, but they can be problematic because they require a waiting period during which progressive renal injury can occur. For example, cortical thinning, an important finding, may develop but is typically a late irreversible finding. Focal cortical loss is easier to detect, though less common than global cortical thinning. Reflecting on Koff and colleagues' study, it is logical to conclude that in patients with unilateral hydronephrosis, contralateral compensatory renal

hypertrophy may indicate a greater risk for continued deterioration of the hydronephrotic kidney.[37] However, reliable sonographic diagnosis of renal hypertrophy requires multiple sequential measurements of renal length or volume, thus limiting its applicability for guiding early intervention.[39]

In summary, renal ultrasound is highly accurate in the diagnosis of hydronephrosis but cannot diagnose obstruction. The degree of hydronephrosis neither specifically indicates the presence or absence of obstruction nor predicts whether the hydronephrosis will improve or progress.[40] A case in point is the neonate, in whom hydronephrosis (by ultrasound) may be transient and is dependent on the degree of hydration and bladder fullness. Most limiting is the fact that ultrasound cannot provide information regarding renal function.

## TECHNETIUM 99m RENAL SCINTIGRAPHY

Differential renal function is one of the most important parameters used in defining significant obstruction and defining the need for surgical correction of congenital UPJ obstruction. It is the present study of choice for estimation of overall and differential renal function. Three radiopharmaceuticals are primarily used in renal scintigraphy, and their characteristics are linked to their biologic activity. Technetium 99m-diethylenetriaminepentaacetic acid ($^{99m}$Tc-DTPA) and technetium 99m-mercaptoacetyltriglycine ($^{99m}$Tc-MAG-3) are preferentially concentrated by the kidney and freely filtered by the glomerulus.[41] **DTPA is neither secreted nor resorbed by the renal tubules, whereas MAG-3 is secreted by the tubules.** Because each is nearly completely excreted, they can be used to estimate differential renal function and urinary drainage. The third agent, technetium 99m-dimercaptosuccinic acid **($^{99m}$Tc-DMSA), is tightly bound to renal tubular cells and is, therefore, useful for the detection of differential renal function and clinically significant cortical lesions such as renal scars.**

At least three consensus statements have been published to decrease the wide clinical variance in protocols: (1) the Society of Nuclear Medicine's Nuclear Medicine *Procedure Guidelines for Pediatric Diuretic Renography,* (2) the *Well Tempered Diuretic Renogram,* and (3) the consensus statement from the Ninth International Meeting of the Society of Radionuclides in Nephrourology, Committee on Diuretic Renography.[42–44] They are all similar in methodology and interpretation. Basically, a collecting system without significant obstruction will have a clearance half-time (i.e., the time for half the radiopharmaceutical to clear) after furosemide administration of less than 10 minutes. Longer than 20 minutes is abnormal and associated with significant obstruction. Clearance half-times between 10 and 20 minutes are considered indeterminate. The half-time should not be the only criterion on which to define obstruction. As in most studies, interpretation requires the use of other available data: curve analysis, differential renal function, and, of course, the clinical context (Fig. 113-7).

Currently, renal scintigraphy is the most popular modality for determining the functional significance of UPJ obstruction, mainly because several investigators have shown that most cases of severe hydronephrosis (SFU grades 3 to 4) demonstrate obstruction on diuretic renography.[28,45] As a result of these studies, the differential renal function of a hydronephrotic kidney, as determined by $^{99m}$Tc-DTPA or $^{99m}$Tc-MAG-3 renal scan, creates an arbitrary threshold for surgical intervention.[46] Thirty-five percent is the pivotal function around which intervention or observation is determined. If the initial ipsilateral differential renal function is greater than

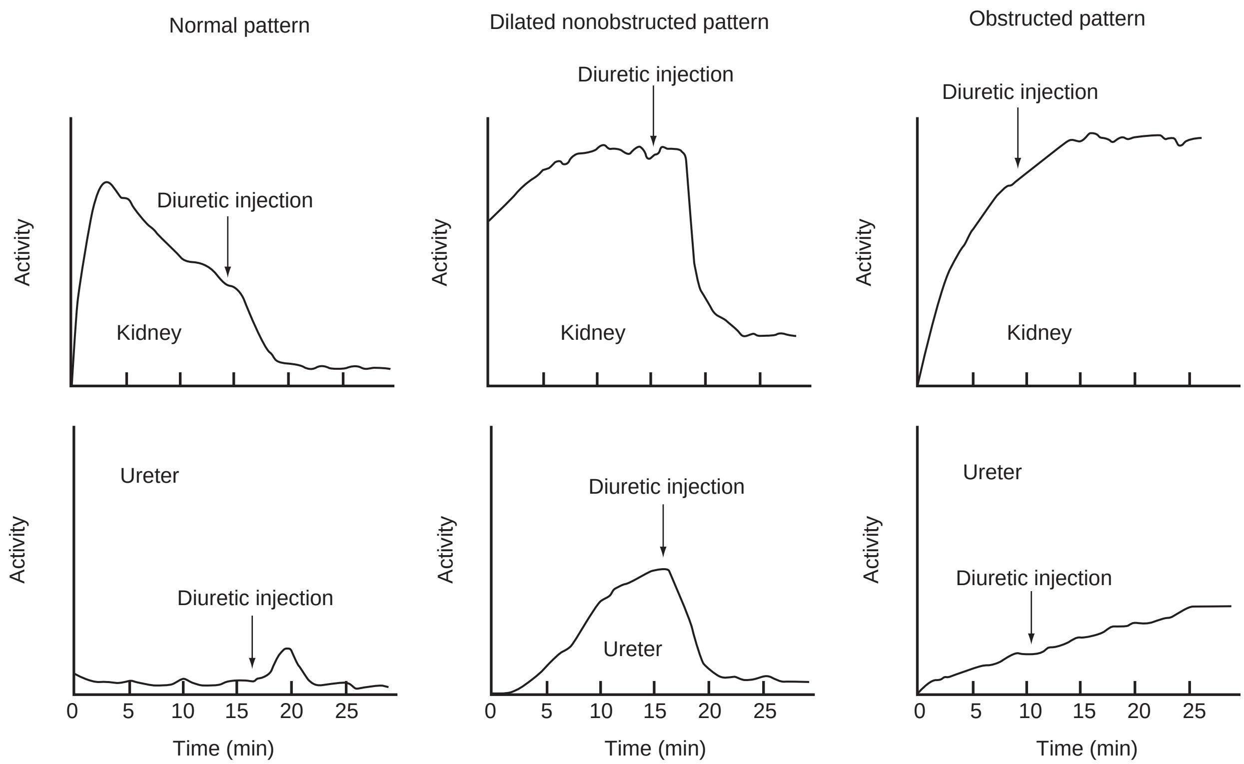



FIGURE 113-7 Lasix renography, classic patterns: normal, dilated nonobstructed, and obstructed. (From Fung LCT, Lakshmanan Y: Anomalies of the renal collecting system: Ureteropelvic junction obstruction [pyelocalyectasis] and infundibular stenosis. In Belman AB, King LR, Kramer SA [eds]: Clinical Pediatric Urology, 4th ed. London, Martin Dunitz, 2002, p 594.)

35%, the neonate may be monitored conservatively by renal ultrasound every 3 months. In contrast, if the differential renal function is less than 35% on the initial study or if there is a decremental change in function of 10% by repeat renal scan, consideration should be given to surgical intervention.[47]

Renal scintigraphy is the study of choice for the estimation of overall and differential renal function, except in patients with poor or immature renal function and those with capacious collecting systems. Other determinates that affect renal scintigraphy include the region of interest, time of measurement, state of hydration, bladder fullness, reservoir effect, type of protocol, renal response to furosemide, and the concept of supranormal function (Fig. 113-8).[42,43,48–51] Supranormal function is defined as greater than 55% of differential renal function in the hydronephrotic kidney in children with unilateral hydronephrosis. It has not been confirmed whether supranormal differential renal function is an artifact or a true finding, nor is there a consensus on how to manage these patients (Fig. 113-9). Oh and colleagues[83] examined supranormal function in human subjects and determined that supranormal function of the ipsilaterally obstructed kidney may not be true hyperfunction but merely a pathologic compensatory mechanism in response to chronic obstruction. For this reason, they warned that interpretation of differential renal function should be made with this caveat in mind. Khan and colleagues[52] believe that supranormal function is an artifact that can be avoided by using MAG-3 and appropriate computer software to account for multiple algorithms.

## VOIDING CYSTOURETHROGRAPHY

It is well known that VUR, the most common problem of the lower urinary tract in children, can coexist with UPJ obstruction, the most common pediatric problem of the upper urinary tract.[53] The exact reason for this association has not yet been established.[54] However, what is known is that approximately 9% to 14% of patients with UPJ obstruction have VUR. Historically, voiding cystourethrography (VCUG) is the standard of practice for the clinical evaluation of all infants with prenatal hydronephrosis, regardless of age or gender.[55,56]

However, several investigators have challenged this standard.[57] In a retrospective review of 106 patients who underwent pyeloplasty for UPJ obstruction, low-grade reflux coexisting with UPJ obstruction spontaneously resolved after pyeloplasty. Additionally, they found that all cases of high-grade VUR coexisting with UPJ obstruction were easily detected by renal ultrasonography. They concluded that VCUG should be limited to children with UPJ obstruction who also have a dilated ureter on ultrasonography. However, patients with a history of febrile UTI and hydronephrosis all should undergo VCUG regardless of dilatated ureter on ultrasonography. Caution should be practiced when evaluating children with this diagnostic dilemma because the approach to management is subtle yet complex.

## MAGNETIC RESONANCE UROGRAPHY

Most recently, dynamic, gadolinium-enhanced magnetic resonance urography (Gd-MRU) has been advocated for its nonionizing radiation and its unparalleled, three-dimensional views of anatomic obstruction. Wen and colleagues[58] used Gd-DTPA-enhanced magnetic resonance imaging in rats and determined that it could distinguish between an obstructed and nonobstructed collecting system. Using a similar technique, Kirsch recently reviewed a cohort of 200 children with hydronephrosis who underwent systematic evaluation

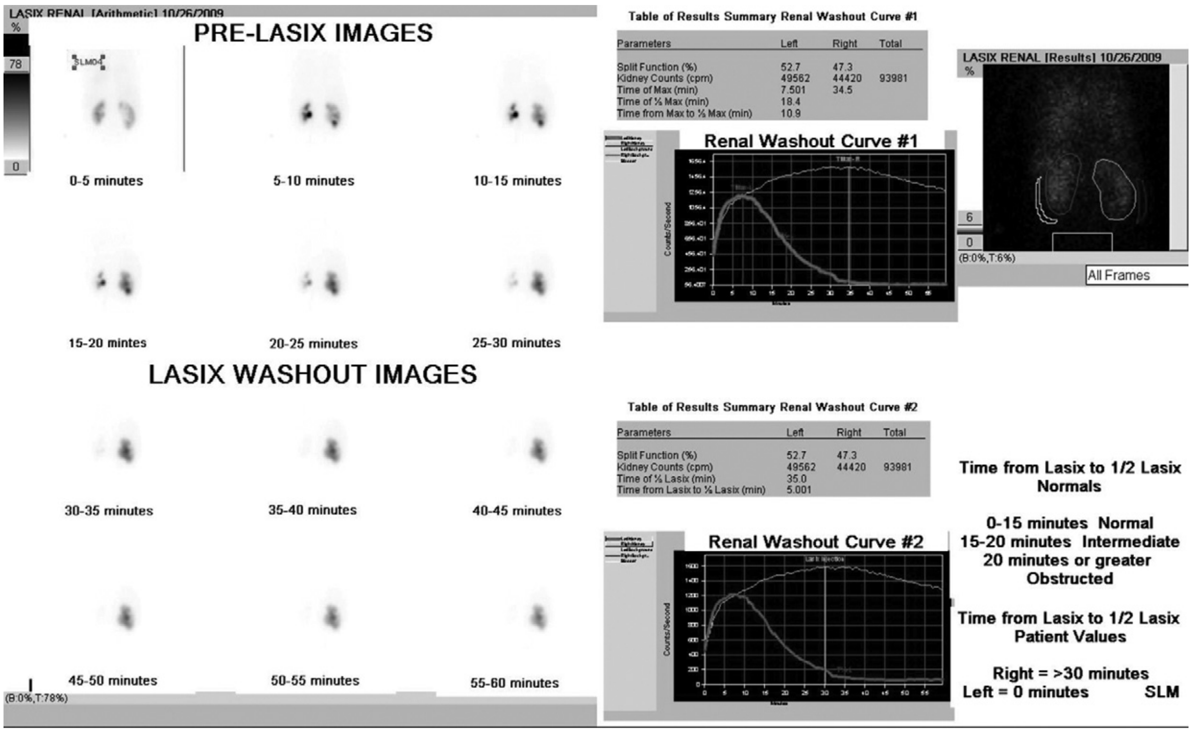



**FIGURE 113-8** MAG-3 lasix renal scintigraphy of a patient with ureteropelvic junction obstruction with delayed washout pattern and excretion of contrast with preserved renal function on the right side. (Courtesy Children's Hospital of Wisconsin, Milwaukee.)

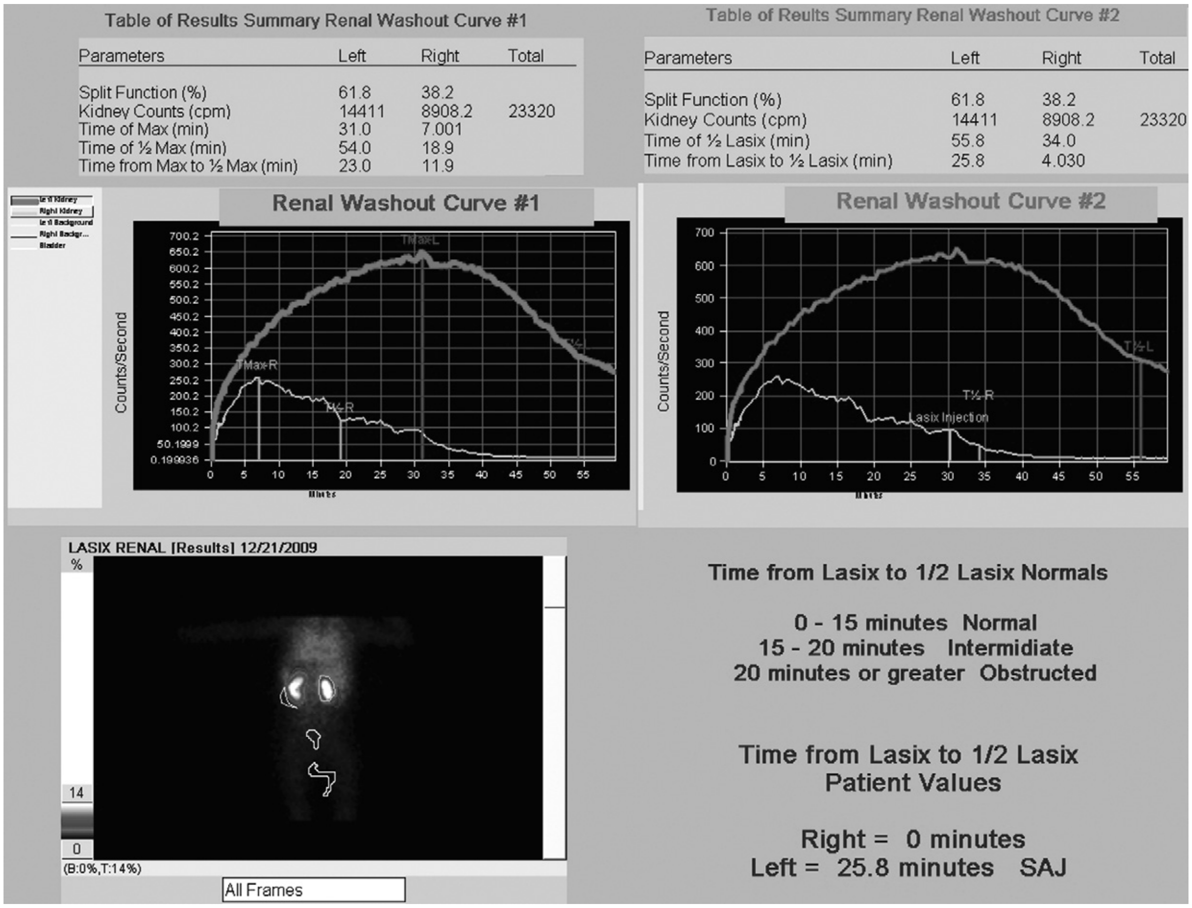



**FIGURE 113-9** MAG-3 lasix renal scintigraphy: Supranormal renal function of a 6-month-old baby who had the SFU grade 3 hydronephrosis, found postnatally to have high-grade left ureteropelvic junction obstruction. (Courtesy Children's Hospital of Wisconsin, Milwaukee.)

**FIGURE 113-10** Three-dimensional maximal intensity projection reconstruction after Gd-DTPA infusion showing classic left ureteropelvic junction obstruction. (From Perez-Brayfield MR, Kirsch AJ, Jones RA, Grattan-Smith JD: A prospective study comparing ultrasound, nuclear scintigraphy and dynamic contrast-enhanced magnetic resonance imaging in the evaluation of hydronephrosis. J Urol 2003;170:1331.)

with Gd-MRU.[59] When compared with sonography and renal scintigraphy, Gd-MRU provided superior anatomic images of the genitourinary system and excellent spatial resolution (Fig. 113-10). The study has been shown to be robust and reproducible with a linear regression coefficient of 0.99. The limitations of the study are that it requires general anesthesia or sedation and involves cumbersome interpretation of the images.[60] Although the technique is not yet widely available, MRU has been considered by some investigators to be a more reliable determinant of renal anatomy and function in cases of UPJ obstruction.

## RETROGRADE PYELOGRAPHY

This radiographic study is rarely necessary to diagnose UPJ obstruction. In a series of 108 children undergoing pyeloplasty, retrograde pyelography (RPG) did not change the surgical approach or planned procedure in any of the cases.[61] However, RPG is still commonly performed before open pyeloplasty. The reason for this is simple. During the diagnostic process, information regarding the exact anatomic location of the UPJ in relation to other anatomic structures is lacking. Therefore to precisely identify the location of obstruction and perhaps exclude the presence of another distal obstruction, RPG is performed (Figs. 113-11 and 113-12).[62]

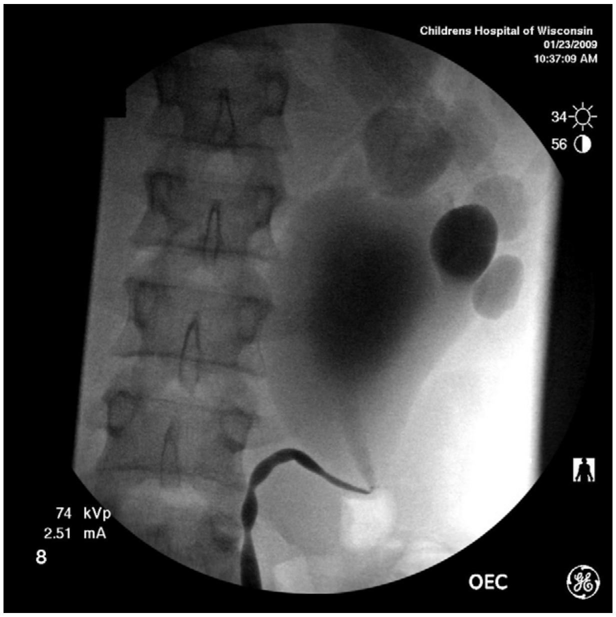



**FIGURE 113-11** Left retrograde pyelogram demonstrating left ureteropelvic junction obstruction. Note the dilation of renal pelvis and small jet of contrast at the ureteropelvic junction. (Courtesy Children's Hospital of Wisconsin, Milwaukee.)

## PRESSURE-FLOW STUDY

The perfusion provocation study, introduced by Bäcklund and colleagues[63] in 1965 and popularized by Whitaker in 1973, is the standard pressure-flow study and is simply referred to as the *Whitaker test* (Fig. 113-13).[64] It detects the resistance of the ureter to a known flow rate by simultaneously measuring manometric pressure between the renal pelvis and bladder. The test is unaffected by the kidney's GRF, and its antegrade pyelography offers excellent anatomic location of the suspected obstructing segment. The study is most useful when

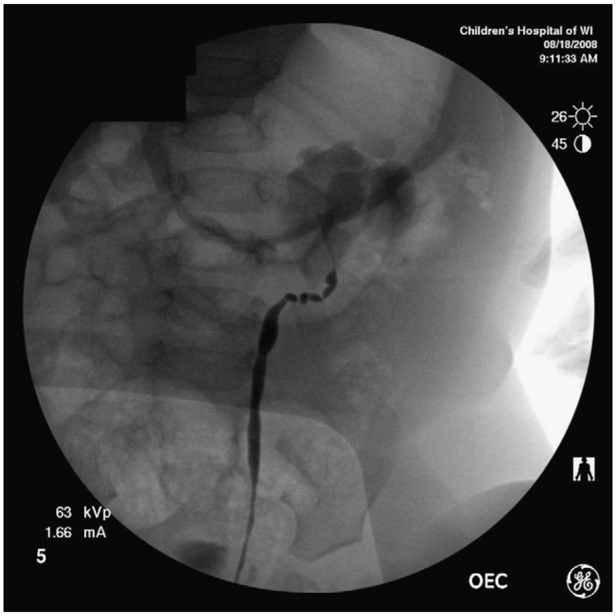



**FIGURE 113-12** Left retrograde pyelogram demonstrating left ureteropelvic junction obstruction along with infantile appearing proximal ureter. (Courtesy Children's Hospital of Wisconsin, Milwaukee.)

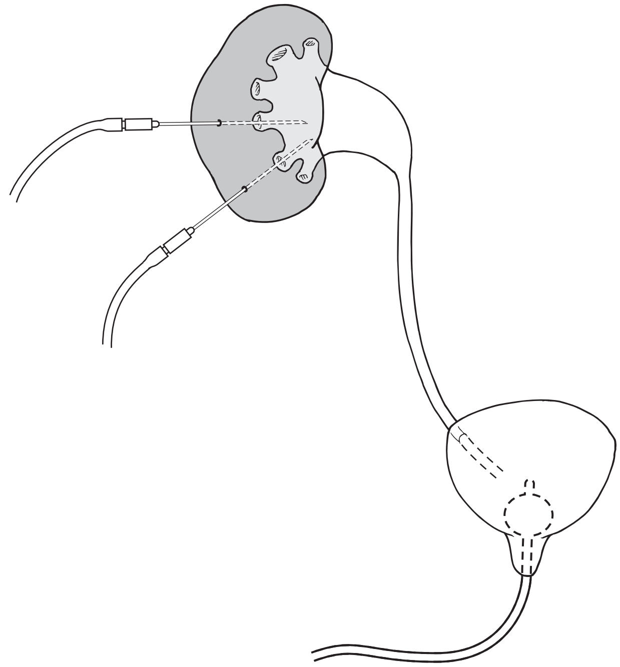


**FIGURE 113-13** Whitaker pressure perfusion study. (From Fung LCT, Lakshmanan Y: Anomalies of the renal collecting system: Ureteropelvic junction obstruction [pyelocalyectasis] and infundibular stenosis. In Belman AB, King LR, Kramer SA [eds]: Clinical Pediatric Urology, 4th ed. London, Martin Dunitz, 2002, p 596.)

there are equivocal studies regarding obstruction in a hydronephrotic kidney. High renal pelvic pressure relative to bladder pressure at a given flow rate confirms the presence of obstruction. According to this test at a flow rate of 10 mL/min, a differential pressure between the renal pelvis and the urinary bladder of less than 13 cm $H_2O$ is considered to be normal. Arbitrary values of 14 to 20 cm $H_2O$ indicate mild obstruction; values in excess of 35 cm $H_2O$ indicate severe obstruction. The Whitaker test requires percutaneous access to the kidney and usually requires general anesthesia in the pediatric population. Consequently, it is undesirable for a routine test. It is typically indicated for equivocal cases of obstruction and is, therefore, rarely performed. In addition, the Whitaker test requires a rigid protocol and exacting measurements to avoid technical errors. The most common error is failure to achieve an equilibrium (what goes in comes out). A physiologic pressure/flow test would be the ideal means of diagnosing "obstruction," but unfortunately one test does not presently exist.

## BIOCHEMICAL MARKERS

A biomarker is something that can be used as an indicator of a disease. Researchers have used proteomics, which is defined as the characterization of protein content within tissue, cells, or fluid, to try to find new biomarkers. It has been well established that ureteral obstruction results in renal injury on a cellular level.[65] Studies have led investigators to surmise that there might be potential biochemical markers detected in the urine that may be predictive of significant postnatal renal injury in patients with elevated hydronephrosis.[66] Prospective markers include urinary sodium, calcium, and $\beta_2$-microglobulin, or appropriate urinary proteins (proteomics) unique to obstruction.

Clearly, it has been demonstrated that persistently elevated collecting system pressure induces renal abnormalities including an increase in tubular pressure, decrease in renal blood flow, decrease in GFR, and renal tubular dysfunction.[67,68]

Recently, there have been several potential biomarkers that have been shown to be increased in the urine of children with UPJ obstruction. These include transforming growth factor β1 (TGF-β1), monocyte chemotactic protein 1 (MCP-1), and endothelin-1.[69–73] Also, urinary epidermal growth factor (EGF) was shown to decrease during obstruction.[72] Fung and Atala, using a nonobstructed porcine model in which urine drained against a predetermined pressure gradient, demonstrated a progressively elevated level of urinary N-acetyl-β-D-glucosaminidase, an indicator of acute renal cell injury.[74] There has yet to be any prospective studies or clinical studies that demonstrate if these biomarkers will be of clinical value. At present, however, because of the lack of standard biochemical or physiologic markers to measure renal obstruction, serial radiographic studies are necessary to evaluate the function and anatomy of a kidney with suspected UPJ obstruction. Proteomics has great potential to help discover new biomarkers that could in theory dramatically change how patients with hydronephrosis are followed and treated. It may be that the profile of a marker of different urinary proteins will reveal a reproducible and dependable measure of ongoing renal injury related to obstruction. Because these markers require vigorous clinical validation, which has been limited to date, and need to be reproducible, their future role in management remains undetermined.

### PREOPERATIVE VASCULAR IMAGING

Once the diagnosis of UPJ obstruction has been determined from the history and basic radiographic studies, there is often a question regarding the possibility of involvement of a crossing polar vessel in the obstructive process. This particular anatomic problem is primarily important in older children or adults with UPJ obstruction because it can influence the surgical approach and require radiographic studies focused on defining the vascular anatomy.

The incidence of crossing vessels in patients with UPJ obstruction is inconsistent in the literature and ranges from 11% to 79%, mainly because of the variable definitions used to describe UPJ obstruction.[7,75] Polar vessels crossing immediately adjacent to the UPJ are designated as "crossing vessels." They are thought to exacerbate rather than initiate the obstructive process, although this remains a controversial issue.[76] Crossing vessels have the potential to cause significant morbidity if not recognized before an endourologic procedure. Several imaging modalities can be used to search for a crossing vessel including digital subtraction intra-arterial angiography, helical computed tomography, contrast-enhanced color Doppler imaging, endoluminal sonography, and magnetic resonance angiography. The anatomic peculiarity of polar crossing vessels makes vascular imaging important, especially when minimally invasive techniques are proposed for the management of UPJ obstruction.[77] An extensive historical review addressing crossing vessels has been published.[78] Among pediatric urologists, the concept of preoperative vascular imaging to verify a crossing vessel is controversial, if not moot. Surgical management of children with UPJ obstruction is open surgery, laparoscopy, or robotic surgery, but not endopyelotomy, which, if used blindly, could inadvertently disrupt an unsuspected crossing vessel. To this date, endourologic procedures are limited in children for several reasons: (1) the available endourologic equipment is not small enough to accommodate children younger than 3 years; (2) most pediatric surgeons are trained to perform an open dismembered pyeloplasty, with the recognition that laparoscopy is an excellent choice in the proper hands; (3) both open and laparoscopic approaches would identify an anterior crossing vessel intraoperatively; and (4) the open surgery, laparoscopy, or robotic surgery for UPJ obstruction success rate is much greater than the reported success rate for endopyelotomy as a primary procedure in children.

## Management

The management of possible UPJ obstruction remains controversial because the natural history of UPJ obstruction still remains unclear in children. Management of unilateral hydronephrosis cannot be based on either the degree of pelvic dilation on ultrasound or obstruction on diuretic renography.[45,79] Several investigators have demonstrated that nearly 50% to 80% of all cases of prenatal hydronephrosis will resolve spontaneously with postnatal follow-up.[80,81] Others, however, have demonstrated progressive hydronephrosis with diminution of function in follow-up 3 years postpartum.[82] These different outcomes are unsettling and, as yet, unanswered. Currently, watchful waiting and early intervention are two main options regarding the management of UPJ obstruction.

### WATCHFUL WAITING

Conservative management of unilateral UPJ obstruction involves sequential radiographic studies and cautious patience. The fact that so many algorithms have been devised for the management of UPJ obstruction is a sure indication that no single algorithm is absolute. In general, however, the typical evaluation of an infant with the prenatal diagnosis of hydronephrosis begins with a directed physical examination and postnatal ultrasound. The physical examination should determine the child's vital signs, general health, and overall appearance. Respiratory distress or vomiting may be associated with a palpable abdominal mass in some cases. In most instances, however, an abdominal mass is not identified.

Postnatal ultrasound should be performed at least 2 days after birth because relative dehydration of the fetus and physiologic oliguria may result in a false-negative study after birth. The one exception to this 2-day rule is a male neonate with bilateral hydronephrosis and a thickened bladder wall, which would be suggestive of a more urgent problem such as bladder outlet obstruction secondary to posterior urethral valves.

Renal sonography suggesting UPJ obstruction should be followed by additional diagnostic studies to confirm or exclude the obstruction. Further radiologic tests should be based on other possible causes of hydronephrosis. Several conditions can produce dilatation of the collecting system with or without urinary tract obstruction such as physiologic pelviectasis, UPJ obstruction, duplication of the collecting system with an ectopic ureter (or an associated ureterocele),

megaureter, MCDK, UVJ obstruction, posterior urethral valves, prune-belly syndrome, renal cystic diseases, parapelvic renal cysts, and megacalicosis. In addition, the diagnosis of hydronephrosis may be falsely diagnosed because of the sonolucent appearance commonly seen in the neonatal renal medullary and pyramids. This curious finding resolves with renal parenchymal maturation, which usually occurs within the first 6 months of life. Follow-up ultrasound reveals no apparent evidence of hydronephrosis (Fig 113-14).

Postnatal renal ultrasound can eliminate several of the aforementioned diagnoses. If a dilated ureter is demonstrated on postnatal ultrasound, the diagnosis of UPJ obstruction is less likely and the differential diagnosis would include ectopic ureter, megaureter, UVJ obstruction, posterior urethral valves, vesicoureteral reflux, or prune-belly syndrome (bilateral). Sonographic evidence of multiple, noncommunicating cysts is typical of parapelvic cysts or MCDK and not UPJ obstruction. Parapelvic cysts are rare in the pediatric population and should not be mistaken for hydronephrosis.[83] MCDK can be confirmed by nuclear scintigraphy, typically a DMSA scan, which reveals no evidence of ipsilateral renal function.

Historically, if the postnatal sonogram confirms characteristic findings consistent with hydronephrosis, the newborn was placed on a once-daily prophylactic dose of oral antibiotics with amoxicillin, 15 mg/kg, but the necessity of this has come into question and frequently these patients will be followed without prophylactic antibiotics, especially in the circumcised male. The use of prophylactic antibiotics in infants with postnatal hydronephrosis in the absence of VUR continues to be controversial.[84–86]

## OPEN SURGERY

The goal of surgery for UPJ obstruction is to preserve renal function by assisting unobstructed drainage of the renal pelvis. Several techniques have been designed for this purpose. The first is the flap techniques, which include Y-V-plasty, spiral flap, or Scardino-Prince vertical flaps. These flaps all use renal pelvic tissue to augment the narrowed UPJ segment (Fig. 113-15). The second type of technique, the dismembered pyeloplasty (Anderson-Hynes pyeloplasty), is the most popular.[8] It involves complete removal of the narrowed (dysfunctional) segment, tailoring of the renal pelvis (if necessary), and reapproximation of the ureter to the renal pelvis in a dependent position. Because neither technique sufficiently treats all the possible anatomic variations, it is imperative to be familiar with all techniques. The anatomy of the renal pelvis, in association with other intraoperative findings, dictates the technique of choice. Dismembered pyeloplasty is appropriate for most repairs of intrinsic and extrinsic obstruction. The flap technique may be useful in the patient with a long narrowed segment. Each technique can provide a solution to UPJ obstruction with success rates in excess of 90% to 95%.[13,87]

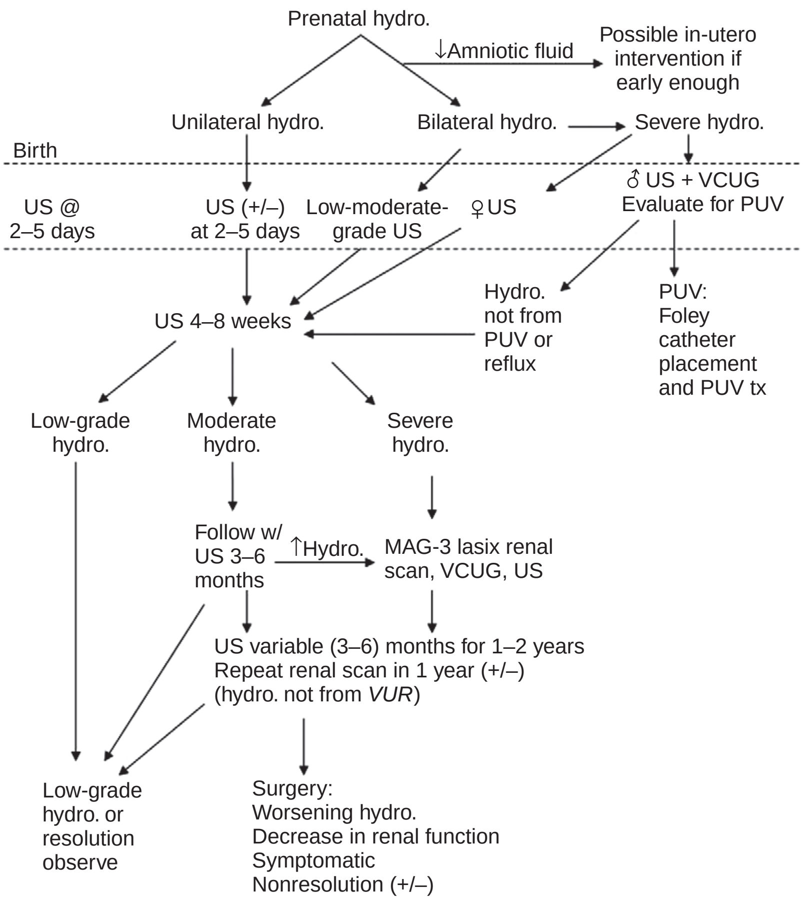



**FIGURE 113-14** A flow chart for workup and management of prenatal-detected hydronephrosis (*hydro.*) without ureteral dilation. *Low-grade hydro.*, SFU grade 1; *moderate hydro.*, SFU grade 2; *PUV*, posterior urethral valves; *renal scan*, MAG-3 lasix renal scan; *severe hydro.*, SFU grades 3-4; *US*, renal and bladder ultrasound; *VCUG*, voiding cystourethrogram; *VUR*, vesicoureteral reflux.

To perform a pyeloplasty, the child is given adequate general anesthesia, with the option of using a regional block. We routinely perform an RPG (retrograde pyelogram) at the onset of the procedure. Although some have challenged the necessity of this, we believe an RPG helps to characterize the lesion and distal ureter and to assist in defining the appropriate site for optimum exposure. After RPG, a Foley catheter is placed in a sterile manner and the child is repositioned for surgery with respect to the particular approach that is planned.

A number of approaches can be used to obtain access to the retroperitoneal space to perform an open pyeloplasty including anterior subcostal, flank, and dorsal lumbotomy. In infants we prefer an anterior subcostal, muscle-splitting approach,

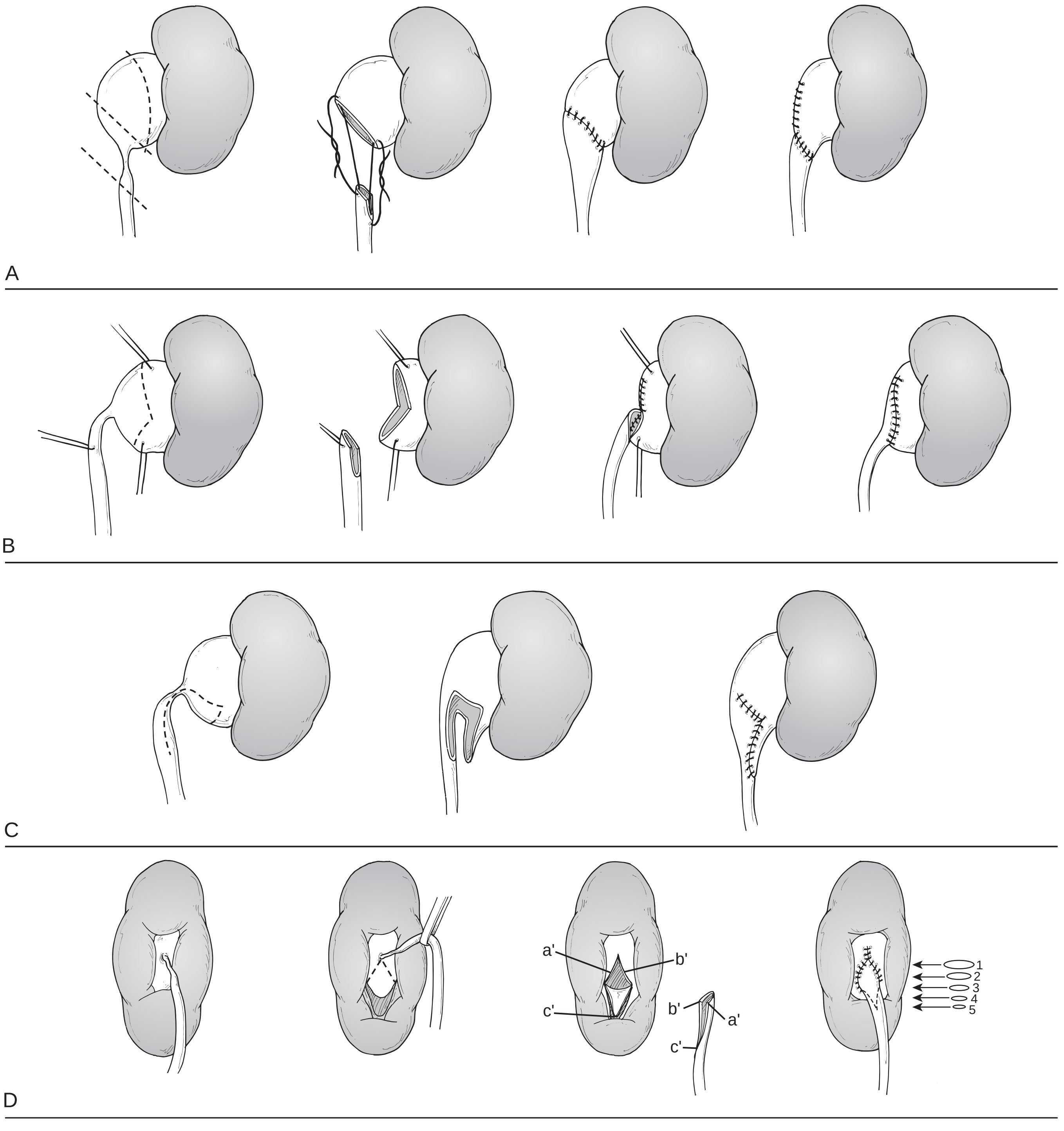



**FIGURE 113-15** **A,** Dismembered pyeloplasty. **B,** Anderson-Hynes pyeloplasty. **C,** Foley Y-V-plasty. **D,** Variation of the Foley Y-V-plasty for proximal ureteral high insertion.

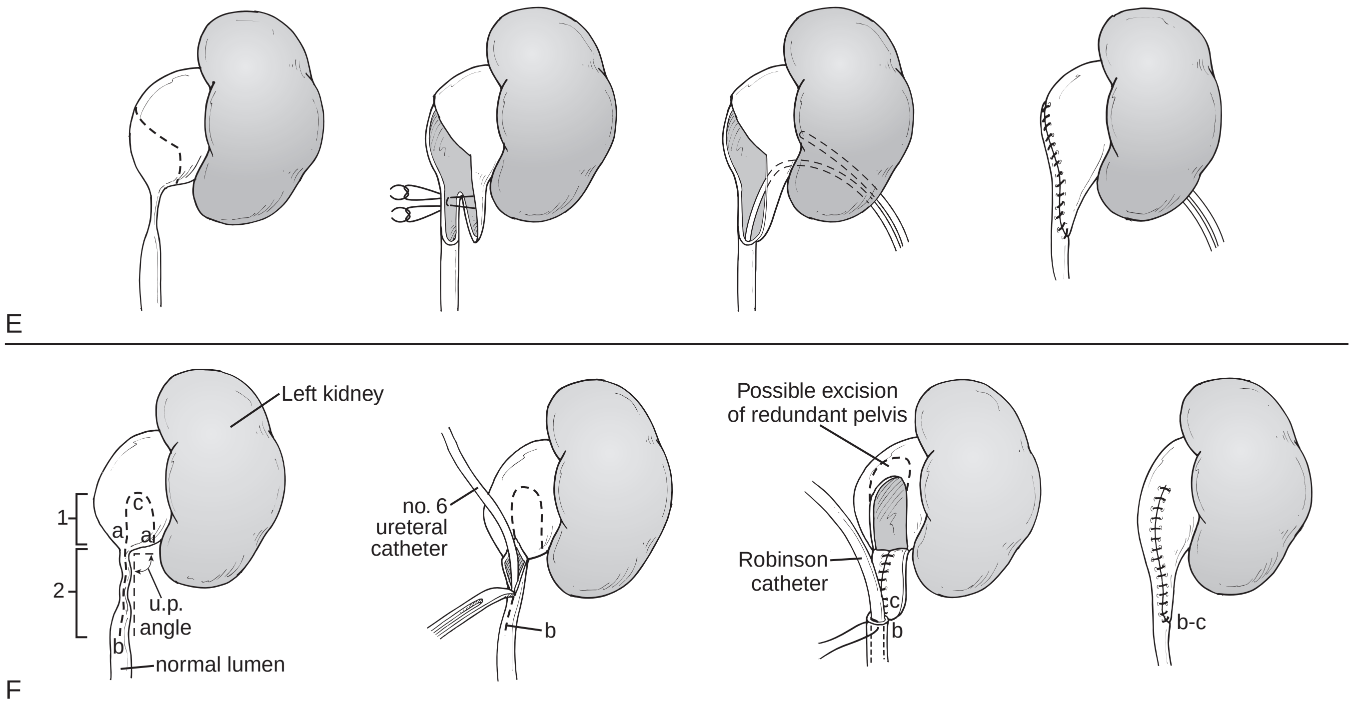



**FIGURE 113-15—CONT'D** **E,** Spiral flap. **F,** Scardino-prince vertical flap pyeloureteroplasty for long proximal ureteral narrowing. (From Fung LCT, Lakshmanan Y: Anomalies of the renal collecting system: Ureteropelvic junction obstruction [pyelocaliectasis] and infundibular stenosis. In Belman AB, King LR, Kramer SA [eds]: Clinical Pediatric Urology, 4th ed. London, Martin Dunitz, 2002, p 612.)

which provides excellent exposure through a small incision. (In older children, a flank incision might be preferential given the lateral displacement of the peritoneum and the frequently thicker muscle bundles.)

The child is then placed in a modified supine position with the ipsilateral side at an approximately 15- to 20-degree angle to the operating table. Small children may have both upper extremities at their sides. The operating table is flexed at the level of the child's anterior superior iliac spine, which exposes the anterior abdominal area and flank. Approximately two fingerbreadths below the subcostal region, a 3- to 4-cm incision is made along Langer's lines. A "muscle-splitting" technique is used to separate the muscle layers without transecting them. This technique provides adequate exposure and reduces postoperative pain. After the fascia is opened, the peritoneum is reflected medially. The Gerota fascia is incised in a plane vertical to the patient. A self-retaining ring retractor provides adequate exposure to the kidney and renal pelvis.

Once the kidney and renal pelvis have been exposed, careful inspection of the anatomy should allow a decision to be made regarding the best technique to use. A dismembered pyeloplasty is performed for most UPJ obstructions. However, there are three anatomic situations that may be treated appropriately with three different flap procedures: Foley Y-V-plasty, spiral flap, or Scardino-Prince vertical flaps. The first situation occurs when the obstructing segment is longer than 1.5 to 2 cm. The second situation occurs in a child with a small extrarenal pelvis, and the renal pelvis does not need to be reduced. The last situation, in which a Foley Y-V-plasty may be the preferred technique, is when the ureter has a high insertion into the renal pelvis. In these cases, the pelvis can be funneled to construct a dependent drainage system.

When a decision is made to perform a dismembered pyeloplasty, the renal pelvis should be evaluated for possible reduction in size. The ureter is transected between stay sutures at the UPJ. Care is taken to not excessively dissect the blood supply from the proximal ureter. Stay sutures are strategically positioned in a "diamond" pattern, and tenotomy scissors are used to excise redundant renal pelvis within the borders of the stay sutures. The narrowed ureteral segment should be incised laterally along the longitudinal axis of the ureter to the point of healthy ureteral tissue of normal caliber. The proximal ureter at the UPJ obstruction level should be excised from and removed before reapproximation. The anastomosis is begun at the inferior apex of renal pelvis and opened ureter, with continuous running 7-0 absorbable monofilament suture used in the infant and 5-0 to 7-0 absorbable sutures used in older patients. During the anastomosis, care should be taken to include adequate adventitial tissue with less mucosal tissue to provide a watertight anastomosis. A temporary ureteral stent may be used when performing the anastomosis to reduce the risk for obstruction as a result of "back-walling." Alternatively, a double-J ureteral stent may be positioned in the distal end of the ureter and bladder with the Seldinger technique. This is typically removed in 4 to 6 weeks.

The dorsal lumbotomy approach provides excellent exposure, especially in the rare case of bilateral UPJ lesions (Fig. 113-16). As in the subcostal approach, a muscle-splitting technique can be used to access the retroperitoneum through a relatively short distance. The dorsal lumbotomy approach requires that the ureteral anatomy be precisely defined before embarking on the technique because it provides limited exposure to the distal part of the ureter.

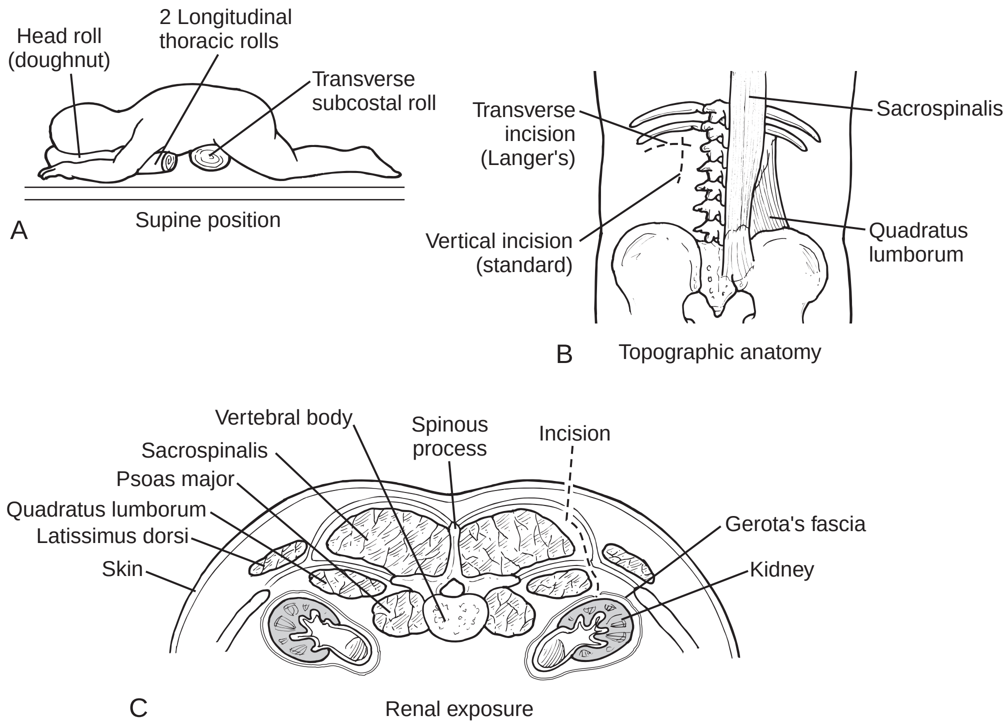



**FIGURE 113-16** Dorsal lumbotomy approach. (From Sheldon CA, Duckett JW: Infant pyeloplasty. AUA Update Series 1988;7[Lesson 37]:293.)

## MINIMALLY INVASIVE SURGERY FOR URETEROPELVIC JUNCTION OBSTRUCTION IN CHILDREN

Unlike in adults, open pyeloplasty is considered the gold standard in the management and treatment of UPJ obstruction. The success rate has been reported to be between 90% and 100%.[88,89] However, open surgery can result in postoperative morbidity because of pain, prolonged length in recovery, and significant scar formation. Minimally invasive surgery evolved to decrease the morbidity of pyeloplasty while maintaining the efficacy of treatment. Minimally invasive techniques to correct UPJ obstruction in adults include balloon dilation, percutaneous antegrade endopyelotomy, retrograde cutting-wire balloon endopyelotomy, ureteroscopic retrograde endopyelotomy, and laparoscopic pyeloplasty.

Techniques such as antegrade and retrograde endopyelotomy, although less invasive, have a significantly decreased success rate when compared with open surgery, with a reported success rate of 61% to 89%. They can also carry a risk of bleeding in patients with crossing vessels.[90,91] The endopyelotomy success rate decreases to 39% to 44% with UPJ obstruction associated with crossing vessels.[92,93] Laparoscopic pyeloplasty was first introduced in adults in 1993 and has a success rate approaching 95%.[94,95] In the adult population, studies have demonstrated decreased pain and decreased length of hospital stay.[96] Laparoscopy in children has shown similar success rates, but the benefit from recovery for the younger patient has been less well established.

Pediatric laparoscopic pyeloplasty faces the same challenges as the other minimally invasive techniques in children.[97] Much of pediatric urologic surgery is reconstructive rather than extirpative, which limits the ability of many practitioners to gain experience in basic laparoscopic skills. Peters reported the first case of pediatric laparoscopic pyeloplasty in 1995.[98] There have been several series demonstrating comparable success rates with laparoscopic dismembered pyeloplasty to open pyeloplasty in the pediatric population.[99–106] Recently, several authors have demonstrated that laparoscopic pyeloplasty is a viable option in infants and children younger than 2 years of age and not solely limited to older children.[107,108]

The two main laparoscopic techniques to pyeloplasty are transperitoneal versus retroperitoneal approaches. The transperitoneal approach is used more frequently in the pediatric patient because it allows for increased working space along with the benefit of easy identification of crossing vessels and readily identifiable anatomic landmarks. The two main procedures used to treat UPJ obstructions laparoscopically include dismembered pyeloplasty and Foley Y-V flap for UPJ obstructions secondary to high inserting ureters. There have been a limited number of reports of higher success rates with a dismembered approach when compared with a nondismembered approach in the laparoscopic setting and thus is the more commonly used.[103]

Various techniques are used to achieve pneumoperitoneum including the Veress needle technique versus the open Hasson technique. The patient is placed at 30 to 45 degrees in a modified flank with the affected side elevated. Peritoneal access is obtained through the umbilicus via Hasson technique. The abdomen is then insufflated to 10 to 12 mm Hg to allow for adequate pneumoperitoneum. The 5- or 10-mm camera port is placed at the umbilicus, and two 5-mm (in infants sometimes 3-mm ports can be used instead) working ports are placed in the midline between the umbilicus and xyphoid and in the midclavicular line 2 cm below the umbilicus on the affected side. Initially, the colon is then mobilized medially by incising the line of Toldt and reflecting the colon to gain

access to the retroperitoneum and kidney. On the left side, a transmesenteric approach can sometimes be undertaken. A ureteral stent is placed either antegrade during laparoscopy or in a retrograde fashion during initial cystoscopy at the start of the procedure depending on surgeon preference. The type of absorbable suture varies between 5-0 and 4-0 depending on the patient's age and surgeon's preference. There is a significant learning curve to laparoscopic pyeloplasty, and it is technically challenging secondary to the intracorporeal suturing and knot tying required. This is why it has been relegated to specialized centers and not universally adopted.

The recent implementation of robotic laparoscopic systems has increased the availability of laparoscopic reconstructive surgery including pyeloplasties. The most commonly used robotic system is the da Vinci robotic system (Intuitive Surgical, Sunnyvale, Calif.). The benefits of robotic laparoscopy include increased magnification, three-dimensional vision, articulating robotic Endowrist with six degrees of articulation, tremor filtering, and an ergonomic surgeon's position. These benefits to robotic laparoscopy assist dissection and suturing, allowing for greater applications with decreased learning curve in reconstructive surgery. The patient is placed at 30 to 45 degrees in modified flank with the affected side elevated. Peritoneal access is obtained similar to conventional laparoscopy through the umbilicus. The 12-mm camera port is placed at the umbilicus, and two robotic working ports (5 mm or 8 mm) are placed in the midline between the umbilicus and xyphoid and in the midclavicular line 2 cm below the umbilicus. The absorbable suture used varies with age but ranges between 7-0 and 4-0 similar to sutures used in an open repair. Robotic surgery has the potential to advance minimally invasive surgery by allowing urologists with limited laparoscopic experience to rapidly master the endocorporeal skills necessary to treat UPJ obstruction.[109,110]

## Outcome

A successful pyeloplasty is most specifically measured by preservation of or improvement of renal function. Several investigators have reported improvement in renal function in children with obstruction detected early and surgery performed before renal impairment occurs.[1,111] Meticulous attention to surgical principles contributes to operative success. The use of proper pediatric instruments is important. Atraumatic tissue handling, careful dissection, and preservation of ureteral blood supply all contribute to a successful anastomosis. The ureteropelvic anastomosis should be watertight and tension free. The retroperitoneal space should have adequate passive drainage.

Finally, the routine use of ureteral stents and percutaneous nephrostomy tubes after an open pyeloplasty remains controversial.[112] The most common reasons to leave a stent in place after pyeloplasty are to ensure proper urinary diversion, maintain ureteral caliber, and ensure anastomotic alignment. The main reasons against leaving a temporary stent in situ are that they are foreign bodies and may be a nidus for infection, they may erode through the anastomotic site, and in children, internalized stents require general anesthesia for removal.

The goal of pediatric pyeloplasty is to reduce hydronephrosis and preserve renal function. This goal is evaluated by radiographic studies and clinical considerations. Renal ultrasound defines a successful pyeloplasty as improvement in SFU-graded hydronephrosis, temporal axial growth of the ipsilateral kidney, and a gradual increase in renal parenchyma. Diuretic renography should demonstrate improved urinary drainage and differential renal function. In older children, successful pyeloplasty is determined by the absence of symptoms.

Depending on the definition, the success rate of pyeloplasty for UPJ obstruction is as high as 98%.[13,113,114] The success rate is so high, in fact, that one investigator suggested that a satisfactory diuretic renogram 3 months after pyeloplasty eliminated the need for further urologic follow-up. Other investigators claim that ideally, follow-up should be extended to 2 years, which would include the period when initial symptoms of recurrence are most likely to take place.[115] Subsequently, renal ultrasound is performed annually for 2 years. Of course, after pyeloplasty, primary care physicians should monitor any patient with renal scars on a preoperative DMSA scan by annual blood pressure reading. We recommend renal ultrasound 3 months after pyeloplasty and diuretic renography if improvement is not obvious by ultrasound.

Complications of pyeloplasty can be categorized as acute and late. Acute complications have a higher incidence in infants.[6] Postoperative pyelonephritis is most commonly seen in children who had a positive intraoperative urine culture. It is treated with intravenous antibiotics. Delayed opening of the ureteropelvic anastomosis typically occurs as a result of edema and may lead to a prolonged leak around the anastomotic site. Interestingly, a transanastomotic ureteral stent does not reduce the frequency of this complication. Patients with persistent hydronephrosis or symptoms after pyeloplasty may be salvaged with placement of a percutaneous nephrostomy tube. In some of these children, a secondary procedure may be necessary such as revision pyeloplasty or nephrectomy. Late complications can be manifested as clinical symptoms or progressively worsening radiographic studies. In either case, evaluation should determine whether optimizing drainage via a nephrostomy tube or ureteral stent improves the clinical symptoms or renal function. Typically, surgery for a failed pyeloplasty should not be considered for at least 2 months. There are five basic approaches to the treatment of secondary UPJ obstruction: revision pyeloplasty, ureterocalicostomy, endopyelotomy, laparoscopy, and nephrectomy.[116]

## Summary

UPJ obstruction is the most common congenital urinary obstruction, and management remains complex because of the variability of the lesion and the unpredictability of the manifestations. In many cases, observation alone is a viable option because the obstruction is not progressive. In other cases, radiographic studies reveal renal deterioration or progressive hydronephrosis, and surgery is required. Unfortunately, the factors that determine which kidneys require surgery have not been clearly defined at this point. However, with future developments in biochemical markers and improvements in radiographic studies, timing of surgical intervention will be defined earlier so that renal deterioration in children with suspected UPJ obstruction might be prevented.

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 114

# Renal Infection, Abscess, Vesicoureteral Reflux, Urinary Lithiasis, and Renal Vein Thrombosis

Leslie T. McQuiston and Anthony A. Caldamone

## Urinary Tract Infection, Renal Abscess, and Vesicoureteral Reflux

The urinary tract is the second most common site of infection in infants and children after the respiratory tract. The true incidence of urinary tract infection (UTI) in children is difficult to determine because of the challenges of diagnosis. Young children may present with only fever or failure to thrive, with no specific urinary symptoms or signs. Diagnosis and treatment of UTI are of particular importance in children, given the long-term complications including renal scarring, hypertension, and decreased renal function. On the basis of several studies, the incidence of renal scarring in young children with febrile UTI may be as high as 40% to 50%.[1] Among infants between the ages of 2 months and 2 years who present with fever, approximately 5% are diagnosed with a UTI.[2,3] Age and gender are significant factors in the incidence of UTI in the pediatric population. The incidence of UTI is greater in girls than in boys; in prepubertal girls, the incidence is reported to be 3%, whereas in prepubertal boys it is only 1%.[1] Some studies have demonstrated that the incidence of UTI in uncircumcised males, particularly boys younger than 1 year, is 5 to 20 times higher than in circumcised males.[4,5] Over the past few years, there have been advances in the understanding of the pathogenesis of UTI and the identification of risk factors that predispose patients to renal damage.

### PATHOGENESIS

There are four major pathways by which bacteria gain access to the urinary tract: ascending, hematogenous, lymphatic, and direct extension. Hematogenous access is most commonly seen in immunocompromised children or in neonates, owing to their immature immune systems. Direct extension can occur in the setting of fistulas from the vagina or the gastrointestinal tract to the genitourinary tract. The ascending route is considered the most common pathway, with bacteria colonizing the periurethral area and then entering via the urethra. Host factors including the ability to resist infection are important elements in the pathogenesis of UTI. There is a higher incidence of UTI in infancy, likely due to the immaturity of the neonatal immune system and the higher periurethral bacterial colonization in the first year of life.[6] Bacteria from the gastrointestinal tract colonize the periurethral mucosa and may ascend into the bladder and then the kidneys (Table 114-1).[7] Certain bacterial traits such as the presence of fimbriae mediate bacterial adherence to uroepithelial cells and increase bacterial virulence.

Differentiation of pyelonephritis from lower UTI is difficult because there is poor correlation between clinical symptoms and localization of bacteria to the upper versus lower tract. In older children, however, the diagnosis of pyelonephritis may be suggested by fever, flank pain, and systemic symptoms. Persistent fever for more than 48 hours after the initiation of appropriate antibiotics may be indicative of upper tract infection. Infants with a febrile UTI should be considered to have pyelonephritis and evaluated and treated accordingly. Alternatively, if one has access to dimercaptosuccinic acid (DMSA) nuclear scanning at the time of the illness, more specific identification of pyelonephritis is possible, which may modify the evaluation and treatment. Studies have demonstrated that 40% to 60% of children with a febrile UTI have a positive DMSA scan.[8,9]

### RISK FACTORS

Although bacterial virulence plays an important role in the development of UTI, a variety of host characteristics may predispose to UTI including age, gender, colonization factors, constipation, genitourinary abnormalities, sexual activity, genetic factors, and iatrogenic factors (Table 114-2).[10] The most important factors influencing prevalence are age and gender. Males are five to eight times more likely than girls to have UTIs during the first 3 months of life.[11] Beyond that age, girls have a

**TABLE 114-1**
**Pathogens Associated with Infections**

| *Organism* | *Comment* |
|---|---|
| *Escherichia coli* | Accounts for 70%-90% of infections |
| *Pseudomonas aeruginosa* | Most common nonenteric gram-negative pathogen<br>Occasionally seen in immunocompromised patients |
| *Enterococcus* | Most common gram-positive pathogen |
| Group B streptococci | Occasionally seen in neonates |
| *Staphylococcus aureus* | Suggests additional site (abscess, osteomyelitis, bacterial endocarditis) |
| *Proteus mirabilis* | Boys > 1 yr old |
| *Candida*, coagulase-negative staphylococci | Seen after instrumentation of urinary tract |
| *Klebsiella* | Occasionally seen in immunocompromised patients |

Modified from Handel LN, Caldamone AA: Urinary tract infections in the pediatric population. Lebanese Med J 2000;52:194.

greater incidence of UTIs than boys. Symptomatic infections are 10 to 20 times more likely in preschool girls than boys.[5]

UTI often serves as a marker for anatomic abnormalities of the genitourinary tract. It is important to identify these abnormalities early because, if uncorrected, they may lead to recurrent infection and possible loss of renal parenchyma. Obstructive malformations such as ureteropelvic junction obstruction, posterior urethral valves, ectopic ureters, ureteroceles, and urethral diverticula can increase the risk of UTI. Renal abnormalities such as papillary necrosis, nonfunctioning kidneys, and unilateral medullary sponge kidney also predispose patients to UTI.

Vesicoureteral reflux (VUR), which is the abnormal flow of urine from the bladder to the kidney, allows bacteria from the bladder to gain access to the kidney. By itself, VUR does not cause UTI; bacteriuria must be present in the setting of VUR for UTI to develop. The exception to this rule is a child with massive VUR who may have a significant postvoid residual from refluxed urine. VUR occurs in approximately 1% of the general population and is estimated to occur in 20% to 35% of children evaluated for bacteriuria.[12,13] More than 60% of children younger than 1 year are found to have VUR after their first UTI.[3] This percentage decreases to 30% in 2- to 3-year-olds and is 5% or less in adults.[3] As children grow, the submucosal tunnel elongates and the ratio between the submucosal tunnel length and the ureteral diameter increases. In addition, filling and voiding pressures change over time, which can also improve VUR. These factors, along with changes in bladder dynamics and voiding patterns, account for the spontaneous resolution rate of VUR. VUR is graded I to V on the basis of the International Reflux Grading System. Grades I and II generally resolve or improve over time, whereas grades IV and V typically do not resolve spontaneously and may require intervention.

**TABLE 114-2**
**Risk Factors for Urinary Tract Infection**

| |
|---|
| Anatomic abnormalities |
| Vesicoureteral reflux |
| Obstruction |
| Other: diverticulum, labial adhesion |
| Female gender |
| Uncircumcised male |
| Voiding dysfunction |
| Constipation |
| Instrumentation |
| P-fimbriated bacteria |
| Toilet training |
| Sexual activity, pregnancy |

From American Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Urinary Tract Infection: Practice parameter: The diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. Pediatrics 1999;103:843.

Functional abnormalities such as a neuropathic bladder predispose to UTI as a result of increased urinary tract pressures, incomplete bladder emptying, and increased frequency of instrumentation. UTI is also more common in patients with bladder and bowel dysfunction (BBD). These children commonly have incomplete bladder emptying, urinary stasis, and abnormally high urinary tract pressures, as well as bladder instability, infrequent voiding, Hinman syndrome, and constipation. Periurethral colonization and preputial colonization also may increase the risk of UTI. Preputial aerobic bacterial colonization is highest during the first month after birth, decreases after 6 months, and is uncommon after 5 years of age.[10,14]

## CLINICAL PRESENTATION

Children with UTIs, especially those younger than 2 years, do not always present with the typical symptoms of dysuria, frequency, or pain, and the physical examination may be of limited value. Thus it is important to maintain a high index of suspicion in infants and young children. In children younger than 2 years, parents may describe nonspecific symptoms such as fever, fussiness, vomiting, or diarrhea; patients may present with failure to thrive or difficulty feeding. In infants, often the only presenting symptom is fever. Children 2 to 5 years of age often present with fever and abdominal pain coincident with upper respiratory infection. After toilet training, children may start to demonstrate more specific symptoms such as fever, dysuria, flank pain, and urgency.

## DIAGNOSIS

Accurate diagnosis of UTI in children is critical. The method of collection can affect the accuracy of diagnosis (Table 114-3). In toilet-trained children, clean-catch specimens have a contamination rate of approximately 30%.[15] The method least likely to be contaminated is suprapubic aspiration; this method, however, is often not favored by parents or by primary practitioners. Suprapubic aspiration may be contraindicated in patients with certain anatomic abnormalities of the genitourinary tract.

Transurethral bladder catheterization is the preferred method, with a lower false-positive rate than perineal bag collection. The sensitivity of positive urine culture is 95%, and the specificity is 99%.[2] In children not yet toilet trained, perineal bag collection is more common but has a high probability of contamination. False-positive results occur in 85% of specimens collected in this manner.[2] Perineal bag collection may be used when there is low suspicion of UTI. Current recommendations are urethral catheterization or suprapubic

**TABLE 114-3**
**Criteria for the Diagnosis of Urinary Tract Infection**

| *Method of Collection* | *Colony Count (Pure Culture)* | *Probability of Infection (%)* |
|---|---|---|
| Suprapubic aspiration | Gram-negative bacilli: any number | >99 |
| | Gram-positive cocci: >a few thousand | |
| Transurethral catheterization | >100,000 | 95 |
| | 10,000-100,000 | Infection likely |
| | 1000-10,000 | Suspicious, repeat |
| | <1000 | Infection unlikely |
| Clean-voided (boy) | >10,000 | Infection likely |
| Clean-voided (girl) | 3 specimens >100,000 | 95 |
| | 2 specimens >100,000 | 90 |
| | 1 specimen >100,000 | 80 |
| | 50,000-100,000 | Suspicious, repeat |
| | 10,000-50,000 | If symptomatic, suspicious, repeat; if asymptomatic, infection unlikely |
| | <10,000 | Infection unlikely |

aspiration following a positive urinalysis or a positive urine culture from a bag specimen to eliminate the possibility of contamination.

On urinalysis, the combination of urine nitrite, leukocyte esterase, bacteria, and white blood cells on microscopy yields a sensitivity of 99.8% and a specificity of 70%.[2,15] However, UTI cannot be ruled out if any of these findings is absent on urinalysis or microscopy. A urine culture is the only way to accurately diagnose a UTI; however, prompt treatment before final culture results are obtained is recommended due to the increased risk of renal scarring in children younger than 5 years, as well as the possibility for rapid clinical deterioration.

## IMAGING

The role of imaging after a UTI is controversial.[10,13,16] The primary goal of imaging is to identify children who are at risk for subsequent UTIs and renal damage. Imaging includes an anatomic evaluation of the kidney and bladder, as well as a functional study to identify the presence of VUR. The current American Academy of Pediatrics guidelines recommend renal and bladder ultrasonography (US) for all children younger than 2 years with a first UTI.[2] The National Institute for Health and Clinical Excellence (NICE) recommends renal and bladder US for all children younger than 3 years of age, but only for those with atypical or recurrent UTI for those older than 3 years of age.[17] The purpose of US in these cases is to assess for the presence of any congenital structural abnormalities of the urinary tract such as hydronephrosis (Fig. 114-1). Additionally, US allows the visualization of any renal parenchymal abnormalities such as cysts and identifies the presence of perinephric fluid collections. Ureteral dilatation, bladder wall thickening (Fig. 114-2), a duplicated collecting system (Fig. 114-3), ureteroceles (Fig. 114-4), bladder diverticula, and calculi are also identifiable with US. In cases of acute pyelonephritis, US may demonstrate focal or diffuse renal enlargement, as well as abnormal cortical echogenicity. Multiple studies have demonstrated obstructive lesions in 5% to 10% of patients and VUR in 20% to 50% following a UTI.[18] Thus imaging should be considered after a first UTI. Imaging for VUR using cystourethrography (VCUG) is the standard of care

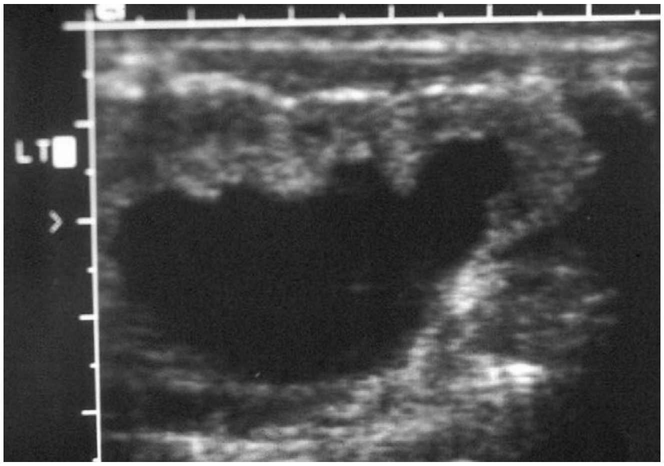


**FIGURE 114-1** Sagittal ultrasonography of a kidney demonstrating hydronephrosis of the renal pelvis and calices. (Modified from Handel LN, Caldamone AA: Urinary tract infections in the pediatric population. Lebanese Med J 2004;52:194.)

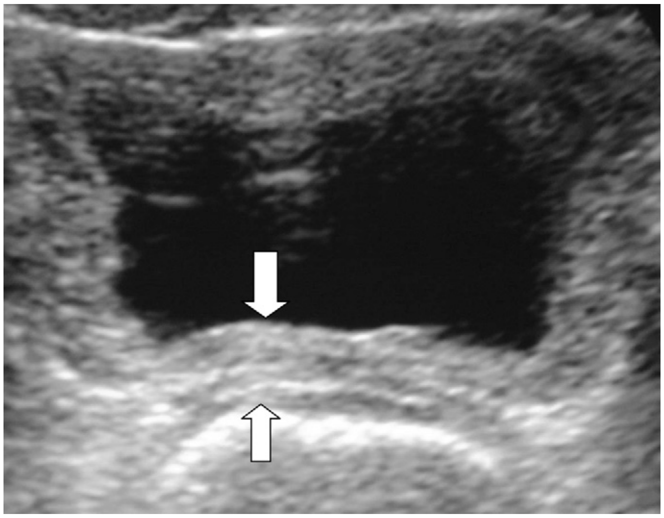

**FIGURE 114-2** Transverse ultrasonography of the bladder demonstrating posterior wall thickening (*arrows*).

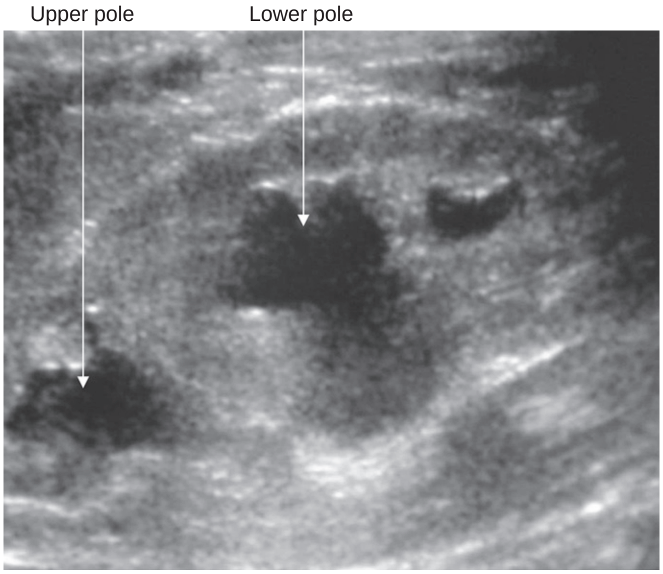


**FIGURE 114-3** Sagittal ultrasonography of a kidney demonstrating a duplicated collecting system.

in infants and children younger than 3 years or not yet toilet trained. In older children, the data to support VCUG are less clear because it is not certain, on the basis of available data, that the treatment of children with VUR provides a clinically significant benefit with respect to reduction in long-term renal damage.[19] The "Top-Down Approach" has suggested that initial DMSA scintigraphy may help to identify children at highest renal risk and therefore those who need further investigation by VCUG.[9] This approach is based on evaluation with DMSA scan as close to the acute episode of febrile UTI as possible, preferably within the first 10 days of diagnosis, and further imaging with VCUG for those with a positive scan. Several studies have shown that a negative DMSA scan decreases the probability that there is high-grade VUR.[8] Children with a negative scan may not require further evaluation unless UTI recurs. Further studies are necessary to clarify the best evaluation strategy to detect children who are at risk of progressive renal damage from UTI. Currently based on age and gender, the recommendation is US and VCUG for all boys with their first UTI regardless of age and for girls younger than 5 years with their first UTI. Additionally, for girls older than 5 years, imaging should be done in those with pyelonephritis or recurrent UTIs (Table 114-4). The type and timing of imaging may depend on the patient's response to initial antibiotic therapy and the availability of DMSA scintigraphy.

The most common anomaly associated with UTI in children is VUR, which is noted in about 20% to 35% of children evaluated after UTI. VCUG is used to detect the presence of VUR (Fig. 114-5). Standard VCUG is performed by instilling iodinated contrast into the bladder and then imaging during filling and voiding. The American Academy of Pediatrics recommends VCUG as the initial study of choice in VUR, especially in male patients to rule out posterior urethral valves (Fig. 114-6).[2] Previous recommendations were that VCUG should be done 4 to 6 weeks after UTI because of possible false-positive results owing to inflammation of the bladder wall causing VUR. More recent studies have shown no difference between early (within 7 days of infection) and late VCUG.[20] VCUG can be performed once the child is afebrile, and cultures are negative to prevent the risk of infected urine being forced in a retrograde fashion during the study.

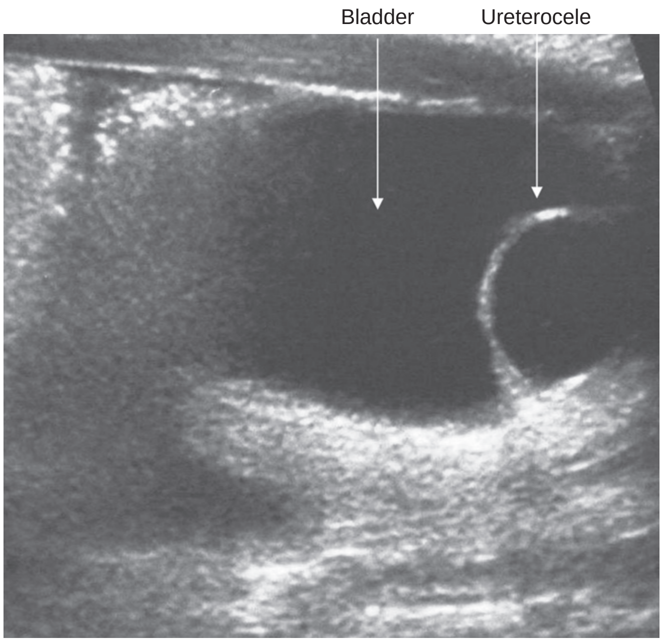


**FIGURE 114-4** Transverse ultrasonography of the bladder demonstrating a left ureterocele.

**TABLE 114-4**
**Pediatric Genitourinary Imaging**

| *Study* | *Findings* | *Indications* |
|---|---|---|
| Renal/bladder US | Abscess<br>Presence of 2 kidneys<br>Renal size<br>Presence of hydronephrosis (see Fig. 114-1)<br>Bladder wall thickening (see Fig. 114-2)<br>Postvoid residual<br>Duplicated collecting system (see Fig. 114-3)<br>Ureterocele (see Fig. 114-4) | All boys with first UTI |
| VCUG | Vesicoureteral reflux (see Fig. 114-5)<br>Posterior urethral valves (see Fig. 114-6) | All boys with first UTI; girls <5 yr with first UTI |
| MAG3 diuretic scan | Renal function | Hydronephrosis on US, no reflux on VCUG |
| | Renal obstruction | |
| DMSA renal scan | Pyelonephritis | To diagnosis acute pyelonephritis ("top-down" approach)<br>To assess for renal scarring |

DMSA, dimercaptosuccinic acid; MAG3, mercaptoacetyltriglycine; US, ultrasonography; UTI, urinary tract infection; VCUG, voiding cystourethrography.

Modified from Handel LN, Caldamone AA: Urinary tract infections in the pediatric population. Lebanese Med J 2004;52:194.

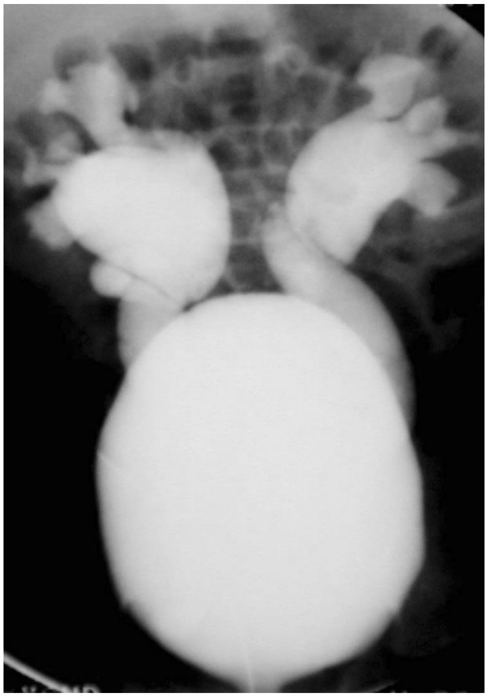

**FIGURE 114-5** Voiding cystourethrogram demonstrating vesicoureteral reflux.

Renal cortical imaging with dimercaptosuccinic acid (DMSA) is both sensitive and specific for the detection of pyelonephritis in children.[18,21] Areas with decreased uptake may represent acute pyelonephritis or renal scarring. Before the availability of DMSA, imaging techniques demonstrated that approximately 17% of children with bacteriuria had renal scarring; current studies using DMSA demonstrate that the percentage is likely twice that.[1] The use of DMSA should be limited to those patients with suspected acute UTI in whom the diagnosis is unclear but there is a high suspicion of pyelonephritis. DMSA can also be used to assess for renal scarring after UTI if the results would change the management of the patient.

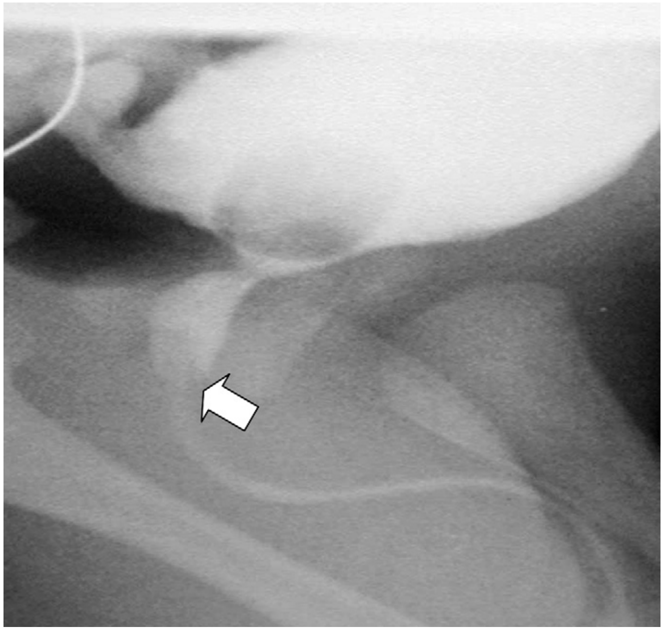

**FIGURE 114-6** Voided cystourethrogram demonstrating posterior urethral valves (*arrow*).

Mercaptoacetyltriglycine (MAG3) or diethylenetriamine pentaacetic acid (DTPA) with a diuretic is used to assess renal function and excretion in patients with hydronephrosis without VUR and to determine the presence or absence of obstruction. Both false-positives and false-negatives are possible, so caution must be used when interpreting the study and clinical correlation is essential.

Renal abscess is a potential complication of pyelonephritis regardless of the underlying cause. Abscess is more common in compromised patients. Gram-positive organisms such as *Staphylococcus aureus* and streptococci may be the causative agents. The diagnosis is best made by US or computed tomography (CT). Treatment may involve long-term antibiotics, percutaneous drainage and antibiotic instillation, or open surgical drainage. Sequential follow-up with radiographic imaging is essential.

## TREATMENT

Because of the risk of renal scarring in children, prompt diagnosis and treatment are critical (Fig. 114-7). The treatment strategy depends on various factors, particularly the child's age and the severity of illness. Children younger than 4 weeks with fever are at increased risk for bacteremia and sepsis and may require hospitalization for parenteral antibiotics. Similarly, any child younger than 5 years with a suspected UTI who appears systemically ill should be hospitalized. The American Academy of Pediatrics recommends that children who are dehydrated, are unable to tolerate oral medication, and appear toxic should receive intravenous antibiotics.[2] Additionally, children who are immunocompromised, are suspected of having urosepsis or bacteremia, or have failed oral therapy should be hospitalized. If the child can tolerate oral antibiotics and has reliable parents who will maintain follow-up and contact with the physician, the child may be managed as an outpatient.

Initial antibiotic treatment needs to be broad spectrum to cover the more common pathogens. Once culture results and sensitivities are complete, treatment can be tailored specifically to cover the identified organism. In patients who have had previous UTIs, the prior culture results should be considered when selecting the initial therapy. For children who are hospitalized, parenteral treatment such as a combination of aminoglycosides and ampicillin or cephalosporins is continued for 48 to 72 hours until the child is afebrile and stable and sensitivities are available. Once the child is stable, oral antibiotics can be initiated on the basis of sensitivity results. Most studies recommend treating febrile UTIs in young children for 7 to 10 days in total,[22,23] although more recent studies suggest that shorter-duration therapy may be equally effective.[24–26] The American Academy of Pediatrics recommends that the treatment duration be 7 to 10 days for uncomplicated UTI and 14 days for children with presumed renal involvement or who are toxic.[2] In infants younger than 6 weeks, ampicillin and gentamicin or ampicillin and a cephalosporin are good initial choices. The exception is ceftriaxone, which can increase the risk of kernicterus in young infants. For children likely to be infected with *Pseudomonas* or *Enterococcus*, ampicillin and gentamicin are the agents of choice because

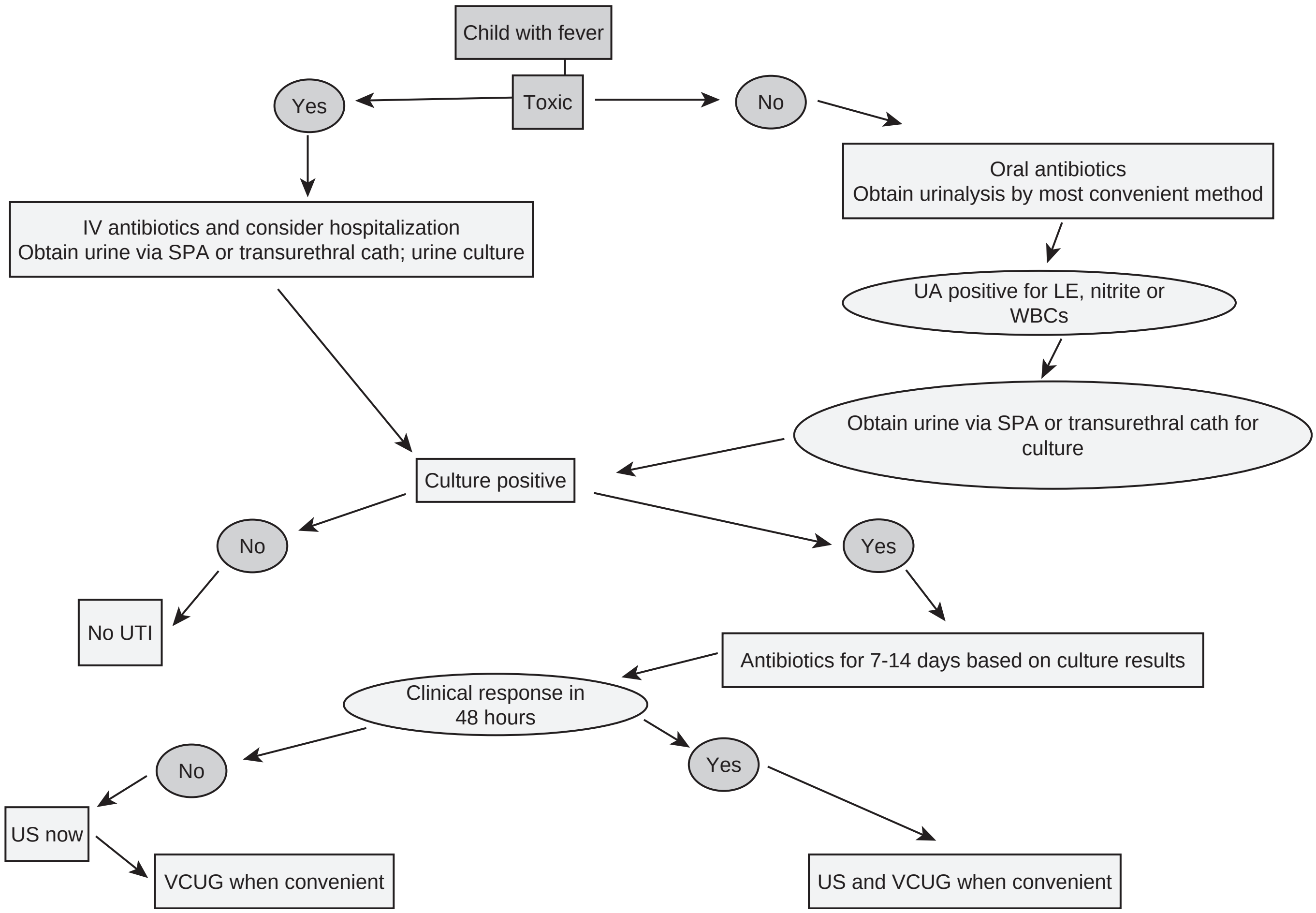


**FIGURE 114-7** Algorithm for management of urinary tract infection (UTI). LE, leukocyte esterase; SPA, suprapubic aspiration; UA, urinalysis; US, ultrasonography; VCUG, voiding cystourethrography; WBC, white blood cell.

cephalosporins have no effect on enterococci. Gentamicin levels should be monitored closely, particularly in children with impaired renal function.

In patients who are clinically stable, a broad-spectrum oral antibiotic is recommended. In a well-appearing child, a cephalosporin, trimethoprim-sulfamethoxazole (TMP-SMZ), or nitrofurantoin is a common choice. TMP-SMZ should not be used in children younger than 2 months because of the increased risk of kernicterus and blood dyscrasias. Nitrofurantoin, which is excreted in the urine and does not achieve therapeutic concentrations in the bloodstream, should not be used in febrile infants with UTI or in children in whom there is concern about renal involvement. The fluoroquinolones have recently been authorized for pediatric use.[11,27] Table 114-5 provides a summary of the commonly used antibiotics.

Low-dose antibiotic prophylaxis should be considered in all children with a febrile UTI awaiting a full evaluation with renal US and VCUG. Children with VUR, recurrent UTIs, or partial obstruction or who are immunocompromised should be considered for prophylactic antibiotics, although the clinical benefit remains in question.[17,19] The ideal prophylactic agent provides high urinary antibiotic excretion with low serum levels. Amoxicillin, nitrofurantoin, and TMP-SMZ are the most commonly prescribed agents. However, *Escherichia coli* has demonstrated increasing resistance to amoxicillin, thus limiting its use in children with symptomatic UTI. Generally, the antibiotic used for prophylaxis should be different from the antibiotic used to treat the acute infection.

**TABLE 114-5**

**Antibiotics Used to Treat Pediatric Urinary Tract Infections**

| ***Method of Delivery*** | ***Antibiotic*** | ***Additional Information*** |
|---|---|---|
| Parenteral | Ampicillin and gentamicin | Check gentamicin levels |
| | Ampicillin and cephalosporin | No *Enterococcus* or *Pseudomonas* coverage |
| | Ceftriaxone/ cefotaxime | Contraindicated in infants < 2 mo old |
| Oral | TMP-SMZ | Contraindicated in infants < 2 mo old |
| | Amoxicillin | Increasing resistance by *Escherichia coli* |
| | Nitrofurantoin | Inadequate if renal involvement |
| | Cephalosporins | No *Enterococcus* or *Pseudomonas* coverage |
| | Ciprofloxacin | Recently approved in children |

TMP-SMZ, trimethoprim and sulfamethoxazole.
Modified from Handel LN, Caldamone AA: Urinary tract infections in the pediatric population. Lebanese Med J 2004;52:194.

In patients with normal studies and recurrent UTIs—defined as three or more infections within a 6-month period—prophylactic antibiotics may be indicated. In these cases, one must consider other factors such as the patient's age, as well as the patient's biologic predisposition for UTIs and voiding pattern. For children started on prophylactic antibiotics, the rate of infection usually decreases; however, the risk of developing another UTI returns to baseline once prophylactic antibiotics are discontinued. These patients should be carefully screened for bladder and bowel dysfunction. In cases of asymptomatic bacteriuria, current recommendations include strict follow-up without antibiotic treatment.

VUR treatment depends on several factors: age at presentation, grade of reflux, presence or absence of voiding dysfunction, comorbidities, family compliance with a treatment protocol, and choice. It is helpful to divide VUR into primary and secondary categories. Primary reflux refers to a congenital abnormality of the vesicoureteral junction resulting in a foreshortened ureteral tunnel and poor detrusor backing of the ureter. The lack of detrusor backing prevents the ureter from being collapsed as the bladder fills (Fig. 114-8). Secondary reflux refers to other anatomic or functional abnormalities that may lead to reflux such as bladder outlet obstruction or an abnormality of the vesicoureteral junction (Table 114-6).

In the majority of patients with VUR, antibiotic prophylaxis, UTI surveillance, a regular voiding pattern, constipation management, and regular follow-up US and VCUG are the mainstays of therapy.[28] Indications for surgical correction are debatable, but most would agree with the following: breakthrough upper UTIs, renal scarring developing on antibiotic prophylaxis, poor renal growth, failure to follow a treatment plan, high-grade VUR (except in young infants), a fixed anatomic defect of the ureterovesical junction, and persistence of VUR followed for 2 years or longer associated with symptoms of BBD or UTI.[28]

VUR in a child with a recognized bladder and bowel dysfunction requires special mention. It is clear that if the bladder and bowel dysfunction (including constipation, if present) is managed well, the incidence of breakthrough UTIs and renal scarring and the need for surgical correction of VUR are significantly reduced.[28–31] Voiding dysfunction is a common cause of failed ureteral reimplantation.[32]


FIGURE 114-8 Anatomy of the normal and refluxing ureterovesical junction (UVJ). Note the lack of detrusor backing of the refluxing UVJ.

**TABLE 114-6**

| Causes of Secondary Reflux |
|---|
| Anatomic |
| Posterior urethral valves |
| Ureterocele |
| Diverticulum |
| Ectopic ureter |
| Prune-belly syndrome |
| Bladder exstrophy |
| Functional |
| Voiding dysfunction |
| Neuropathic bladder |
| Myelodysplasia |
| Sacral agenesis |

Many surgical techniques exist using intravesical and extravesical approaches. They all require the establishment of an intramural ureter with sufficient muscular backing to provide adequate ureteral wall coaptation with filling and contraction of the bladder such that retrograde flow of urine is prevented (Figs. 114-9 to 114-11). This approach requires an average hospital stay of 48 hours or less and has a complication rate of about 4%, 2% to 2.5% due to ureteral obstruction and 2% to 2.5% due to persistent VUR. The Pediatric Vesicoureteral Reflux Guidelines Panel delineated an open surgical success rate of 98% and a rate of 50% to 92% with endoscopic correction of VUR.[28]

In 1981 Matouschek[33] introduced the concept of endoscopic correction of urinary incontinence and VUR by polytetrafluoroethylene (Teflon) paste injection. This method was developed and popularized by Puri and O'Donnell, initially in a piglet model in 1984 and then applied to children with VUR.[34,35] This procedure causes little postoperative discomfort and can be performed as an outpatient procedure (Figs. 114-12 and 114-13). Owing to the potential risks of particle migration and malignancy induction,[36] Teflon is not in current use.[32] Many other injectable materials have been investigated and applied to animal models and humans for VUR correction. Success rates approach 75% to 80%, depending on the grade of reflux and the number of injections.[37–40] Today, the most commonly used materials worldwide are dextranomer macrospheres (Deflux, Oceana Therapeutics, Edison, N.J.) and polydimethylsiloxane with a water-based biocompatible carrier gel.

# Urinary Lithiasis

## HISTORY AND INCIDENCE

Urinary stones, in both the bladder and the kidney, have been reported in Egyptian mummies dating from 4800 BC,[41] and urolithiasis has long been studied in an effort to understand its pathogenesis and to refine treatment strategies. Although urolithiasis has been recognized in children for centuries, the clinical picture, evaluation, and management continue to evolve.

Approximately 7% of all stones occur in children younger than 16 years.[42] Traditionally, urolithiasis was characterized by bladder calculi in children of developing countries; the

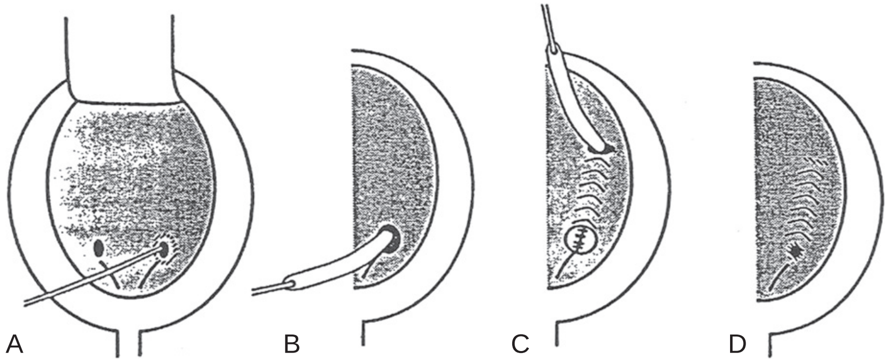


**FIGURE 114-9** Leadbetter-Politano ureteral reimplantation. **A,** The ureter is catheterized through a midline bladder incision. **B,** The ureter is dissected from the surrounding detrusor until it is totally mobilized. **C,** A neohiatus is created by passing a right-angle clamp into the bladder. A subepithelial tunnel is created, and the detrusor defect is closed. **D,** The ureter is then passed through the tunnel, and its orifice is matured. (From Rowe M, O'Neill JA, Grosfeld JL, et al: Essentials of Pediatric Surgery. St Louis, Mosby-Year Book, 1995.)

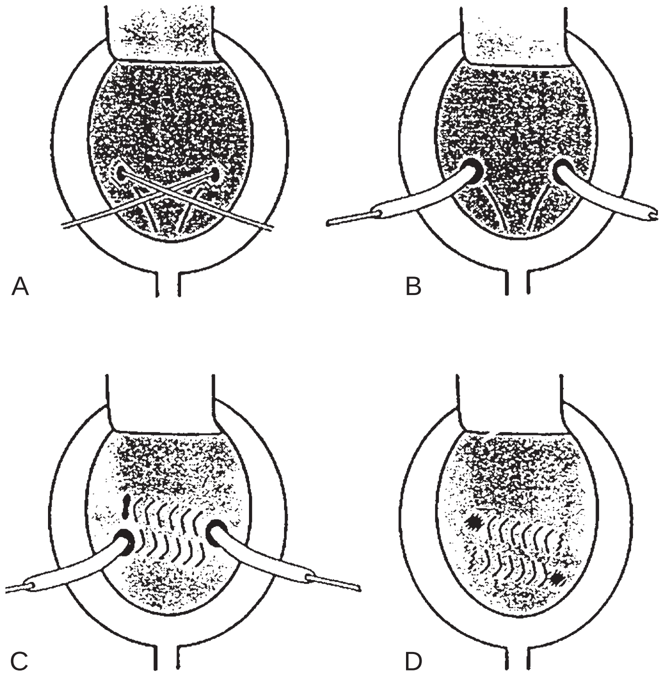


**FIGURE 114-10** Cohen cross-trigonal ureteral reimplantation. **A,** Both ureters are catheterized. **B,** Both ureters are fully mobilized, as in the Leadbetter-Politano procedure. **C,** The detrusor is approximated around the ureter to create a normal neohiatal caliber, and two transtrigonal tunnels are created. **D,** The ureters are then passed through the respective tunnels, and the orifices of the ureters are matured. (From Rowe M, O'Neill JA, Grosfeld JL, et al: Essentials of Pediatric Surgery. St Louis, Mosby-Year Book, 1995.)

incidence of upper tract calculi, occurring mainly in industrialized areas, was much lower in children than in adults. Also, in comparison with adult stone formers, children were more likely to demonstrate risk factors outside the metabolic realm such as UTI, anatomic abnormalities, and surgical alterations in the urinary tract. Currently, the incidence of upper tract calculi in children without these predisposing factors is on the rise worldwide,[43,44] and the paradigms are changing. The importance of metabolic evaluation in children with urolithiasis has been shown, even in countries thought to have primarily endemic bladder stone disease based on diet. With the introduction of smaller endoscopic instruments and the refinement of extracorporeal shock wave lithotripsy (ESWL) technology, treatment of pediatric stone disease now closely parallels stone management in adults.

## SPECTRUM OF DISORDERS

Although there are a number of contributing factors, the central concept in urolithiasis is urinary supersaturation. When a solute is added to a solvent, it dissolves until a certain concentration is reached, at which point the solution is saturated. Beyond this point, the solute may form crystals in the solution, and those crystals may aggregate. Supersaturation occurs when this point is surpassed and crystal precipitation occurs in the urine in the form of nucleation, the basis of urinary stones. Crystallization and aggregation must also occur for stones to form. These processes are influenced by the presence of inhibitors and promoters. Citrate, magnesium, pyrophosphate, glycosaminoglycans, nephrocalcin, and Tamm-Horsfall proteins are inhibitors of crystallization and aggregation. Bacterial infections and anatomic abnormalities such as obstruction or stasis may encourage crystal aggregation and retention, thus increasing the risk of clinically significant urolithiasis.[45,46] Multiple studies of urolithiasis in children have shown metabolic abnormalities in up to 92% of patients, with hypercalciuria and hypocitraturia the most common.[46–52] Interestingly, even in children with urolithiasis and anatomic obstruction, the prevalence of urinary metabolic abnormalities is high.[45,49,53] The prevalence of infection-related stones is especially high in children younger than 6 years.[54] Approximately 12% of children with urolithiasis have no identifiable risk factor.[55] Urinary stone disease can, therefore, be classified as metabolic, anatomic, infectious, or idiopathic, on the basis of underlying factors. The relative contribution of these factors, which may overlap in some cases, is shown in Table 114-7.

Stones can also be classified on the basis of their location in the upper urinary tract (kidneys and ureters) or lower urinary tract (bladder and urethra) and as symptomatic or asymptomatic. These classifications may influence the decision-making process with regard to treatment options.

## CLINICAL PRESENTATION

In adults, upper tract calculi present in a characteristic fashion in the form of renal colic. This severe, intermittent, refractory pain, often accompanied by nausea and vomiting, is a less common presentation in children. Although classic renal colic does occur in children, more commonly, stones involving both the upper and lower tract are detected during the radiologic evaluation for UTI or hematuria. Younger children in

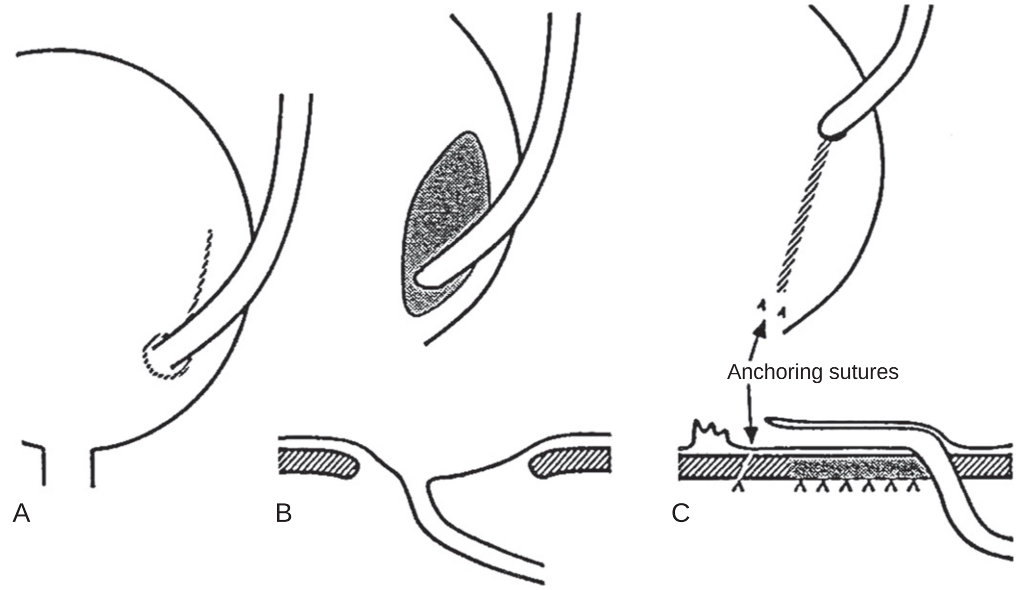


**FIGURE 114-11** Extravesical detrusorrhaphy—a modification of the Lich-Gregoir procedure. **A,** The ureter is mobilized for several centimeters externally. The detrusor is then incised in a caudal direction and carried around the ureteral insertion. **B,** The ureter is left attached only to the underlying bladder mucosa. **C,** The distal ureter is advanced and fixed with two sutures. Then the detrusor is approximated over the ureter to recreate the tunnel, which is now longer than before. (From Rowe M, O'Neill JA, Grosfeld JL, et al: Essentials of Pediatric Surgery. St Louis, Mosby-Year Book, 1995.)

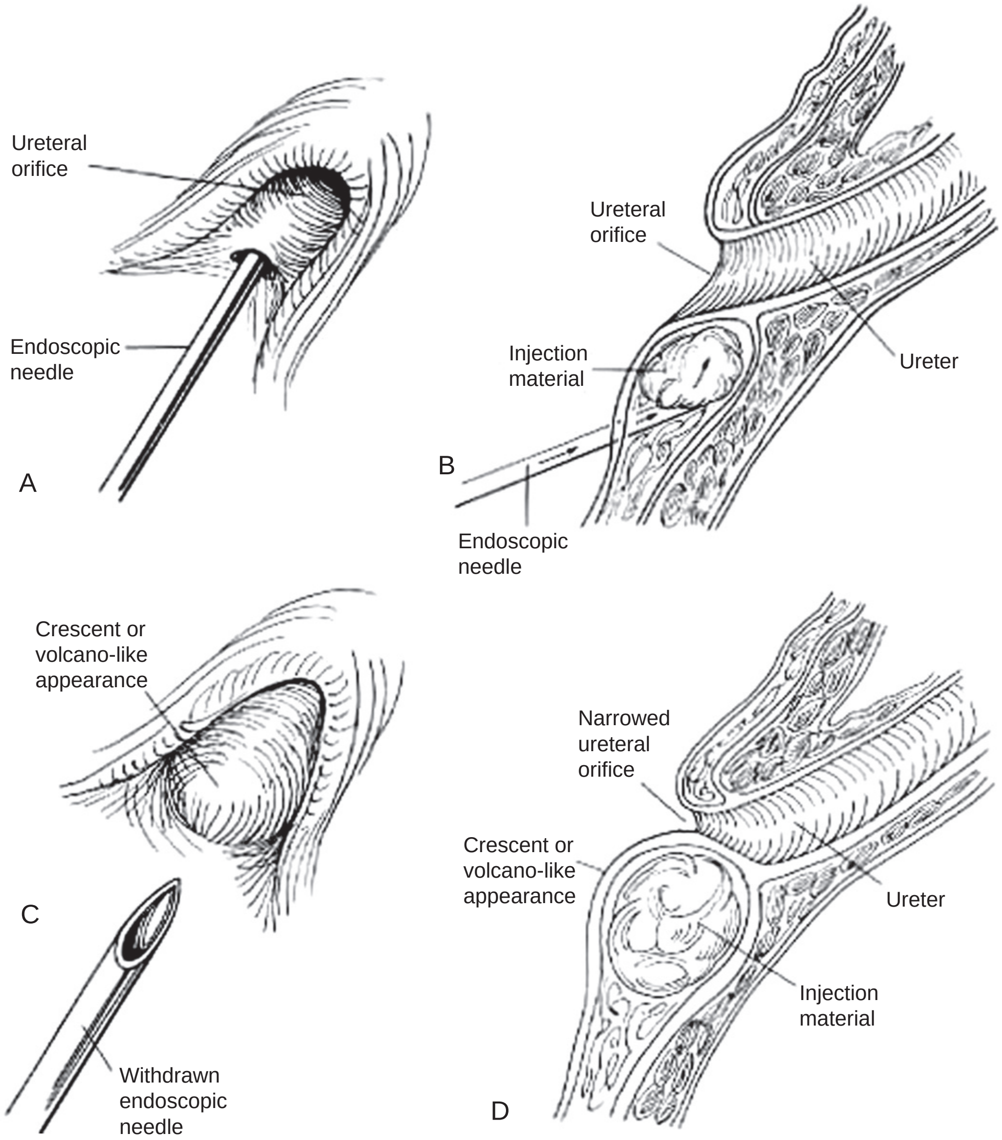


**FIGURE 114-12** Endoscopic technique for reflux connection. **A,** The needle is placed at the 6 o'clock position, bevel up. **B,** Slow injection in subureteral space. **C,** Postinjection appearance. **D,** Appropriate position of injected material. (From Russinko PJ, Tackett LD: Endoscopic correction of reflux. In Caldamone AA [ed]: Atlas Urol Clin North Am 2004;12:55.)

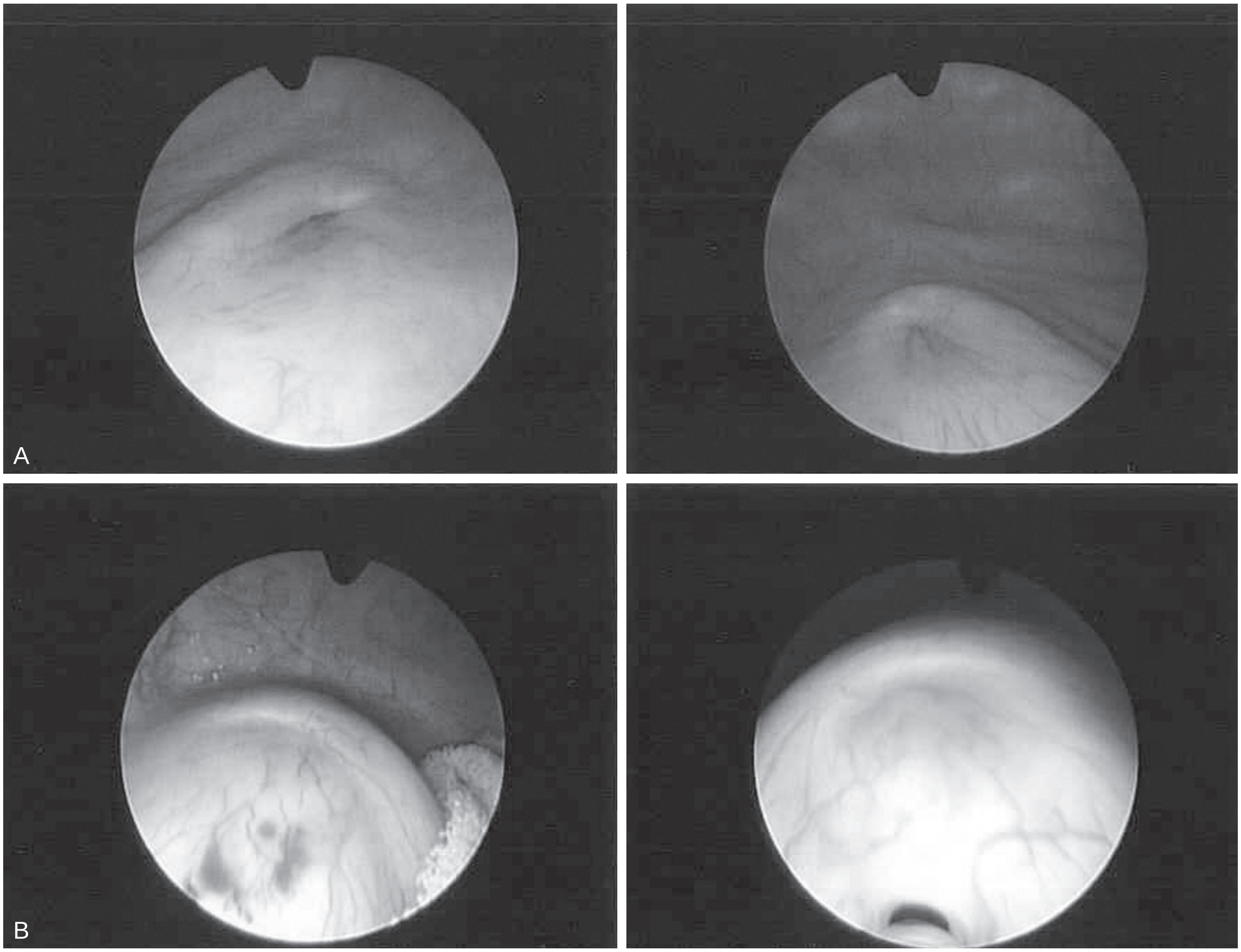


FIGURE 114-13 Endoscopic injection. **A,** Left and right ureteral orifices before injection. **B,** Left and right ureteral orifices demonstrating the crescent appearance after injection.

**TABLE 114-7**
**Clinical Diagnoses in Children with Urolithiasis**

| *Diagnosis* | *Mayo Clinic (N = 221) No. of Patients (%)* | *North America (N = 492)* No. of Patients (%)* | *Europe (N =481)* No. of Patients (%)* |
|---|---|---|---|
| Metabolic disorder | 115 (52.0)† | 162 (32.9)‡ | 59 (12.3) |
| Idiopathic hypercalciuria | 38 | 39 | 36 |
| Immobilization | 8 | 39 | 4 |
| Uric acid stones | 8 | 22 | 2 |
| Endemic stones (urate) | 0 | 10 | 0 |
| Cystinuria | 15 | 15 | 9 |
| Hyperoxaluria | 25 | 12 | 5 |
| Renal tubular acidosis | 4 | 10 | 2 |
| Other | 38‡ | 25 | 1 |
| Developmental anomalies of genitourinary tract | 66 (29.9)† | 160 (32.5) | 145 (30.1) |
| Infection | | | |
| Primary | 41 (18.6)† | 21 (4.3) | 209 (43.5) |
| All causes | — | 215 (43.7) | 358 (74.4) |
| Unknown cause | 55 (24.9) | 139 (28.3) | 68 (14.1) |

*Data from Polinsky MS, Kaiser BA, Bacuarte HJ: Urolithiasis in childhood. Pediatr Clin North Am 1987;34:683.
†Metabolic disorders often coexisted with genitourinary tract anomalies and infections.
‡More than one disorder in some patients.
From Liebermann E: Importance of metabolic contributions to urolithiasis in pediatric patients [editorial]. Mayo Clin Proc 1993;68:313.

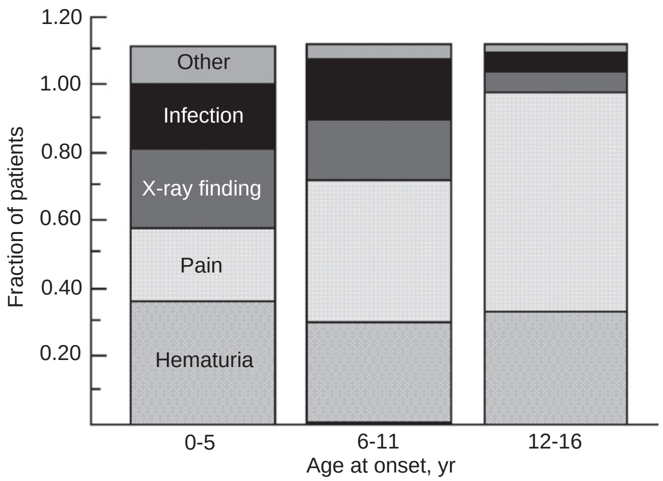


**FIGURE 114-14** Clinical features at the time of initial assessment of 221 children and adolescents with urolithiasis who were examined at the Mayo Clinic between 1965 and 1987. (From Milliner DS, Murphy ME: Urolithiasis in pediatric patients. Mayo Clin Proc 1993;68:241.)

particular may also present with nonspecific abdominal pain accompanied by microscopic hematuria or, less frequently, with outlet obstruction (Fig. 114-14).

## DIAGNOSIS

History and physical examination are key components to rule out other causes of abdominal and back pain. The history should include a dietary and urologic history. One clue to the presence of urolithiasis is a positive family history for kidney stones, which may be present in up to 37% of children with stone disease.[56] Other underlying medical conditions that may predispose children to urolithiasis include hyperparathyroidism, renal tubular acidosis, inflammatory bowel disease, seizure disorders treated with a ketogenic diet,[57] cystic fibrosis, and Dent disease.[58] Urinalysis and urine culture should be obtained to assess for microscopic hematuria, urine pH, crystals in the sediment, and UTI. Baseline serum electrolytes, blood urea nitrogen, creatinine, calcium, uric acid, phosphorus, and magnesium levels should also be obtained. A 24-hour urinalysis for stone risk assessment should be obtained after treatment of the presenting stone.

Radiologic evaluation may include plain abdominal radiography, US, intravenous pyelography, and noncontrast CT. In adults, the standard imaging study is noncontrast CT because of its sensitivity and specificity. In children, however, these studies are limited, although some authors recommend CT as the first-line imaging study.[59,60] Others recommend initial abdominal US because of the varied presentation of urolithiasis in children and because of concerns about radiation exposure.[61,62] Plain abdominal radiography may not be helpful in the initial diagnosis but may assist in planning treatment on the basis of the ability to visualize the stone.

## TREATMENT

Four main factors affect initial treatment decisions: the clinical scenario, stone composition, stone size, and stone location (Table 114-8). In the setting of potential urinary tract obstruction with fever or complete obstruction, urgent relief of the obstruction is warranted, either by placement of a ureteral stent or by percutaneous nephrostomy. The decision between ureteral stent placement and percutaneous nephrostomy is dependent on physician preference, available resources, and patient size and anatomy. In children, nephrostomy drainage may be performed without general anesthesia and may be the procedure of choice. After relief of the obstruction and subsequent treatment of infection, definitive therapy directed at stone clearance can be undertaken.

The most common composition of upper tract calculi is calcium oxalate. The stones are radiopaque and do not respond to dissolution therapy. Calcium oxalate monohydrate stones may be resistant to ESWL, whereas calcium oxalate dihydrate

**TABLE 114-8**
**Factors Affecting the Treatment of Stones**

| *Factor* | *Treatment Consideration* |
|---|---|
| Clinical scenario | |
| Bilateral obstruction | For all scenarios, urgent relief of obstruction via stent or nephrostomy |
| Obstruction of a solitary kidney | |
| Fever/UTI with potential obstruction | |
| Intractable pain | |
| Stone composition | |
| Uric acid | Consider chemodissolution |
| Struvite | Continue antibiotic therapy throughout treatment |
| Cystine | Responds poorly to ESWL |
| Calcium oxalate | Radiopaque; may respond well to ESWL |
| Stone size | |
| <4 mm | Approximately 90% chance of spontaneous passage |
| 4-6 mm | Approximately 50% chance of spontaneous passage |
| >6 mm | Approximately 10%-20% chance of spontaneous passage |
| Stone location | |
| Renal | ESWL or PCNL |
| Proximal ureteral | Ureteroscopic extraction (antegrade) or ESWL |
| Distal ureteral | Ureteroscopic extraction (retrograde) or ESWL |
| Bladder | Cystolithotomy or cystolitholapaxy |

ESWL, extracorporeal shock wave lithotripsy; PCNL, percutaneous nephrostolithotomy; UTI, urinary tract infection.

calculi, which are more common, generally respond well. Uric acid calculi are radiolucent and form at a low urinary pH. They are often identified by their characteristic Hounsfield units on noncontrast CT. Uric acid stones may be dissolved and prevented by alkalinization of the urine (pH $> 6.5$) using sodium bicarbonate or potassium citrate. If symptoms are present, a ureteral stent or nephrostomy tube may be used for temporary relief during dissolution therapy. Struvite stones are usually associated with infection, and antibiotics should be continued throughout treatment. Because struvite stones are generally large or staghorn in shape, percutaneous nephrostolithotomy (PCNL) is often the first-line treatment for these stones. Cystine stones are typically difficult to treat and frequently recur. Small renal cystine stones may be treated by ESWL, whereas larger stones will likely require PCNL or ureteroscopic extraction.[63]

Stone size can be used to predict whether the stone will pass without intervention. In adults, the likelihood of passing a stone less than 4 mm is 90%, a stone between 4 and 6 mm has an approximately 50% rate of spontaneous passage, and one greater than 6 mm has a 10% to 20% rate. Interestingly, small stones and stone fragments after ESWL have shown the same passage rate in the pediatric population, theoretically because of ureteral pliability and peristalsis.[46,64,65] Therefore supportive care in the form of vigorous hydration (oral or intravenous, as needed) and analgesic therapy is a reasonable first step in a child with a small stone in the absence of fever or complete ureteral obstruction. Studies demonstrate that partial obstruction is well tolerated in the short term; thus this treatment may be continued for 3 to 4 weeks on an outpatient basis to allow spontaneous passage of the stone. In the case of an obstructing stone 4 mm or greater in size, the likelihood of spontaneous passage is significantly lower, and intervention may be indicated sooner. Nonobstructing stones can be treated electively. Stones larger than 2 cm have demonstrated a poor stone-free response to ESWL, and a National Institutes of Health Consensus Conference in 1998 recommended that stones larger than 2 cm be approached by PCNL as first-line treatment. "Sandwich therapy," which is a combination of PCNL and ESWL, is an addition to the treatment armamentarium for large calculi.

Calculi are most commonly located within the renal pelvis or calices, proximal ureter, distal ureter, or bladder. Each location lends itself to different treatment approaches. For renal calculi, ESWL or PCNL is suitable. ESWL or ureteroscopic stone extraction is an appropriate choice for ureteral stones, whereas cystolitholapaxy or cystolithotomy is recommended for bladder calculi.

ESWL, first described in the early 1980s,[66] is noninvasive and well-tolerated but requires general anesthesia in many young children and special precautions in infants. Children who weigh as little as 6.8 kg have been successfully treated. This procedure may be suitable for proximal ureteral stones and even some distal ureteral stones; however, treatment of calculi more distal than the midureter is contraindicated in females because of the unknown effects of shock waves on the developing ovary. Stone-free rates after one to two treatments generally range from 70% to 97% (mean 85%).[67–71] Complications of ESWL therapy include incomplete fragmentation of the stone, retained fragments, Steinstrasse, perinephric hematoma, fever, renal colic, and abrasion or ecchymosis at the site of shock wave entry and exit.[72] Although the distant and long-term effects of ESWL are unknown, short-term follow-up studies suggest no demonstrable complications with regard to renal function or hypertension.[42,72–74]

PCNL requires nephrostomy tube placement, general anesthesia, and inpatient hospitalization. Once the nephrostomy tube is placed, the tract is dilated to a size appropriate for the nephroscope and electrohydraulic or ultrasonic lithotriptor.[75] It is a good choice for a large renal stone associated with hydronephrosis or one refractory to ESWL treatment (cystine or calcium oxalate monohydrate). PCNL and ESWL can be combined for optimal treatment in some cases, so-called *sandwich therapy*. Stone-free rates may approach 100%; however, multiple procedures may be required to render a child stone free.[68,76] Complications of PCNL include perforation of the collecting system, bleeding, extravasation of irrigant, pneumothorax, intestinal injury, and retained fragments.

Ureteroscopic stone extraction in children has become feasible with the development of progressively smaller ureteroscopes and working instruments. Ureteroscopic treatment of ureteral calculi may be approached in an antegrade or retrograde fashion, and the stone may be extracted intact or fragmented using a laser, ultrasound, or hydraulic lithotriptor (Swiss Lithoclast). Success rates for ureteroscopic stone extraction may exceed 95%.[68,69,77–80] An indwelling ureteral stent may be left in place for 24 to 72 hours to prevent obstruction secondary to ureteral spasm or edema. Complications include ureteral perforation, ureteral stricture, reflux, proximal migration of the stone, and loss of the stone through a perforated ureter.

Despite the success of minimally invasive treatment for pediatric stone disease, open surgical treatment is still required in up to 17% of patients,[69] which may result in decreased renal function in up to 45%.[81] Anatomic abnormalities such as ureteropelvic junction obstruction or obstructed megaureter may be addressed concurrently with stone treatment and must be dealt with eventually to prevent recurrence and optimize renal function.[82,83]

Cystolitholapaxy, or transurethral lithopexy of bladder stones, has been the preferred approach for all but large bladder calculi. The stone is fragmented using the electrohydraulic lithotriptor, and the fragments are irrigated from the bladder. Bladder calculi are becoming more common in children who have undergone augmentation cystoplasty, and in this population, open removal of the intact calculi may be a more prudent approach to minimize the risk of recurrence due to retained fragments, although this remains controversial.[84–86]

## RECURRENCE

Children who present with urolithiasis are at risk for recurrence for a longer time than adults. Thus the cumulative likelihood of recurrent stone disease is higher in children. Therefore a thorough metabolic evaluation is strongly encouraged in children after their first presentation with urolithiasis. A 24-hour urinalysis for stone risk should be obtained including, at a minimum, urinary volume, pH, and calcium, creatinine, uric acid, citrate, oxalate, and magnesium levels. The cornerstones for preventing stone recurrence as the child enters adulthood are the ability to render the patient stone free, elucidate and treat metabolic abnormalities, control urinary infection, and correct anatomic anomalies.

# Renal Vein Thrombosis

Renal vein thrombosis is a variable clinical disorder related to the acuteness and extent of venous occlusion of the main or intrarenal veins. Rayer[87] first described renal vein thrombosis more than 150 years ago. For many decades, the condition was rarely diagnosed clinically but was discovered at operation or autopsy. Once the condition was clinically recognized, treatment initially consisted of simple nephrectomy; this procedure was advocated until the early 1960s.[88,89] In 1964 Stark[90] reported excellent recovery after conservative management, suggesting that aggressive surgical intervention was unnecessary. The use of anticoagulants or thrombolytic agents still remains controversial because of the limited number of pediatric cases and the absence of controlled trials evaluating the risks and benefits of these therapeutic interventions.

## CAUSE

Renal vein thrombosis is a disease of infancy; approximately 80% of patients present during the first month of life.[91] It results from diminished renal blood flow, increased blood viscosity, and hypercoagulability. The neonatal kidney is particularly vulnerable because of its low renal perfusion pressure and double intrarenal capillary network. Many factors also lead to hemoconcentration, with a sluggish venous flow that predisposes patients to thrombosis. In addition, up to 50% of these patients may have prothrombotic abnormalities.[92,93] The thrombotic process may originate in the main renal vein or in the small intrarenal veins.[94] Thrombosis may be unilateral or bilateral, but thrombosis from the inferior vena cava is rare.[95]

Clinical conditions predisposing neonates to thrombosis include preterm delivery[92]; perinatal asphyxia, polycythemia, and cyanotic congenital heart disease[96]; maternal diabetes[97,98]; septicemia and congenital nephrotic syndrome[99,100]; cytomegalovirus infection[101]; shock, diarrhea, and dehydration[102]; activated protein C resistance[92]; factor V Leiden heterozygosity[93]; and maternal use of diuretics and corticosteroids.[103] Renal vein thrombosis has been noted in association with adrenal hemorrhage and has been recognized on prenatal US.[104–106]

In infants older than 1 month, renal vein thrombosis is usually associated with hypovolemia such as with gastrointestinal fluid losses or burns[99,102,107] or renal disease such as nephrotic syndrome.[108,109] Renal vein thrombosis may occur secondary to prolonged inferior vena cava catheterization, with thrombus extending into the renal vasculature.[108]

## CLINICAL PRESENTATION

Clinical presentation varies, depending on the age, extent, and acuity of the thrombosis. In the neonatal period, males are affected predominantly (62%) and most cases are unilateral (70%) and on the left side (63.6%).[110] Renal vein thrombosis may present prenatally or in a healthy newborn with no predisposing illness. In neonates, classic features include a palpable mass and gross hematuria; however, these signs may be found in only 13% of patients at the time of diagnosis.[101] Caval thrombosis may be suspected when the lower extremities are swollen and the superficial abdominal veins are dilated. Renal vein thrombosis may also present in infancy after a predisposing illness, or it may develop in an older child who has preexisting renal disease (nephrotic syndrome). Presentation in older children generally includes acute flank pain, hematuria, and a palpable mass.

## DIAGNOSIS

Renal vein thrombosis is frequently associated with thrombocytopenia (platelet count $< 75{,}000$ cells/mm$^3$) as a result of platelet entrapment in the renal thrombus. A consumptive coagulopathy characterized by a prolonged prothrombin time and increased fibrin degradation products may also be present. Leukocytosis is often present, and the presence of anemia varies. Serum electrolyte levels vary, depending on predisposing illness and renal function. Urinalysis usually shows blood and protein. Screening for prothrombotic abnormalities should be considered.

## IMAGING

An abdominal radiograph may show an enlarged renal shadow or have a lacelike pattern, similar to the renal vascular tree, but it is usually normal.[111] Renal Doppler US is the test of choice to evaluate the renal mass and image the renal vein and inferior vena cava. Diagnostic features include thrombus in the vein and renal enlargement.[112] Renal function can be monitored initially and during recovery with radionuclide scintigraphy using technetium 99m DMSA or technetium 99m MAG3. CT, magnetic resonance imaging, or inferior venacavography may be indicated to determine the extent of a thrombus (with inferior vena cava involvement) or to rule out rare causes of thrombus or thrombosis (e.g., external venous compression or thrombus from a renal tumor).

## TREATMENT

Because of the relative infrequency of renal vein thrombosis and the lack of controlled trials, no general consensus on optimal treatment exists. Although nephrectomy and thrombectomy were previously performed during the acute phase, this was rarely necessary on an emergent basis and is now limited to patients with anatomic obstruction of the inferior vena cava.[90] Management of renal vein thrombosis should include a multidisciplinary team including neonatologist or pediatrician, radiologist, hematologist, and nephrologist. Initial treatment should include correction of and therapy for all predisposing conditions, aggressive fluid and electrolyte repletion, and prevention of propagation of the venous thrombus. The use of anticoagulants or thrombolytic agents is controversial because of the absence of controlled trials. In a retrospective study of 16 patients with renal vein thrombosis, renal function was normal in 6 of 9 patients treated with heparin or enoxaparin or both, compared with 0 of 7 patients who did not receive anticoagulation therapy.[93,113] In a review of the English-language literature from 1992-2006, no difference in the rate of significant renal atrophy (70.6% overall) was seen between groups treated with supportive care only (72.5%) and heparin (75.3%).[110] A reasonable approach includes aggressive supportive measures in cases of unilateral renal vein thrombosis without caval extension, especially for those at increased risk of hemorrhagic complications.

For unilateral renal vein thrombosis with caval extension or bilateral renal vein thrombosis, heparin therapy may be considered because of the risk of pulmonary emboli or renal failure.[91] Thrombolytic therapy may be considered for bilateral renal vein thrombosis and renal failure. Although heparin has been used successfully, hemorrhagic complications have been reported in neonates.[114,115] Low-molecular-weight heparin may be a safer alternative, with careful attention to special dosing requirements in preterm and full-term newborns.[93,116] Thrombolytic therapy with streptokinase and urokinase by systemic and regional routes has been reported.[95,99,114] Potential complications with the systemic use of streptokinase include hemorrhage and allergic reactions; these occur less often with selective regional use. Route, rate, and length of infusion of thrombolytic agents differ among various reports; thus standardized protocols are difficult to establish.

## OUTCOME

With improved recognition and management of renal vein thrombosis and the various predisposing conditions, the overall survival rates have improved to about 80% to 85% or higher.[91,110] Most deaths are due to underlying disease rather than renal infarction. Long-term morbidity including conditions such as hypertension, renal atrophy, and chronic UTI has not been systematically assessed. In terms of renal function, the outcome can vary from full recovery to nonfunction. Periodic monitoring with radionuclide scintigraphy permits detailed follow-up evaluation of renal recovery. Renin-mediated hypertension in association with a small, atrophic kidney or recurrent UTIs localized to the shrunken renal unit are reasonable indications for nephrectomy.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 115

# Ureteral Duplication and Ureteroceles

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A duplex (duplicated) system is a kidney with two pelvicaliceal systems. Complete duplication refers to a kidney with two ureters that drain separately into or below the bladder. Incomplete duplication refers to a kidney with two ureters that fuse into a unit proximal to the bladder and then drains into the bladder through a single orifice. A bifid system is a form of incomplete duplication with two renal pelves that join into a single ureter.

The upper or lower pole ureter refers to the ureter draining the upper or lower pole (moiety) of the kidney, respectively. The upper or lower pole orifice refers to the ureteral orifice associated with the upper or lower pole ureter, respectively. An ectopic ureter refers to a ureter that drains into an abnormal site.

The greater majority of duplicated systems are incomplete, and these forms rarely give rise to clinical problems. In contrast, complete duplication anomalies are rare, affecting less than 0.1% of individuals (most females), and are more commonly of clinical significance.[1] Patients with urinary symptoms such as those associated with urinary tract infection (UTI), have about a 4% incidence of ureteral duplication.[2] Two thirds of children with duplex systems who present with UTI have vesicoureteric reflux (VUR).[3] This is particularly true of complete duplex systems, which are associated with higher grades of reflux and renal dysplasia with poor renal function in the affected moieties.[4] A significant familial predisposition exists—between 12.5% and 30% of siblings of affected patients have duplications.[5–7] It has been suggested that the mode of inheritance is autosomal dominant with incomplete penetrance.[5,8]

Less common types of ureteral duplications are (1) the “inverted Y” ureter, consisting of a single pelvis and a proximal ureter that bifurcates distally into two ureters ending with two separate orifices, one of them being frequently ectopic; and (2) the “blind-ending” duplication of the ureter, which occurs when one limb of a bifid ureter does not drain a portion of renal parenchyma.[9,10]

A ureterocele is a cystic dilatation of the lower end of the ureter where it joins the epithelium of the lower urinary tract. An intravesical ureterocele lies entirely within the bladder, whereas an ectopic ureterocele has a portion that lies below the bladder neck.

## Embryology

Ureteral duplication is the consequence of the abnormal development of the ureteral bud from the mesonephric (wolffian) duct. Premature branching of the bud causes incompletely duplicated ureters. Complete ureteral duplication occurs when two separate ureteral buds arise independently from the mesonephric bud and induce the development of a duplex kidney.

The cloaca is divided into the urogenital sinus anteriorly and the alimentary tract behind. Around the eighth week of gestation, the distal end of the mesonephric duct plus a short segment of this duct above the ureteric bud expands and, by differential growth, is incorporated into the lower end of the posterior wall of the developing bladder and urogenital sinus. At this stage the mesonephric duct lies below and medial to the ureteral orifice and is referred to as the wolffian duct. As a result of this “migration,” the normal ureteral orifice is situated at the superolateral angle of the bladder trigone (Fig. 115-1, *A*).[11]

In the male the mesonephric duct becomes the epididymis, vas deferens, and seminal vesicle and enters the posterior urethra above the external urethral sphincter at the verumontanum. The associated ureteric bud must, therefore, also join the developing bladder and urethra above the external sphincter. The testis that initially arises from a region medial to the developing kidney becomes attached to the mesonephric duct. As it descends to the deep inguinal ring, the vas deferens (mesonephric duct) crosses the origin of the ureter superiorly as it arches medially and inferiorly to the seminal vesicle at the level of the verumontanum.[11]

In the female the mesonephric duct becomes the Gartner duct, which lies close to the lateral wall of the vagina. The paramesonephric ducts (müllerian ducts) develop medial to the mesonephric duct. At the caudad end of the embryo, these incorporate the distal end of the remnants of the mesonephric duct where they penetrate the cloaca near the midline. Thus owing to differential growth, the ureteric bud may migrate

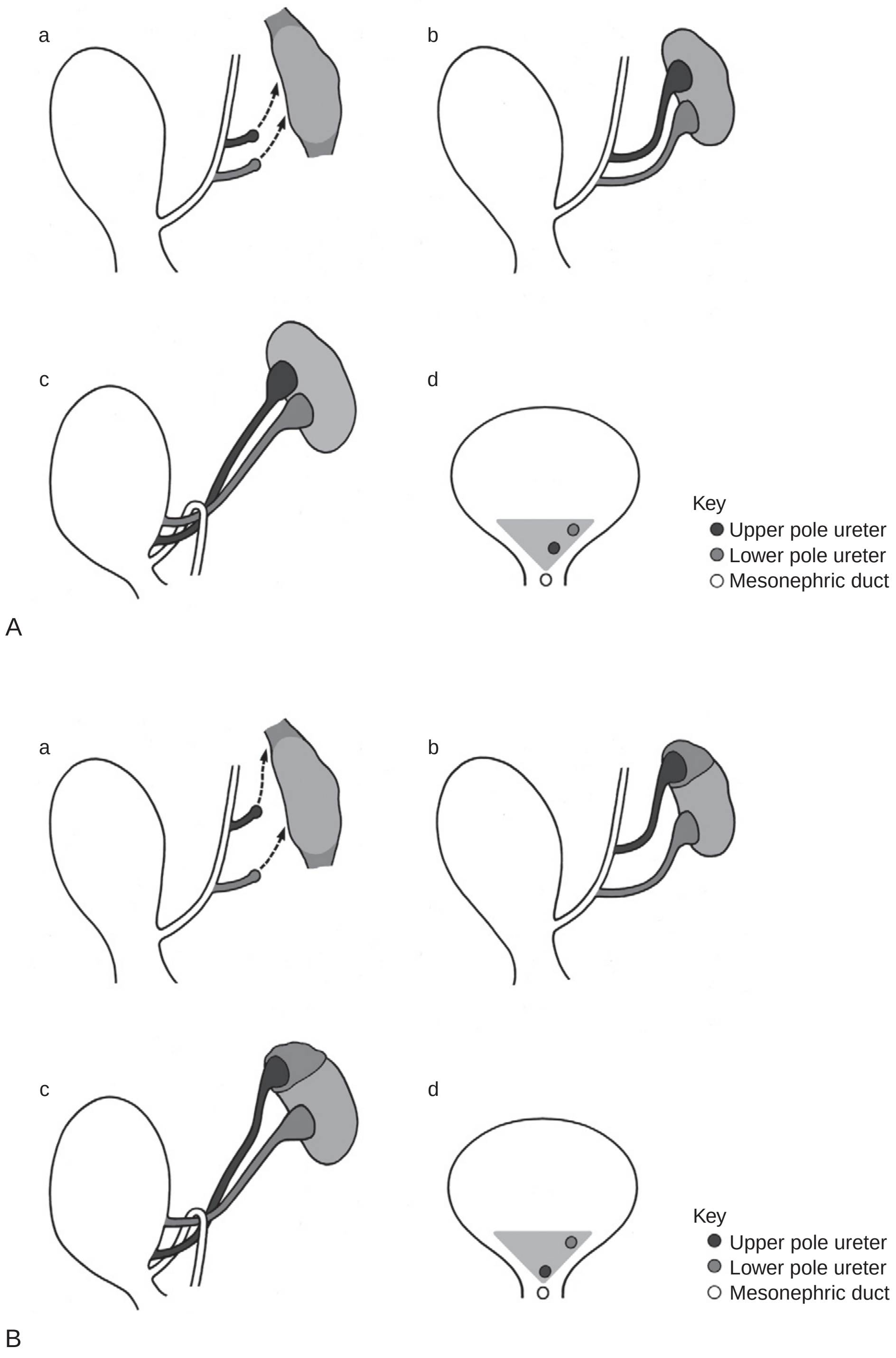


**FIGURE 115-1** **A,** The normal relationship between the mesonephric duct and the ureteric buds and the subsequent positions of their orifices within the bladder (Weigert Meyer law). Also note the area where the buds come in contact with the renal blastema. **B,** Compare with **A** and you will notice that the upper ureteric bud reaches the renal blastema late and into the periphery, thus inducing dysplasia of the upper renal moiety (shaded); also note the position of the upper ureteric orifice in this scenario is caudal in comparison with the situation in **A.**

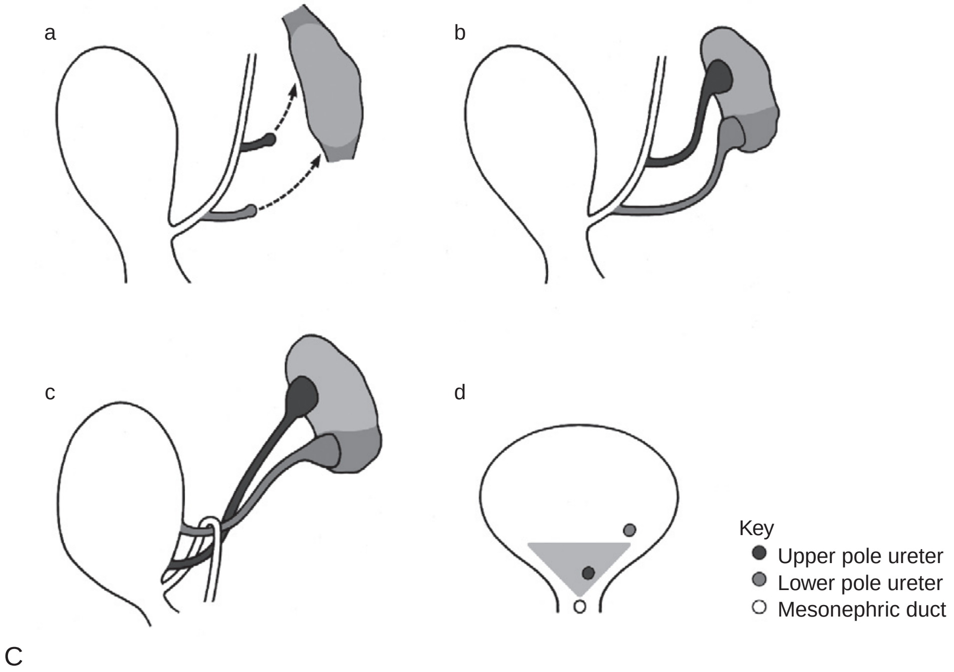


**FIGURE 115-1—CONT'D.** **C,** Compare with **A** and you will notice the lower ureteric bud reaches the renal blastema in the periphery and thus induces abnormal dysplastic development of the lower renal moiety; also note that the position of the lower ureteric orifice in this case is superolateral in comparison with the situation in **A.** Here the submucosal tunnel of the lower pole ureter is relatively short and therefore more prone to reflux.

with the associated paramesonephric duct structures to sites such as the vestibule, vagina, cervix, uterus, and rectum.[11]

The induction of the metanephric blastema by the ureteral bud in a central position is critical to normal renal development. If the ureteral bud meets the metanephric blastema either too caudal or too cranial along the metanephric blastema, renal dysplasia will result.[12] The more superior of the two ureteric buds may make contact with the blastema of the upper pole of the kidney too late to induce normal development. In clinical practice, renal dysplasia affecting the upper pole of the kidney is often encountered in duplex systems (see Fig. 115-1, *A* and *B*).

During development of the trigone, the most cranial ureter that drains the upper moiety of the duplex kidney rotates inward on its long axis and crosses the lower pole ureter. Therefore the upper pole ureter opens in the urogenital sinus in a more distal and medial position than the lower pole ureter that opens more proximally. This relationship between the two ureteral orifices is constant and is called the Weigert-Meyer rule (Fig. 115-1, *A*).

When the two ureters originate close to each other and in a near normal position, both ureteral orifices open in the trigone (see Fig. 115-1, *A*). Conversely, when the two ureteral buds originate at widely separate positions on the mesonephric duct, the upper pole ureter, which is located at a more cranial position on the mesonephric duct, is incorporated into the urogenital sinus at a later stage of development. As a result, the ureteral orifice is situated in an ectopic position, inferior to the trigone (see Fig. 115-1, *B*). In the male in this situation, the location of the ureteral orifices can be anywhere along the lower mesonephric duct or its derivatives below the bladder neck in the posterior urethra but always above the external urethral sphincter. Therefore urinary incontinence due to duplex systems with ectopia of the upper pole ureter does not occur in boys. In girls, however, the situation is different. During development, the mesonephric duct derivatives can open anywhere caudally from the developing bladder, commonly into the vault of the vagina.

The lower pole ureter, which joins the mesonephric duct closer to the urogenital sinus, is incorporated into the developing trigone at an early stage and consequently migrates laterally and cranially, leaving a relatively short intravesical tunnel (Fig. 115-1, *C*). VUR into the lower pole ureter may be present because of the short length of the intramural tunnel.

Occasionally, in either complete or incomplete duplication, one of the ureters fails to meet the developing blastema of the metanephros. In this case, a blind-ending ureter occurs, with no attachment to the kidney.[10] Rarely, an inverted Y abnormality is encountered. It is presumed to be caused by double ureteric buds arising from the mesonephric duct caudally and fusing cranially before merging above with the blastema of the metanephros.[9]

Recently, there has been a shift from classic theories to the cell biology view of congenital anomalies of the kidney and urinary tract (CAKUT).[13] The process of ureteral budding and metanephric differentiation into the final kidney is under the control of the renin-angiotensin system through the Agtr-2 receptor, which is intensely expressed in the mesenchymal cells surrounding the wolffian duct at the time of the initial budding of the ureter. Most recently it has been shown that ectopic budding and ureteral duplication may occur in Agtr2 null mice.[14] The formation of a double collecting system has also been observed in another group of experimental animals that are heterozygous mutants for the bone morphogenetic protein 4 (BMP4). BMP4 is a member of the transforming

growth factor-beta (TGF-β) superfamily and is credited to be part of the navigating system that allows the budding of the ureter from the mesonephric duct at a precise site.[13] Abnormalities in the number and site of the initial ureteral buds preceding a duplex collecting system and ectopic ureteral orifice with concurrent renal abnormalities are constantly observed in mice that are homozygous mutants for the *FOXC1* gene, which encodes for a transcription factor playing an essential role in embryonic development.[13]

# Incomplete Duplicated Systems

Uncomplicated duplex kidneys may be detected incidentally on ultrasound scans done for unrelated reasons. Bifid pelvis is never responsible for any symptoms. Incompletely duplicated ureters are also often completely asymptomatic but in rare cases are associated with distinct clinical problems.

Three clinical problems may affect an incompletely duplicated ureter: (1) VUR, (2) ureteropelvic junction obstruction, and (3) retrograde ureteral peristalsis (yo-yo phenomenon).

Treatment depends on the function of the affected renal moiety and on the length of the lower limb. If the function is poor, a partial lower pole nephroureterectomy is the appropriate choice, removing the lower moiety and its ureter down to the junction with the upper pole ureter. If the lower moiety is worth saving, the type of repair depends on the length of the ureter. If the ureter is very short, the upper and lower pelvis may be joined side by side (pyelopyelostomy) to create a single pelvis drained by the upper ureter. Conversely, if the lower ureter is long, a conventional dismembered pyeloplasty can be done, but, if the junction between the two limbs is close to the bladder, a ureteroureterostomy with excision of the distal ureter is a better solution in order to avoid the possibility of uretero-ureteral reflux.

Even when uretero-ureteral reflux (yo-yo reflux) is demonstrated, it is difficult to relate the frequently vague complaints of the patient to the peristaltic disorder. Clinical judgment is required before proceeding to a surgical repair, which may consist of a proximal pyelo-ureteral anastomosis with removal of one ureter or, if the ureteral junction is close to bladder wall, excision of the common limb and reimplantation of the two ureters into the bladder side by side.

## COMPLETE DUPLICATION ANOMALIES

### Vesicoureteric Reflux

The most frequent anomaly detected in completely duplicated ureters is VUR. As a rule, it always affects the lower pole ureter either independently or with VUR into the upper pole ureter because it opens in the trigone in a more cranial and lateral position with a shorter submucosal tunnel, causing incompetence of the ureterovesical junction. When VUR rarely occurs into both moieties, the ureteral orifices are usually close together and in a lateral ectopic location.

The most common presentation is UTI, with more than 60% of children with UTIs and a duplex kidney having vesicoureteral reflux.[15] Therefore when ultrasound reveals a duplex kidney in a child with a history of a UTI, a micturating cystourethrogram is mandatory.

**FIGURE 115-2** Drooping lily appearance of a refluxing right lower pole ureter. Note that the contralateral ureter is also refluxing with all its calyces intact, but the calyces are missing on the right, giving it a characteristic lower pole appearance.

Cystourethrogram often reveals the pelvis in a lower than normal position with an abnormal renal axis. The upper calyces are missing, and the lower ones often show signs of chronic reflux nephropathy, resulting in the appearance of a drooping lily (Fig. 115-2).

The affected lower pole on dimercaptosuccinic acid (DMSA) renal scan may be nonfunctioning or poorly functioning, indicating severe dysplastic changes or parenchymal scarring due to repeated episodes of UTI. In this relatively rare case, the treatment of choice is lower pole partial nephrectomy and ureterectomy (Fig. 115-3). It is recommended that the lower pole ureter be removed completely down to the bladder wall in order to avoid leaving a refluxing stump. In most cases, however, the lower pole is worth saving and several options are available for treatment.

Contrary to popular belief, a significant proportion of refluxing units associated with duplex systems resolve spontaneously with time. This is more likely with grade 1 and 2 VUR (up to 85%) than with higher grades.[16–19]

Provided the child remains asymptomatic (as with primary VUR), antibiotic prophylaxis is justified initially. These patients must be followed carefully to assess the kidneys for scarring and its progression. VUR can be assessed using either indirect MAG3 cystography or a micturating cystourethrogram (MCUG). If progressive renal scarring with deteriorating renal function is identified, or if symptomatic upper renal UTIs cannot be controlled by antibiotic prophylaxis, operative intervention is indicated.[20,21]

Endoscopic treatment of VUR in a duplicated system is not as successful as with a single-unit VUR, with a permanent resolution rate of only 46%.[22] However, it is still worthwhile to

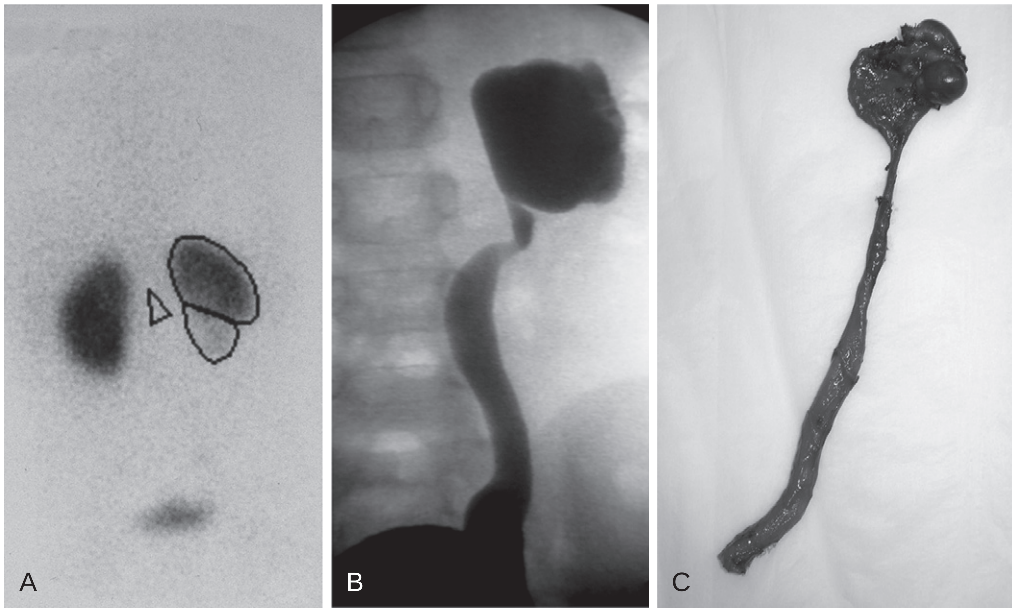


**FIGURE 115-3** A case of poorly functioning lower pole **(A)** on dimercaptosuccinic acid scan and refluxing on micturating cystourethrogram **(B).** The specimen after lower pole heminephroureterectomy **(C);** note that the refluxing ureter has been removed as low as possible to avoid a refluxing stump.

consider it as an effective option in selected cases.[17,23] In duplex systems in which the ureteral orifices are close together, the implant is injected under the upper pole moiety orifice (inferomedial). The needle is advanced below both orifices, and the injection is commenced under direct vision until both moiety orifices are compressed. When the ureteral orifices are separated by more than a few millimeters, they can be individually injected; however, caution is required when placing the injection under the lower pole orifice because the upper pole ureteral lumen may be entered in error.

The procedure of choice, when the refluxing ureter is not excessively dilated, is "double barrelled" or common sheath ureteroneocystostomy. When the ureteral orifices are situated relatively normally on the trigone, both should be mobilized from the bladder base together, even if only the lower pole ureter is refluxing. This is necessary because the ureters share the same adventitial sheath and blood supply.[24] Attempts to mobilize only the affected ureter will result in ischemia of one or both ureters. Alternatively, both ureters can be mobilized to a level above the common sheath. The ureters can then be rerouted through the bladder wall using either an intravesical cross-trigonal technique or an extravesical approach. The objective in both instances is to create a sufficiently long submucosal tunnel for the ureters (preferably three times their diameter), in order to create a satisfactory "flap valve" antireflux mechanism.

When one or both ureters are massively dilated, they can be safely reduced in size, plicating or excising the side away from the common wall.[25] When both ureters need to be reduced in size, excisional tapering is a better choice in order to avoid an excessive bulk of tissue that may make subsequent ureteroneocystostomy difficult.

Other surgical options, when only one ureter needs to be addressed, include uretero-ureterostomy. Recent literature indicates it is effective and has a low incidence of complications.[26–28] The size of the ureter does not seem to be a problem with this technique, which has also been performed via an inguinal incision with good results.[29] It is important to make sure there is no reflux in the ureter draining into the bladder. There is a theoretical risk of inducing yo-yo reflux. Such a risk can be avoided with pyelo-ureterostomy, which is a highly successful procedure, but a second lower abdominal incision is required to completely remove the refluxing stump or the stump can be dealt with by endoscopic correction.

### Ectopia of the Upper Pole Ureter

Another common anomaly in complete duplications is ectopia of the upper pole ureter.

Approximately 80% of all ectopic ureters occur in duplicated systems. The upper pole drained by an ectopic ureter commonly has severe dysplasia. In addition, findings consistent with obstructive changes are the rule in the male, where ectopic ureters are always obstructed. In females, obstruction affects only ureters ending inside the urinary tract.

Ureters ending on the bladder neck or in the posterior urethra are obstructed when the bladder neck is closed but may occasionally reflux during micturition; in such cases UTI is common. In the male, ectopic ureters generally cause infections and are identified during the evaluation for UTI. Epididymo-orchitis is a frequent presentation when the ureter opens in the genital tract in association with the vas or seminal vesicle.[30–32]

Many infant girls with ureters opening inside the urinary tract and, as a consequence, obstructed, present with UTI. Conversely, an ectopic ureter opening in the müllerian derivatives, having its orifices outside the realm of the urinary sphincter, causes urinary pseudo incontinence. A constant dribbling of urine in the interval between normal micturition is frequently observed.[33] This symptom is generally overlooked until the girl is fully toilet trained and has normal voiding habits. If the ectopic upper pole function is poor and little urine is produced, dribbling may not be observed and the patient may present with constant vaginal discharge. When the urine pools in a dilated ureter, especially at night when the patient is in a recumbent position, urinary losses may assume different features and mimic stress or urge incontinence.

Physical examination is often completely normal. Rarely, close and careful scrutiny of the external female genitalia reveals that the ectopic ureter is located in the urethro-vaginal septum. In addition, a dilated ureter is occasionally palpated during rectal examination.

Diagnosis of a suspected ureteral ectopia is straightforward when the ectopic ureter is massively dilated and may be easily identified on an abdominal ultrasound or when the upper pole functions sufficiently to excrete contrast material on intravenous urography (IVU).

Difficulties arise when the upper pole function is so poor that contrast is not excreted and the ureter is not dilated or when the ectopic ureter is associated with other malformations like massive reflux in the ipsilateral lower pole ureter or contralateral pathology that confuses the picture.

Ultrasound, the first-line investigation, may reveal a dilated duplex ureter and upper pole or, when the ureter is not dilated, show changes in the echogenicity of an otherwise normal upper pole that help in defining the correct diagnosis. MCUG should be included in the diagnostic workup. Associated reflux either in the ipsilateral lower pole ureter or in the ectopic upper pole ureter may be demonstrated; in the latter case MCUG delineates the anatomy of the ureter, making more sophisticated imaging studies unnecessary. An ectopic ureter should always be suspected in cases of isolated reflux into the upper pole of a duplicated system, which most commonly occurs on the voiding phase of the MCUG. Excretory urography is useful for defining the anatomy in a ureter associated with a functioning renal unit.[34] However, when the affected moiety is nonfunctioning, the findings are more subtle and changes on ultrasonography, DMSA scans, and excretory urography are easily missed.[19,34] Magnetic resonance imaging (MRI) scanning is particularly useful in these circumstances and provides both anatomic detail and functional analysis (Fig. 115-4)[35–38]; however, anesthesia is required in children.

The choice between the different treatment options largely depends on the function of the affected segment, on the coexistence of associated malformations, and, to a lesser degree, on the size of the affected ureter.

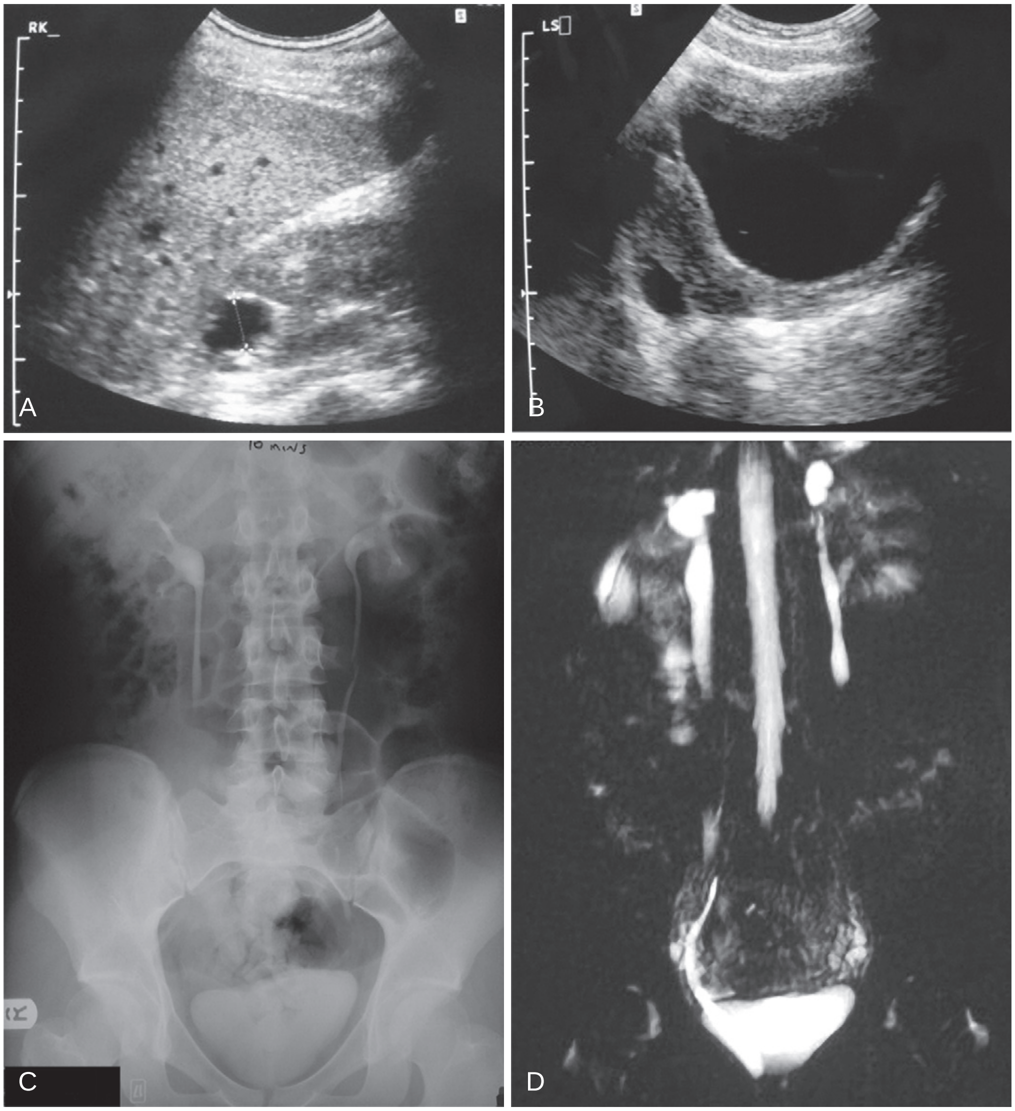


FIGURE 115-4 A case of ectopic ureter causing incontinence in a young girl. The ultrasound shows a dysplastic upper pole **(A)** with a dilated ureter behind the bladder **(B).** Excretory urogram is unremarkable **(C),** but magnetic resonance imaging (MRI) shows the ureter opening well below the bladder **(D).** This girl had bilateral ectopic upper pole ureters as diagnosed on the MRI.

In the great majority of cases when the involved upper pole contributes to less than 5% total function, open surgical, laparoscopic, or, even better, retroperitoneoscopic removal of the upper pole along with its ureteral segment is the treatment of choice.

Partial nephrectomy involves identifying the demarcation between the normal lower pole and the nonfunctioning upper pole and excising the ureter of the affected renal unit inferiorly as near the bladder as possible without compromising the lower pole ureter. The potential problems of excising the lower end of the affected ureter are well recognized and are discussed in more detail later.

The operation may be undertaken by either open or endoscopic techniques. The important steps are to clearly identify the ureter and pelvis of the affected upper pole moiety. After dividing the blood supply to the upper pole of the kidney, it is then possible to identify the limit of the affected upper pole, and a relatively bloodless plane can be developed between the abnormal and normal renal tissue without entering the caliceal system of the lower pole.[39] The ureter can then be excised down to the pelvic brim.

This upper tract approach lends itself well to minimally invasive surgery because access to the kidney and ease of defining the vascular anatomy, particularly with the retroperitoneoscopic approach, are excellent.[40–43] Secondary surgery at the bladder level to remove the stump or to reimplant the refluxing lower pole ureter is necessary only in a small number of cases.[44,45]

If the upper pole retains some function and is considered worth saving, then proximal ureteropyelostomy or distal uretero-ureterostomy is advisable. In a series of 11 infants who underwent ureteropyelostomy for obstructed duplicated ureters with satisfactory results, only 3 children needed secondary surgery at the bladder level for persisting reflux in the lower pole ureter.[46] When ipsilateral lower pole reflux is present, a "double-barrelled" ureteroneocystostomy may allow resolving both obstruction and reflux with a single operation. It requires a meticulous and tedious extravesical dissection in order to isolate enough length of both ureters and perform a safe reimplantation. Moreover, both ureters are usually markedly dilated and need tapering before ureteroneocystostomy. A possible, easier alternative is to perform a distal end-to-side anastomosis of the obstructed ureter to the refluxing one and to reimplant the lower pole ureter into the bladder.

However, in the great majority of cases an upper tract approach is strongly recommended, either by an upper pole partial nephrectomy or a ureteropyelostomy. If VUR is present preoperatively or develops postoperatively, it can be safely managed conservatively with antibiotic prophylaxis or treated endoscopically at a later stage. With such an approach the number of surgical procedures and complications can be substantially reduced, allowing, when possible, the preservation of a functioning upper pole.

### Ureteropelvic Obstruction

In duplex systems, the obstruction usually affects the lower pole and is more common in boys.[47,48] The decision to operate is guided by the size and function of the renal unit involved. An increase in hydronephrosis or decreased function of the affected part of the kidney on isotope study is an indication to intervene. However, these parameters are sometimes difficult to assess objectively in a growing child. Loin pain in older children, typically preadolescents, associated with objective evidence of ureteropelvic junction obstruction on MAG3 isotope scan, is a common indication for operation. The surgical options are pyeloplasty or pyeloureterostomy to the unaffected upper pole ureter, with excision of the distal ureter of the affected lower pole.[47–49] Partial nephroureterectomy is undertaken when the function of the affected renal unit is severely impaired.

# Ureteroceles

The term *ureterocele* describes the cystic dilatation of distal intravesical portion of the ureter. A single-system ureterocele is associated with a kidney with only one ureter, whereas a duplex system ureterocele is associated with the upper pole of a kidney with a complete ureteral duplication.

Most frequently the pelvicaliceal system drained by the ureterocele is also obstructed. The malformation may be further complicated by VUR into the ipsilateral lower pole or into the contralateral ureter or by ureteral obstruction.

The incidence of ureteroceles is approximately 0.02% of individuals with 80% occurring in females.[50,51] A slight majority are left sided and bilateral in 10%.[52] Some 80% of ureteroceles are associated with the upper pole of a complete duplication,[53] and in most series 60% to 80% are ectopic.[54] Bilateral ureteroceles or those associated with contralateral duplicity occur in 15% of cases.[55] Single-system ureteroceles are uncommon, occur most often in males, and can be associated with other anomalies including abnormalities of the kidneys such as fusion, ectopia,[56] or multicystic dysplasia.[57]

## CLASSIFICATION

The Committee on Terminology of the Urologic section of the American Academy of Pediatrics, proposed a simple and widely adopted classification, whereby ureteroceles contained entirely within the bladder are named *orthotopic* or *intravesical* and a ureterocele that has a portion permanently located outside the bladder is called *ectopic*.[58] In 1971 Douglas Stephens classified the ureteroceles associated with ureteral duplication according to the position and/or presence of intrinsic obstruction of the ureteral orifice as shown in Table 115-1.[59]

Stenotic ureteroceles are completely located inside the bladder and have a small, stenotic, often pinpoint orifice; they are usually tense and show a well muscularized wall with predominantly longitudinal muscle fibers. The nonobstructed variety is rather rare; in such cases the ureterocele is visible only when a peristaltic wave fills it.

**TABLE 115-1**

| Douglas Stephens Classification Ureteroceles |
|---|
| Intravesical |
| Extravesical |
| Stenotic 40% |
| Sphincteric 40% |
| Nonobstructed 5% |
| Sphinctero-stenotic 5% |
| Cecoureterocele 5% |
| Blind ureterocele 5% |

In the sphincteric subtypes the ureteral orifice is wide and often gaping, but it is located inside the bladder neck or urethra and is obstructed by the contraction of sphincteric muscle. These ureteroceles decompress during voiding. Sphinctero-stenotic ureterocele is similar to the previous one, but the orifice is both ectopic and stenotic. Because a sphinctero-stenotic ureterocele does not decompress during micturition, it may ball valve and obstruct the bladder outlet. The meatus of the cecoureterocele is in the bladder, but a tongue of the ureterocele extends down in the urethra. Ureteroceles are described as blind when no kidney or upper pole associated with ureterocele can be demonstrated.

In duplex kidneys the upper pole drained by the ureterocele is affected by some degree of dysplasia in 43% to 73% of cases. In 20% the dysplasia is severe, affecting more than 25% of the upper pole.[60,61] The contribution of the affected upper pole to the global renal function ranges from 4% to 8%. Measurable loss after upper pole partial nephrectomy is, on average, around 1% while functional gain after endoscopic incision is around 2%.[62]

## CLINICAL PRESENTATION

Prenatal diagnosis of ureterocele represents approximately 15% of all antenatal diagnosis of duplex kidneys as the number of neonates with prenatally detected ureteroceles has increased from 2% to 28% in the past 20 years.[63] Prenatal ultrasound screening of the kidneys often identifies some degree of hydronephrosis, which is most pronounced with ureteroceles.[64] Although there is no evidence that treatment of these prenatally diagnosed children affects the prognosis for the kidney, symptomatic UTIs can be reduced in frequency.[65–67]

In the postnatal period, infection is the most common presentation for ureteroceles in both sexes; in infants symptoms may vary from a life-threatening gram-negative sepsis to a febrile illness with gastrointestinal symptoms or failure to thrive. In older boys and girls symptoms are more specific and point to a urinary tract infection: fever, malaise, dysuria, foul-smelling urine, and back pain.

Other presenting symptoms in both girls and boys may be hematuria after minimal trauma or a palpable abdominal mass representing the bladder or the obstructed urinary tract.

In girls an interlabial mass or acute urethral obstruction due to the ball valve effect of a ureterocele prolapsing in the urethra is another possible presentation. Rarely, the most distal portion of a cecoureterocele can protrude from the urethra as a pink, interlabial mass without obvious urethral obstruction or retention and, consequently, such cases do not need emergency treatment.

Prolapsing ureteroceles are the most common cause of acute urethral obstruction in girls,[68] but this event has been also reported in males,[69] even if much less frequently. Patients present in obvious pain with an acute urinary retention and a palpable bladder. A purple red or frankly necrotic round mass may be seen protruding from the labia. In such cases emergency treatment to decompress the ureterocele and remove the bladder outlet obstruction is warranted. In extreme cases, when the ureterocele prolapses and obstructs the urethra, it may affect the function of all the renal units.[69,70]

## DIAGNOSIS

The diagnostic workup relies on the use of ultrasound, MCUG, and renal isotope scans.

Excretory urography, the mainstay of ureterocele diagnosis until a decade ago, is much less commonly used now. Computed tomography scan and magnetic resonance urography may be useful, especially the latter, when the urinary tract anatomy is not clear.

Ultrasound of the urinary tract is the first investigation and generally depicts clearly the ureterocele as a sonolucent round image that sits on the bladder base and occupies a portion of the bladder. One or more dilated ureters can be seen behind the bladder (Fig. 115-5). Ultrasound gives valuable information on the presence of unilateral or bilateral renal duplicity and on the dilatation of the collecting systems, and it helps in identifying which kidney is drained by the ureterocele. Cortical cysts and severe parenchymal thinning, but not increased echogenicity, suggest renal dysplasia that is confirmed by isotope scan.[71]

An MCUG is an essential part of a ureterocele evaluation. The ureterocele is seen in the first films as a negative shadow in the bladder, with a rim of contrast around it. If the ureterocele is not tense, it may be obscured with the progressive filling of the bladder because it may be compressed or, if it is small, may be obscured by the contrast medium around it. MCUG may also reveal VUR in the lower pole ureter (50%) or in the contralateral ureter (25%).[53,72,73] In less than 10% of cases, reflux can be identified in the ureterocele if it is ruptured or if it has a large open meatus placed on the bladder neck that allows

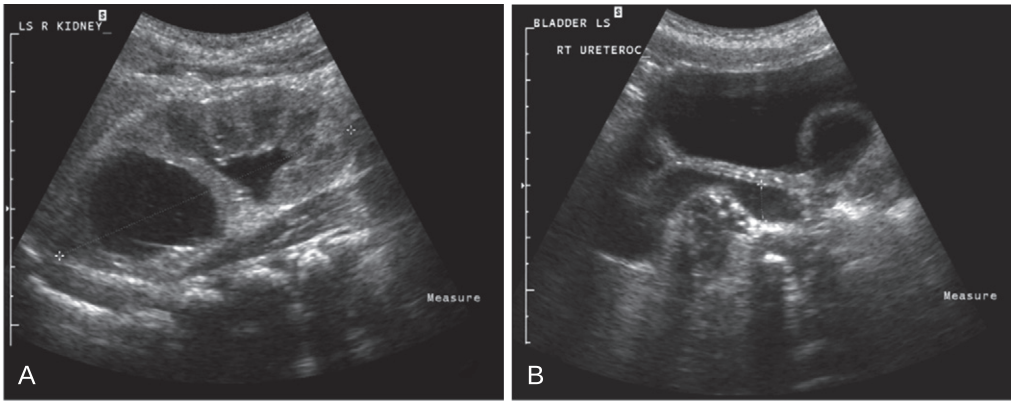


FIGURE 115-5 Ultrasound images of a dysplastic dilated upper pole **(A)** with corresponding dilated ureter and ureterocele in the bladder **(B).**

**FIGURE 115-6** Voiding cystourethrogram demonstrating retrograde prolapse of a ureterocele into the upper pole ureter and vesicoureteral reflux into the lower pole ureter on the left side in a complete duplex system. This appearance may be confused with a bladder diverticulum.

reflux during voiding.[33,73] The MCUG is also useful to ascertain the degree of the detrusor backing for the ureterocele. If the detrusor support is poor, the ureterocele may evert during micturition, mimicking a bladder diverticulum (Fig. 115-6). During voiding, the ureterocele may also be seen prolapsing through the urethra and obstructing the urinary flow.

IVU was the most important diagnostic step in the past. More recently, however, the progress of ultrasonography, DMSA, and MRI has made this examination obsolete in most cases. Nevertheless, when the anatomy is confusing, excretory urography may still play a role.

If the renal parenchyma associated with the ureterocele retains some function, which most commonly occurs in single systems, a characteristic "cobra head" or "spring onion" deformity of the intravesical ureter is produced due to opacified urine in the ureterocele being surrounded by a radiolucent halo that represents the wall of the ureter. More commonly, when the ureterocele is associated with the upper pole of a duplex kidney, function is absent or minimal in 90% of cases; therefore the radiographic signs are mainly negative, reflecting the displacement of the lower pole renal unit by the hydronephrotic upper pole ureter. The lower pole pelvis is often laterally and downward displaced, producing the characteristic "drooping lily" appearance; the number of calices is reduced; and the upper calices are missing (Fig. 115-7).

At the bladder level a negative shadow may be seen, suggesting the presence of a ureterocele (see Fig. 115-7). The shadow may vary from a large, tense, round shadow occupying most of the bladder to a minor irregularity in the base of the bladder.

Excretory urogram also shows the condition of the contralateral kidney collecting system that may be duplex (see Fig. 115-7) or may be obstructed at the bladder level by a large and tense ureterocele compressing the ureteral orifice.


**FIGURE 115-7** Excretory urogram appearances of a ureterocele in the bladder as a negative shadow. Please note bilateral duplex with nonfunctioning right upper pole corresponding to the ureterocele. The lower pole of the right and both the poles on the left are functioning. The lower pole on the right is dilated and possibly refluxing (back flow of contrast during the study).

The function of the pole or of the kidney associated with the ureterocele is best assessed by a DMSA renal scan that shows the quality and quantifies the amount of functioning renal tissue (Fig. 115-8).

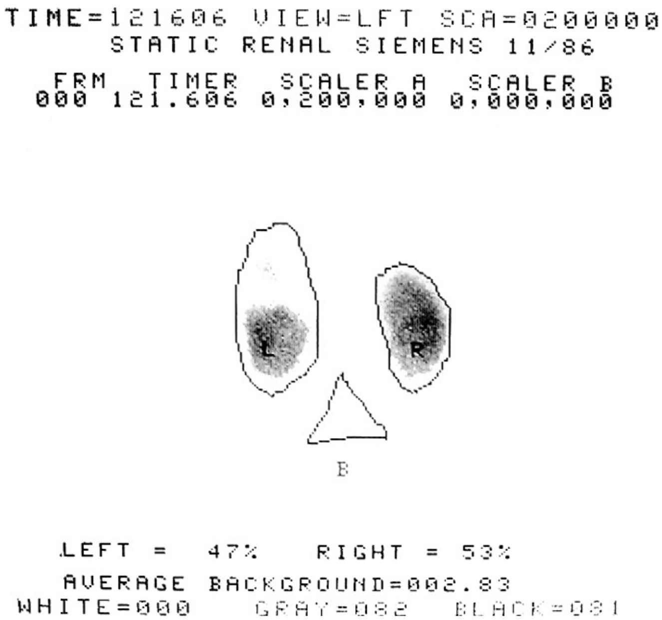


**FIGURE 115-8** Dimercaptosuccinic acid isotope scan demonstrating poorly functioning upper pole moiety in a left-sided complete duplex system. The upper pole ureter was associated with a ureterocele.

## PRINCIPLES OF TREATMENT

The goals of the ureterocele treatment are to preserve renal function by providing unobstructed drainage of all functioning renal tissue, removing any potential source of infection and treating VUR; prevent bladder outlet obstruction and/or urinary incontinence; and prevent and treat any bladder wall deficiency (e.g., diverticula, poor detrusor backing).

The surgical strategy should be optimized in order to attain these goals with minimal surgical morbidity. Few cases of prenatal treatment of a prolapsing obstructing ureterocele with anhydramnios have been recently reported with a view to restore amniotic volume.[74–76] In a small number of prenatally detected cases of ureteroceles with no obstruction or reflux, a nonoperative watchful waiting approach has been attempted successfully.[65,77,78]

Postnatally, the treatment options are endoscopic incision, upper pole partial nephrectomy (upper tract approach), complete reconstruction at the bladder level, or nonoperative (conservative) treatment. These methods cannot be compared easily, and the choice must be appropriately applied to patients with different clinical presentations. Skill in all methods of management is important, and an understanding of when to apply these methods is critical because the management of each patient with a ureterocele must be individualized.[79]

The factors that influence treatment choice are type of presentation (prenatally diagnosed or symptomatic), age of the patient, type of ureterocele (intravesical versus ectopic), differential function of the renal moieties, and presence of VUR and UTI.

## ENDOSCOPIC DECOMPRESSION

Wide, open deroofing of the ureterocele was performed in the past. The problem with this technique is that if the ureterocele arises from the urethra, epithelial remnants that have not been completely excised may result in urethral obstruction owing to the valvelike nature of these folds.[80] In addition, with this type of operation, postoperative VUR is almost inevitable. Therefore deroofing usually requires a subsequent antireflux procedure that is normally best undertaken as part of the initial surgery. This more aggressive approach is potentially difficult and is associated with increased morbidity, especially in the very young child with a small bladder.[81]

Endoscopic techniques have been used for some time to simply incise the ureterocele. At any age endoscopic incision has the advantage of being a simple, quick, and minimally invasive procedure that can be performed with a minimal hospital stay.

This can take the form of either diathermy incision or simple puncture of the cyst.[82–84] During this procedure it is important not to overfill the bladder; otherwise, the ureterocele may be compressed, making it difficult to identify. If this occurs, loin compression on the affected side may assist in refilling the ureterocele. The planned decompression point on the ureterocele is important and, if possible, should not overlie the ureteral lumen where it is attached to the bladder base. Recently a novel technique of fulgurating the internal layer of the ureterocele has been described to achieve and maintain collapse of the ureterocele.[85] This technique is challenging and tedious, especially when the postoperative outcomes following endoscopic incision depend on anatomic and functional characteristics rather than the technique used.[86]

Simple decompression obviates obstruction and allows a better evaluation of the function of the kidney or pole involved by the ureterocele. It often reduces the size of the ureter so that secondary procedures (such as excision of the ureterocele and ureteroneocystostomy), if required, are less difficult and may reduce the need for ureteral tapering. In addition, associated VUR into the lower pole ureter may subside spontaneously.[72]

Endoscopic incision of intravesical ureterocele is the definitive treatment in 77% to 93% of cases; therefore it can be considered to be the initial treatment for this type of ureterocele.[79] A recent meta-analysis looking at endoscopic management of ureteroceles confirmed what others have suggested that the risk of reoperation after endoscopic incision of ectopic ureteroceles was significantly higher than with intravesical ureteroceles.[73,87]

There is no consensus about the effectiveness of endoscopic incision in ectopic ureteroceles because it rarely represents the definitive treatment modality[88,89]; seldom ameliorates the function of the involved upper renal pole; and, if an iatrogenic reflux is created in the ureterocele, it may unnecessarily commit the patient to future lower tract surgery. Alternative treatment options are represented by the upper tract approach, which includes either an open or retroperitoneoscopic upper pole partial nephrectomy and ureterectomy, leaving the upper ureteral stump open in order to decompress the ureterocele, or, if the upper pole is considered worth being kept, a uretero-pyelostomy or uretero-ureterostomy, joining the upper pole ureter to the lower one.

The preservation of the upper pole affected by an ectopic ureterocele is rarely warranted because its function is often minimal, the severity of renal dysplasia being directly proportional to the degree of ectopia of the ureterocele.[62] There is little hope of recovery of function after relief of obstruction in most cases because the upper pole is often dysplastic with irreversible changes, neither progressive nor amenable to any type of treatment.

The upper tract approach may be recommended when there is no associated VUR and the choice between removing and keeping the upper pole is dictated by its relative function.

With this approach, the rate of secondary procedures on the bladder ranges from 15% to 20% if preoperative VUR was absent.[90,91]

When VUR is associated with an extravesical ureterocele, no matter which approach is used first, a second stage at the bladder level to remove the ureterocele and reimplant the ureters is necessary in the majority of cases. As the number of renal units affected by VUR in a duplex system with an ectopic ureterocele increases, the higher the incidence of surgery at the bladder level.[61,92]

The reoperation rate in patients with duplex system ectopic ureterocele and VUR varies from approximately 50% to 100% after endoscopic incision[93] and from 84% to 90% after upper pole partial nephrectomy.[90]

## BLADDER BASE RECONSTRUCTION

As mentioned earlier, bladder base reconstruction including excision of ureterocele and ureteroneocystostomy may be required. This usually produces a significant defect that necessitates a precise anatomic reconstruction; otherwise, disruption of the bladder neck and posterior urethra could lead to incontinence. Fortunately, it is unusual for the ureter to open directly into the urethra; this most often occurs at a

level at or just above the bladder neck. Recently, it has been suggested that the ureterocele can be excised or marsupialized without much effect on clinical outcome.[94] The ureterocele, however, often involves the urethra, requiring that the epithelial edges of the cyst be excised completely and then meticulously repaired. Otherwise, obstruction of the urethra may result from either the residual "valvular" remnants of the ureterocele or stricturing due to excessive scarring.[80] Therefore it is usually necessary to mobilize the unaffected lower pole ureter with that associated with the ureterocele. If the upper pole ureter is to be excised, mobilization of both ureters should be extended above the common adventitial sheath. Alternatively, the two ureters can be separated by preferentially taking the adventitia of the affected ureter, thus preserving the blood supply to the "normal" ureter. In any case the defect in the bladder base and outlet must be repaired without narrowing the outlet. The remaining lower pole ureter can then be reimplanted using either a cross-trigonal or an extravesical method as described earlier.

Proponents of complete primary lower urinary tract reconstruction early in the neonatal period or infancy argue that the need for secondary surgery in patients affected by duplex system ectopic ureteroceles with preoperative VUR ranges from 0% to 32%.[95–97] They have reported that this approach in patients with ectopic ureterocele with VUR appears to have better results than a staged approach with initial endoscopic treatment. Moreover, they conclude and have been supported by others that extensive reconstructive bladder surgery in neonates and infants does not lead to bladder function deterioration at a later age.[98] However, severe bladder dysfunction was observed in 7 of 10 girls who underwent bilateral ureterocele repair in their first 2 years of life,[81] suggesting that due to the gross abnormality of the bladder base in duplex systems, there is a significant risk of damaging the bladder outlet in the course of mobilizing the ureters. The difficulty is in determining whether these children's problems are a primary abnormality of bladder function or congenital and unrelated to surgical intervention.[99,100]

# Summary

Ureteral duplications and ureteroceles represent a spectrum of often overlapping embryologic and anatomic abnormalities. Most unobstructed or nonrefluxing duplications are of no clinical significance along with incomplete duplications; others are associated with significant morbidity. Complete duplications are often asymptomatic but can be associated with VUR or ureteroceles with a predominance in girls.

VUR is the most common anomaly of duplications, occurring in about 65% of those with symptomatic UTIs; the reflux is usually into the lower pole ureter. Ectopia of the ureter is not uncommon, and a detailed history is often useful in pointing toward the cause of incontinence. Specialized imaging techniques are often required, however, to identify the precise anatomic abnormality; these include ultrasonography, isotope scanning, MCUG, excretory urography, and MRI.

On the basis of these data, a planned, individualized approach to each case can be taken, with an emphasis on preventing deterioration in renal function, controlling symptoms, and avoiding surgical interventions that could risk bladder function.

### *Acknowledgments*

I would like to acknowledge the contribution of Dr. Victor Boston, the previous author of this chapter, because parts of the previous version and some figures are retained. I would also like to thank my friend and colleague Dr. Emilio Merlini for allowing me to refer to previous educational materials on duplication anomalies that we produced together.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 116

# Disorders of Bladder Function

Martin Kaefer

Disorders of bladder function can range from the most mundane problem of dysfunctional voiding to complex disorders involving neuropathic bladder dysfunction. The typical symptom with which the patient presents is that of wetting. Although of great concern to parents and child alike, this relatively benign-appearing outward sign of bladder dysfunction may in the extreme case reflect a far more insidious and occult problem involving injury to the lower and upper urinary tracts. This chapter begins with the physician's initial assessment of the child with voiding symptoms. Radiographic and dynamic studies relevant to bladder dysfunction are covered next. Finally, specific disorders and their treatment are discussed.

## History and Physical Examination

The evaluation of the child with bladder dysfunction should begin with establishing both day and nighttime voiding patterns. Voiding symptoms have classically been divided into irritative and obstructive, examples of which can be found in Figure 116-1. It should be noted that nearly every disorder discussed in this chapter can have a combination of these symptoms. For example, parents of a boy with obstructing posterior urethral valves may not report that their child is suffering from urinary retention but rather that he is experiencing urinary frequency and urgency (secondary to increased bladder irritability from overdistention). It should be established whether the child has had a urinary tract infection (UTI) and, if so, whether there has been associated fever. This latter symptom will help distinguish an episode of cystitis from the more significant episode of pyelonephritis. The physician should inquire as to whether the child suffers from constipation in that it may reflect a form of retentive behavior (as in the case of dysfunctional elimination) or neuropathic bowel dysfunction (as in the various forms of spinal dysraphism). As pertains to the latter diagnosis, it is also important to record any symptoms of lower extremity weakness or change in sensation.

The physical examination of the child with bladder complaints should include evaluation of the abdomen, back, genitalia, and lower extremities. In examining the abdomen, special note should be made of palpable feces and whether the bladder is palpable and/or percussible, especially if the child has just voided. What has become a common pediatric urology office procedure and an extension of the physical examination is a postvoid bladder scan to check for residual urine.

Examination of the back is critical. Cutaneous findings of a hair patch or nevus overlying the lumbar spine reflect abnormal migration of the neuroectoderm, which can often signal abnormal formation of the lumbosacral spinal cord. A dimple over the lumbosacral spine may likewise signal such an abnormality (Fig. 116-2). An asymmetric gluteal crease is a further sign of potential problems of the spinal cord. This asymmetry reflects differing degrees of impaired innervation to the two groups of gluteal muscles. For example, if the right gluteal nerves are affected to a greater degree than those on the left, then a greater degree of atrophy may ensue and the crease would deviate to the right. With respect to this last outward sign of occult spinal cord dysraphism, it is critical to note that gluteal asymmetry may be an acquired finding as the child matures and grows in axial length. Therefore the back should be examined not only on the initial patient evaluation but during return visits in children with continued voiding complaints. Figure 116-3, *A* and *B*, demonstrates the concept of spinal cord tethering. Patients who possess any of these cutaneous findings should undergo a magnetic resonance imaging (MRI) of the lumbosacral spine.

Examination of the male genitalia should include palpation along the entire urethra. Induration may be a sign of urethral inflammation and stricture. Position of the testicles should be noted because there is an increased incidence of cryptorchidism in children with myelodysplasia.[1,2] The anus should be examined to ensure that there is good tone and proper location on the perineum. Finally, any deficits in lower extremity reflexes or motor strength should be noted in that they are outward signs of neuromuscular disorders, especially disorders of the lumbosacral spinal cord.

A urinalysis should be obtained in every child with voiding symptoms. The presence of red cells, white cells, glucose, and protein should be noted. A low specific gravity may reflect poor concentrating ability secondary to renal dysfunction.

Voiding Symptoms

Irritative

- Dysuria
- Urgency
- Frequency

Obstructive

- Retention
- Hesitancy
- Staccato voiding (starting and stopping)
- Straining to void
- Feeling of incomplete emptying

**FIGURE 116-1** Irritative and obstructive voiding symptoms.

**FIGURE 116-2** Cutaneous findings suggestive of occult spinal cord tethering: picture of a 10-year-old child with neuropathic bladder who was found on physical examination to have a cutaneous lumbar birthmark, a lumbar dimple and asymmetry of the gluteal cleft. Magnetic resonance imaging of the lumbosacral spinal cord revealed an intraspinal lipoma responsible for cord tethering.

# Radiographic and Dynamic Assessment of Bladder Dysfunction

## BLADDER ULTRASOUND

Although it is the most basic of radiographic imaging modalities, the bladder ultrasound can provide many clues about whether there is significant bladder pathology. In the absence of infection, a thickened bladder wall may reflect a compensatory response on the part of the bladder to either an anatomic (e.g., posterior urethral valves) or functional (e.g., detrusor sphincter dyssynergy) form of bladder outlet obstruction (Fig. 116-4).[3] Calculation of postvoid residual urine volume is an excellent means of assessing whether the patient can efficiently empty the bladder.

## VOIDING CYSTOURETHROGRAPHY

The instillation of radiographic contrast into the bladder provides information regarding bladder, bladder neck, and urethral anatomy. Figure 116-5 demonstrates the classic radiographic findings seen in neuropathic bladder dysfunction. Because of chronic high-pressure urine storage, the bladder wall becomes thick and multiple diverticuli may form. In many conditions the voiding phase provides the most useful information because it is only during this time that the bladder neck and urethra can be properly evaluated. The importance of obtaining oblique imaging during voiding cannot be overemphasized because this may be the only image that reveals urethral pathology. A classic example of this is the patient with posterior urethral valves. The bladder neck and urethra proximal to the site of obstruction are markedly dilated, and the bladder itself can demonstrate findings of trabeculation and diverticuli formation. Vesicoureteral reflux is a common finding in both anatomic and functional causes of bladder dysfunction.

## URODYNAMIC EVALUATION

The urodynamic evaluation is the one test that provides in-depth functional information regarding the bladder. It establishes bladder capacity, bladder filling pressures, the patient's perception of bladder filling, and the ability of the bladder neck to empty efficiently and in proper coordination with external sphincter relaxation.

Normal values for various urodynamic parameters have been published. Two parameters are especially useful to mention. Early formulas for calculating expected bladder volume gave reasonable estimates of bladder capacity. One of the most commonly used is Age (years) $+ 2 =$ Capacity (in ounces).[4] However, data in the studies were obtained in large part from patients undergoing evaluation for functional bladder pathology.[5] More recently, Kaefer and colleagues, in measuring the bladder capacity of 2000 healthy children without bladder pathology, demonstrated that bladder capacity was not a linear function of age.[6] The curvilinear relationship $4.5 \times \text{age}^{0.4} =$ capacity (ounces) is similar to the relationship between age and other morphometric parameters (e.g., height and weight). This nonlinear relationship can be approximated by two practical linear formulas that have excellent predictive value when applied prospectively ($2 \times$ Age [years] $+ 2 =$ capacity [ounces] for children younger than 2 years old, and Age [years] $\div 2 + 6 =$ capacity [ounces] for those older than 2 years old).

Neurologic modulation combined with the viscoelastic properties of the healthy detrusor muscle allow the bladder to maintain fairly constant pressure throughout the filling phase. As a result, intravesical pressures in the healthy bladder remain at or below 5 to 10 cm $H_2O$ pressure until capacity is achieved. When various pathologic processes alter the composition of the bladder wall (e.g., collagen deposition following mechanical outlet obstruction) or affect neurologic control of the bladder (e.g., loss of upper or lower motor neuron function in myelomeningocele) compliance can be adversely affected, resulting in increased intravesical storage pressures.

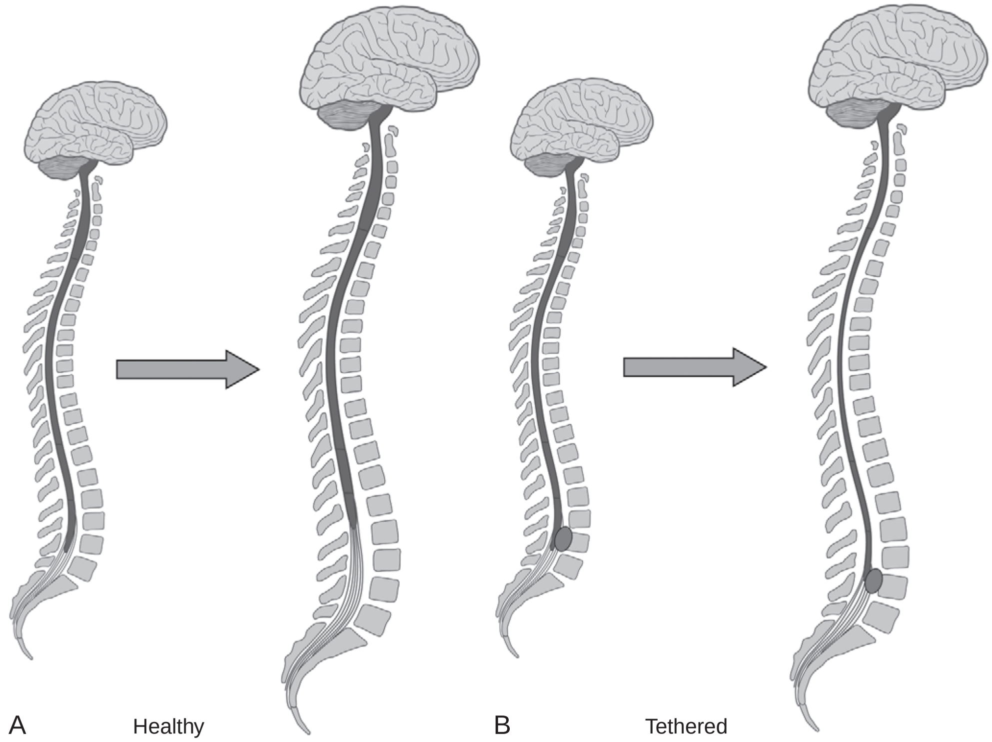


**FIGURE 116-3** **A,** Normal spinal cord. Spinal column increases in axial length at a greater rate than does the spinal cord. As a result, the spinal cord rises to a higher position. **B,** Abnormal spinal cord anatomy with spinal cord lipoma. As the spine grows, the spinal cord is unable to float upward and the cord is stretched. This stretching results in a relative state of hypoxia in the area of the distal cord and subsequent nerve injury to the distal spinal cord segments.

If intravesical storage pressures reach levels higher than 40 cm $H_2O$, renal injury is likely to ensue.[7]

Before undergoing placement of the urodynamic catheter, the child is asked to void into a toilet that measures urinary flow rate. The catheter is then placed through the urethra (or alternatively through a suprapubic site if one is available), and the intravesical pressure is measured. The bladder is then emptied and residual urine determined, yielding a pressure at residual volume.[8] This measurement may prove useful in determining whether the bladder is experiencing high resting

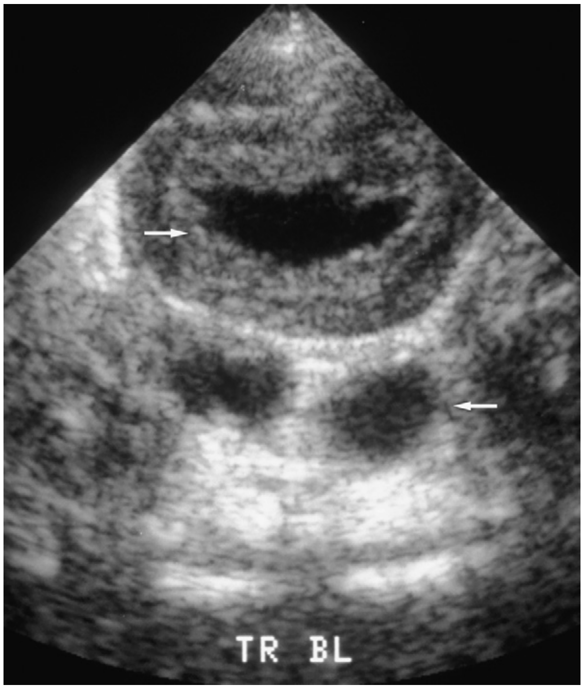


**FIGURE 116-4** Bladder ultrasound from a child with posterior urethral valves. Note the markedly thickened bladder wall *(left arrow)* and the dilatation of the distal ureters *(right arrow)*.

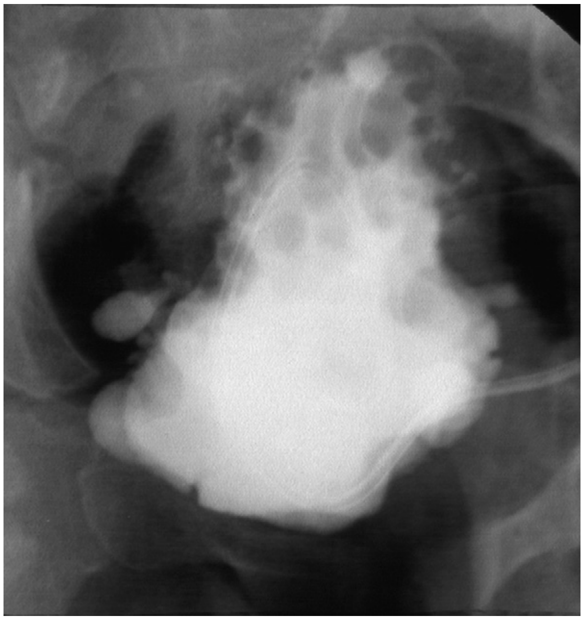

**FIGURE 116-5** Typical voiding cystourethrogram from a child with neuropathic bladder dysfunction secondary to myelomeningocele. The "Christmas tree" appearance is a result of greater bladder wall thickening at the dome relative to the bladder base.

pressures. Next, electromyographic (EMG) electrodes are placed on the perineum either in the form of patch surface sensors or needle sensors, the latter of which is placed directly into the external sphincter complex. These electrodes record the electrical activity of the muscle in order to determine the function of the external sphincter during bladder filling and emptying. Under normal conditions the external sphincter is active during periods of urine storage. Just before voiding there should be silencing of external sphincter activity as the bladder neck relaxes (Fig. 116-6, *A*). Failure of the sphincter to relax before a voiding contraction is termed *detrusor sphincter dyssynergy* (DSD) and is commonly noted in patients with neuropathic bladder dysfunction (Fig. 116-6, *B*), as well as in patients with functional urinary incontinence.

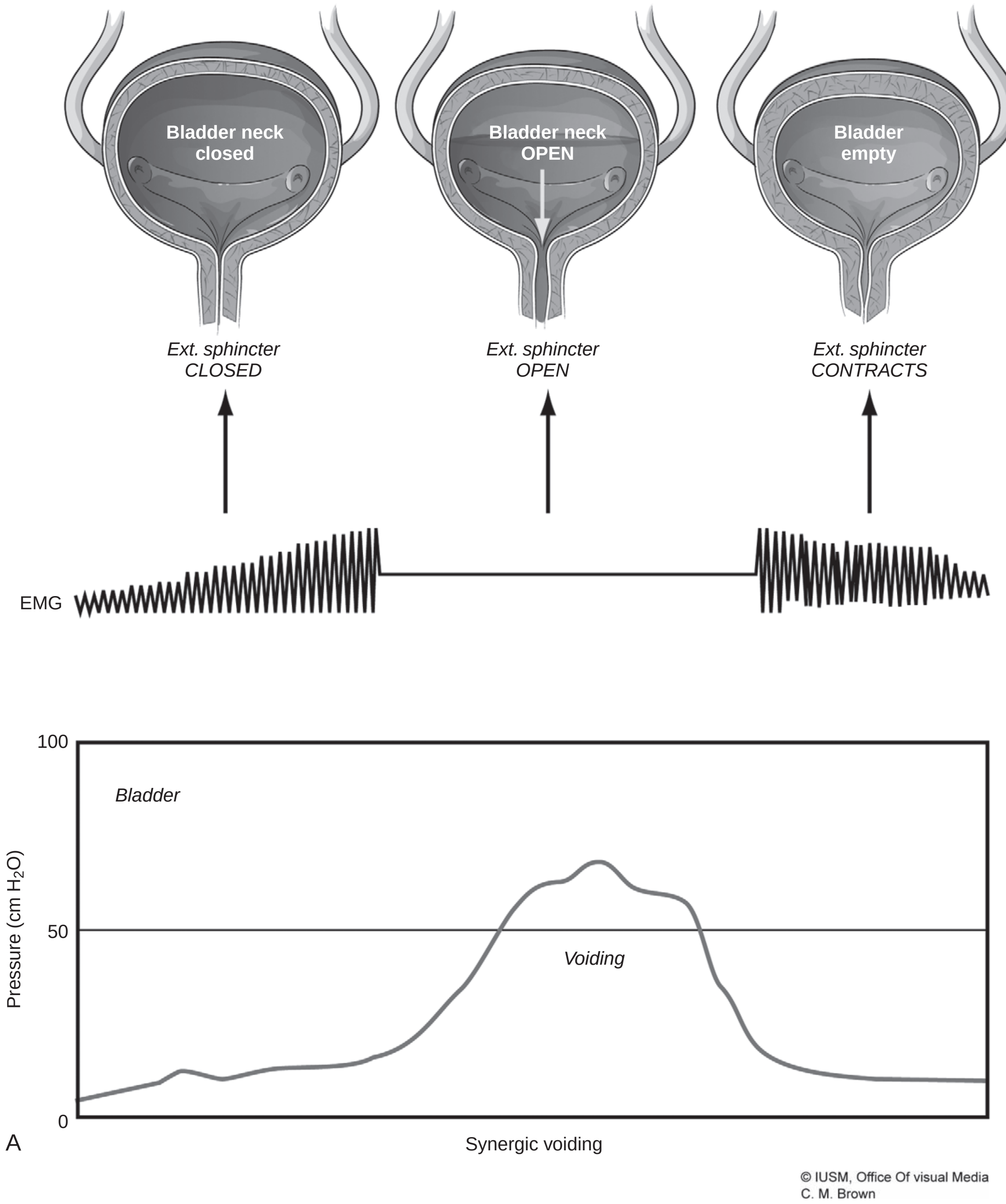


**FIGURE 116-6** **A,** Coordinated synergic voiding: Electrical activity of the external urethral sphincter is chronically active. Just before experiencing a detrusor contraction, the activity of the external sphincter is silenced, providing a marked decrease in urethral resistance and thereby facilitating emptying. Intravesical pressure is shown in the bottom panel.

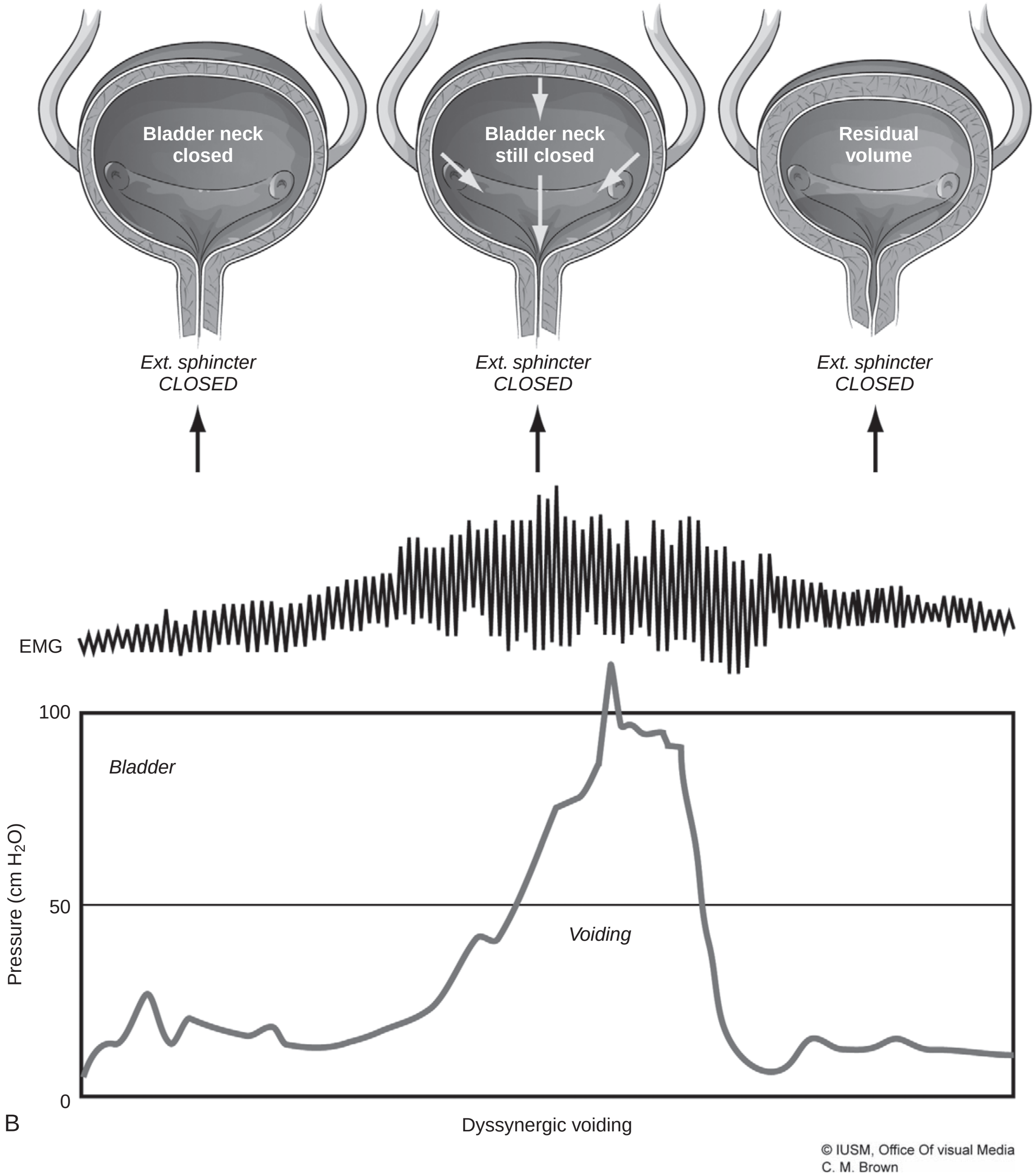


**FIGURE 116-6—CONT'D** **B,** Dyssynergic voiding: In cases of neuropathic bladder dysfunction discoordination between bladder and sphincter activity can often be appreciated. As the bladder begins to contract the activity of the external sphincter actually increases resulting in high outlet pressures and ineffective voiding. Intravesical pressure shown in bottom panel.

The bladder is next filled slowly with normal saline to determine bladder capacity, and the pressure-volume relationship is measured in order to establish bladder wall compliance. Percent expected bladder capacity is calculated by dividing the patient's actual capacity by the expected normal bladder capacity for age.[9] During the filling phase, any uninhibited contractions should be noted because they are a reflection of bladder irritability. Figure 116-7 shows a comparison between pressure tracings from a compliant bladder with those of a poorly compliant, irritable bladder. During the filling phase, the leak point pressure is also noted.

# Neuropathic Causes of Bladder Dysfunction

## NEUROPATHIC BLADDER SECONDARY TO MYELODYSPLASIA

Myelodysplasia, defined as abnormal development of the spinal canal and spinal cord, is the most common etiology of neuropathic bladder dysfunction in children. A genetic component appears to be partially responsible for this

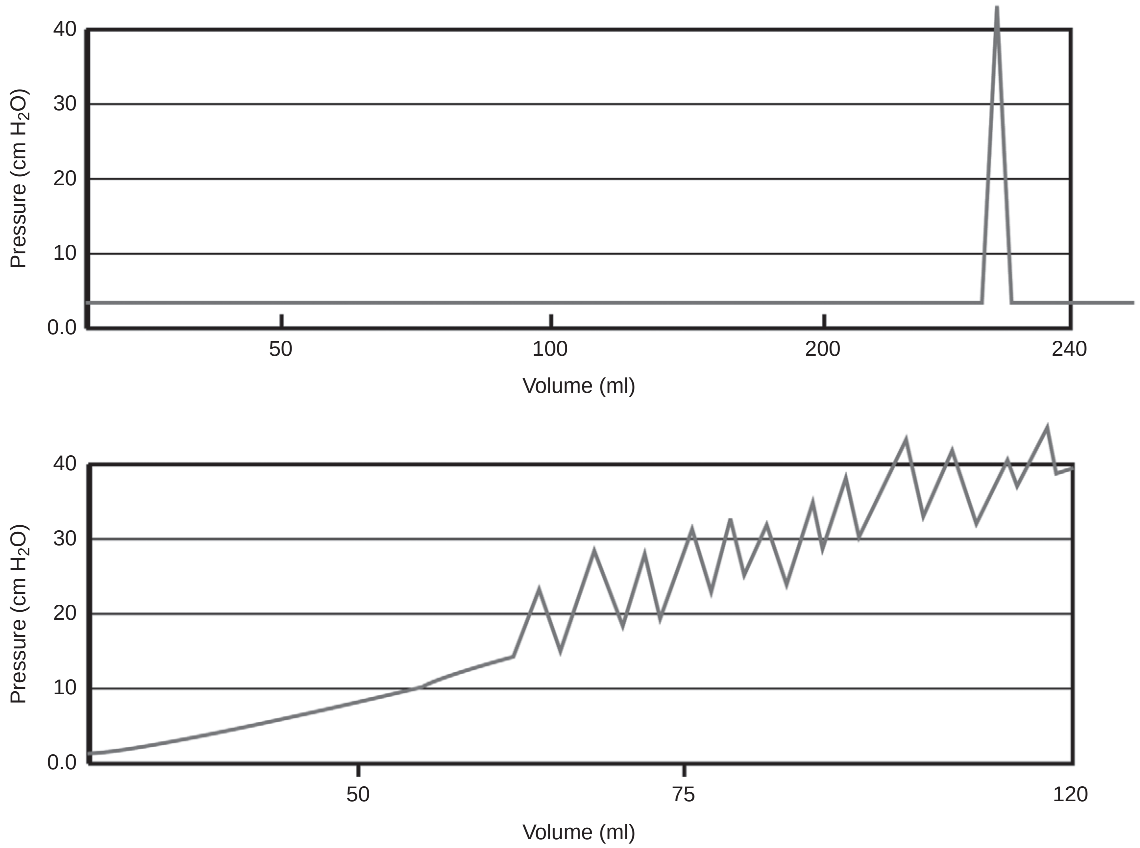


**FIGURE 116-7** Representation of typical urodynamic tracings from a compliant bladder and a poorly compliant bladder. Upper tracing demonstrates a compliant bladder: As the bladder fills, numerous factors serve to maintain low intravesical pressure until a voiding contraction is initiated. Lower tracing demonstrates a poorly compliant bladder with detrusor hyperreflexia. As the bladder fills, intravesical pressure rises precipitously. Irritability of the dysfunctional detrusor muscle is reflected in numerous small pressure spikes (i.e., uninhibited contractions).

**FIGURE 116-8** Photograph of spinal dysraphism.

disorder. In a family with one child with myelodysplasia, there exists a 2% to 5% chance that each subsequent sibling will suffer from the same condition. Early studies reported the incidence at 1 in 1000 live births.[10] However, over the past 20 years there has been a steady decrease in this rate. Reasons cited for this decrease include the widespread perinatal supplementation of folic acid (a metabolite important for proper spinal cord formation) and pregnancy termination.[11,12] Dietary supplementation with folic acid can reduce the incidence of myelodysplasia by approximately 50%.

The most common forms of myelodysplasia consist of prolapse of the meninges (meningocele) and in many cases neural tissue (myelomeningocele) beyond the confines of the bony vertebral canal. Initial urologic evaluation of the child found to have spinal dysraphism (Fig. 116-8) should include a renal ultrasound, voiding cystourethrogram, and determination of postvoid residuals by clean intermittent catheterization (CIC). The renal ultrasound will detect the presence of hydronephrosis. Up to 15% of newborns will be found to have an abnormal urinary tract; 3% have hydroureteronephrosis secondary to spinal shock from the closure procedure; and 10% have abnormalities that developed in utero as a result of abnormal lower urinary tract function in the form of outlet obstruction, thus resulting in high intravesical pressures.[13,14] The renal ultrasound serves the additional purpose of evaluating for renal fusion anomalies, which are known to be more common in patients with myelodysplasia.[15]

The voiding cystourethrogram serves the purpose of detecting vesicoureteral reflux, which is present in 3% to 5% of newborns with myelodysplasia.[16] Reflux is typically seen in children with detrusor hypertonicity or detrusor sphincter dyssynergy. New reflux will develop in approximately 30% of children with unfavorably high-pressure bladder dynamics if proper treatment is not taken to lower intravesical pressures. As mentioned earlier, several postvoid residuals (PVRs) are obtained in order to determine the efficiency of emptying. If the postvoid residuals average greater than 10 mL, the parents are taught CIC to be performed three times daily after discharge to home. Alternatively, because it may be difficult to obtain exact PVRs in newborns, random catheterized volumes can be measured. Random catheterized volumes consistently below expected bladder capacity imply efficient bladder emptying.

Follow-up urologic evaluation consists of a urodynamic evaluation at 3 months of life. Performing urodynamics at an earlier time point is often discouraged due to the fact that the infant may experience a degree of spinal shock from spinal closure that may last for up to 2 months. The urodynamic evaluation serves two purposes. First, it serves as a baseline against which all future urodynamic evaluations can be compared. Changes in the urodynamic profile may be the first indication (often before lower extremity function changes) that postmyelomeningocele closure spinal cord tethering is occurring and that surgical intervention may be required.

The second purpose of the urodynamic evaluation is to determine the overall storage characteristics of the bladder and sphincteric function. Three specific combinations of bladder contractility and external sphincter activity are seen. Bauer demonstrated that 19% of patients will demonstrate synergic voiding, 45% will have dyssynergic voiding, and the remaining 36% will suffer from complete denervation.[17] This system of classification is of great importance in predicting long-term renal and bladder function and thereby determining who will benefit from aggressive measures to minimize progressive urinary tract injury. Bauer has shown that within the first 3 years of life, patients with a dyssynergic voiding pattern have a much higher incidence of urinary tract deterioration. He found that 71% of newborns with DSD had urinary tract deterioration on initial assessment or subsequent studies, whereas only 17% of synergic children and 23% of completely denervated individuals developed similar changes. Notably, the small percentages of children with synergic or denervated voiding patterns that did go on to demonstrate urinary tract deterioration all had subsequent conversion to a high outlet resistance.

Frequent follow-up of patients with neuropathic bladder dysfunction secondary to myelomeningocele is mandatory because bladder dynamics (and thereby the effect on the upper urinary tract and continence) can change with time. Many reasons for a change in bladder dynamics exist, the most important being spinal cord tethering.[18]

The primary goal of treatment of the neuropathic bladder is the preservation of renal and bladder function. An additional goal of achieving urinary continence is addressed once the child reaches the age at which his or her peers are achieving this developmental milestone. CIC and the use of anticholinergic medications are the cornerstones of medical therapy to provide a low-pressure storage environment for urine. Edelstein and colleagues[19] demonstrated that if one aggressively and proactively treated high-risk patients who are defined as having either high outlet resistance, detrusor sphincter dyssynergy, and/or bladder hypercontractility (so-called *hostile bladder dynamics*) with CIC and anticholinergic medications that the rate of upper urinary tract injury could be substantially reduced. Kaefer and colleagues[20] subsequently demonstrated that long-term bladder function is similarly preserved in a greater number of patients if such measures are taken (Fig. 116-9). In this later study the incidence of long-term bladder deterioration requiring surgical bladder augmentation was reduced 2.5-fold. If these medical measures do not adequately reduce intravesical pressures and progressive hydronephrosis is noted in the first few years of life, then surgical intervention in the form of a cutaneous vesicostomy is indicated.

Urinary incontinence is likewise treated initially with conservative measures (i.e., CIC and anticholinergic medications) to decrease intravesical pressures. If such measures do not result in adequate improvement in bladder capacity and compliance, it may become necessary to enlarge the bladder by means of enterocystoplasty.[21,22] Additional surgical maneuvers may be required to provide adequate outlet resistance in order to achieve a state of urinary continence.[23]

## OCCULT SPINAL CORD TETHERING

A number of congenital defects affect the formation of the spinal column yet do not result in an open vertebral canal. These conditions occur in approximately 1 of every 4000 live births.[24] These lesions may result in no obvious outward neurologic signs, but in many there is a cutaneous abnormality overlying the lower spine (see earlier section on physical examination). There is an increased incidence (up to 50%) of these conditions in individuals with anorectal malformations,[25,26] with earlier reports demonstrating that the incidence varied proportionately in relation to the height of the

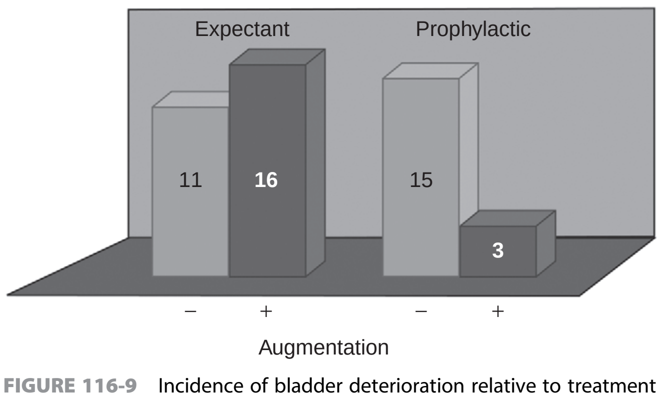


FIGURE 116-9 Incidence of bladder deterioration relative to treatment regiment in myelomeningocele patients. The expectant group comprised patients with hostile bladder dynamics noted at birth who were started on clean intermittent catheterization and anticholinergic medications to lower bladder pressure only after signs of upper tract deterioration or worsening incontinence became evident. On average treatment was initiated at age 4.1 years in this group. The prophylactic group comprised patients with hostile bladder dynamics noted at birth who were treated with measures to lower intravesical pressures beginning in the first 3 months of life. The greater than twofold higher incidence of bladder augmentation in the expectant group is highly statistically significant (41% vs. 17%). (From Kaefer M, Pabby A, Kelly M, et al: Improved bladder function after prophylactic treatment of the high risk neurogenic bladder in newborns with myelomeningocele. J Urol 1999;162(3 Pt 2):1068-1071.)

rectal lesion.[27] However, one recent study suggests that the incidence may not differ significantly between patients with supralevator and infralevator lesions.[25] All patients with a cutaneous abnormality overlying the lower spine or an anorectal malformation should undergo an MRI to evaluate for an intraspinal lesion.[28] In the first 6 months of life it is also possible to evaluate for spinal cord tethering with a spinal ultrasound.[29] When using ultrasound, one expects to see the conus medullaris at the level of the L2 vertebrate. In addition, the nontethered spinal cord should move with respiration. After 6 months of life, ossification of the vertebral segments limits the ability of ultrasound to penetrate to the level of the spinal cord and achieve adequate visualization of the distal spinal cord.

Urologic symptoms of occult spinal cord tethering may include difficulty with toilet training, urinary incontinence after an initial period of dryness (especially during the pubertal growth spurt when the most stress is put on the tethered cord), recurrent urinary infections, and/or fecal soiling.

Although the majority of newborns evaluated for occult spinal cord tethering have a perfectly normal physical examination, urodynamic testing will reveal abnormal lower urinary tract function in about one third of babies younger than 18 months of age.[30] In contrast, practically all individuals older than 3 years of age who have not been operated on or in whom an occult dysraphism has been belatedly diagnosed have abnormal urodynamic profiles.

Once it has been shown on MRI that there are signs of spinal cord tethering (e.g., the conus medullaris lies below the second lumbar vertebrae or there is a significant intraspinal lipoma), then a judgment is made as to the need for neurosurgical intervention. Often, the first sign of neurologic impairment is an abnormal urodynamic profile. Therefore urodynamics are performed on all patients with positive MRI findings. If a decision is made not to perform spinal cord tether release, then follow-up with biannual renal ultrasound and yearly urodynamic evaluations is indicated so that any future neurologic deficits can be identified early and appropriate intervention can be instituted in a timely fashion before irreversible nerve injury occurs.

## SACRAL AGENESIS

Patients with sacral agenesis frequently suffer from neuropathic bladder dysfunction. The etiology of sacral agenesis is still uncertain. It is, however, known that insulin-dependent mothers have a 1% chance of giving birth to a child with this disorder and that 16% of children with sacral agenesis have a diabetic mother.[31,32] Because these children have normal sensation and little or no orthopedic deformity in the lower extremities, the underlying lesion is often overlooked. Up to 20% of children with this condition escape detection until the age of 3 or 4 years.[33] Typically, the only outward sign of this condition is flattened buttocks and a low, short gluteal cleft (Fig. 116-10, *A*). The diagnosis is confirmed with a lateral film of the lower spine, which reveals the missing sacral vertebrae. MRI of the lumbosacral spine, which is recommended in all patients, consistently reveals a sharp cutoff of the conus at T12[34] (Fig. 116-10, *B*). Urodynamic testing shows that an almost equal number of individuals manifest a primarily upper (i.e., hypertonic, hyperreflexic) or lower (i.e., atonic) motor neuron type lesion (35% vs. 40%, respectively), while 25%

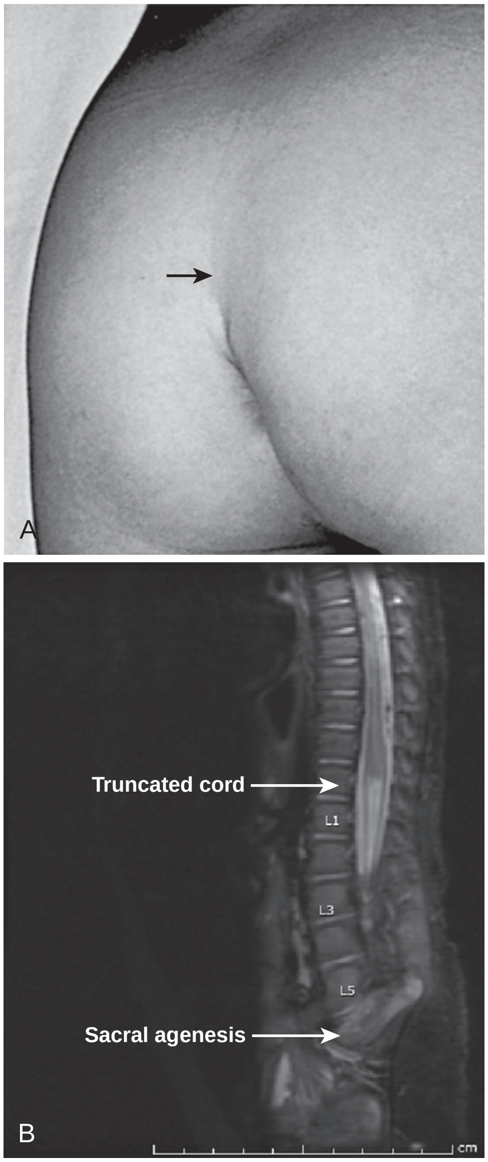


**FIGURE 116-10** **A,** Photograph of buttocks of patient with sacral agenesis. Note flattened buttocks and a low, short gluteal cleft. **B,** Magnetic resonance imaging of the lumbosacral spine in patient with sacral agenesis. Note sharp cutoff of the conus at T12 *(arrow)*.

have no sign of bladder dysfunction.[35] The number of affected vertebrae does not correlate with the type of motor neuron lesion. In contrast to the lesions noted in myelodysplasia or occult spinal cord anomalies, the injury is most frequently found to be stable. Although it is rare to see signs of progressive denervation such as a changing urodynamic pattern in these children as they grow, there can occasionally be a progressive renal impairment.[36,37] Anticholinergic agents are used to treat uninhibited contractions and/or relax the hypertonic detrusor, whereas CIC is used in patients with impaired bladder emptying.

## CEREBRAL PALSY

*Cerebral palsy* is the term used to describe a nonprogressive injury of the brain (e.g., hypoxic) occurring in the perinatal period that frequently produces a neuromuscular disability.[38]

Its incidence is approximately 1 in 1000 births. However, the incidence of cerebral palsy appears to be increasing as smaller premature infants survive in intensive care units. Although a high percentage of children will be found to have uninhibited contractions on urodynamic evaluation, the majority of children with this diagnosis have the capacity to develop total urinary control.[39] Incontinence is most commonly related to the physical handicap, making it difficult for the child to get to the bathroom in time. For this reason continence is often achieved at a later than expected age, once the child has become adept at transferring. Properly addressing the issue of adequate access to handicapped facilities may be extremely helpful in many of these children.

As a result of the many physical issues facing the child with cerebral palsy, urodynamic evaluation is typically reserved for those children who appear to be trainable, do not seem to be hampered too much by their physical impairment, and have not achieved continence by late childhood. For similar reasons, upper and lower urinary tract imaging is not recommended unless UTI has occurred.

Treatment focuses on providing an appropriate setting to allow the patient to easily access a toilet where they can properly relax while voiding. Individualized orthotics and upper body stabilization can help in this regard. If urodynamic data reveal uninhibited bladder activity, one can use anticholinergic medications but residual urine must be monitored closely to ensure complete evacuation with each void. CIC may be required for those who cannot empty their bladder. These children are also prone to severe constipation largely due to their poor fluid intake and limited physical activity. Insofar as constipation can adversely affect bladder stability and emptying, treatment to improve fecal elimination can prove beneficial in treating incontinence in these children. In a small subset of patients who do not respond to conservative measures, selective dorsal rhizotomy has improved bladder capacity, reduced the number of uninhibited contractions, and increased compliance.[40]

# Anatomic Causes of Bladder Dysfunction

## POSTERIOR URETHRAL VALVES

The most common form of anatomic bladder outlet obstruction in the pediatric population is posterior urethral valves (PUVs) in boys. Other etiologies of bladder outlet obstruction include urethral stricture, anterior urethral diverticulum, and an obstructing ureterocele situated at the bladder outlet.[41–43]

The incidence of posterior urethral valves is between 1 in 5000 and 1 in 8000 male births. Children present in a variety of ways depending on the degree of obstruction. Newborn children with severe outlet obstruction from posterior urethral valves typically present with a palpable midline abdominal mass (a distended bladder) and/or ascites (from urinary leak at the level of the kidney). In the most extreme cases children may experience respiratory distress from pulmonary hypoplasia due to the lack of adequate amniotic fluid volumes during lung development. Children who are identified later in life as having PUVs generally do not suffer from as severe an obstruction. These children typically present with voiding dysfunction, UTI, and on rare occasion with signs of renal failure (e.g., short stature). Today, with the widespread use of prenatal sonography, the majority of boys with bladder outlet obstruction are identified before delivery.[44]

Anatomic obstruction of the urethra results in pathologic changes at both the level of the kidney and the bladder. The bladder wall hypertrophies, diverticuli can form, and the posterior urethra becomes variably dilated (Fig. 116-11). Vesicoureteral reflux is seen in between 30% and 50% of patients. In approximately one third of these cases the reflux resolves once the obstruction has been relieved.[45] However, even in the absence of vesicoureteral reflux the upper urinary tract may still suffer injury due to lower urinary tract dysfunction that arises as a result of bladder wall thickening.

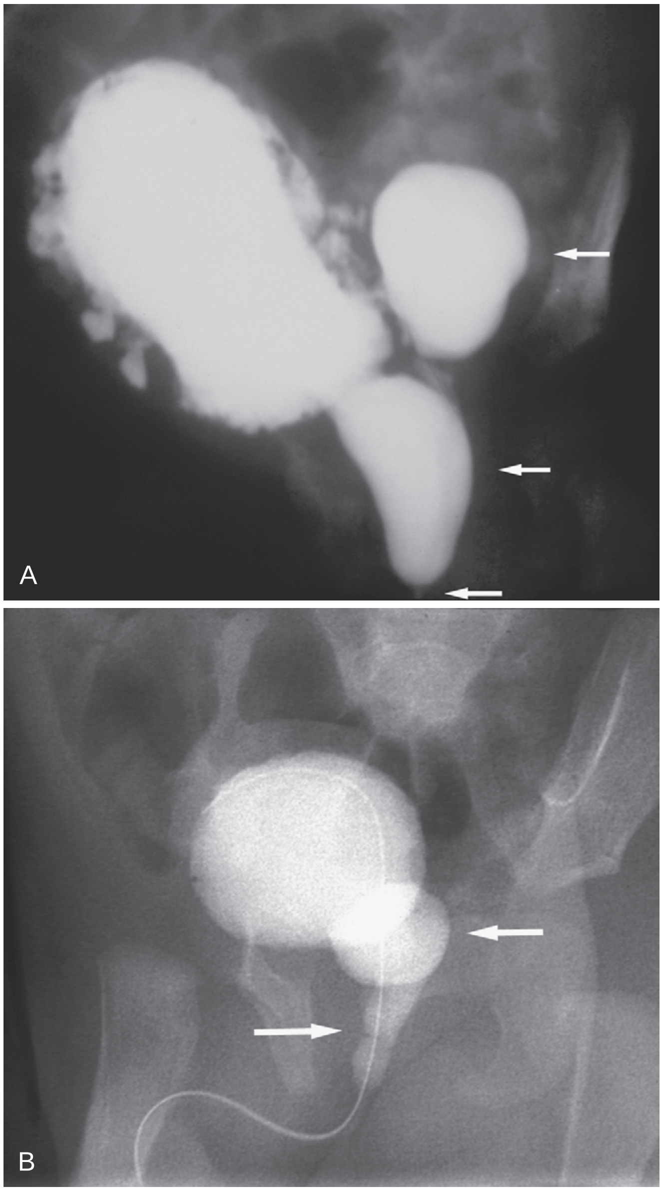


**FIGURE 116-11** Voiding cystourethrograms in children with posterior urethral valves. **A,** Severe case in which there is dramatic bladder decompensation with multiple small and large diverticuli *(uppermost arrow)* and dilated posterior urethra *(middle arrow)*. The site of valvular obstruction is shown by the inferior arrow. **B,** Mild case in which there is little evidence of bladder deterioration. *Upper arrow* points to the distended posterior urethra. *Lower arrow* points to the negative impression resulting from the posterior urethral valve itself.

Both cellular hypertrophy and the increased deposition of extracellular matrix are seen histologically in a bladder that is of lower capacity and decreased compliance.

Endoscopic destruction of the valve leaflets can be performed safely in nearly all term infants. An antegrade approach to valve destruction has been used in patients whose urethra is too small to accept a cystoscope.[46] Although cautery electrodes are the most frequently used device for disrupting the obstructing leaflets, cautery hooks, the neodymium: yttrium laser, and the antegrade withdrawal of a balloon catheter have also been used effectively for this purpose.[47–49]

Once the urethral obstruction has been relieved, bladder dysfunction may persist. Most often the bladder dysfunction manifests itself as daytime urinary incontinence that persists after the child has reached school age. Initially it was felt that persistent incontinence was due to injury to the urethral sphincter during endoscopic ablation of the valves and/or abnormal bladder sphincter development as a result of the initial obstruction. However, urodynamic assessment of these children has clearly shown that persistent bladder dysfunction is frequently seen well after the valves have been ablated. Several investigators have demonstrated that there are three primary abnormalities of detrusor function: bladder hypertonia, detrusor hyperreflexia, and myogenic failure.[50–53] Furthermore, evidence suggests that urodynamic patterns can change as the child matures. A study by Holmdahl and colleagues[54,55] has demonstrated that many children who are initially shown to have a hypercontractile, poorly compliant bladder as newborns will later have a urodynamic pattern that is more consistent with myogenic failure. Many children with bladder dysfunction secondary to posterior urethral valves also appear to have abnormal bladder sensation and an inability to sense when their bladder is full.[56] Adding to the problem of persistent bladder dysfunction is the common finding of renal injury and associated poor urinary concentrating ability. The large volumes of urine that result put a further stress on the dysfunctional lower urinary tract.

The treatment of bladder dysfunction in children with posterior urethral valves depends on the severity and form of bladder dysfunction, as well as the efficiency of bladder emptying. Patients with high-pressure voiding dynamics often benefit from the use of anticholinergic medications to improve compliance. In younger patients with an impaired ability to empty the bladder spontaneously, CIC may be required. Daytime catheterization can often be avoided in older children if they can adhere to a strict schedule of timed voiding. Recently Koff and colleagues have advocated the use of a nighttime indwelling catheter to provide optimal bladder drainage. By improving nighttime drainage, the authors have documented significant improvement in hydronephrosis and bladder compliance.[56,57] Although conservative measures are usually effective in modifying bladder dynamics (i.e., keeping bladder volumes sufficiently low to maintain acceptable bladder pressures), a small number of patients may still require bladder augmentation to improve bladder volume and compliance.[52] Patients with posterior urethral valves do not have altered urethral sensation, and many of these children will find catheterization through the penis painful. Creation of a continent catheterizable channel to the anterior abdominal wall can therefore improve the quality of life and result in improved compliance with catheterization in these children.[58]

# Nonneuropathic, Nonanatomic Causes of Bladder Dysfunction

## DYSFUNCTIONAL ELIMINATION SYNDROMES

Bladder dysfunction in the absence of anatomic bladder outlet obstruction or neurologic disease is frequently termed *dysfunctional voiding*. This term encompasses children who fit along a spectrum of relative urinary retention. At the most severe end of this spectrum are children who retain urine to such a great degree that they demonstrate altered bladder anatomy, upper urinary tract dilatation, and scarring, which is virtually indistinguishable from that seen in neuropathic bladder dysfunction (the so-called *non-neurogenic neurogenic bladder*) (Fig. 116-12).[59,60] The severity of the radiographic findings leads the physician to obtain an MRI of the lumbosacral spine, which by definition shows no abnormalities suggestive of spinal cord tethering. Urodynamic evaluation classically demonstrates a low-capacity, high-pressure bladder. Treatment of Hinman syndrome parallels that used in true neuropathic bladder dysfunction. An attempt should be made to lower intravesical pressures with the combined use of anticholinergic medication and CIC. If conservative measures fail to adequately reduce storage pressures, bladder augmentation is performed. Unlike patients with true neurologic lesions, many of these children will find catheterization painful and will benefit from creation of a continent catheterizable channel to the anterior abdominal wall.

At the opposite end of the spectrum is a large population of otherwise healthy children who, as a result of relative urinary retention experience, increased irritative voiding symptoms and a higher propensity toward developing UTIs. In the past decade it has become clear that constipation can be seen in many of these individuals and that a large fecal burden can have a significant impact on bladder function. As a result, the more encompassing term *dysfunctional elimination syndrome* (DES) has largely supplanted the term *dysfunctional voiding*.

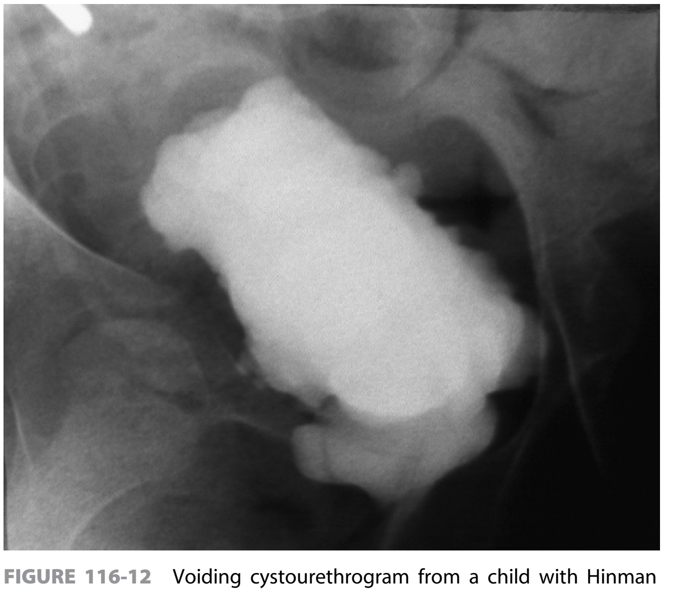

**FIGURE 116-12** Voiding cystourethrogram from a child with Hinman syndrome. Note the significant irregularity of the bladder outline secondary to bladder wall thickening.

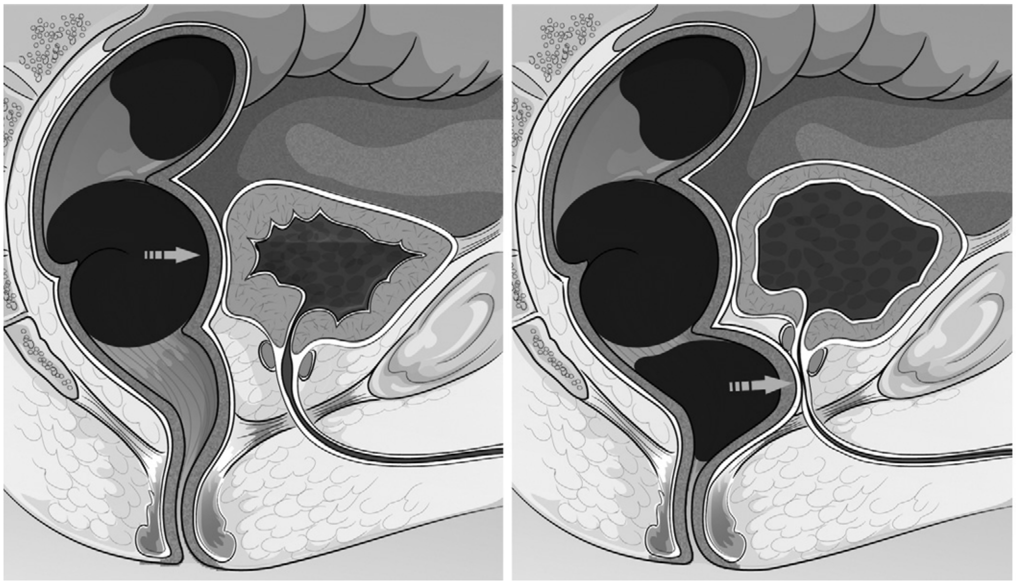



**FIGURE 116-13** The effect of constipation on bladder function. *Left,* Stool in the rectum may push up on the posterior aspect of the bladder, resulting in bladder instability. *Right,* Severe forms of constipation have the potential to externally compress the bladder neck and inhibit bladder emptying.

Children affected by this condition do not empty their bowel or bladder as often or as completely as they should, or they require high bladder pressures to empty their bladders. As a result of poor bladder emptying, the bladder is constantly distended and as such leaves the patient prone to urge incontinence. If children fail to empty completely, they will reach a state of fullness more often and this may be reflected in the symptom of urinary frequency. The maintenance of a high postvoid residual leaves the patient more prone to UTIs and incontinence. Constipation can contribute bladder irritability from the mass effect on the posterior aspect of the bladder and in severe cases may also inhibit bladder emptying (Fig. 116-13). Poor bladder emptying has been shown by Dohil and colleagues[61] to improve following bowel treatment in constipated children, with postvoid residual urine dropping from 66% at baseline assessment to 21%. Chronic constipation is associated with significant hypertrophy of the internal anal sphincter and abnormal anal sphincter EMG activity.[62] This may generate increased urethral sphincter and pelvic floor activity and explain the association between voiding dysfunction and incomplete voiding.

Radiographic findings that are highly suggestive of this diagnosis include a large stool burden on the plain abdominal film or evidence of a full rectosigmoid segment behind the bladder on ultrasound, a large postvoid residual on bladder ultrasound, and the "spinning top" image of the bladder neck on voiding cystourethrogram (Fig. 116-14).

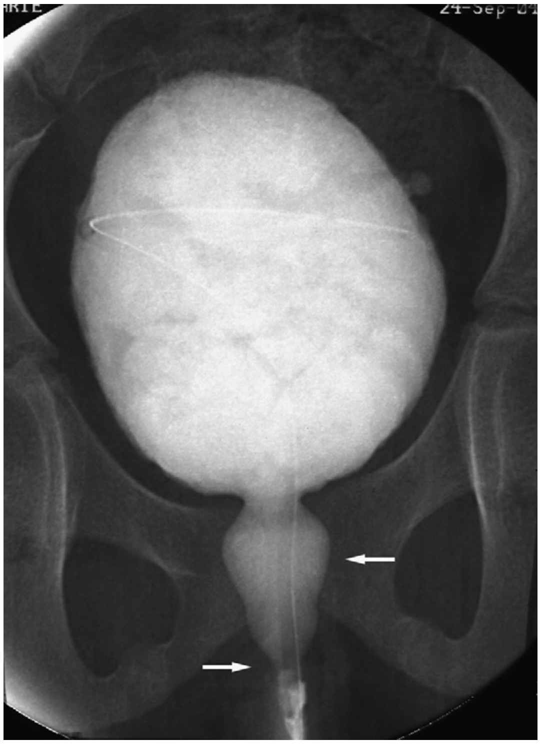

**FIGURE 116-14** Voiding cystourethrogram from a child with dysfunctional elimination syndrome demonstrating a full bladder with a small diverticulum and a distended proximal urethra *(uppermost arrow)*. The *lowermost arrow* depicts the site of the external sphincter. Because of failure to relax, the result is proximal urethral ballooning (the so-called *spinning top deformity*).

Treatment of the child with DES includes (1) timed voiding in which the child is asked to void every 2 hours, (2) double voiding in which the child is asked to attempt to void a second time after emptying the bladder (in an attempt to minimize the chances of carrying a large postvoid residual), and (3) establishing good bowel emptying habits. The latter behavior can be supported by increasing dietary fiber, using stool softeners, and taking plenty of time to defecate completely. Providing adequate foot support can be beneficial in achieving a state of balance and thereby enhancing adequate relaxation. Should these conservative measures fail to result in adequate relaxation during voiding/defecating, biofeedback may prove beneficial. Many ingenious methods for performing biofeedback including the use of videogames have been developed.[63] Although biofeedback has proven to be highly beneficial in

many patients, this modality may require multiple office visits with skilled nursing care, which can often be difficult due to time and/or financial constraints. An alternative that has recently gained much attention is treatment with α-adrenergic inhibitors. The exact mechanism and site of action for α-blocker therapy in children with poor bladder emptying remains in question. There are documented reports of $\alpha_1$-adrenergic receptors at the bladder outlet and in the proximal urethra.[64,65] It is felt that the primary mechanism of action is smooth muscle relaxation at the base of the bladder and decreased outlet resistance in the proximal sphincter complex. Both tamsulosin and doxazosin have been studied in the pediatric setting.[66] Selective α-blocker therapy appears to be effective for improving bladder emptying in children with wetting, recurrent infection, and increased PVR urine. Early treatment of increased postvoid residual urine volumes with α-blockers may significantly reduce the number of patients who will need biofeedback therapy. The more commonly reported side effects of these medications are nasal congestion, dizziness, and postural hypotension. We recommend administering the medication before bedtime so as to minimize the potential for experiencing dizziness during the waking hours. It is also imperative that the blood pressure be evaluated 3 days following initiation of the medication to ensure that the child is not experiencing orthostatic hypotension.

## OVERACTIVE BLADDER SYNDROME

Although the majority of children who present to the pediatrician with wetting and urinary frequency will have a retentive behavior as the etiology, a smaller population will demonstrate these symptoms due to a state of relative detrusor overactivity in the absence of demonstrable neurologic impairment. As a result, bladder filling even to moderate volumes will often trigger a bladder contraction. This group of children does not demonstrate retentive bladder or bowel behavior and carries minimal postvoid residual when evaluated by bladder ultrasound. An effective treatment for this condition is the use of anticholinergic medications. Anticholinergic medications are competitive inhibitors of acetylcholine that block the neurotransmitter's muscarinic effects. Anticholinergic medications are typically titrated to effect. Common side effects consist of dry mouth, flushing, and constipation. Constipation especially may pose a problem because children with detrusor overactivity have a predilection for constipation, and the development of constipation may aggravate detrusor overactivity and thus counteract the beneficial effects of the drug. Oxybutynin (0.2 mg/kg twice daily or three times daily) has been the most often used anticholinergic medication. The newer antimuscarinic drug tolterodine has, in adults, shown a more favorable therapeutic profile, with the same clinical efficacy and a lesser frequency of side effects compared with oxybutynin.[67] Tolterodine has also been shown to be safe and effective in children.[68] A commonly used dosage for tolterodine in children is 0.1 mg/kg twice daily. Sustained release formulations, which can be taken once daily, are also a choice for children who can tolerate medication in pill form. In patients who experience minimal side effects, studies have shown increased effectiveness by doubling the recommended daily dosage.[69,70] Overactive bladder symptoms are typically self-limiting with even the most recalcitrant cases showing resolution within an 18-month period.[71] Failure to improve on anticholinergic medication may warrant a more thorough investigation of the patient in the form of a urodynamic evaluation.

## NOCTURNAL ENURESIS

Whether a true problem of bladder function, a failure of adequate nocturnal urinary concentrating ability, or an issue related to a relatively poor state of nocturnal arousal, nighttime wetting is often discussed in chapters on bladder dysfunction.[72] Various series have reported the incidence of isolated nocturnal enuresis as between 6% and 10% in children who have reached age 7 years. The spontaneous cure rate in children between the ages of 5 and 20 is 15% annually.[73] Most children who are enuretic eventually obtain normal control.

Nocturnal enuresis is a genetically complex and heterogeneous disorder. Genetic factors play an important role in the etiology. A positive family history may be elicited in more than 50% of cases. Within families different members can show the same or different forms of wetting. Studies evaluating the incidence of nocturnal enuresis in twins have shown 46% for monozygotic pairs and 19% for dizygotic pairs.[74] The most common mode of transmission appears to be autosomal dominant.

Various pathophysiologic mechanisms appear to be at play including nocturnal polyuria, bladder overactivity at night with a small functional bladder capacity, and disorder of arousal.[75] Furthermore, these groupings show considerable overlap. In humans there is a marked circadian rhythm of urine production so that there is a nighttime reduction in diuresis of up to 50% of daytime levels.[76] In children this is controlled by increased nocturnal release of arginine vasopressin, as well as angiotensin II and aldosterone.[77,78] It has long been known that children with nocturnal enuresis have significantly larger nocturnal urine production than nonenuretic children. This group of patients has a favorable response to the arginine vasopressin analogue dDAVP.[79] Although a certain subset of enuretics has a smaller nocturnal functional bladder capacity, the incidence of functional abnormalities seems rather low in children with isolated nocturnal enuresis. Whether wetting is primarily due to a problem of urinary concentrating ability, functional bladder capacity, or other as of yet unrecognized etiology, a prerequisite for wetting is failure to awake when micturition is imminent. This has caused many to conclude that sleep disturbance per se is the major pathophysiologic factor in enuresis, and it is still a widely held belief that enuretics are deep sleepers. However, a number of studies have been unable to convincingly show abnormalities in sleep patterns.

Treatment of nocturnal enuresis takes many forms. If present, daytime symptoms should be treated. The child should be asked to void regularly and not to delay urinating after experiencing a sense of bladder fullness. Symptoms of urgency and frequency, as well as constipation, should be addressed. A rate of enuresis cure up to 72% has been reported after constipation has been adequately addressed.[80] To minimize the possibility of nocturnal polyuria, fluids should be limited several hours before bedtime. A low calcium and sodium dietary content of the afternoon and evening meals may also be useful. The child should be instructed to void before bedtime. This helps to minimize the nocturnal bladder volume.

Enuresis that persists after age 6 may be treated with medication and/or a bed alarm device. Desmopressin (dDAVP) is easy to administer and has an immediate effect on urinary

volume. Dosing is between 0.2 and 0.6 mg orally. Intranasal dDAVP has recently lost its indication for nocturnal enuresis by the U.S. Food and Drug Administration due to the side effect of water intoxication. In most trials response to desmopressin (defined as >50% reduction of the number of wet nights) was noted in 60% to 70% of patients.[81] Another pharmacologic option is the tricyclic antidepressant imipramine (Tofranil), which exerts a direct effect on bladder smooth muscle and has sympathomimetic effects. Unlike anticholinergic medications, which have a relatively short half-life, the blood levels of imipramine build up over a period of several days. The true beneficial effect of this medication may therefore not become apparent for up to 2 weeks. Approximately 50% of enuretic children improve with imipramine, yet a significant number will relapse after treatment is discontinued. It has been reported that only 17% of children who were dry during imipramine medication stay dry 6 months after cessation of the medication.[82] The major drawback to imipramine therapy is its cardiotoxic side effects, even in therapeutic doses.[83] Although anticholinergic medications should not be expected to be effective in true isolated nocturnal enuresis, this medication can occasionally be of help.

Alarm therapy is the most effective method for treating nocturnal enuresis. A meta-analysis of the world literature revealed an average success rate of 68%.[72] Efficacy is reported to increase with duration of therapy to as high as 90% by 6 months.[84] Although most children will not awaken, they will stop emptying the bladder at the onset of the alarm. It therefore requires that a parent assist the child in awakening and proceeding to the toilet to finish voiding. Once the undergarments have been changed, the alarm should be reset. The exact mechanisms of alarm treatment are not known, although it is clearly an operant type of behavioral approach.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 117

# Reconstruction of the Bladder and Bladder Outlet

Eugene Minevich and Curtis A. Sheldon

Effective surgical management of the abnormal bladder requires a thorough understanding of both normal micturition and dysfunctional voiding (see Chapter 116). Urinary continence is a complex balance between intravesical pressure and bladder outlet resistance. Several variables determine intravesical pressure, only one of which is compliance, which reflects both muscular tone and interstitial elasticity. This measure is not static but rather varies with bladder capacity. Consequently, urine output, postvoid residual volume, and frequency of bladder emptying determine the working compliance range of the bladder. Pathologic alterations (e.g., uninhibited detrusor contraction or interstitial fibrosis) may markedly alter compliance and resultant intravesical pressure characteristics.

Bladder outlet resistance also depends on several variables and must be highly coordinated in order to prevent incontinence but allow voiding to occur. Reflex contraction of the sphincteric mechanism helps prevent incontinence after sudden increases in intra-abdominal pressure. Conversely, bladder outlet sphincteric mechanisms reflexively relax at the time of detrusor contraction. At this point, volitional voiding ensues. In addition, voluntary contraction of the striated muscle of the urinary sphincter adds supplementary support to prevent incontinence. In some circumstances, however, reflex contraction of the bladder sphincteric mechanism or inappropriate voluntary contraction (e.g., dysfunctional voiding) can result in dangerously high intravesical pressures. Furthermore, the bladder outlet sphincteric mechanism may fail to relax during attempts at voiding, a condition known as *detrusor-sphincter dyssynergy*. Pathologic bladder outlet resistance may be caused by congenital anatomic obstruction (e.g., posterior urethral valves) or acquired lesions (e.g., stricture).

The structural consequences of unbalanced voiding are highly variable and ominous. Bladder consequences include hypertrophy of detrusor musculature with trabeculation. Sacculation and diverticula may develop, leading to urinary tract infection (UTI) and urolithiasis. Interstitial fibrosis may also occur and cause a progressive loss of bladder compliance. Of particular concern are the consequences of high bladder pressure on renal function. Even without vesicoureteral reflux, a close correlation exists between intrapelvic renal pressure and intravesical pressure.[1] Renal pelvic pressures greater than 40 cm of $H_2O$ deform the renal papillae, which may distort the orientation of the tubules draining into the papillae and result in intrarenal reflux.[2] This increases the vulnerability of the kidney to pyelonephritis.

In patients with neurogenic bladder (such as those with myelodysplasia), bladder pressure and renal prognosis are closely correlated. Spontaneous urine leakage through the bladder outlet mechanism at a bladder pressure greater than 40 cm $H_2O$ has been associated with poor prognosis for the upper urinary tract.[3] A similar correlation with the maximal urethral pressure on urodynamic testing has also been demonstrated.[4] Furthermore, elevated intravesical pressure has been shown to adversely affect the renal allografts.[5]

Otherwise healthy children with increased intravesical pressure have an increased risk for UTI and vesicoureteral reflux (VUR).[6] Anticholinergic medications, which reduce intravesical pressure, can dramatically alleviate reflux and UTI.[7,8]

The surgeon must realize that the cause of bladder injury cannot be reliably determined from end-stage abnormalities because the ability of various primary diseases to cause bladder injury overlaps considerably. Secondary changes due to chronic retention, infection, stones, or surgery also confound the issue. Therefore one cannot predict the degree of bladder function on the basis of knowledge of such primary diseases as myelodysplasia, posterior urethral valves, prune-belly syndrome, and imperforate anus. Measurement of physiologic properties of the bladder by formal urodynamic investigation is essential in planning any major surgical intervention.

Although it is accepted that bladder dysfunction can damage the kidney, it is less well recognized that renal disease can contribute to bladder injury. Polyuria caused by primary renal disease can substantially alter bladder function. It can result in a hypertensive bladder with extensive detrusor hypertrophy or, if decompensated, a massively dilated, flaccid, hypotonic bladder that cannot empty completely. These effects can also accompany secondary renal disease (e.g., polyuria accompanying posterior urethral valves). Such lesions injure the renal medulla and lead to a loss of concentrating capacity; the resulting polyuria may further damage the bladder.

Bladder outlet obstruction is a major factor in progressive bladder and kidney injury. Structural lesions such as posterior urethral valves or urethral strictures are particularly problematic. Also important is detrusor-sphincter dyssynergy. This condition may be volitional or nonvolitional. With the latter, the sphincteric periurethral muscle inappropriately contracts (rather than relaxes) during detrusor contraction. In the former, the child closes the bladder outlet to prevent incontinence that results from uninhibited detrusor activity or to delay the need for voiding when the bladder has become overfilled. Such activity may also be used to prevent painful voiding. This activity is often manifested clinically by the occurrence of Vincent curtsy, in which the child sits on a foot, squats, or squeezes the legs together to help prevent voiding.

The "valve bladder" best exemplifies the interplay of these factors (Fig. 117-1). Even after valve resection, the bladder may still operate at high pressures because of residual bladder wall changes such as altered compliance and uninhibited detrusor contractions. The bladder may not empty completely, and substantial VUR may be present. During voiding, urine is emitted through the urethra but also refluxes into the kidneys. When the patient completes voiding, this urine immediately drains back into the bladder. This drainage, along with elevated postvoid residual urine volume caused by abnormal bladder function, forces the bladder to continuously work within a range that results in high storage pressure with subsequent adverse effects on the kidneys.

Recent advances in surgical technique, the successful application of intermittent catheterization to the reconstructed urinary tract, and the lessons learned from the pioneering work on urinary undiversion[9] allow even the most anatomically devastated children to be reconstructed for continence, as well as preservation of renal function. Such reconstructive principles may now be applied to virtually all urinary tract anomalies with a good expectation of success. Reconstructive options are presently available even for children with end-stage renal disease for whom renal transplantation will ultimately be required. Reconstruction involves many challenges in achieving the goals of low-pressure storage of urine and complete bladder emptying. Most frequently, such reconstruction is necessary for treatment of bladder exstrophy; posterior urethral valves; and neurogenic bladder related to myelomeningocele, other sacral dysraphisms, or the VATER complex (*v*ertebral defects, imperforate *a*nus, *t*racheoesophageal fistula with *e*sophageal atresia, and *r*adial and renal dysplasia). Other disease states necessitating reconstruction include urogenital sinus and cloacal anomalies, cloacal exstrophy, and bilateral single ectopic ureters. All of these are commonly associated with abnormal storage pressures of urine or problems with emptying.

# Disorders of Bladder and Urethra

## ANATOMIC DISORDERS OF BLADDER AND URETHRA

Primary structural abnormalities are important and are best exemplified by posterior urethral valves (Fig. 117-2), the most common cause of structural lower urinary tract obstruction in male infants. As a consequence of obstruction, the proximal urethra is elongated and dilated, and the bladder neck is relatively narrowed because of secondary detrusor hypertrophy. The distal urethra is of normal caliber, resulting in an abrupt transition between the dilated proximal urethra and the thin anterior urethra. The bladder exhibits detrusor hypertrophy and is irregular because of trabeculation, sacculation, and the presence of diverticula. The upper urinary tracts typically show severe hydronephrosis with or without vesicoureteral reflux. Renal impairment is frequent and often presents from birth; recovery is incomplete even after valve ablation.

Most patients are recognized during infancy, and more than two thirds are identified within the first year of life. With the

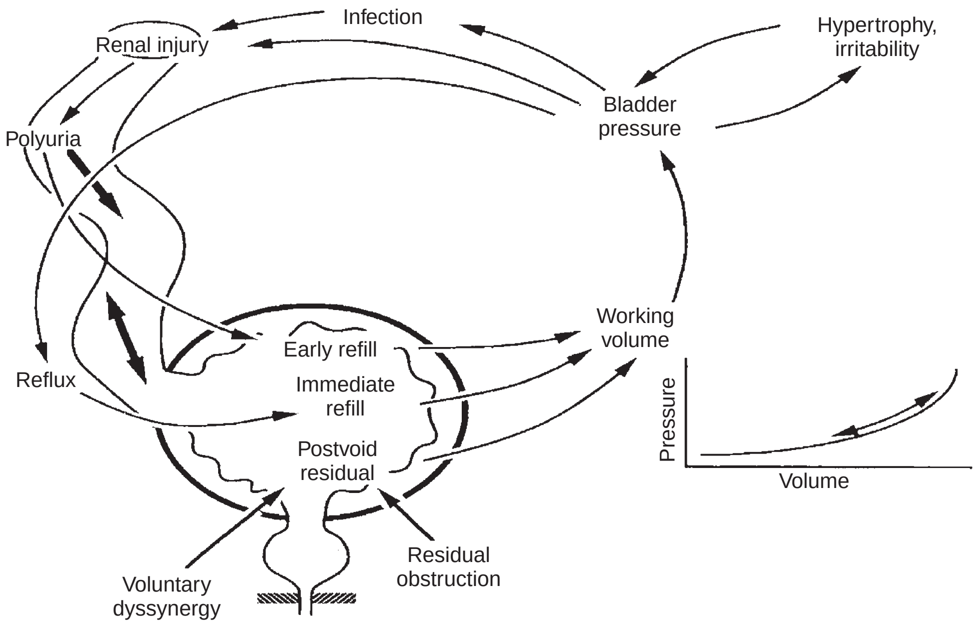


FIGURE 117-1 Pathophysiology of the valve bladder. (From Minevich E, Sheldon CA: Structural disorders of the bladder, augmentation. In Grosfeld JL, O'Neill J, Fonkalsrud E, Coran A [eds]: Pediatric Surgery. St. Louis, Mosby, 2006.)

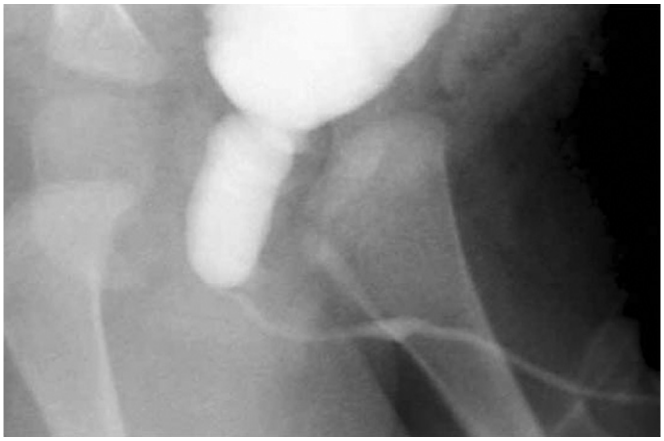

FIGURE 117-2 Radiographic appearance of posterior urethral valves. (From Minevich E, Sheldon CA: Structural disorders of the bladder, augmentation. Grosfeld JL, O'Neill J, Fonkalsrud E, Coran A [eds]: Pediatric Surgery. St. Louis, Mosby, 2006.)

advent of perinatal ultrasonography, in utero diagnosis has become common. A newborn may have an enlarged palpable bladder or kidneys as a result of hydroureteronephrosis. An infant may have UTI or failure to thrive because of azotemia, whereas in older children the initial manifestation may be incontinence. Diagnostic evaluation includes ultrasonography of the upper urinary tract and radiographic voiding cystourethrogram (VCUG). Renal function can be evaluated by renal scanning. Urodynamic investigation may later be indicated if hydronephrosis, reflux, azotemia, or incontinence persists in a child whose valves have been ablated successfully.

Infants should initially be stabilized by catheter drainage of the bladder, intravenous resuscitation, and respiratory support when needed. Urine is drained with a 5- or 8-French infant feeding tube because larger catheters or catheters with balloons may cause intense detrusor contraction, which may impede urine flow through the ureterovesical junction. Most patients are subsequently treated by valve ablation. In premature infants with a urethra too small for endoscopic fulguration, either antegrade ablation or a vesicostomy may be created; with current miniaturized cystoscopes, however, these procedures are rarely necessary. Patients with massive reflux, particularly when accompanied by azotemia, are also candidates for vesicostomy.

The rare infant with profound azotemia who is unresponsive to catheter drainage may benefit from upper urinary tract diversion by way of cutaneous pyelostomy. Such low-pressure drainage may allow sufficient return of renal function so that dialysis or renal transplantation can be deferred until the child is older. Both cutaneous vesicostomies and cutaneous pyelostomies are readily reversed. It is important to avoid fulguration of valves in a dry urethra (e.g., in the patient who has undergone diversion by vesicostomy or pyelostomy), which may result in urethral stricture.

Anterior urethral valves, Cowper duct cysts, urethral polyps, urethral duplication (Fig. 117-3), and urethral diverticula can produce structural changes in the bladder that are related to obstruction. Acquired obstructive lesions include stricture and meatal stenosis. Exstrophic bladder abnormality, epispadias, and hypospadias are other structural lesions, discussed elsewhere in the textbook.

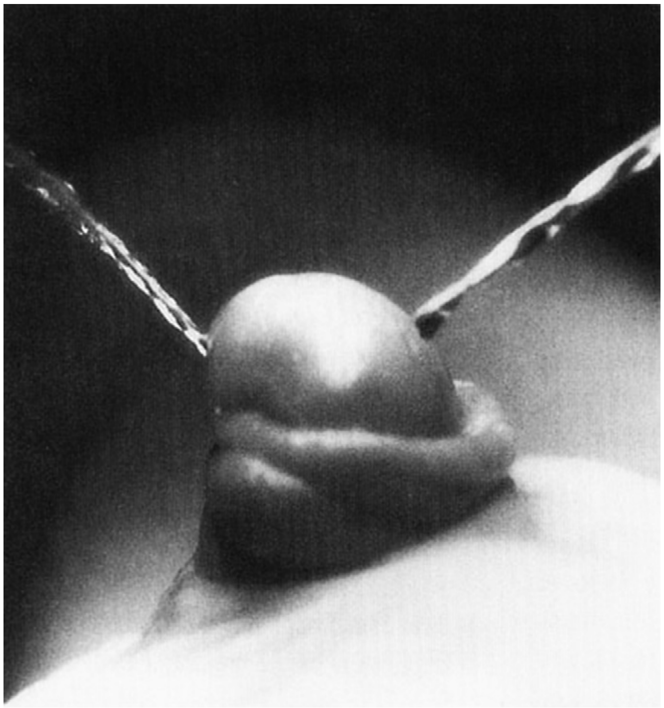

FIGURE 117-3 Urethral duplication. (From Sheldon CA, Bukowski TP: Male external genitalia. In Rowe MI, O'Neill J, Grosfeld JL, et al [eds]: Essentials of Pediatric Surgery. St Louis, 1995, Mosby-Year Book, p 779.)

## NEUROGENIC DISORDERS OF THE BLADDER AND URETHRAL FUNCTION

The surgeon is commonly faced with a primary abnormality of bladder innervation (a neurogenic bladder). Myelodysplasia, an open dystrophic state, is particularly common. Myelomeningocele, in which neural tissue and the meninges protrude beyond the confines of the vertebral canal, is the most common defect. The neurologic effect of these entities on the lower urinary tract varies and cannot be predicted by the observed level of the anomaly; urodynamic testing is, therefore, essential. The risk for upper urinary tract deterioration can be predicted urodynamically. Both a leak point pressure exceeding 40 cm $H_2O$[3] and the presence of dyssynergy[10] have been clearly shown to be associated with poor prognosis for the upper urinary tract (Figs. 117-4 and 117-5). The risk for deterioration exceeds 70% in the presence of dyssynergy; sphincteric synergy or sphincteric denervation is associated with an incidence of deterioration of 15% and 25%, respectively. Unfortunately, the neurologic defect is often a dynamic one in which dyssynergy, if not present initially, may develop over time. The development of dyssynergy is often related to tethering of the spinal cord, which may result in spinal injury or spinal root injury as the child grows. The greatest risk occurs within the first 2 years of life, especially the first year, but such injury can occur throughout childhood.

Occult (closed) spinal dysraphisms include tethered cords, intradural lipomas, dermoid cysts or sinuses, diastematomyelia, and cauda equina tumors. These children commonly have urologic manifestations as UTIs and incontinence. Fortunately, however, cutaneous manifestations are obvious in most patients. Such lesions as cutaneous dimpling, the presence of a skin tag, a subcutaneous lipoma or a patch of hair over the bony sacrum, dermal vascular malformation, and pigmentation may

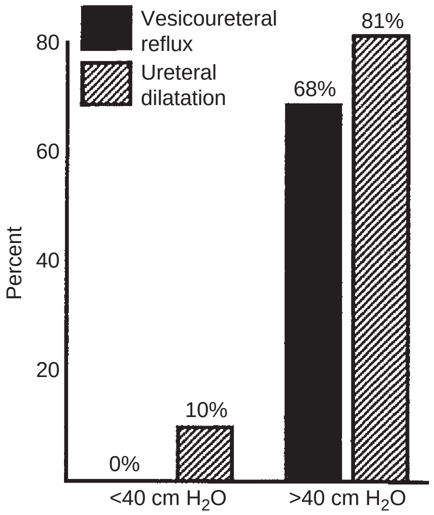


FIGURE 117-4 Risk for upper urinary tract injury as a function of urethral opening pressure. (From McGuire EJ, Woodside JR, Borden TA, Weiss RM: Prognostic value of urodynamic testing in myelodysplastic patients. J Urol 1981;126:208.)

indicate an underlying spinal disorder. The presence of these findings in any child with urinary incontinence or other evidence of bladder dysfunction requires exclusion of occult spinal diastrophism. These diagnoses may be confirmed by urodynamic investigation and spinal magnetic resonance imaging (MRI) or, in the first 6 months of life, ultrasonography of the spinal cord. Abnormal urinary tract function occurs in approximately 40% of patients.[11]

Another important cause of neurogenic bladder is sacral agenesis, often seen in imperforate anus or in the infant of a diabetic mother. This condition is characterized by congenital absence of all or part of two or more sacral segments. The lesion may be suggested on physical examination by the presence of an abnormal gluteal cleft or detection of an incomplete sacrum on direct palpation. The diagnosis may be confirmed by anteroposterior and lateral lumbosacral spine radiographs. Approximately 75% of such patients have abnormal urinary tract function.[12]

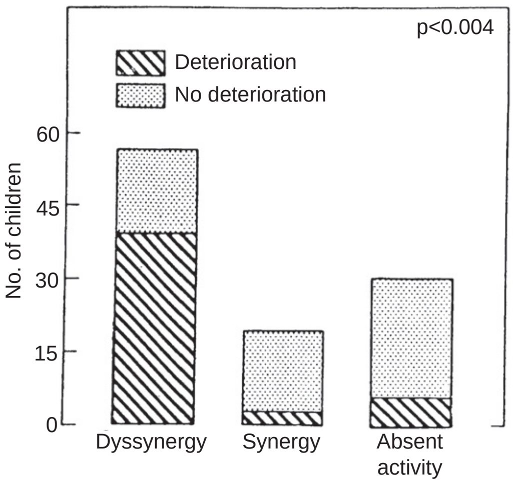


FIGURE 117-5 Urinary tract deterioration as a function of dyssynergia, synergy, and absent sphincteric activity. (From Bauer SB: Early evaluation and management of children with spina bifida. In King LR [ed]: Urologic Surgery in Neonates and Young Infants. Philadelphia, WB Saunders, 1988, p 256.)

## COMBINED ANATOMIC AND NEUROGENIC DISORDERS

A third group of infants requiring bladder reconstruction are those with both functional and structural bladder abnormalities such as imperforate anus or cloaca. In these cases, a full anatomic assessment must be done early in life, which at a minimum requires renal ultrasonography, radiographic VCUG, and ultrasonographic assessment of the spinal cord. The combination of both anatomic and functional abnormalities creates a high risk for substantial urologic morbidity. A study by McLorie and colleagues involving 484 consecutive patients revealed a high risk for end-stage renal disease.[13] Nonfistula genitourinary anomalies were encountered in 60% of patients with high lesions and 20% of those with low lesions. Substantial upper urinary tract abnormalities were encountered in more than one third of cases, and bilateral upper urinary tract abnormalities occurred in 14%.

Our review of 90 consecutive cases of imperforate anus showed an 18% incidence of significant neurovesical dysfunction.[14] The greatest risk was encountered in patients with a high imperforate anus. However, neurovesical dysfunction was also encountered in some patients with low lesions. In many patients, a tethered spinal cord must be addressed because of the risk for progressive injury to innervation of the bladder, urethra, anorectum, and lower extremities.

The importance of these anomalies was demonstrated in a review of 23 of our patients with imperforate anus reconstructed for either upper urinary tract preservation or achievement of continence.[15] As shown in Figure 117-6, 9% of patients presented with end-stage renal disease, 65% had significant renal abnormalities, and 57% had vesicoureteral reflux. Ureteral anomalies were encountered in 30% of patients, and neurovesical dysfunction was encountered in 70%. A wide spectrum of urologic reconstructive procedures was required for these patients (Fig. 117-7). Of particular note, 43% required ureteral reimplantation, 43% required bladder augmentation, 35% required a Mitrofanoff neourethra, and 22% required bladder neck reconstruction. The urethra in boys with imperforate anus may be difficult to catheterize because of urethral irregularity related to the congenital rectourethral fistula. This, along with intact urethral sensation, may necessitate the creation of a Mitrofanoff neourethra to assist intermittent catheterization.

Other lesions, described elsewhere in this text, may also require bladder reconstruction. Patients with urogenital sinus anomalies, in which the bladder and vagina drain through a common channel, often have associated neurovesical dysfunction. In addition to urethral and vaginal reconstruction, these patients may have an incompetent bladder outlet, necessitating reconstruction. As with other conditions associated with neurovesical dysfunction, bladder augmentation may be required. Patients with exstrophy or cloacal exstrophy characteristically require complex urinary tract reconstruction. Patients with the prune-belly syndrome can usually be managed medically but sometimes require surgical intervention. These patients typically have a hypotonic bladder that operates at low pressure but empties incompletely, is highly irregular, and is prone to infection. Some patients, however, lose capacity and compliance over time. Consequently, urodynamic investigation is often necessary to facilitate therapy.

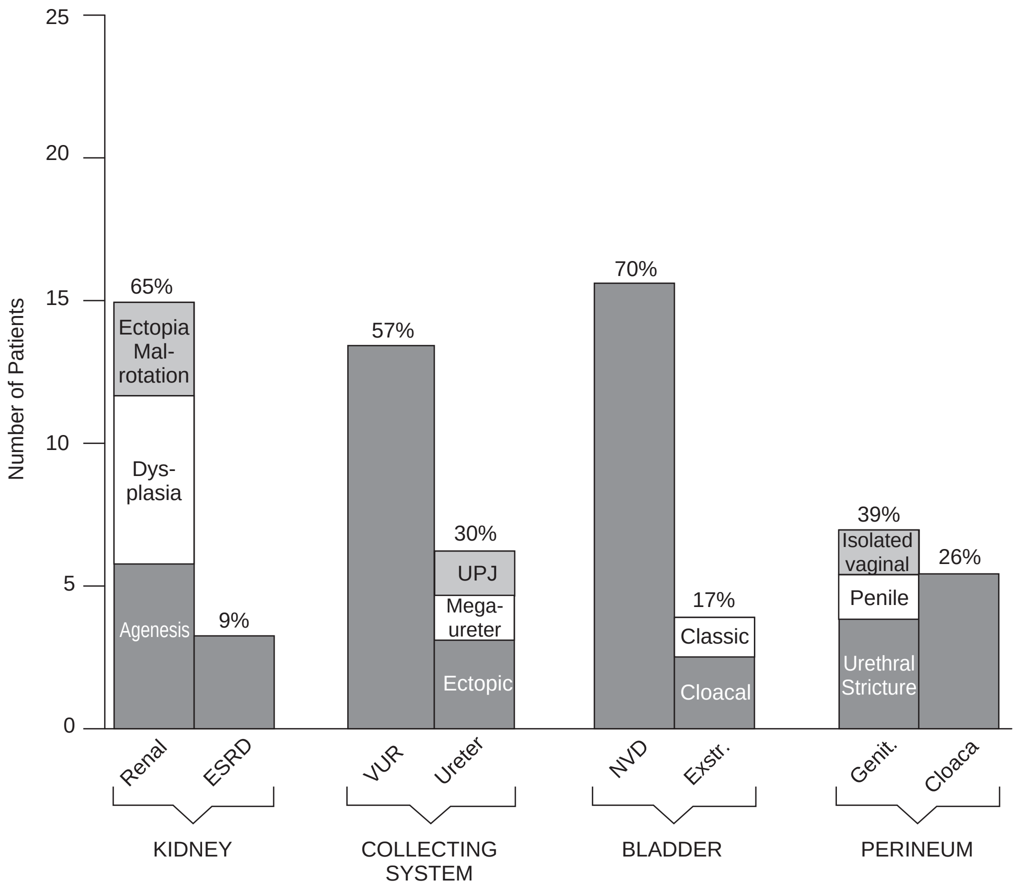


**FIGURE 117-6** Genitourinary anomalies associated with imperforate anus. *ESRD,* End-stage renal disease; *NVD,* neurovesical dysfunction; *UPJ,* ureteropelvic junction; *VUR,* vesicoureteral reflux. (From Sheldon CA, Gilbert A, Lewis AG: Surgical implications of genitourinary tract anomalies in patients with imperforate anus. J Urol 1994;152:196.)

# Reconstructive Philosophy

The goals of urinary reconstruction are to preserve the upper urinary tract, attain socially acceptable continence, and maximize the child's ease of care and potential for self-care. Patients at risk for upper urinary tract injury are evaluated during the newborn period, and therapy to protect the upper urinary tracts is initiated at that time. Urinary incontinence is evaluated and treated just before school age in order to make social integration easier. In general, an attempt is made to manage the urinary tract with medical therapy before subjecting the child to surgical intervention. Such therapy may include intermittent catheterization to facilitate bladder emptying, anticholinergic therapy to diminish intravesical pressure, and α-adrenergic agents to enhance bladder outlet resistance. Surgical therapy is undertaken only if medical therapy is unsuccessful. When contemplating urinary tract reconstruction, meticulous preoperative evaluation is critical, and it is essential to tailor the reconstruction to the individual needs of the patient.

Four components of balanced urinary tract function must be achieved to ensure long-term success with urinary reconstruction.[16] The first component is that of adequate bladder (reservoir) capacity and sufficient compliance to provide low-pressure storage. Optimal bladder capacity should allow a 4-hour catheterization or voiding interval during the day and an 8-hour interval at night without reaching excessive pressure or precipitating incontinence. The second component is adequate bladder outlet resistance to maintain urinary continence. Third, there must be a convenient, reliable mechanism for bladder (reservoir) emptying. Ideally, this should be achieved by spontaneous voiding; otherwise, intermittent catheterization is necessary. The native urethra may be an acceptable conduit for this maneuver, although should catheterization of it prove excessively difficult or uncomfortable (preventing patient compliance), an alternative catheterizable conduit may be necessary. Finally, unobstructed and nonrefluxing sterile upper tract drainage of urine into the bladder (reservoir) is desirable in order to protect the upper tracts.

# Compensating for Inadequate Bladder Capacity or Compliance

## PHYSIOLOGIC CONSIDERATIONS

Bladder capacity and compliance are increased by bladder augmentation. Indicators that augmentation is necessary include clinical symptoms, such as incontinence caused by bladder dysfunction unresponsive to medical therapy, and upper urinary tract deterioration due to inadequate low-pressure storage volume. Also suggestive is a measured bladder capacity that is significantly less than that expected for the patient's age. Caution must be exercised because with an incompetent

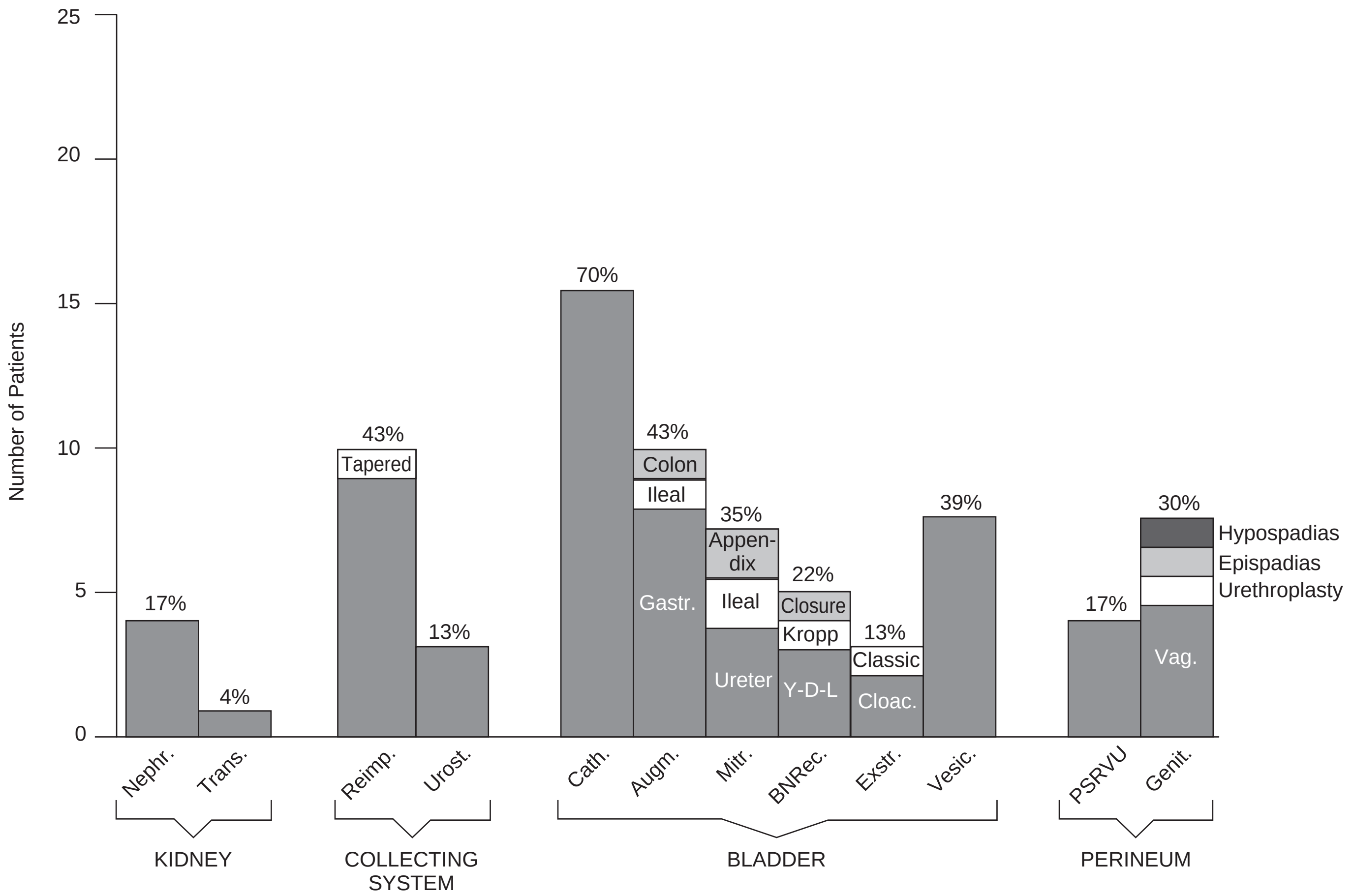


**FIGURE 117-7** Surgical procedures performed in patients with imperforate anus. *Augm.*, Augmentation; *BNRec.*, bladder neck reconstruction; *Cath.*, intermittent catheterization; *Exstr.*, exstrophy; *Gastr.*, gastrocystoplasty; *Mitr.*, Mitrofanoff neourethra; *Nephr.*, nephrectomy; *Reimp.*, reimplantation; *Trans.*, renal transplantation; *Urost.*, ureterostomy; *Vag.*, vaginoplasty; *Vesic.*, vesicostomy; *Y-D-L*, Young-Dees-Leadbetter procedure. (From Sheldon CA, Gilbert A, Lewis AG: Surgical implications of genitourinary tract anomalies in patients with imperforate anus. J Urol 1994;152:197.)

bladder outlet, the bladder may drain at low pressure, making determination of functional bladder volume more difficult. Performing cystometrography with a Foley catheter balloon that occludes the bladder neck may provide more reliable data on functional bladder capacity. The generation of pressure exceeding 35 to 40 cm $H_2O$ with urine volumes equal to those anticipated during 4 hours of urine production during the day or 8 hours of urine production during the night during maximal medical therapy further suggests that bladder augmentation should be considered.

Several important reconstructive concepts are pertinent to bladder augmentation. The first regards management of the recipient bladder. If bowel augmentation is performed, with the detrusor essentially left intact to generate high pressure, the former will act urodynamically as a capacious diverticulum.[17] The problem can be avoided by an extended sagittal opening of the bladder from the level of the bladder neck anteriorly to the trigone posteriorly ("clam cystoplasty"). Essentially, this is a reconfiguration of the bladder from a sphere into a flat plate so that the detrusor is no longer capable of generating a contraction that produces a significant pressure elevation.[18,19]

Just as pressure generated by the bladder detrusor is an important contributor to the pressure generated in an augmented urinary reservoir, so also is the pressure generated by the tubularized bowel segment itself. With peristaltic contractions, pressures ranging from 60 to 100 cm $H_2O$ may be encountered.[20] This observation led Kock to develop his concept of turning the intact bowel into a reservoir incapable of effective peristalsis by creating a "pouch."[21] Opening the bowel along its antimesenteric border and closing it with disruption of the circular muscle ("detubularization") inhibits peristalsis. Once unable to undergo peristalsis, the reservoir dilates and stores urine at a low pressure (Fig. 117-8).[22,23] Additionally, there is a significant increase in the geometric capacity of the intestinal segment.[23] A third important concept is accommodation (Fig. 117-9). It is well known that the reconstructed bladder will gradually enlarge over time. At a constant pressure, a structure with a larger radius will accommodate a greater volume—again, an advantage of detubularized bowel segments.

Several considerations must be entertained when choosing an augmentation donor site. Anatomic considerations such as mobility of the blood supply favor the use of ileum, sigmoid, the ileocecal region, and the greater curvature of the stomach. The ability to implant a ureter or a Mitrofanoff neourethra may also be a consideration. Additionally, it may be important to avoid the peritoneal cavity so that the option of performing peritoneal dialysis or placement of a ventricular peritoneal shunt is preserved. Such considerations favor the use of ureteral augmentation or autoaugmentation.

The choice of augmentation donor site may be limited by the patient's primary disease. Patients with short gut may not tolerate a loss of the ileocecal region or a significant length of ileum. Patients with borderline fecal continence (such as

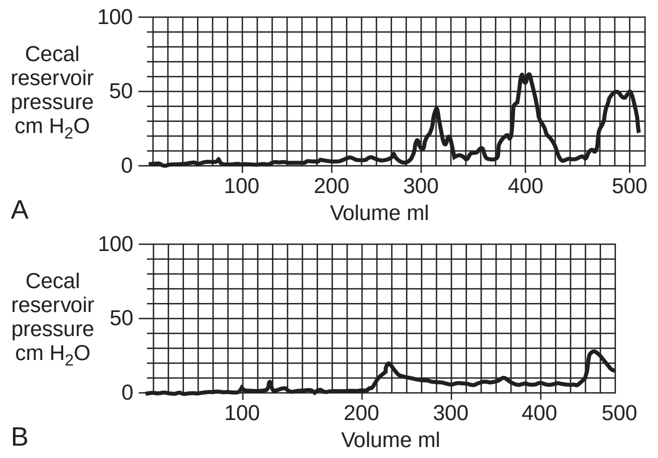


**FIGURE 117-8** Urodynamics of cecal reservoir. **A,** A tubular bowel produces high-pressure peristaltic waves. **B,** A cup patch bowel with disrupted peristalsis stores large volume without pressure rise. (From Goldwasser HR, Webster GD: Augmentation and substitution enterocystoplasty. J Urol 1986;135:221.)

those with imperforate anus or myelodysplasia) may not tolerate loss of the ileocecal valve or the water reabsorptive capacity of the right colon. Metabolic consequences may assume an overriding influence: The risk of absorptive acidosis and growth retardation, which may be exacerbated by chronic renal insufficiency, may favor the use of autoaugmentation, ureteral augmentation, or gastrocystoplasty techniques. Because the reconstruction must be tailored to the individual needs of the patient, the surgeon must be familiar with a wide variety of reconstructive alternatives and prepare the patient accordingly including bowel preparation even when gastrocystoplasty, autoaugmentation, or ureteral augmentation is anticipated.

## SMALL BOWEL PROCEDURES

Ileocystoplasty (Fig. 117-10) is one of the most commonly used bladder augmentation techniques.[24,25] The bladder is prepared by a "clam" cystoplasty incision, and a segment of ileum 20 to 40 cm in length is isolated and incised along its antimesenteric border. It is reconfigured as a "cup patch" and anastomosed to the bladder plate with running 3-0 Vicryl suture (inner-layer interlocking). Bowel continuity is reestablished by end-to-end anastomosis. Advantages of this procedure include its technical simplicity. However, antirefluxing implantation of the ureter or Mitrofanoff neourethra into the ileal segment is less reliable than implantation into the native bladder or other augmentation donor segments.

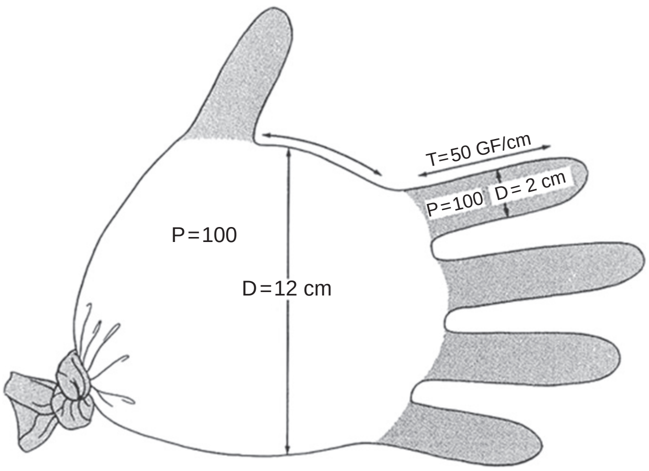


**FIGURE 117-9** Inflated surgeon's glove illustrates the LaPlace relationship. Although pressure (*P*) is equal throughout, tension (*T*) is greater in portion with greater diameter (*D*). (From Hinman F: Selection of intestinal segments for bladder substitution: Physical and physiological characteristics. J Urol 1988;139:522.)

Other techniques of bladder augmentation or replacement using small bowel include the Camey procedure (Fig. 117-11),[26] Kock pouch (Fig. 117-12),[21] and ileal neobladder.[27,28] These procedures are less successful in achieving continence and have a significant rate of complications and reoperation.

## ILEOCECAL SEGMENT PROCEDURES

The ileocecal bowel segment has been favored by urologists for bladder reconstruction because of the natural configuration of the cecum, which gives it the appearance of an ideal substitute for the bladder.[29] This technique is technically simple to perform and also has the major advantage of allowing antirefluxing implantation of massively dilated ureters into the ileum. Reflux is prevented by the ileocecal valve, bolstered by intussusception. Unfortunately, the intussusception antireflux mechanism is inherently unstable. Consequently, various surgical modifications of the ileocecal valve have been introduced in an effort to try to lessen the incidence of reflux. Of greater impact is the fact that loss of the ileocecal valve from fecal continuity risks devastating fecal incontinence in patients with marginal anorectal continence (e.g., myelomeningocele or the VATER complex).

When the cecal or ileocecal segments have been used intact for bladder augmentation, nighttime incontinence has been a significant problem in most series.[30] This problem most likely reflects peristaltic waves in the intact bowel segment because enuresis is rare when the cup patch technique is used. Other continent diversions using the ileocecal valve have included the Maintz pouch,[31] the Penn pouch,[32] the Indiana pouch,[33] and the Florida pouch.[34] Of these techniques, the Indiana pouch has been applied most frequently in pediatric practice and has met with variable results.[35]

## LARGE BOWEL PROCEDURES

Mathisen[36] reported sigmoid augmentation of the bladder performed in a manner similar to that described for ileocystoplasty earlier. This procedure, too, is relatively simple to perform but allows a better antirefluxing implantation of the ureter or Mitrofanoff neourethra into the tenia. This technique did not appear to differ from other bowel segments with respect to ability to empty, infections, or surgical complications.[37] In patients who have previously undergone reconstruction for imperforate anus, this procedure may interrupt blood supply to the rectum because the anorectum depends on a descending blood supply. Positive experiences with construction of a colonic neobladder have been reported,[38,39] although nocturnal incontinence continues to be a problem in up to 33% of patients.[39]

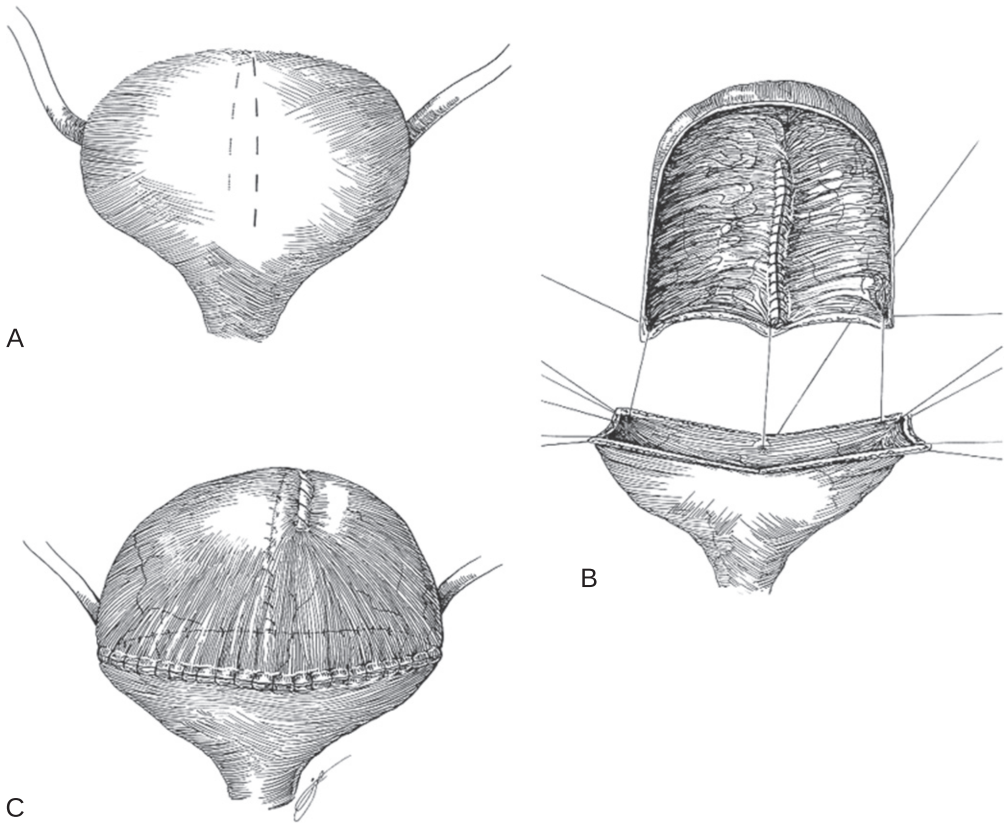


**FIGURE 117-10** Technique of "clam" ileocystoplasty. **A,** Small, high-pressure bladder. **B,** Bladder has been prepared by a long, longitudinal incision, and a segment of ileum has been detubularized and fashioned into a cup patch. **C,** Cup patch is anastomosed to bladder. (From Minevich E, Sheldon CA: Urinary tract reconstruction for continence and renal preservation. In Ziegler MM, Azizkhan RG, Weber TR, et al [eds]: Operative Pediatric Surgery. Norwalk, Conn, Appleton & Lange, 2003, p 915.)

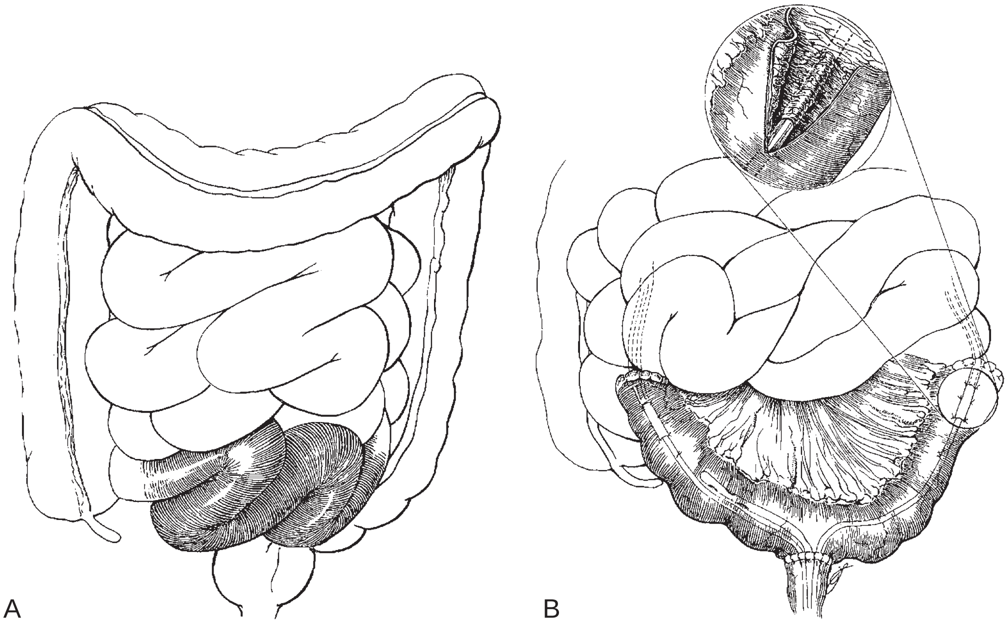


**FIGURE 117-11** Camey enterocystoplasty: **A,** A 35- to 40-cm segment of intact ileum is anastomosed to the urethral stump to create a continent intestinal reservoir. **B,** Ureters are sutured into a 3- to 4-cm trough in the bowel mucosa in each limb of the reservoir to create effective antireflux flap valves. (From Minevich E, Sheldon CA: Urinary tract reconstruction for continence and renal preservation. In Ziegler MM, Azizkhan RG, Weber TR, et al [eds]: Operative Pediatric Surgery. Norwalk, Conn, Appleton & Lange, 2003, p 916.)

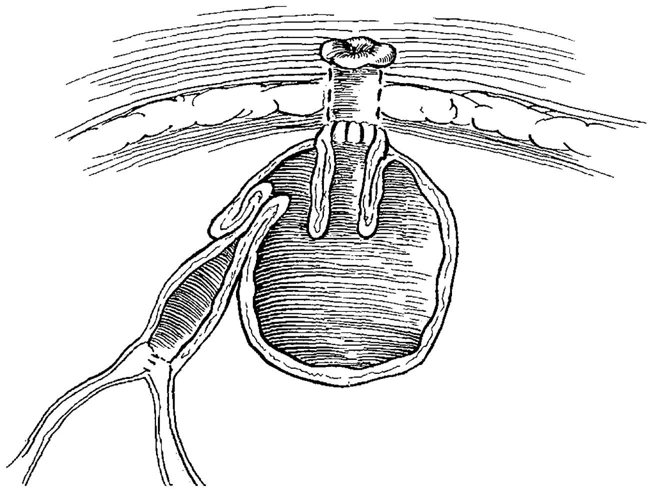

**FIGURE 117-12** Kock pouch. A 70-cm segment of ileum is reformed into a peristaltic pouch with two nipple valves. The most recent modification involves fixation of a nipple valve to the reservoir wall to change it to a fixed flap valve. (From Minevich E, Sheldon CA: Urinary tract reconstruction for continence and renal preservation. In Ziegler MM, Azizkhan RG, Weber TR, et al [eds]: Operative Pediatric Surgery. Norwalk, Conn, Appleton & Lange, 2003, p 917.)

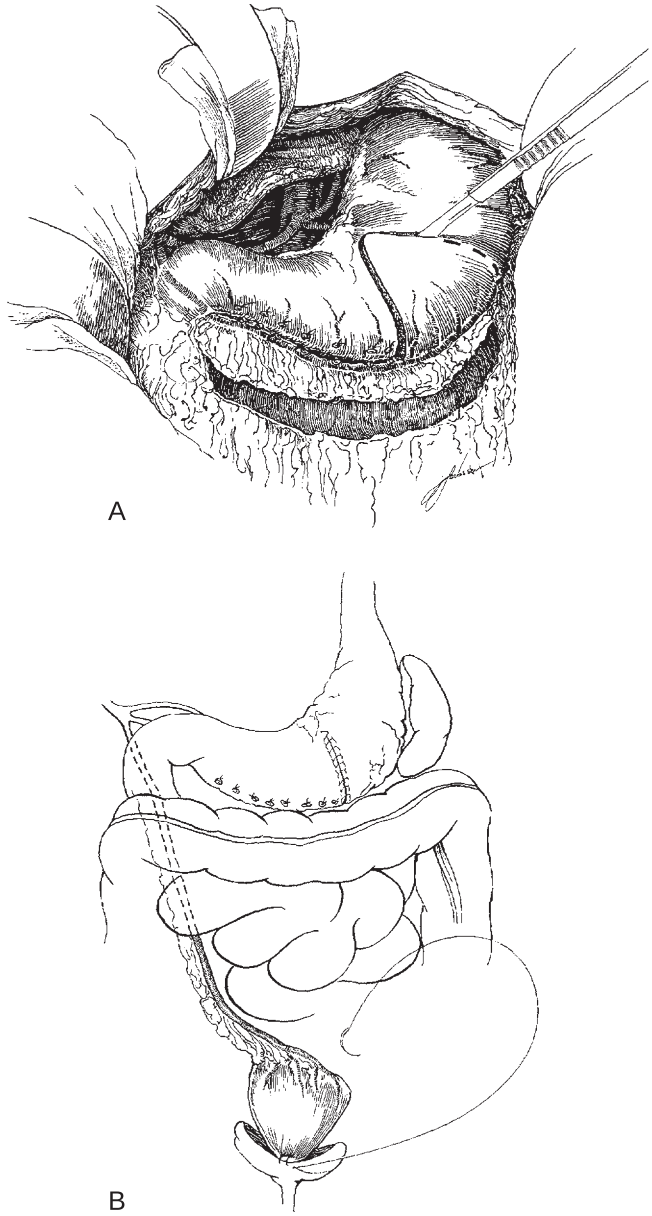


**FIGURE 117-13** Gastrocystoplasty. **A,** Development of right gastroepiploic pedicle and isolation of wedge of gastric fundus. **B,** Mobilization of right gastroepiploic pedicle through retroperitoneal plane into augmentation position. The stomach is closed. (From Minevich E, Sheldon CA: Urinary tract reconstruction for continence and renal preservation. In Ziegler MM, Azizkhan RG, Weber TR, et al [eds]: Operative Pediatric Surgery. Norwalk, Conn, Appleton & Lange, 2003, p 918.)

### GASTRIC SEGMENT PROCEDURES

The work of Mitchell and colleagues[40] ushered in the modern era of the use of stomach in urinary reconstruction (Fig. 117-13). They demonstrated gastrocystoplasty to be highly successful, versatile, and well tolerated even in the face of azotemia. This procedure is associated with a reduced risk for infection, mucus production, and urinary stone formation and provides excellent compliance characteristics. Implantation of a ureter or Mitrofanoff neourethra is technically easy. Our long-term follow-up with gastrocystoplasty or gastric neobladder reveals a continence rate of 91%, stable renal function in all patients, and upper tract deterioration in only one patient who became noncompliant with intermittent catheterization.[41,42] Additionally, gastrocystoplasty has proved to be an excellent alternative for patients with end-stage renal disease facing subsequent transplantation.[41,42] The gastric or composite neobladder has been successfully used for reconstruction[43] with the native urethra,[44] the orthotopic ureteral neourethra,[41,45] and the orthotopic appendiceal neourethra.[41] The major complication and limiting application of the gastrocystoplasty is the development of hematuria-dysuria syndrome, which can be refractory to medical management and may require reversal of the augmentation.

### URETERAL AUGMENTATION AND AUTOAUGMENTATION

Ureteral augmentation[46] (Fig. 117-14) and autoaugmentation[47] (Fig. 117-15) hold great promise because of their ability to prevent absorptive metabolic disorders and to be performed via an entirely extraperitoneal approach.[48] However, these procedures are more likely to fail to attain adequate capacity and compliance because of an inherent restriction in the availability of surface area.[49] In case of ureterocystoplasty the ureter is made available either by nephrectomy or transureteroureterostomy. Unfortunately, a sufficiently dilated ureter is rarely available for this procedure. In addition, some reports indicate that the long-term ability of ureteral augmentation to maintain low storage pressure and adequate capacity may be suspect.[50]

## Procedures to Correct Deficient Bladder Outlet Resistance

Urinary continence is maintained by a complex relationship between bladder outlet resistance and pressure. In order to maintain dryness, the bladder outlet resistance must exceed

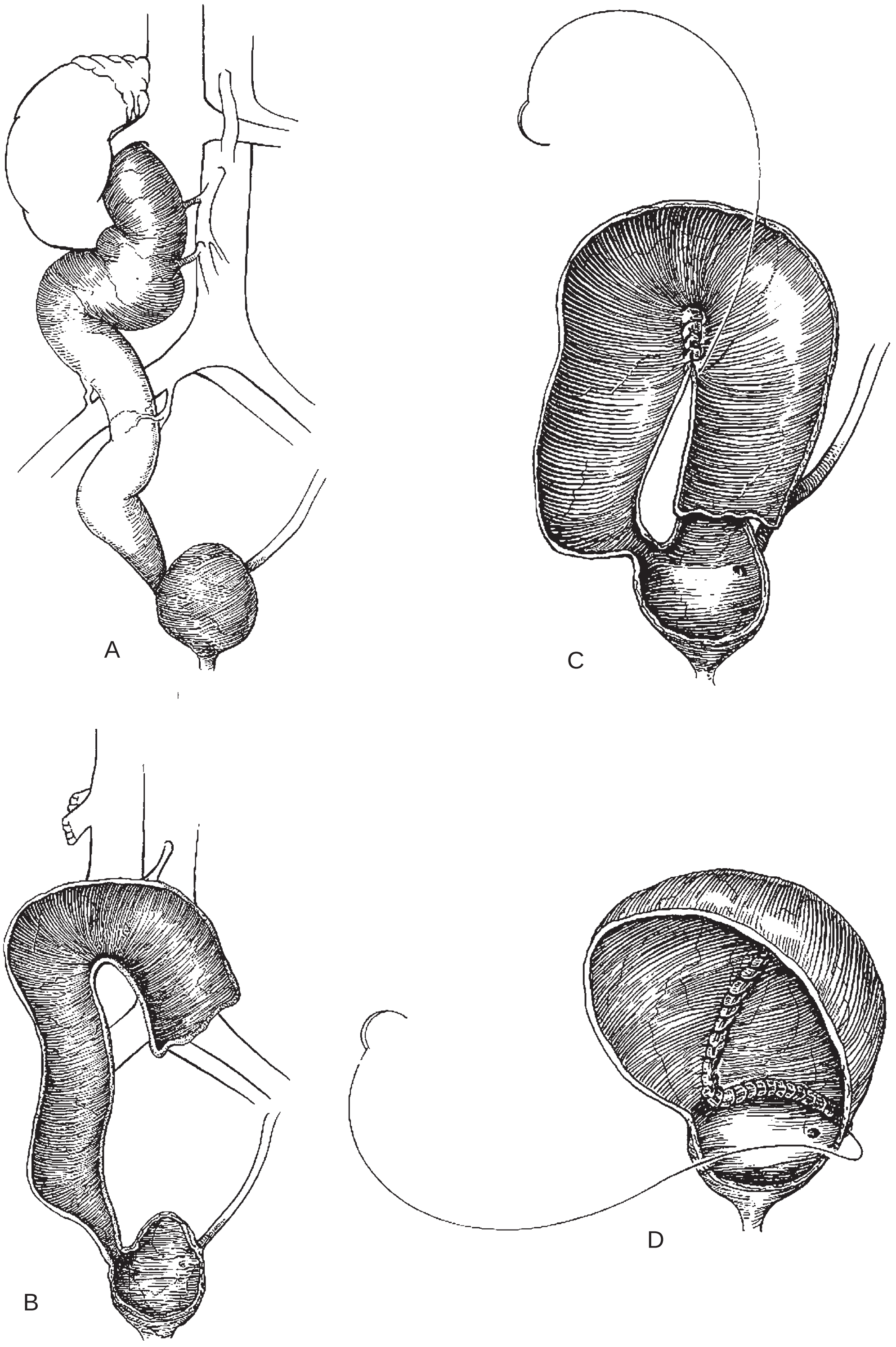


**FIGURE 117-14** Operative stages of ureteral bladder augmentation. **A,** Normal blood supply to ureter. **B,** Ureteral detubularization following mobilization. **C,** Reconfiguration of ureter into U-shaped patch. **D,** Anastomosing ureteral patching to native bivalved bladder. (From Minevich E, Sheldon CA: Urinary tract reconstruction for continence and renal preservation. In Ziegler MM, Azizkhan RG, Weber TR, et al [eds]: Operative Pediatric Surgery. Norwalk, Conn, Appleton & Lange, 2003, p 919.)

intravesical pressure not only at rest but also during changes in posture, coughing, sneezing, and straining. Bladder outlet reconstruction is necessary in patients with incontinence despite low-pressure storage of urine in the bladder. The bladder outlet in patients who have a high-pressure or low-capacity bladder is more difficult to assess because incontinence may be caused by these storage characteristics alone. The likelihood of a competent sphincteric mechanism in this setting is suggested by a stress leak point pressure greater than 100 cm $H_2O$.[51] Urethral pressure profilometry and static leak point pressure have not proven to be reliable, independent indicators of sphincteric competence. Most surgical interventions designed for the

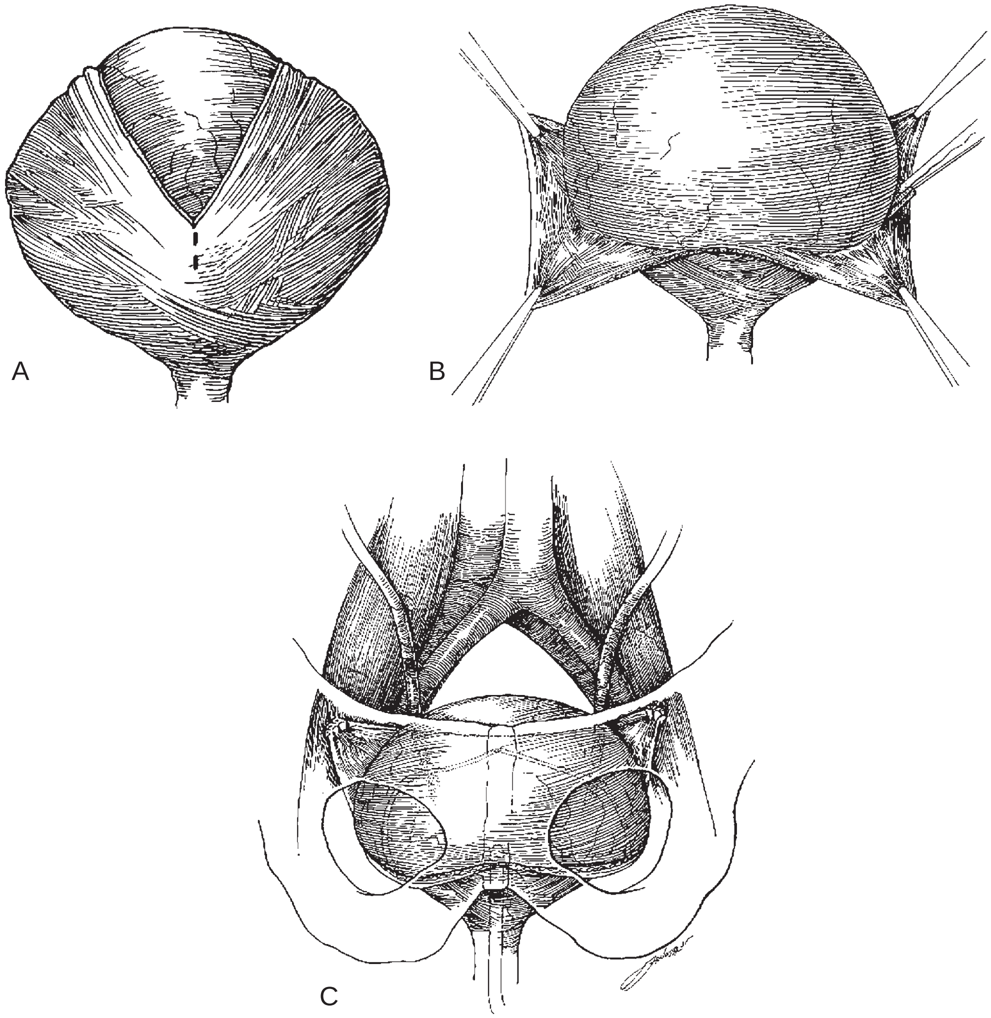


**FIGURE 117-15** Autoaugmentation. **A,** Detrusor incised. **B,** Detrusor stripped from intact bladder epithelium. **C,** Epithelium bulges with bladder filling. (From Minevich E, Sheldon CA: Urinary tract reconstruction for continence and renal preservation. In Ziegler MM, Azizkhan RG, Weber TR, et al [eds]: Operative Pediatric Surgery. Norwalk, Conn, Appleton & Lange, 2003, p 920.)

achievement of continence include procedures to lengthen the urethra, suspend the bladder neck, or compress or completely close the urethra.

Efforts to proximally lengthen the existing urethra through tubularization of the posterior detrusor grew out of the early work of Young.[52] In the procedure, which was later modified by Dees[53] and Leadbetter,[54] the urethra is lengthened by tubularization of a long (4- to 5-cm) segment of the posterior bladder wall. Two triangular sections of urothelium are excised, and the resultant urothelial strip is approximated over a small catheter (8- or 10-French)[55] to fashion the neourethra. The adjacent detrusor is approximated to itself over this mucosal tube to add muscular support (Fig. 117-16). Anterior urethral suspension is usually performed by suture fixation and may be supplemented by the placement of a compressive fascial sling. Several variations in technique have been described.[56,57]

The specific goals of this procedure are to achieve continence and allow spontaneous voiding if the detrusor can contract. Intermittent catheterization must also be attainable if the detrusor cannot effectively contract to empty the bladder. Benefits of this technique are that it may allow spontaneous voiding, uses native tissue, and affords a “pop-off” mechanism. The procedure does, however, reduce bladder capacity and may make the urethra difficult to catheterize. Further, catheterization may injure the continence mechanism and result in reconstructive failure.

The placement of an adjuvant Mitrofanoff neourethra in patients undergoing Young-Dees-Leadbetter bladder neck reconstruction allows a channel for intermittent catheterization, which has been useful for all such reconstructions.[58] With time, as the patient learns to void through the reconstructed urethra, the Mitrofanoff neourethra can be removed in a simple outpatient surgical procedure or, because it does not leak, it can be left in situ.

The Kropp procedure (Fig. 117-17) involves the creation of an extended length of urethra by tubularization of an anterior strip of bladder wall that is left in continuity with the urethra. This tube is then implanted suburothelially into the bladder.[59] This procedure allows reliable continence and uses native tissue. It can, however, lead to difficulty in catheterization. The Pippi Salle modification,[60] which uses an onlay detrusor strip (with preservation of the posterior bladder strip), may permit easier catheterization. Neither the Kropp tube nor the Salle

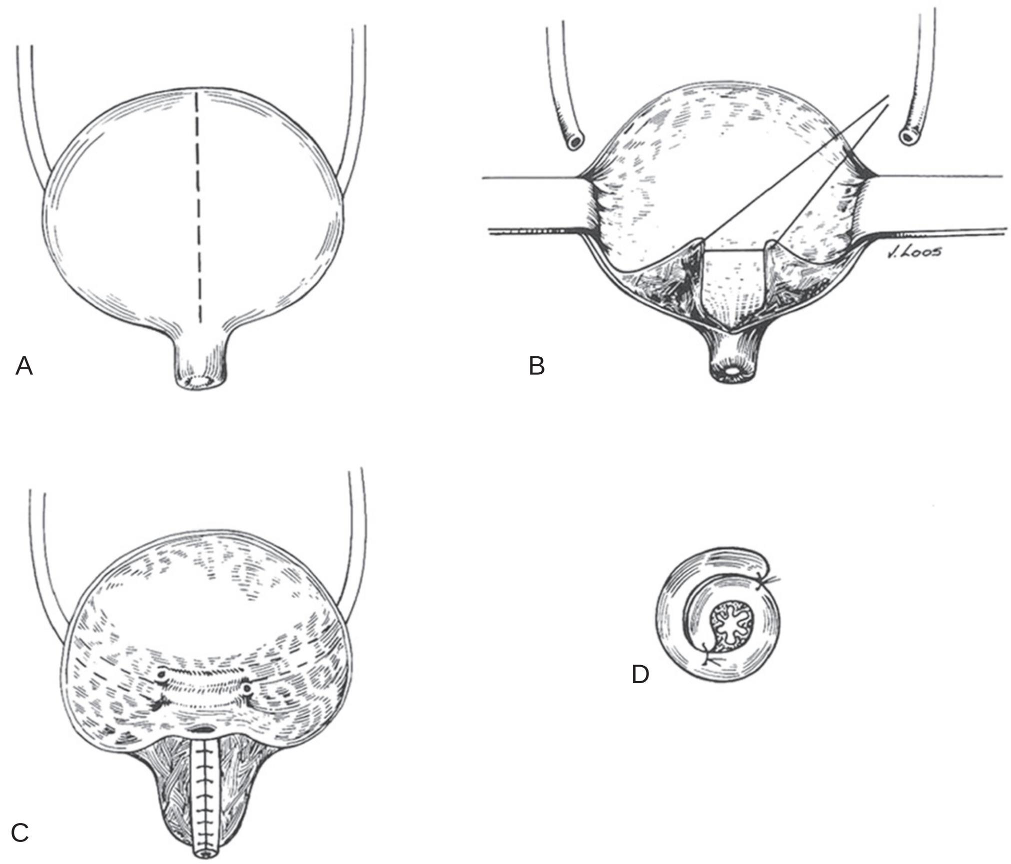


FIGURE 117-16 Young-Dees-Leadbetter bladder neck reconstruction. (From Sheldon CA, Bukowski TP: Bladder function. In Rowe MI, O'Neill JA, Jr., Grosfeld JL, et al, [eds]: Essentials of Pediatric Surgery. St Louis, Mosby-Year Book, 1995, p 742.)

onlay allows a "pop-off" mechanism; thus the potential for spontaneous voiding is eliminated and bladder capacity is reduced.

Another option for the creation of bladder outlet resistance is the fascial sling. A free fascial graft is frequently used; the graft may be placed transvaginally with an endoscopically assisted technique[61] or by open retrourethral dissection.[62] Alternatively, the fascial strip may be developed in such a way that it remains attached to the ipsilateral pyramidalis (Fig. 117-18).[63] The latter approach is particularly applicable to children who have a denervated but anatomically intact sphincteric mechanism and require concomitant bladder augmentation. These procedures are technically fast and relatively simple to perform, involve native tissue, and are readily reversible. They can also be used as an adjunct to the Young-Dees-Leadbetter procedure. Spontaneous voiding is possible if angulation is not excessive, and a "pop-off" mechanism is maintained. Excessive angulation may, however, interfere with spontaneous voiding or catheterization.

The artificial urinary sphincter (Fig. 117-19) has been shown to be effective for compressing the urethra and thus contributes to bladder outlet competence. The most popular model consists of a cuff placed around the bladder neck or bulbar urethra, a reservoir placed intra-abdominally, and an activating pressure bulb located in the scrotum or labia. Controlled pressure is maintained in the cuff until the pump is squeezed, transferring fluid from the cuff into the reservoir balloon and permitting bladder emptying to take place. A delay-fill resistor in the control mechanism provides 1 to 2 minutes of lowered intraurethral pressure before automatic refilling of the cuff takes place from the reservoir balloon. Pressure-regulating balloons of various pressure ranges are available, and a 60 to 70 cm $H_2O$ balloon is generally selected for pediatric reconstruction.[64]

Several series have documented the utility of the artificial urinary sphincter in patients who have bladder augmentation.[65–68] The advantage of this procedure is that it allows spontaneous voiding, but there are several disadvantages. Multiple mechanical problems have occurred in patients with the artificial sphincter in place. The most common problems have been fluid leaks from the cuff or tubing kinks requiring surgical revision. The most serious complications are erosion of the sphincter into the urethra or the development of infection around the cuff. The latter problems generally require removal of the device. Consequently the artificial sphincter is recommended primarily for those patients who have a chance of maintaining spontaneous voiding.

Finally, surgical urethral closure may be necessary. This is obviously a highly effective means of ensuring urethral continence but should be a last resort.[69,70] Simple oversewing of the mucosa at the level of the bladder neck is insufficient because recanalization occurs. Urethral division, which allows muscular approximation (proximally and distally), eliminates this risk. This procedure requires the placement of an alternate catheterizable conduit as discussed later. The advantages of this procedure are that it is definitive and technically simple. It does, however, place the patient at increased risk for bladder calculi and is difficult to reverse. In addition, the lack

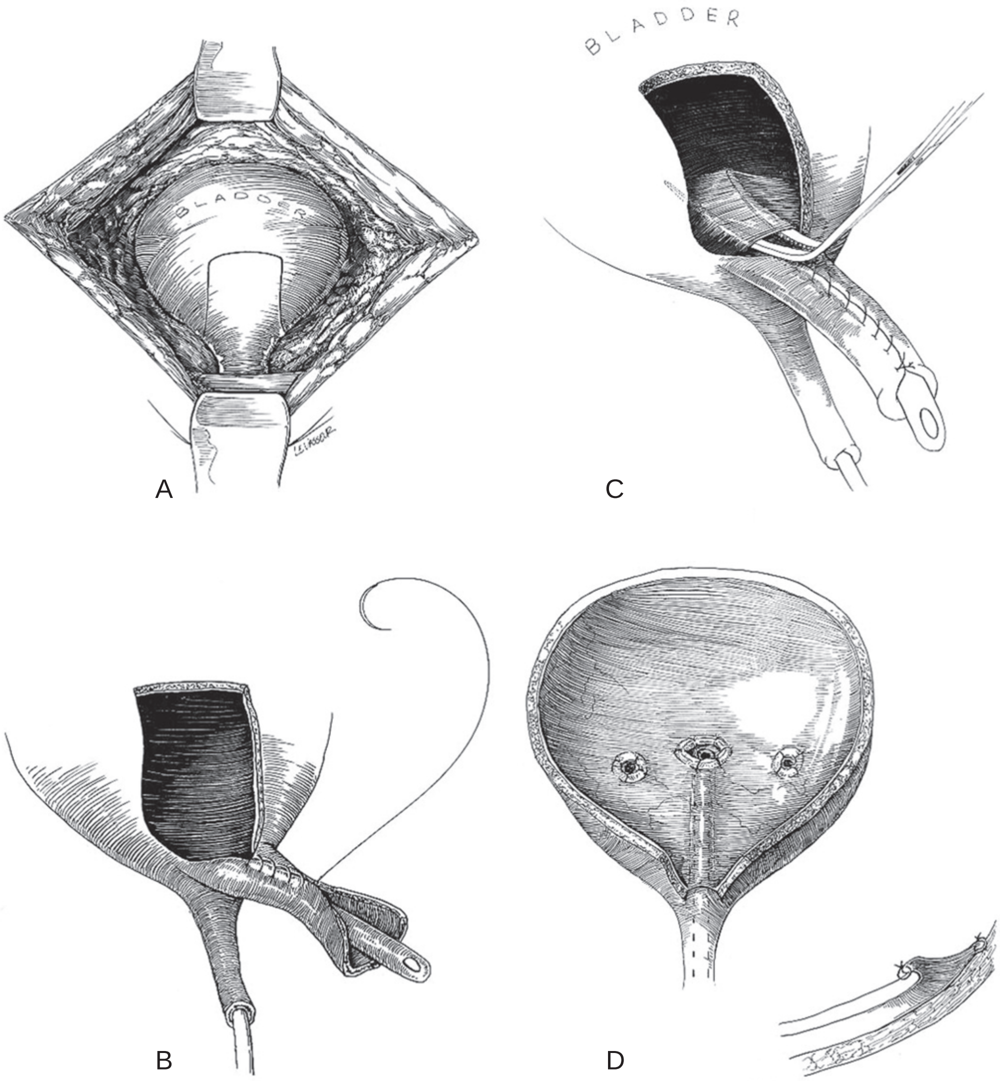


FIGURE 117-17 The Kropp procedure. A detrusor tube is created (anterior shown, posterior tube also possible) and tunneled submucosally in the bladder to create a competent flap valve. (From Minevich E, Sheldon CA: Urinary tract reconstruction for continence and renal preservation. In Ziegler MM, Azizkhan RG, Weber TR, et al [eds]: Operative Pediatric Surgery. Norwalk, Conn, Appleton & Lange, 2003. p 925.)

of a "pop-off" mechanism increases the risk for bladder rupture if the patient does not comply with regular catheterization to empty the bladder.

## Providing for Alternate Continent Urine Drainage

The procedures discussed in the preceding section require the creation of a continent catheterizable conduit that connects the bladder to the skin of the abdominal wall or perineum. An alternative to catheterization of the native urethra is indicated when a urethra is difficult to catheterize because of (1) tortuosity from either previous urethral surgery or congenital irregularity or (2) physical limitations of the patient that impede access to the native urethra. Procedures directed at urethral functional replacement are based on the creation of a tubular conduit of sufficient length that is exposed to external compressive forces, thereby providing outlet resistance that cannot be overcome by intravesical (intrareservoir) pressure. The success of these procedures in terms of continence relies on attaining controlled reservoir-neourethra balance. Neourethral resistance to reservoir outflow must be sufficient to exceed both resting and intermittently elevated intravesical pressure associated with gravity (upright posture), as well as episodic additive intra-abdominal pressure spikes (coughing, sneezing, straining, and sudden postural changes). The creation of neourethral resistance must be complemented by low intravesical (intrareservoir) pressure. This may entail bladder augmentation or replacement by bowel and should include reconfiguration by detubularization. A large capacity is imperative, as is intermittent catheter drainage before the low compliance portion of the reservoir's pressure-volume curve is entered.

Alternate techniques include those associated with a nipple valve (procedures involving the ileal-cecal junction or ileal-ileal intussusception) or those associated with a flap valve (Fig. 117-20). The nipple valve is inherently unstable because wall tension causes distraction of the base of this continence

mechanism over time, often resulting in a loss of effectiveness of the valve and thus incontinence. The flap valve mechanism is considerably more durable because the continence mechanism is a stable component of the reservoir wall.

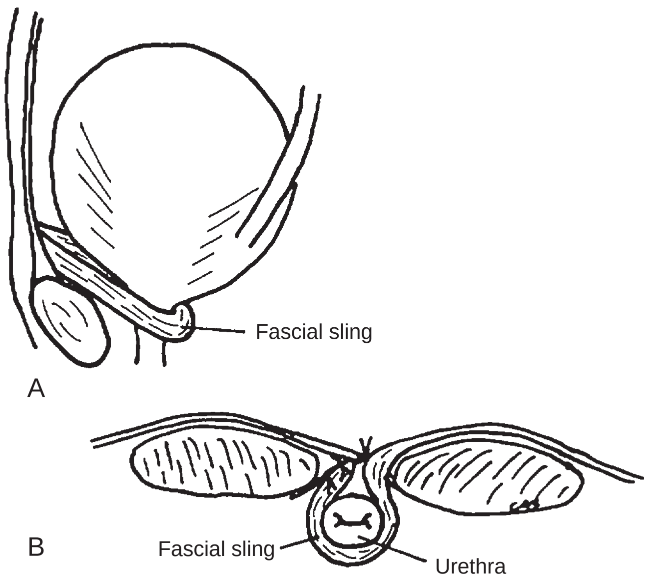


**FIGURE 117-18** Placement of a fascial sling to enhance bladder outlet competence. (From Sheldon CA: Urinary reconstruction (rather than diversion) for continence in difficult pediatric urologic disorders. Semin Pediatr Surg 1996;5:10.)

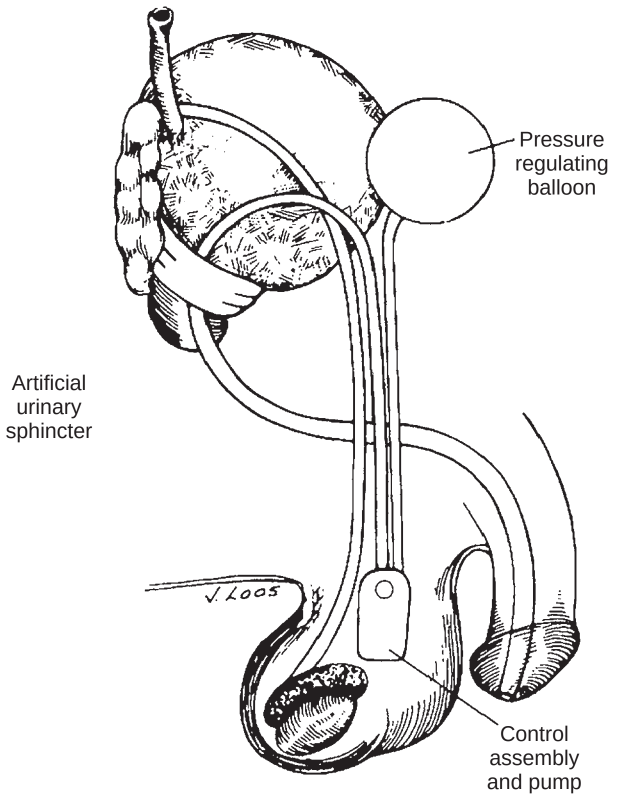


**FIGURE 117-19** Artificial urinary sphincter. (From Sheldon CA, Bukowski TP: Bladder function. In Rowe MI, O'Neill JA, Jr., Grosfeld JL, et al [ed]: Essentials of Pediatric Surgery. St Louis, Mosby-Year Book, 1995.)

The Mitrofanoff neourethra is an example of a flap valve mechanism that is particularly applicable to children.[71] In this procedure, a continent, catheterizable tubular conduit (neourethra) connecting the urinary bladder to the skin is achieved. This provides a one-way flap valve mechanism that permits a catheter to be easily passed into the bladder. The flap valve is also a secure mechanism to prevent incontinence (Fig. 117-21). The appendix, the most common type of Mitrofanoff tube used, is removed from its cecal origin and the appendiceal mesentery is preserved. A submucosal plane is developed in the bladder by either detrusor incision or cystotomy with creation of a long submucosal tunnel. The cecal end of the Mitrofanoff neourethra is exteriorized to the skin; a U-insertion flap technique is used to help minimize the risk for stomal stenosis. The Mitrofanoff neourethra concept has proven extremely versatile and has been implanted into the bladder, colon, and stomach with equal efficiency.[58,72] Multiple sites for exteriorization are possible including the lower abdomen, umbilicus, and perineum.[58] The versatility of this technique has been enhanced by extending the length of the appendix using tubularized cecum.[58,73,74] Mitrofanoff's concept and extension of these principles have permitted successful continent reconstruction of the lower urinary tract in a wide variety of situations.[71,75,76]

If the appendix is unavailable, a tapered segment of ileum (over a 12- to 14-French catheter) can be used, although currently a transverse retubularized segment of ileum is more commonly used.[71,77,78] The length of these ileovesicostomies is limited by the circumference of the bowel segment used, which is inadequate in some cases. Casale introduced a technique that allows a doubling in length of the continent conduit.[79] The ureter also provides a source for a Mitrofanoff conduit when available (this conduit can be created if nephrectomy had been or is being done or if a transureteroureterostomy is being performed).[80] Because an ileal conduit is readily constructed, a transureteroureterostomy is not recommended unless otherwise indicated. If the ureteral segment is refluxing, concomitant ureteral reimplantation may be required. Other continent, catheterizable mechanisms are available including the Benchekroun procedure,[81] the Indiana pouch,[33] the Kock pouch,[82] and the hemi-Kock.[83] Although used less commonly in children than the Mitrofanoff flap valve, they may prove useful in selected circumstances.

The most common complication of the Mitrofanoff conduit is that of stomal stenosis, requiring stomal revision.[76,84,85] Mitrofanoff neourethras that could not be negotiated or were lost due to ischemic necrosis were only rarely encountered.

## Interface with Fecal Incontinence

The urinary tract should not be reconstructed without consideration of anorectal function. Achievement of urinary continence in the patient who will still require a diaper for fecal incontinence can hardly be considered a success. Further, persistent fecal soilage may potentiate the risk of UTI and progressive deterioration of the reconstructed bladder and upper urinary tracts. Therapy for urinary continence can significantly compromise gastrointestinal function. For example,

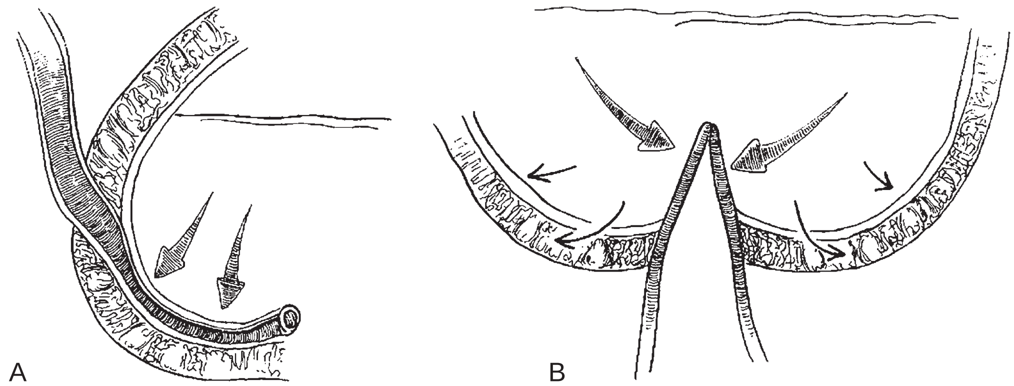


**FIGURE 117-20** **A,** Flap valves. **B,** Nipple valves. Nipple valves are continent because the nipple is circumferentially compressed by pressure within the reservoir. Unfortunately, the intrareservoir pressure also has a laterally destructive force on the base of the nipple, causing a shortening or total effacement of the valve with loss of the continence mechanism. Flap valves are continent because the submucosal segment is compressed by filling of the reservoir (as for a reimplanted ureter for vesicoureteral reflux). Unlike nipple valves, flap valves are stable because they are fixed to the wall of the reservoir. Thus reservoir filling does not tend to cause loss of the continence mechanism. (From Minevich E, Sheldon CA: Urinary tract reconstruction for continence and renal preservation. In Ziegler MM, Azizkhan RG, Weber TR, et al [eds]: Operative Pediatric Surgery. Norwalk, Conn, Appleton & Lange, 2003, p 928.)

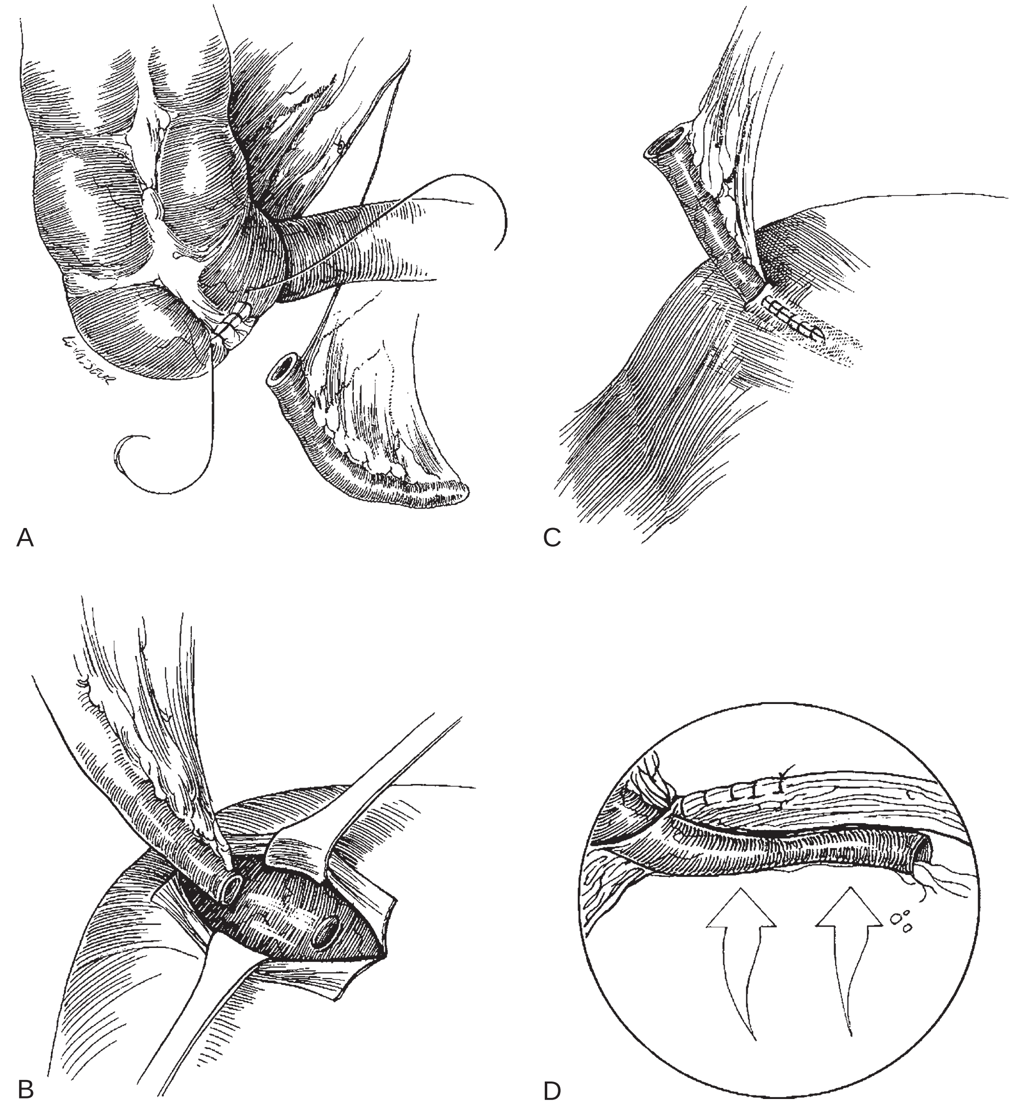


**FIGURE 117-21** Mitrofanoff procedure. **A,** The appendix has been mobilized on its mesentery, and cecal segment is closed. **B,** Extravesical dissection shows mucosal orifice in which the distal end of the appendix will be implanted. **C,** The detrusor is closed over implanted appendix, and its proximal end is then brought to the skin to serve as a catheterizable stoma. **D,** This diagram depicts the resulting continent flap-valve mechanism of the Mitrofanoff procedure; a rise in intravesical pressure compresses the conduit against the detrusor, thereby occluding its lumen and achieving continence. (From Minevich E, Sheldon CA: Urinary tract reconstruction for continence and renal preservation. In Ziegler MM, Azizkhan RG, Weber TR, et al [eds]: Operative Pediatric Surgery. Norwalk, Conn, Appleton & Lange, 2003, p 929.)

anticholinergic therapy may result in severe constipation, and ileocecocystoplasty may facilitate fecal incontinence.

The management of intractable fecal incontinence may be addressed at the time of urinary reconstruction and thus should be evaluated before this undertaking. Because most patients can be managed nonsurgically by dietary restrictions, bulking agents, behavior modification, and expansion enemas, an exhaustive trial of these interventions should be undertaken before surgical reconstruction. In the patient who is refractory to these treatments, the antegrade continence enema (Fig. 117-22) has been shown to be an excellent alternative.[86–89] This procedure is indicated when nonoperative management is ineffective or when expansion enemas prove effective but cannot be administered by the patient.[90]

The technique is similar to the Mitrofanoff neourethra. The appendix or a retubularized ileal segment[91] is implanted into a tenia in the cecum, and the other end is exteriorized to skin. The appendix or ileal segment is prepared in a manner identical to that described for the Mitrofanoff procedure. An incision is made along the anterior tenia of the cecum; an anastomosis is performed between it and the conduit; and a mucosal defect is created distally in the mucosal trough. The muscle is covered over the conduit while the other end is exteriorized to skin. Once daily a catheter is inserted into the continent cecostomy while the patient sits on the commode. An antegrade enema consisting of tap water and table salt is administered by gravity flow. If this is unsuccessful, additives of mineral oil, polyethylene glycol (MiraLax), or glycerin can be added to the irrigant daily.[92]

## Urinary Reconstruction and End-Stage Renal Disease

Congenital urologic disease is reported to occur in 20% to 30% of pediatric end-stage renal disease patients.[5,93] The adverse effects of congenital urologic disease on the success of

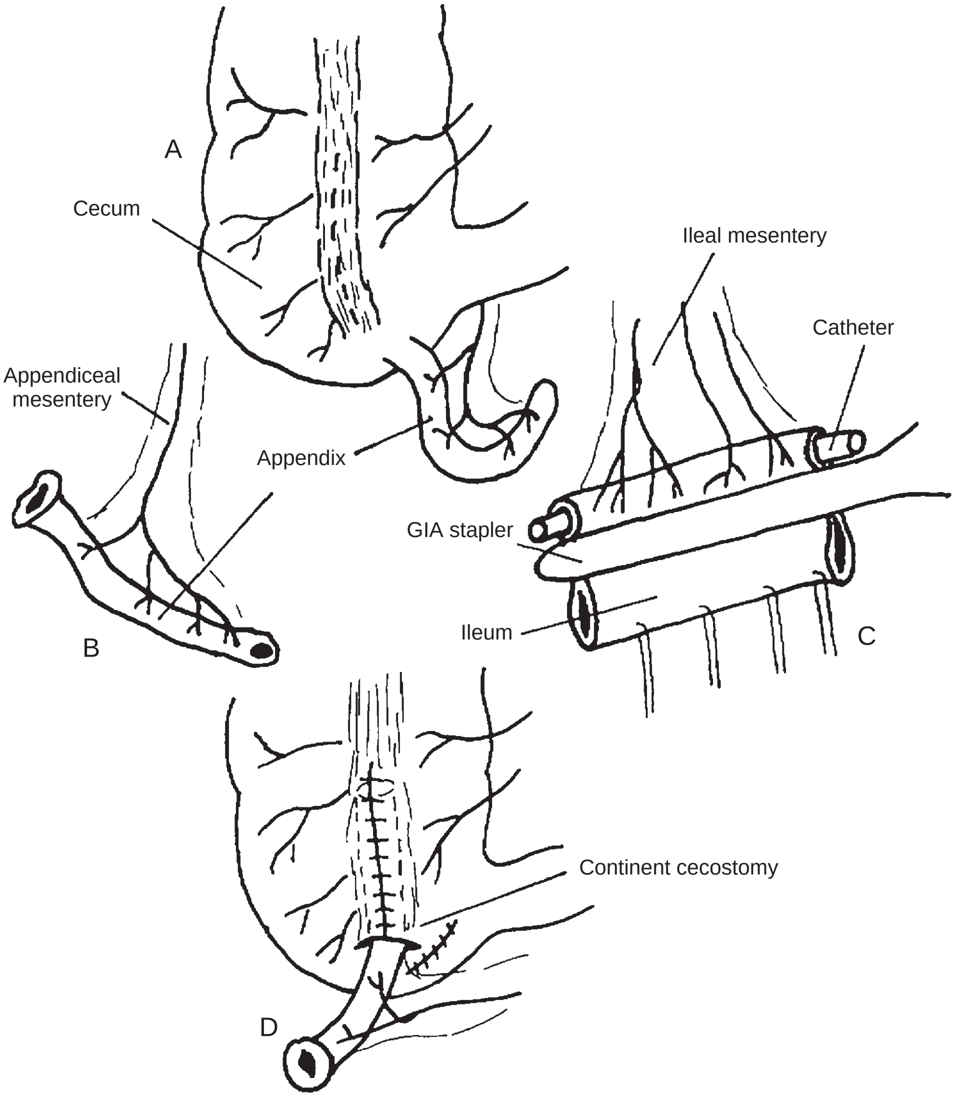


**FIGURE 117-22** Technique for performing continent cecostomy for antegrade continence enema. **A,** Anatomy of the appendix and the anterior cecal tenia. **B,** Appendix is mobilized on its vascular pedicle. **C,** Alternatively, a segment of ileum is tapered and mobilized on its vascular pedicle. **D,** Final appearance of continent cecostomy. (From Sheldon CA: Urinary reconstruction [rather than diversion] for continence in difficult pediatric urologic disorders. Semin Pediatr Surg 1996;5:14.)

renal transplantation are demonstrated by the increased incidence of UTI, allograft dysfunction, technical complications, and graft loss in such patients. UTI can be particularly deleterious to both graft and recipient in the face of immunosuppression. The risk of UTI is higher in transplant recipients with posterior urethral valves as the etiology of their renal failure.[94,95] An analogous problem is seen in patients whose primary disease is vesicoureteral reflux and who continue to have reflux into the native kidneys at the time of transplantation.[96]

These data demonstrate that patients with a history of significant urologic disease must be extensively evaluated before transplantation.[97] Significant vesicoureteral reflux should be resolved either by ureteral reimplantation or nephrectomy. Whenever possible, nephrectomy is avoided to allow the production of urine output so that a functionalized bladder is maintained and dialysis therapy is still an option, either before transplantation or after, should the graft fail. Any endogenous erythropoietin production will be maintained, and this may help avoid presensitization from frequent transfusions. In addition, the ureters are preserved, which may be necessary for subsequent transplant reconstruction should a ureteral complication occur. Indications for nephrectomy include the presence of recurrent UTIs, UTI-prone upper tract anatomy, refractory hypertension, severe proteinuria, and severe polyuria.

When necessary, nephrectomy is performed via lateral flank incisions or dorsal lumbotomy incisions, through which the peritoneal cavity is rarely, if ever, entered. Such procedures can be performed without interrupting peritoneal dialysis. Alternatively, a laparoscopic approach is applicable. If bilateral nephrectomy is considered necessary and preemptive (to avoid dialysis) transplantation is desired, one may remove the worst-functioning kidney first, and if the second kidney provides adequate function, dialysis can be avoided. At the time of transplantation the remaining kidney can be removed via the transplant incision.

Elevated intravesical pressure must be stabilized by either pharmacologic measures or intermittent catheterization (or both) and, when necessary, augmentation cystoplasty. When undertaking pretransplant surgery it is important to plan the surgical incision so that it minimizes interference with current or anticipated peritoneal dialysis, as well as the subsequent transplantation itself. The best means for avoiding loss of access to the peritoneal cavity for purposes of dialysis is an extraperitoneal approach to the urinary tract, which can readily be achieved for nephrectomy and ureteral reimplantation.

Surgical reconstruction of a dysfunctional bladder can be successfully performed and has been demonstrated to allow transplantation with acceptable results.[98,99] Such an approach allows optimal allograft preservation and appliance-free continence and is preferable to the alternative of transplantation into an intestinal conduit. Transplantation is applicable to even the most anatomically complicated child with end-stage renal failure.[100,101] The principles of transplantation into a reconstructed bladder include the following: (1) Avoid a dry reconstruction. The capacity and compliance of a reconstructed bladder can be lost if the interval to transplantation is long. This can be avoided by undiversion of native kidneys (if present) or by using a living-related donor allograft where timing can be optimized. (2) The risk of reabsorptive acidosis occurring either before transplantation, with drainage of the native kidneys into the reconstructed bladder, or after transplantation if the allograft fails over time can be minimized by avoiding the use of intestine and colon for bladder reconstruction. Specifically, gastrocystoplasty, augmentation with the ureter and pelvis, and autoaugmentation all have the potential for minimizing reabsorptive acidosis. (3) Autoaugmentation and augmentation using the ureter have the potential for being performed retroperitoneally, thereby avoiding interference with present or future peritoneal dialysis or with ventricular peritoneal shunts. (4) Whenever possible, ureteral implantation into the native bladder is preferable. If not possible, the colon, an ileocecal segment, or the stomach is the only source of augmentation tissue that will permit reliable antirefluxing anastomosis. (5) During the performance of such transplantations, the blood supply of the augmented bladder and any associated Mitrofanoff neourethra must be meticulously identified and preserved.

# Complications

## ACUTE ABDOMINAL SURGICAL ILLNESS

Acute abdominal surgical illness is a grave concern in the patient who has undergone urinary tract reconstruction, particularly when associated with bladder augmentation or creation of an intestinal reservoir. The most common causes of an acute surgical abdomen in this setting are perforation of the augmented bladder or intestinal reservoir or small bowel obstruction. Even though the etiology remains conjectural, the majority of perforations have been associated with augmentation of a remnant of neurogenic bladder.[102] More than two thirds of such patients have been on intermittent catheterization, and total continence appears to be a common factor. Although the clinical findings are usually those of an acute abdomen, the symptoms may be quite nonspecific and a high index of suspicion is essential. It is important to be aware of the fact that the rupture may occur many years after reconstruction. Altered sensation in patients with dysraphic states or spinal cord injury and steroid administration in renal transplant patients may confound the diagnosis. In establishing the diagnosis a cystogram is essential but is associated with a significant false-negative rate.[103,104] A computed axial tomographic study of the abdomen (with contrast in the bladder or reservoir) may be the most accurate method of making the diagnosis. However, any patient with an augmented bladder on intermittent catheterization who has abdominal pain, fever, or vomiting should be presumed to have a bladder perforation unless the symptoms can be conclusively attributed to another etiology. Exploratory laparotomy may be required to make the diagnosis. Less common, but important, etiologies of the acute abdomen include small bowel obstruction, pseudomembranous enterocolitis, toxic shock syndrome, and ventricular-peritoneal shunt complications.[37]

The performance of laparotomy following urinary tract reconstruction is of critical concern. Certainly, elective laparotomy should be preceded by formal bowel preparation in the face of augmentation or continent diversion. The surgeon should have access to a catheter in the bladder to allow insufflation and deflation for identification purposes, and a catheter should be placed in any catheterization conduit

such as a Mitrofanoff neourethra. Efforts must be directed at identification and preservation of mesenteric blood supply to any gastric or intestinal segments used in reconstruction. Whenever possible, an experienced reconstructive urologist should be present.

## METABOLIC COMPLICATIONS

Metabolic alterations may be encountered when gastrointestinal segments are incorporated into the urinary tract.[105,106] These metabolic derangements are due to solute flux, both active and passive, between the urine and blood across the gastrointestinal segment wall. The character and severity of such derangements depend on the nature of the segment used, the absorptive surface area, the dwell time, and the metabolic reserve of the individual patient. Compensatory mechanisms for metabolic changes are provided by the kidneys, liver, and lungs. Significantly compromised function of any of these organ systems may exacerbate an underlying metabolic defect. Syndromes include alterations in acid-base status, disorders of serum electrolyte composition, hyperammonemia, and bone demineralization.

Systemic acidosis may result from the incorporation of jejunal, ileal, or colonic segments into the urinary tract. Jejunal conduits have been found to be associated with acidosis in 20% to 40% of instances.[107,108] In the jejunum, passive diffusion of solutes occurs along their concentration gradients. The passage of hypertonic urine into a jejunal segment will result in a loss of sodium, chloride, and water, resulting in hyponatremia, hypochloremia, and volume contraction, with subsequent contraction acidosis.[109] Additionally, diminished renal blood flow results in secondary hyperaldosteronism, resulting in a more hypertonic urine and hyperkalemia. The latter is further aggravated by the potassium shift as a result of acidosis.

The metabolic consequences of interposing ileal and colonic segments within the urinary tract relate to the active secretion of sodium (in exchange for hydrogen) and bicarbonate (in exchange for chloride), as well as the reabsorption of ammonium, hydrogen, and chloride. Ammonium absorption appears to be quantitatively the most important, explaining many of the abnormalities encountered when ileal or colonic segments have an interface with urine. Hydrogen ion, generated from ammonium, is buffered by serum bicarbonate producing water and $CO_2$. The latter is readily eliminated by the lungs and results in a chronic compensatory respiratory alkalosis. Additional buffering is provided by bone, resulting in a variable degree of demineralization and secondary hyperparathyroidism. This is manifest by hypercalciuria, hyperphosphaturia, hyperoxaluria, hypocitraturia, hypocalcemia, and hypomagnesemia. Osmotic diuresis and acidosis combine to result in total-body potassium depletion.

Metabolic alkalosis is a unique complication of gastrocystoplasty. Though uncommon,[42] hypokalemic-hypochloremic metabolic alkalosis has been reported.[110,111] Excessive bicarbonate absorption is postulated to occur secondary to the combination of mineralocorticoid excess and potassium/chloride depletion.

Hypokalemia, hypocalcemia, and hypomagnesemia are significant potential sequelae of incorporating intestinal segments within the urinary tract.[106] Sufficiently severe hypokalemia to result in muscular paralysis has been reported. Although hypocalcemia is rarely severe enough to be symptomatic, it may present with irritability, tremors, tetany, and coma and may even prove fatal. Hypomagnesemia is also rarely severe enough to be symptomatic, but it may be manifested as altered sensorium, personality changes, delirium, psychosis, weakness, tremors, tetany, and seizures and may likewise be fatal.

Hyperammonemia complicating urinary tract reconstruction with intestine may cause altered sensoria and coma. As previously noted, ammonium ions are actively absorbed from intestinal segments and may be present in large amounts in urine because of their generation by renal tubules and production from urea by urea-splitting organisms.

Perhaps the most overriding concern of incorporating intestinal segments is the effect on childhood growth and development. Several studies have provided data strongly suggestive of defective linear growth in such cases.[112,113] This concern is particularly worrisome in patients with diminished renal function. Here, the metabolic insult is more likely and more severe because growth and development are often already significantly impaired.

Strong evidence exists for a primary effect of incorporating intestinal segments into the urinary tract on bone mineralization.[114] Metabolic acidosis results in defects in bone mineralization, bone disease, and linear growth failure through decreased renal tubular calcium reabsorption, depressed intestinal absorption of calcium and phosphorus, and vitamin D metabolism. Treatment with alkalinizing agents has been partially successful in preventing or reversing demineralization disease.

## HEMATURIA-DYSURIA SYNDROME

Although rare in our own experience[42] the hematuria-dysuria syndrome is an important complication of bladder reconstruction using stomach.[115] This syndrome is characterized by severe pain and urinary bleeding as a result of urothelial erosion from acid secreted in the urine after gastrocystoplasty.[116] Endoscopic evaluation of children with the hematuria-dysuria syndrome suggests greater involvement of the urethra than the bladder itself. Three major factors appear to be of importance in the genesis of this complication: acid hypersecretion, profound oliguria,[41] and bladder neck incompetency. True acid hypersecretion appears to be quite rare and, presumably, the predominant mechanism for this would be hypergastrinemia that has been reported in some instances.[117] $H_2$ receptor blockers and proton-pump inhibitors such as omeprazole have been shown to be reasonably effective in this syndrome.

## ALTERED GASTROINTESTINAL FUNCTION

The incorporation of intestinal segments into the urinary tract may result in significant alterations in gastrointestinal tract function. Alterations in gastric function have been reported following gastrocystoplasty.[118] Functional alterations reported include weight loss, feeding intolerance, dumping syndrome, delayed gastric emptying, and esophagitis. Our own review of gastrocystoplasty with emphasis on long-term follow-up (minimum follow-up of 5 years) failed to demonstrate any significant incidence of altered gastric function or altered acid base status in 44 consecutive patients.[42] Technical emphasis must be placed on avoiding the vagus nerves, avoiding significant dissection in the region of the gastric pylorus, and

avoiding traction-distortion of the angle of His (e.g., by gastrostomy tube), which may predispose to gastroesophageal junction incompetence.

Several potentially important sequelae of intestinal malabsorption may accompany intestinal resection including diarrhea, vitamin deficiency, and fecal incontinence. Diarrhea is most frequently a result of alterations in bacterial colonization and impairment of bile acid reabsorption (with or without accompanying steatorrhea).[119] Malabsorption from ileal resection is directly related to the length of resection. Resections of greater than 100 cm of ileum (adult equivalent) diminish bile acid reabsorption to a degree that cannot be compensated by increased hepatic synthesis. As a result, the bile salt pool is diminished and steatorrhea develops. Another important sequela of the diminished bile salt pool in this population is cholelithiasis, which, like urolithiasis, is clinically seen at a significantly increased incidence following ileal resection. Diarrhea induced by altered bile acid reabsorption (with or without accompanying steatorrhea) is further enhanced by the rapid emptying of ileal contents into the colon, causing a tendency for osmotic diarrhea.

Although most of the data involve adult patients, it is estimated that 10% of children undergoing resection of ileocecal valve segments will experience chronic diarrhea. This may be resolved after restoring intestinal continuity by returning the ileocecal segment to its normal position within the gastrointestinal tract.[120]

Despite these data, the use of intestinal and gastric segments appears to be extremely well tolerated in most children. It would, however, appear prudent to avoid the removal of large segments of ileum or removal of the ileocecal valve for purposes of urinary reconstruction, particularly in those already compromised. Such patients include those with preexisting malabsorption or short-gut syndromes and patients with marginal fecal continence, in whom fecal soilage may become incapacitating by loss of stool consistency. The latter patients include those with myelomeningocele and imperforate anus, who commonly require urinary tract reconstruction.

## MALIGNANCY

A majority of our understanding of urointestinal malignancy following reconstruction comes from the experience with ureterosigmoidostomy.[121,122] The incidence of malignancy developing in conduits and continent diversion has been comparably small.[123–125] In most cases there is a long interval between surgery and the onset of cancer. This latency interval has several important implications: A carcinogenic effect is clearly implied. Moreover, there is a potential for early surveillance diagnosis. Clearly, long-term follow-up is mandatory.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 118

# Incontinent and Continent Urinary Diversion

Audrey C. Rhee, Elizabeth B. Yerkes, and Richard C. Rink

Urinary diversion can be either incontinent or continent. With incontinent diversion the reservoir is external to the body (ostomy bag or diaper in children) and is emptied routinely when full. With continent urinary diversion the urinary reservoir is routinely emptied by clean intermittent catheterization (CIC). Classically when the reservoir has been made entirely of gastrointestinal segments, it has been known as a *continent urinary diversion* (CUR). In children, the primary diagnoses requiring urinary reconstruction are spinal dysraphism, exstrophy, posterior urethral valves, or complex cloacal anomalies. In these disorders, the diseased native bladder can be incorporated into the reconstruction so that true CURs are rare in children. However, most will require intestinocystoplasty and a catheterizable abdominal wall channel and therefore they are "continent reservoirs" and are considered as such in this chapter. The term *undiversion* used in this chapter previously refers to the situation in which a child was previously treated with an incontinent urinary diversion and is converted to a continent diversion. Due to the infrequency of this situation, it is not covered in this chapter.

Historically permanent incontinent urinary diversion was used to protect the kidneys from the deleterious effects of increased bladder and renal storage pressures or to manage urinary incontinence. In more contemporary practice, medical management of bladder dysfunction with CIC[1] and anticholinergic agents has limited the indications for surgical intervention. Urodynamic expertise has allowed identification and aggressive management of the high-risk patients.[2] The development of surgical techniques to allow storage of urine at safe pressures has virtually eliminated the use of permanent forms of incontinent urinary diversion, but this still remains an appropriate option for some patients. Temporary diversion is still required for select patients but is rarely first-line management for the bladder or the upper urinary tract.

## Incontinent Urinary Diversion

Although eventual urinary continence is desirable for all children, protection of the integrity of the upper urinary tract is the primary concern. Several forms of incontinent urinary diversion are still occasionally used on either a temporary or permanent basis to prevent upper urinary tract deterioration or to simplify day-to-day care of patients with limited capability for self-care.

Temporary urinary diversion is most commonly performed in infants or very young children, and the urine is easily collected in the diaper. Most permanent incontinent diversions require an ostomy appliance for hygienic collection of the urine. Compared with the alternative of continence by clean intermittent catheterization, the incontinent stoma carries a stigma and body image issues that are better avoided in the pediatric population. For select patients and families, however, this remains a reasonable option.

### CUTANEOUS VESICOSTOMY

Cutaneous vesicostomy is the most common form of incontinent urinary diversion in children today, but it is rarely used as first-line therapy and has limited indications. Infants with a neuropathic bladder and unsafe storage pressures may require a vesicostomy if CIC and anticholinergic medications fail or if the family is unable or unwilling to execute these medical measures. Inability to incise posterior urethral valves safely due to the small urethral caliber in some premature infants is another indication for cutaneous vesicostomy. In these patients the vesicostomy is closed when the child has grown enough for incision of the valves. Young infants with high-grade vesicoureteral reflux and multiple breakthrough urinary tract infections on antibiotic prophylaxis may benefit from vesicostomy.[3–4] Improvement in the efficiency of both bladder and upper tract drainage reduces the incidence of urinary infection. In persistent cloaca refractory hydronephrosis, hydrocolpos or urinary infection despite intermittent catheterization of the common channel is another uncommon indication for vesicostomy.[5]

Ideally the vesicostomy provides low-pressure drainage of the bladder contents with minimal residual volume. Multiple series have confirmed the benefits of vesicostomy.[3–4,6–9] Improvement in upper urinary tract dilation and stabilization or improvement of renal function is achieved. Reflux may

resolve, or the degree of ureteral dilation may improve enough that ureteral tapering is not required at the time of reimplantation.[3–4] Although bacterial colonization of the open system is common, symptomatic infections and urosepsis are reduced. One concern about prolonged vesicostomy drainage in the non-neuropathic population is failure of the bladder to develop normally in the absence of cyclic filling and emptying.[10–11] Several studies have refuted this concern.[4,12–13]

Once the urinary tract is stabilized and the long-term potential of the bladder becomes clearer, the vesicostomy is easily closed. It may be closed primarily or in combination with continent diversion. Some patients and families are not appropriate candidates for vesicostomy closure or find that vesicostomy and diaper drainage is an acceptable low-maintenance permanent option. Vesicostomy, with or without the use of an ostomy appliance, can also be performed in adult patients who are not candidates for continent diversion.[9]

Two techniques for cutaneous vesicostomy have been used for many years. Lapides described elevation of an anterior bladder wall flap with deep insertion of an abdominal skin flap to fashion the cutaneous vesicostomy.[14] The more common technique was described by Blocksom in 1957[15] and modified by Duckett (Fig. 118-1).[16] The Blocksom vesicostomy is fashioned through a small transverse incision halfway between the umbilicus and the pubis. The fascia is incised, and the peritoneum is pushed superiorly off the dome of the bladder. The urachal remnant is divided, and the dome of the bladder is pulled up to the skin. The fascia is secured to the bladder wall to form a 24-Fr defect, and the bladder is matured as a flush stoma.

Complications of cutaneous vesicostomy include stomal stenosis, prolapse, peristomal dermatitis, and bladder calculi. Stomal stenosis is more common with a stiff or thick bladder wall as in posterior urethral valves. Failure to fashion the vesicostomy from the dome of the bladder may allow the posterior bladder wall to prolapse through the vesicostomy. This is one advantage of the Blocksom technique over the Lapides vesicostomy. Prolapse is managed by manual reduction with temporary catheter drainage and revision of the low vesicostomy. Dermatitis is particularly bothersome in some patients and is managed with application of a zinc oxide barrier cream or topical treatment for obvious candidiasis. Bladder calculi are unusual provided that the vesicostomy is functioning well and the upper tracts are drained.

## CUTANEOUS URETEROSTOMY

Ureterostomy for temporary supravesical urinary diversion is rarely performed today. It has been used historically for drainage of a profoundly dilated upper urinary tract in the face of urosepsis[17] or to maximize drainage of the renal units in cases of severe obstruction. Percutaneous or endourologic drainage of these systems is possible now in children, but tube size limits the utility of this in very small infants.[18] Low diversion can be performed as a loop or end cutaneous ureterostomy (Figs. 118-2 and 118-3), and subsequent takedown involves ureteroneocystostomy. The diversion allows the caliber of the ureter to decrease, thereby reducing the complexity of the reimplantation. Diversion at the level of the kidney is performed through a flank incision and can be performed as a

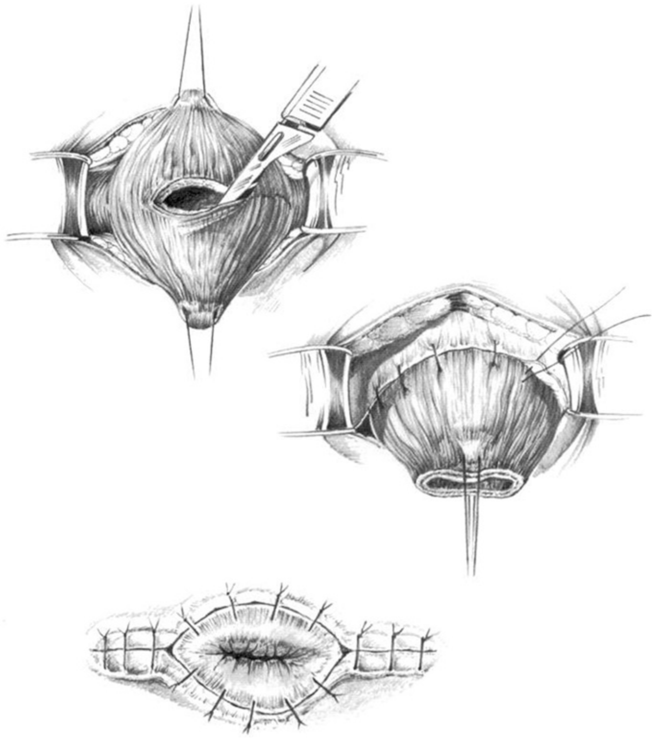

**FIGURE 118-1** The Blocksom vesicostomy, showing the incision in the dome of the bladder, the fixation to the overlying fascia, and the everted stoma.

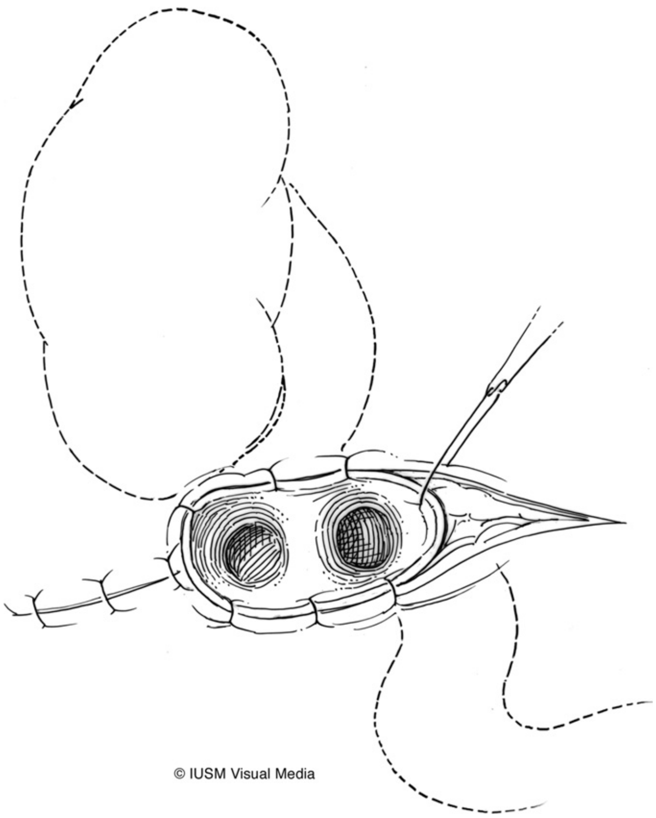


**FIGURE 118-2** The loop ureterostomy is easily taken down and therefore allows for an excellent temporary diversion.

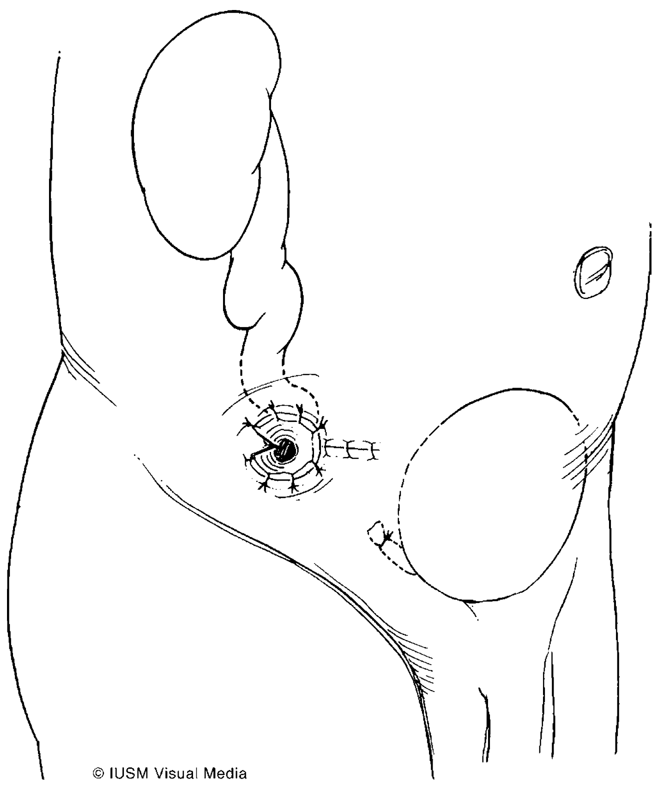


FIGURE 118-3 The end ureterostomy requires formal reimplantation to reverse.

loop ureterostomy, Sober ureterostomy, or end ureterostomy. A loop ureterostomy can easily be taken down and is the more appropriate choice for temporary diversion. End ureterostomy just below the ureteropelvic junction makes reconstitution of the ureter more difficult and should be reserved as a rare permanent form of diversion in cases of severe bladder dysfunction.[18] Sober ureterostomy, with its proximal diverting limb and reanastomosis of the distal limb to the renal pelvis, is rarely used today and is technically much more involved and may therefore be less appropriate for diversion during acute illness. On the other hand, it offers the advantage of diversion and continued antegrade drainage to cycle the bladder.[19] In all cases, care should be taken to preserve the medial blood supply and adventitial vessels and to create a tension-free anastomosis to the skin. Given the profoundly dilated nature of the ureter in most of these cases, stomal stenosis is rarely an issue.

Supravesical diversion may be warranted in select posterior urethral valve patients when renal function fails to improve after bladder drainage.[19] Persistent ureterovesical junction obstruction is the concern. Ureterostomy and pyelostomy would maximize upper tract drainage, but percutaneous nephrostomy is a less invasive temporary means to assess the potential of the affected kidney.[20] Patients who demonstrate improvement in renal function after supravesical diversion may do so because of better drainage or just due to normal renal maturation.[21] As with cutaneous vesicostomy, there is concern that the valve bladder will fail to develop normally if the urine is diverted. In patients with a solitary functioning kidney, a loop ureterostomy or an end ureterostomy would defunctionalize the bladder. Several studies suggest that bladder dysfunction is due to bladder wall abnormalities from infravesical obstruction rather than supravesical diversion of urine.[13,22]

Another method to treat distal ureteral obstruction is creation of a freely refluxing end-to-side or side-to-side ureteral reimplant.[23] This alternative approach, while obviating the continual drainage of urine via a cutaneous stoma, remains controversial.

## CUTANEOUS PYELOSTOMY

As with cutaneous ureterostomy, proximal diversion by pyelostomy has limited indications in current practice. The controversies surrounding this type of diversion are similar. With direct drainage of the renal pelvis, pyelostomy may be used for temporary diversion in select cases of obstruction at the ureteropelvic junction but could also be used as discussed earlier for posterior urethral valves. Pyelostomy requires a dilated extrarenal pelvis to create a tension-free anastomosis to the skin. Takedown of the pyelostomy at the time of a definitive procedure is relatively simple due to reliable blood supply to the renal pelvis.

## ILEAL CONDUIT/COLON CONDUIT

Permanent supravesical urinary diversion was popular many decades ago as reliable means to manage neuropathic bladder, bladder outlet obstruction, and severe urinary incontinence. Conduit diversions have been created with most intestinal segments, although the ileum (Fig. 118-4) and colon are used most commonly. Both simple refluxing and tunneled nonrefluxing ureterointestinal anastomoses have been used. The primary advantage of the colon conduit over an ileal conduit is the reliable antireflux reimplantation achievable with colon.

The risk of upper tract deterioration after ileal conduit diversion has exceeded 50% in some series.[24–26] Although this is not a tremendous concern in the older patient after cystectomy for bladder carcinoma, the long-term impact on the kidneys is extremely relevant in the pediatric population. The ability to create a nonrefluxing anastomosis between the ureter

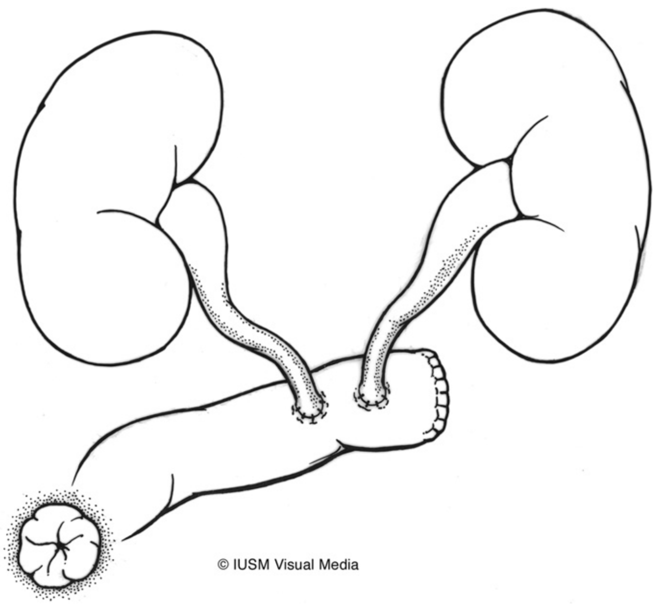


FIGURE 118-4 The ileal conduit is the standard permanent supravesical diversion for patients whose bladder is absent.

and colon gives colon conduits a theoretical advantage over ileal conduits. Unfortunately, deterioration of the upper tracts occurs in 26% to 48% of cases and ureteral reflux persists in 8% to 58% of colon conduits.[27] Anastomotic stricture occurs with similar frequency with ileum and colon (9% to 22%).[24,27]

Koch and colleagues[24] compared a cohort of myelomeningocele patients with ileal conduit diversion to another group managed with CIC. The ileal conduit group suffered renal deterioration, nephrolithiasis, and pyelonephritis significantly more than the catheterization group. Bone density was decreased in both groups and the incidence of fractures was equal, but the diversion group had impaired linear growth, more spinal curvature, and more complications from orthopedic procedures. The metabolic alterations associated with incorporation of intestinal segments into the urinary tract do occur with incontinent diversions.[24]

Other complications of conduit diversion included stomal stenosis, stomal prolapse, peristomal hernia, and peristomal dermatitis. Stomal stenosis occurred in 8% to 61% of cases. Stoma complications are best prevented with careful surgical technique including preservation of intestinal perfusion, creation of a straight and adequate caliber fascial window, and fixation of the conduit to the fascia. A protuberant rosebud stoma enhances the fit of the stoma appliance and prevents stenosis.

Bacteriuria is nearly universal but does not cause upper tract damage if the ureterointestinal anastomosis and the conduit itself function appropriately.[27–28] Stasis of colonized urine, however, may contribute to upper tract stone formation and may have other implications as well. Nitrosamines produced by the mixture of urine and bacteria appear to have some role in induction of malignancy in the isolated intestinal segment.[27,29]

Austen recently reviewed the world literature and identified 81 tumors collectively in a variety of continent and incontinent diversions with incorporated bowel segments. This total is exclusive of the large number of malignancies reported after ureterosigmoidostomy. Neoplasia was reported in 12 ileal conduits and 5 colon conduits with a mean latency of 22 and 10 years, respectively. Colon conduit tumors were exclusively adenocarcinoma, but transitional cell carcinoma, squamous cell carcinoma, and carcinoid and anaplastic tumors were also found in ileal conduits. Chronic inflammation of the intestinal segment may play a role in the malignant changes. Early yearly surveillance for tumor is recommended.[30]

Preoperative preparation for conduit diversion involves a full mechanical and antibiotic bowel preparation and parenteral antibiotic to sterilize the urine on the day before surgery. Patients with severe neuropathic bowel may actually require more than one day of preparation for adequate cleanout. It is critical that an enterostomal therapist mark potential stoma sites bilaterally after examining the patient in multiple positions. The abdominal contour can change significantly in myelomeningocele patients when seated, and an ill-fitting ostomy appliance will be a lasting source of dissatisfaction.

### INCONTINENT ILEOVESICOSTOMY

Incontinent ileovesicostomy, initially described by McGuire and colleagues in 1994,[31] has primarily been used in the adult population with bladder and sphincter dysfunction secondary to spinal cord injury and multiple sclerosis. Patients had failed other efforts to manage the bladder pressures and urinary incontinence and refused or were not candidates for continent diversion. Many suffered severe complications from use of a chronic indwelling urethral catheter. Several series report excellent results with regard to preservation of renal function, incidence of urinary tract infection and urolithiasis, and stomal complications.[32–35] The ileovesicostomy functions as a pop-off valve to maintain safe bladder storage pressures. Stomal leak-point pressures are low, and a moderate residual urine remains.[35]

Incontinent ileovesicostomy is an option to consider in select pediatric patients with limited dexterity and social support. Although it does require a permanent stoma, preservation of renal function appears superior when compared with standard conduit diversion. In addition, the disruption of the ureterovesical junction is not required. Parents may have difficulty accepting permanent diversion even if the child has limited potential to perform self-catheterization in the future. Some families are not ready to assume the care required for bladder augmentation or continent urinary reservoir, despite the fact that the child needs reconstruction to preserve the upper urinary tracts. In these instances, incontinent ileovesicostomy with both an efferent incontinent limb and a large open patch of ileum to augment the bladder can be considered. Consideration could be given to creation of a Mitrofanoff catheterizable channel at the time of the initial procedure. Should the family later embrace continence and the long-term care of bladder augmentation, the ileal chimney can be amputated to leave a continent diversion.[36]

Thorough preoperative bowel preparation and sterilization of the urine are required. A stoma site is carefully preplanned for the right lower quadrant to ensure optimal fit of the stoma appliance. The bladder is bivalved in the coronal plane in preparation for anastomosis to the isolated ileal segment. The proximal end of the ileum is opened widely on its antimesenteric border and anastomosed to the bladder in a running fashion. The length of the ileal segment can be tailored to account for body habitus and for the need to augment the native bladder capacity.[32] A rosebud stoma is fashioned in the right lower quadrant, and a 22-Fr catheter is left in place for 3 weeks to maintain the caliber of the ileovesical anastomosis. If significant augmentation is performed, a suprapubic catheter should be left as well to maximize perioperative drainage. In select patients with perineal excoriation from urinary incontinence, a bladder neck or urethral procedure in conjunction with an ileovesicostomy may be used to create outlet resistance.

## Continent Urinary Diversion

Many different types of continent urinary diversions have been developed to improve or replace the native lower urinary tract. The chosen technique depends largely on the surgeon's experience and preference, but the primary pathology plays a large role in any given patient. Reconstruction is tailored to the specific anatomy and related functional deficits. A fundamental difference exists in pediatric lower urinary tract reconstruction versus that of adults. In adult reconstruction, a particular type of reconstruction (i.e., Kock pouch, Indiana pouch) may

be chosen preoperatively. In children, the principles of a low-pressure reservoir with a means of catheterization without leakage or reflux must be achieved from the tissues available at this time of reconstruction. Whenever possible, enhancement of the native bladder and outlet is preferred to avoid the potential complication associated with ureteral anastomosis to a CUR. CUR would be performed if the native bladder is absent or not salvageable. Patients with bladder agenesis syndromes, the most severe bladder exstrophy, and pelvic organ destruction secondary to trauma or malignancy would be candidates for CUR.

Continent urinary diversion is now common, but one must remember that it requires a broad spectrum of surgical skills and must address the varied underlying diagnoses. By definition, a reservoir that must be emptied by intermittent catheterization is created. This may include the augmentation of an intact but severely diseased bladder or the creation of a reservoir completely from heterologous tissue. The surgical goals and principles are similar: to create the ideal storage reservoir for urine that can be easily emptied with the minimum of complications. Because the gastrointestinal (GI) tract is plentiful and accessible, it is the most common source of tissue. The physiologic variability along the GI tract allows the surgeon to tailor the reconstruction to the patient. However, these complex surgeries are not without complications, and these have to be understood and anticipated.

## BLADDER AUGMENTATION

Bladder augmentation is an essential component of the pediatric urologist's surgical armamentarium. It has a prominent role in the management of many lower urinary tract (LUT) disorders including neurogenic bladder, posterior urethral valves, and bladder exstrophy. The modern application often includes the use of a continent catheterizable abdominal wall stoma based on the Mitrofanoff principle. This is generally performed using either the appendix (appendicovesicostomy) or reconfigured ileum (Monti) and may require an additional procedure to improve the continence mechanism at the bladder neck. Intermittent emptying via the native urethra remains an option.

As previously discussed, children with severe LUT dysfunction were historically treated with urinary diversion. Lapides' introduction of clean intermittent catheterization ensured that any child could safely empty his or her bladder.[1,37] This brought the dawning of lower urinary tract reconstruction and allowed the urinary tract to remain intact and avoid the use of external collecting devices. Advances in urodynamic monitoring improved our ability to predict who would best benefit from bladder reconstruction and therefore prevent renal deterioration.[2] Parallel medical advances ensured the survival of these complex patients and allowed for the shift of focus toward continence as an important aspect of their quality of life.[38–39] Recent advances with cutaneous catheterizable channels continue to simplify care and increase its popularity.[40]

The primary goal of lower urinary tract reconstruction is to store urine safely without leakage. Adequate storage requires a low-pressure, highly compliant reservoir of adequate volume, whereas continence results from limited contractility and an effective sphincter mechanism.

The vast majority of augmentations are performed with gastrointestinal segments because bowel segments are readily available and easily configured. Ileum is currently the most popular segment,[41–43] but sigmoid is often used. Stomach and ileocecal segments have been used but have only a small role in contemporary management.[44–47] Their abundance ensures that adequate capacity is obtained while detubularization and the natural viscoelastic properties allow for the low-pressure reservoir.[48–49] However, the secretive[50–51] and absorptive[52] nature of this tissue is also responsible for most of the common complications associated with this procedure.

Requirements for a successful augmentation include proper patient selection,[53] the ability and willingness to perform CIC,[50,54] proper selection of augmentation material, and recognition and treatment of complications.

## PATIENT EVALUATION AND SELECTION

The patient, family, and entire health care team must be involved in the decision to pursue major surgery. The common risks of incorporating GI segments into the urinary tract include mucus production, urinary tract infection, bladder and renal calculi, and metabolic changes. Life-threatening risks such as malignant degeneration and spontaneous perforation must be explained to the family and child, and they *must* be understood.[50,51,54] Everyone involved in caring for the child must be committed to the appropriate postoperative care including mandatory use of CIC and regular bladder irrigation.[50,54,55]

Clinical evaluation requires a thorough history and physical examination. Particular attention should be paid to latex allergy because this can be a fatal complication. Preoperative evaluation should include a renal-bladder ultrasound (RBUS) and a voiding cystourethrogram (VCUG). Serum chemistries are required because impaired renal function may change the gastrointestinal segment used.[54] Initially, it was suggested that a creatinine clearance of less than 60 mL/minute might be a contraindication for the use of ileum as a continent urinary reservoir,[56–57] but augmentation often stabilizes renal function and reconstruction has been done before renal transplantation. Urodynamic studies are necessary to determine outlet resistance, bladder capacity, and storage pressures. Cystoscopy will confirm anatomy and ensure that no untoward findings that may hinder reconstruction are present.[50]

The net result of these investigations is a comprehensive surgical plan. The exact procedure will depend on which segment is to be used and whether the patient requires concomitant ureteric reimplantation, bladder neck procedure, and a catheterizable channel. Patients with a neurogenic bladder may also undergo an antegrade continence procedure to assist evacuation of their neurogenic bowel.[58]

Preoperative preparation usually involves bowel preparation, as described previously for conduit diversion. Perioperative antibiotics and a sterile urine are required and are particularly important if the patient has a ventriculoperitoneal shunt.[59]

Long-term follow-up is required with all patients. After the postoperative visit, and assuming the absence of complications, the patient should be seen annually with a history, physical examination, creatinine and electrolytes, an ultrasound, and an annual cystoscopy 5 to 10 years out from surgery.[50,54]

## GASTROINTESTINAL CYSTOPLASTY

Most children undergoing lower urinary tract reconstruction for hostile bladder dynamics can have their native bladder preserved but need to have it augmented to lower intravesical pressures, limit contractility, and improve compliance. Gastrointestinal segments are generally used, but this requires reconfiguration and detubularization to prevent their own inherent contractile properties.[44,48,49,60] Maximum storage capacity requires approximation of the spherical shape.[48] A widely bivalved bladder enables this and helps to prevent the augment behaving as a diverticulum (Fig. 118-5). The volume of the sphere is maximized by folding the ileum into a U or an S shape, which increases the potential radius and volume (Fig. 118-6).[54] This reconfiguration, as well as detubularization along the antimesenteric border, is critical to disrupting intestinal contractions because the intact intestine can create pressures of 40 to 100 cm $H_2O$.[61–63] The reconstructive surgeon should err on the side of a larger rather than smaller augmentation.[50] Regardless of the bowel segment selected, a water-tight anastomosis using absorbable suture is done. A suprapubic tube is placed into the native bladder and secured to the abdominal wall, and a perivesical drain is placed.

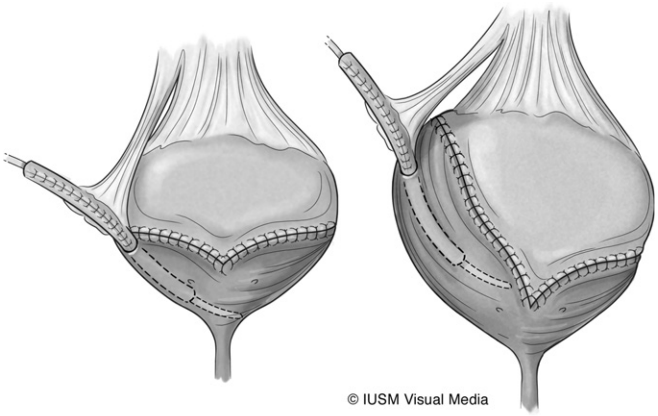


FIGURE 118-5 The offset cystoplasty allows for more mobility of the detrusor muscle and provides better access to the muscular backing that is essential for implantation of the catheterizable channel.

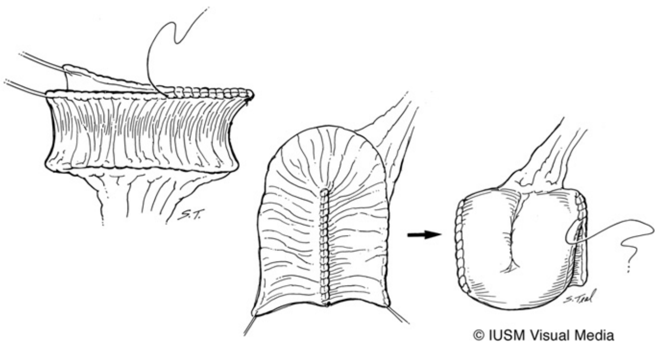


FIGURE 118-6 The ideal bladder augmentation will increase both capacity and compliance, which are required for continence and renal protection.

## ILEOCYSTOPLASTY

Ileum has become the segment of choice due to its inherently low contractility, abundance, and ease of manipulation.[41–43] In children 20 to 30 cm are harvested, with the distal margin located 15 to 20 cm from the ileocecal valve to prevent vitamin $B_{12}$ and bile salt malabsorption.[49,64] Ileum is known to produce less mucus than colon, and we noted a lower rate of perforation when compared with sigmoid.[35] It has the distinct disadvantage of being difficult to create submucosal tunnels for ureteral reimplantation or catheterizable channel placement.

## SIGMOID CYSTOPLASTY

Advantages of the sigmoid include its proximity to the bladder and its marked dilation in the neuropathic population. Approximately 15 to 20 cm are isolated and irrigated with an antibiotic solution. Due to the extreme contractile nature of the sigmoid, complete detubularization is essential.[46] Spontaneous perforation rates have been shown to be higher with sigmoid as opposed to ileal augmentations,[65] presumably due to their increased contractile pressure.[66]

## ILEOCECAL CYSTOPLASTY

The main advantage of the ileocecal segment is the consistent blood supply. Two main techniques exist, each with multiple variations. Either both the ileal and cecal segment are tabularized and reconfigured together, or solely the cecum is tubularized and the ileum used to create a continent stoma[47] or for ureteric replacement.[54] This segment is infrequently used in the neuropathic population because loss of the ileocecal valve can result in intractable diarrhea.[67]

## GASTROCYSTOPLASTY

The stomach is much less absorptive than other intestinal segments, and its secretion of hydrogen ions may be beneficial in patients with chronic renal failure and metabolic acidosis.[44,68] A 10- to 15-cm wedge from the greater curvature is mobilized along the right gastroepiploic vessel and passed through the mesentery of the transverse colon to the bladder. Originally felt to be an option for all augmentation candidates, its role is now limited primarily due to the hematuria dysuria syndrome, which occurs in up to 70% of patients.

# Autoaugmentation

Described by Cartwright and Snow,[69] in order to decrease intravesical pressures and increase bladder capacity, a large diverticulum is created at the dome of the bladder by a detrusorectomy while leaving the bladder mucosa intact. Unfortunately, although the initial reports of urodynamic improvements seemed promising, the results were not as durable as those patients treated with an enterocystoplasty and seem to do better in adults than in children.[70–72] In general, autoaugmentation will decrease intravesical pressures. It will not reliably increase capacity that is often necessary in children. It does remain an option for a select group of patients.

## SEROMUSCULAR SEGMENTS (WITH UROTHELIAL LINING)

To avoid the incorporation of intestinal mucosa with the urinary tract, Shoemaker and Marcucci described using seromuscular segments of bowel overlying an autoaugmented bladder.[73] Most experiences have demonstrated that whether the segment is facing the bladder lumen or is reversed, significant contracture develops.[74–75] Most recently, some have demonstrated success with demucosalized colon over urothelium with findings of increased bladder capacity and low filling pressures.[76] Long-term results and more experience are necessary to help determine the efficacy of this approach.

## CONTINENT CATHETERIZABLE CHANNELS

Bladder augmentation and bladder neck surgery markedly decrease the patient's ability to empty spontaneously while increasing the consequences of incomplete emptying. Not adhering to a strict CIC schedule can result in an increased risk of urinary tract infection, bladder stones,[77] and spontaneous bladder perforation.[78–79] In 1980 Mitrofanoff introduced the principle of a continent channel by using the vermiform appendix and implanting it submucosally into the bladder.[80] What is now known as the "Mitrofanoff Principle" states that any supple tube implanted submucosally with sufficient muscle backing acts as a flap valve and results in a reliable continence mechanism (Fig. 118-7).

The Mitrofanoff principle has been widely embraced and applied to a variety of tissues because the appendix (Fig. 118-8) is not always appropriate or available, especially if a simultaneous Malone antegrade continence enema (MACE) procedure is being performed. The use of stomach, colon, bladder, ureters, and fallopian tubes have all been reported with good success.[81–92] However, the utility of the tubularized ileal channel was introduced by Yang[87] and Monti[82] and has assumed a leading role in genitourinary reconstruction (Fig. 118-9).[84,93]

The continent catheterizable channel requires a supple tube, straight path, and short intra-abdominal segment. The appendicovesicostomy requires full mobilization of the right colon to ensure adequate mobility. Amputation should include some cecum because this allows for a larger-caliber cutaneous stoma or can be tubularized to increase stomal length.[81,94] The appendix is then carefully mobilized with the mesoappendix to ensure adequate blood supply. The

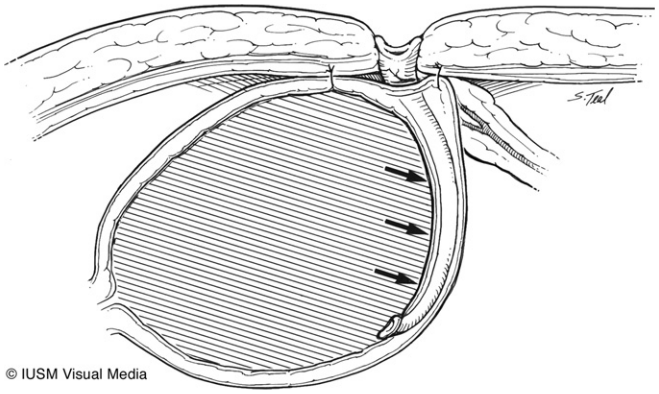


FIGURE 118-7 The Mitrofanoff principle states that a supple tube will compress with increasing intravesical pressure and provide continence.

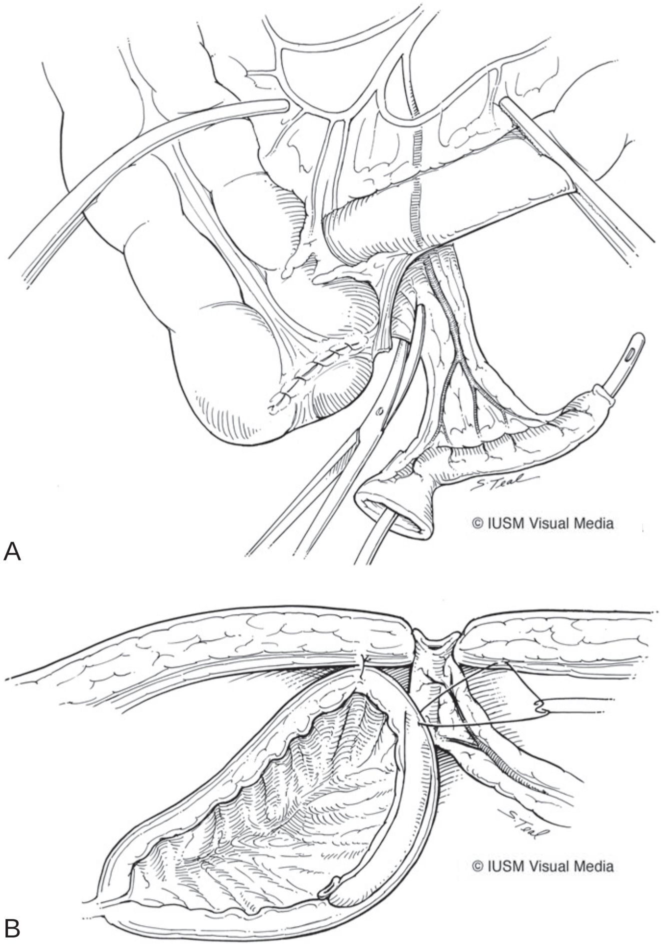


FIGURE 118-8 **A,** The appendix is readily accessible and mobilized with maintenance of its vasculature. **B,** It is implanted easily beneath the bladder mucosa to provide a reliable catheterizable channel.

Monti-Yang technique requires the isolation of 2 cm of ileum, opening it along its antimesenteric border and retubularizing it over a 12-Fr catheter. The channel is then preferentially implanted into the submucosa of the bladder because its thick muscle is ideal for a continent valve; however, stomach and the tenia coli have been successfully used. Reimplantation into ileum is the most challenging and requires the creation of a seromuscular trough. The stoma site can be hidden within the umbilicus or placed in the right lower quadrant, the latter being favored as a shorter and more direct route. Great care is taken to ensure a catheter, usually 12-Fr, passes easily and that the channel is as straight and tension free as possible. When satisfied, the surgeon fixes the channel to the abdominal wall with a permanent suture. Many ingenious skin flap techniques are used to minimize the chance of stomal stenosis, all inserting into the spatulated channel. An indwelling catheter is left for 2 to 3 weeks, and the first catheterization is usually performed in the clinic setting.

Stomal continence is excellent, and rates of 90% to 99% are reported in the two largest published series.[84,95] Complications pertain primarily to difficulties with catheterization, most commonly at the skin level, but may also occur deeper within the channel itself. Stomal stenosis is reported to occur in 5% to 25%,[95–96] with a lower rate potentially seen with tubularized ileum.[84]

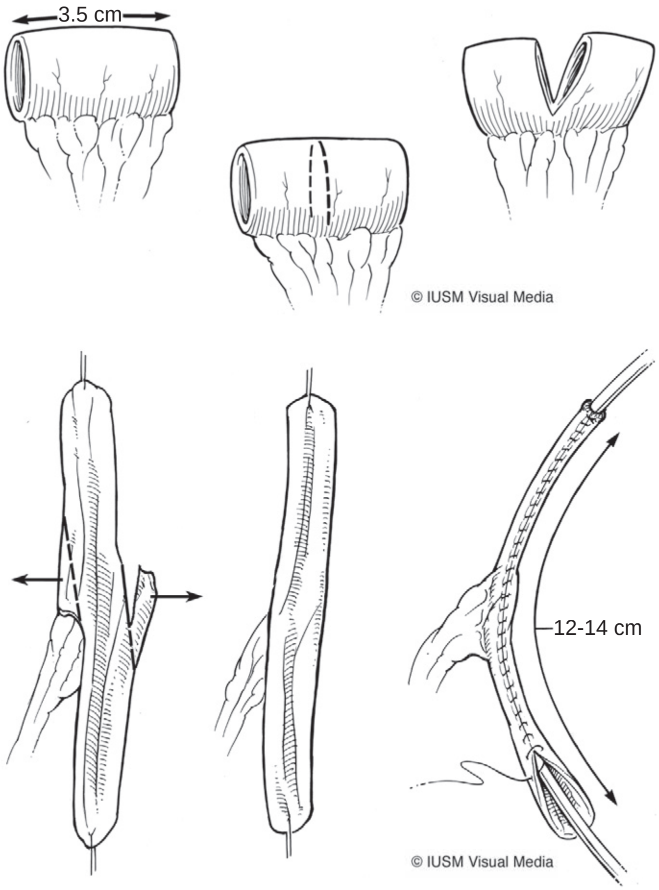


**FIGURE 118-9** Normally, a 2-cm segment of ileum can be opened along its antimesenteric border and tubularized for an effective channel. A slightly longer piece (3.5 cm) can be partially divided, both ends tubularized, and reanastomosed for a spiral Monti, for situations demanding more channel length.

Several authors have described continent catheterizable tubes fashioned from native bladder. Casale's original description of the "intravesical channel"[97] was modified by Rink.[98] Although continence rates of 100% were reported, the technique is hampered by a 45% incidence of stomal stenosis. Although still a useful technique if an intraperitoneal procedure can be avoided, it has been largely replaced by the appendicovesicostomy and reconfigured ileovesicostomies.

These channels provide a more convenient and more socially acceptable means of catheterization. It is especially beneficial for those with a sensate urethra and in the obese or wheelchair-bound female. It also assists caregiver comfort and, most importantly, patient independence.

## CONTINENT URINARY RESERVOIRS

If the entire bladder has been replaced by nonurothelial tissue (usually gastrointestinal) and requires emptying by means other than the urethra, it is referred to as *continent urinary diversion*. Although popular and with many refinements over the past several decades, it is not commonly used in pediatrics today because generally the bladder can be incorporated into the reconstruction.[50]

A few diagnoses such as bladder agenesis or malignancy resulting in cystectomy will require complete bladder replacement. When required, however, it allows the complex patient to achieve continence and enjoy the benefits of such. Patient selection for the procedure is as important as with bladder augmentation because noncompliance will result in the same myriad of complications, despite a technically perfect operation. Preoperative evaluation is similar to the bladder augmentation patient, with the acquisition of sufficient clinical, metabolic, anatomic, and functional data to develop a detailed surgical plan.

The goals of the continent urinary diversion include the creation of a reservoir of adequate capacity and compliance, nonrefluxing ureteric implantations, a continent cutaneous stoma, and a minimum of complications.

Although the gastrointestinal tract again provides for the reservoir, several key differences exist with an augmentation. Colon and stomach have assumed a larger role because the musculature of the tenia coli and stomach allow for more reliable nonrefluxing ureteric and catheterizable channel anastomoses. The three most common types of continent reservoir in children are (1) a reservoir fashioned solely from ileum (Kock pouch), (2) a gastroileal composite, and (3) an ileal reservoir (Indiana pouch).[95] Each has a myriad of variations described, all attempting to decrease complications and assist construction. However, because published reports in children are usually limited to small numbers, each reservoir having subtle variations and no published direct comparisons, it is impossible to determine an ideal reservoir.[55,95,99] Therefore the reconstructive surgeon must be familiar with several techniques because each has advantages that may require exploitation with any clinical situation.

## KOCK POUCH

Kock first described a continent ileostomy in 1971[100–101] and from this developed the Kock pouch in 1982.[102] This continent ileal reservoir was among the original nonorthotopic bladder substitutions used and remains popular today.[103–105] It requires the construction of an efferent nipple for continence and an afferent limb for the prevention of reflux. This technically demanding aspect usually requires the use of stapling devices, and these can be the source of its most significant complications (stone formation) and long-term failure rate.[106]

Approximately 80 cm of ileum is harvested in adults, with the proximal 15 to 20 cm used in an isoperistaltic fashion to create the antireflux mechanism. The distal 12 to 15 cm are used for the continent cutaneous stoma. These lengths are decreased appropriately depending on the size of the child. The bowel is intussuscepted through its full thickness, and this is secured by three rows of gastrointestinal staples, although absorbable mesh has also been described.[107] Significant modifications include removing the distal 6 staples from the device,[106] stripping the distal mesentery,[108] and the use of absorbable staples.[109]

## GASTROILEAL POUCH

The advantages of both gastric and ileal segments can be maximized while offsetting their complications by incorporating them both into a composite reservoir. The metabolic derangements complement each other, as the acidic gastric secretion will neutralize the absorptive properties of the colon or

ileum.[110–112] Furthermore, in patients at high risk for short gut syndrome, as in cloacal exstrophy, it allows a minimum of valuable absorptive tissue to be lost.[50] However, it is a more complex reconstruction, requiring two anastomoses and longer operating time, but is a valuable alternative for select patients.

## INDIANA POUCH

The ileocecal segment has been popularized due to the potential continence or antireflux mechanism inherent to the ileocecal valve. Many surgical techniques have been described, in the attempt to maximize cutaneous continence, simplify the surgical procedure, and minimize complications. The Indiana group modified the pouch described by Gilchrist and Merricks with a unique plication method that has retained its popularity. An Indiana pouch uses the detubularized cecum as its reservoir, with ureters implanted in a nonrefluxing manner into the tenia. The ileum is then plicated to the ileocecal valve, which is reinforced by Lembert sutures (Fig. 118-10). Continence has been reported in 95% to 99%,[113–114] in part due to its large capacity.[115] Complication rates have been acceptable, as low as 0.6%,[113] but not all surgeons have reported such success.[116]

## COMPLICATIONS FROM THE INCORPORATION OF INTESTINE IN THE URINARY TRACT

Despite the popularity of using the gastrointestinal tract as a urinary reservoir, the potential complications are numerous and can be significant. A broad categorization would include (1) complications due to structural defects, (2) complications secondary to the loss of the intestinal segment, (3) complications due to secretions, and (4) complications from absorption.

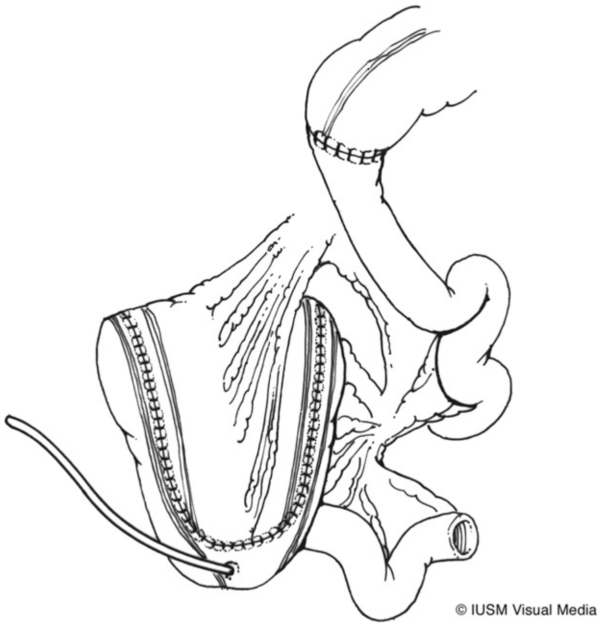


**FIGURE 118-10** The Indiana pouch uses the ileocecal valve as a continence mechanism and the cecum for urinary storage.

## STRUCTURAL COMPLICATIONS

Structural complications include the requirement of a second augmentation, spontaneous perforation, and long-term malignancy potential. A secondary augmentation may be required in up to 6% of patients,[66] and most are due to high intravesical pressures from persistent bowel contractility.[117–118] The hallmark clinical signs are incontinence or hydronephrosis with screening ultrasound, and this is confirmed with urodynamic studies.

A spontaneous perforation can be a fatal complication and must not be underestimated. Early urine leaks are likely due to technical error, but late complications usually originate in the bowel, approximately 1 cm from the anastomotic line.[50] Patients often present later in the course, as their neurologic deficit impedes symptoms. Therefore sepsis and death are realistic possibilities, and a high index of suspicion must prevail. Diagnosis is with a CT cystogram and treatment is usually by laparotomy and primary closure,[78] but conservative treatment with catheter drainage has been successful in select patients.[119]

The development of an adenocarcinoma is concerning due to the well-documented occurrence following ureterosigmoidostomy.[120–124] It arises from the ureterointestinal junction and occurs in these patients with a 7000-fold risk over the general population.[123] Although a tumor has been reported as soon as 3 years after augmentation,[125–126] the mean latency is 21.5 to 26 years.[30,123] At our institution, 3 malignancies have occurred in our series of more than 500 augmentations. All patients died of metastatic disease, with a mean time from augmentation to diagnosis of 19 years.[127] Husmann and colleagues[128] have suggested that patients with neurogenic bladders, exstrophy, and other congenital anomalies requiring CIC are at higher risk for malignancy regardless of whether enterocystoplasty is performed. The risk of carcinoma (both adenocarcinoma and transitional cell) in this patient population is increased with exposure to other carcinogens (e.g., tobacco) and immunosuppression.[129] Although most surgeons appreciate the risk, definitive guidelines for surveillance have not been established. Annual cystoscopy has been recommended to begin 3 to 10 years after augmentation.[30,50]

## LOSS OF INTESTINAL SEGMENT

Removal of an intestinal segment places the patient at risk for a bowel obstruction, and this occurs in approximately 3% of cases.[50,60,65,130] Because many of these are due to internal herniation through the pedicle of the augment, Leonard and colleagues[131] have recommended early exploration to minimize the risk of augmentation ischemia.

The removal of a gastrointestinal segment for CUR or augmentation is usually well tolerated; however, bowel dysfunction has been reported in 10% to 54% of patients.[132–133] Removal of the ileocecal valve can result in problematic diarrhea and rectal incontinence, especially in the neurogenic population.[134–135] Loss of the distal ileum can also result in diarrhea, in these cases due to an interruption in the enterohepatic circulation,[136] but can usually be prevented by leaving the distal 15 to 20 cm intact. Treatment of mild cases is usually successful with anion-exchange resins.[54]

Vitamin $B_{12}$ deficiency can develop in up to 35% of patients following an 80-cm small bowel resection for a Kock

pouch,[137] but it had not been demonstrated following ileocystoplasty in the past.[138–139] More recently, our group in Indiana has demonstrated that vitamin $B_{12}$ deficiency often occurs following standard ileocystoplasty using 25 cm or less of small bowel.[140] Of patients greater than 7 years from ileocystoplasty, 21% had low values of vitamin $B_{12}$ and 41% were found to be low-normal. Vitamin $B_{12}$ levels should be routinely tested, and if found to be low, patients can be adequately treated with oral therapy.[141]

### COMPLICATIONS DUE TO SECRETIONS

The acidic nature of gastric secretions can result in a hematuria-dysuria syndrome (HDS) in 9% to 70% of patients.[50,131,142–143] This troublesome complication can result in bladder spasms, suprapubic pain, dysuria, gross hematuria, and excoriation of genital skin. This is especially troublesome in sensate patients, where nearly 75% will have symptoms.[54,144–145] Treatment of mild cases is with histamine blockers or proton pump inhibitors[144] but may also require bicarbonate irrigations.[146–147] The net acid loss can result in a profound hypokalemic, hypochloremic, metabolic alkalosis and can be especially severe with a coexisting gastroenteritis.

Mucus production continues with all other bowel segments, although less so with ileum,[65,148–149] and can result in incomplete bladder emptying. Mucus production also predisposes the patient to urinary tract infection (UTI) and bladder stone formation.[50] Bladder stones occur in approximately 7% to 52% of augmentations,[77,150–151] with the two largest series recording an incidence of 10% to 15%.[151–153] The increased risk may be due to increased levels of calcium and phosphate in mucus.[154] Their struvite composition implies a common etiology with a urease-producing bacteria. The systemic acidosis common to the augmented population decreases stone inhibitors and promotes stone growth.[77] Prevention is aimed at regular CIC and daily bladder irrigations. Treatment is amenable to open or endoscopic means,[77,150,152,155] with open surgery reserved for the larger stones.

Bacteriuria is nearly universal in any patient performing CIC, especially when combined with an enterocystoplasty. A UTI most frequently presents with malodorous urine, but symptoms may include hematuria, incontinence exacerbation, suprapubic pain, or increased mucus production.[50] A symptomatic urinary tract infection is reported by Rink and colleagues[65] in 22.7% of patients with an ileal augmentation, but in only 8% of patients with a gastrocystoplasty. Overall occurrence of a febrile UTI was reported to be 14%. Treatment of asymptomatic bacteriuria is not indicated unless culture indicates a urease-producing organism or a virulent organism. However, treatment may decrease the risk of stone formation.

### COMPLICATIONS CAUSED BY ABSORPTION

The use of bowel for a urinary reservoir can be associated with profound metabolic changes due to its absorptive nature. Colon and ileum readily absorb ammonium, hydrogen ion, and chloride, and this will result in a hyperchloremic metabolic acidosis. This is tolerated in many patients with normal renal function[156] but may require medical therapy in others. The extent of ion absorption depends primarily on intestinal contact area and length of time for contact; therefore significant acidosis should prompt an investigation into incomplete emptying.[50] Although not all patients will be frankly acidotic, nearly all will have a rise in their serum chloride levels, albeit still in the normal range.[60] The acidosis prompts mobilization of buffers and can result in bone demineralization. Although some believe that somatic growth impairment occurs, it remains controversial. This has been demonstrated in animal models,[157–159] as well as in patients with bladder exstrophy, where there has been a reported 15% to 20% decrease in their overall height.[160] However, in the much more prevalent myelodysplastic population the clinical correlation has been more difficult to prove. The acidosis will also result in hypocitraturia and increase the risk of both renal and bladder stone formation.[77]

Medications such as Dilantin and methotrexate are readily absorbed across the bowel, and levels must be closely monitored.[161] Glucose is also absorbed, making urinary monitoring of hyperglycemia less reliable.[162]

## Summary

The description by Lapides of CIC revolutionized lower urinary reconstruction. It opened the door for primary reconstruction in children, allowing the urinary tract to remain intact. It virtually eliminated permanent incontinent urinary diversion with the social stigma of ostomy drainage, leaving only rare indications for temporary incontinent diversion. The Mitrofanoff principle allowed for an even more aggressive approach to achieving complete dryness in these children. Although there have been enormous gains in independence and social well-being in the affected children, the reconstructions have provided an entire new set of complications, some of which are potentially lethal. It is clear that the most important aspect is patient and family motivation. They must be willing and able to catheterize at 4-hour intervals, daily, forever. These reconstructions require a team approach, from the family, surgeon, and nursing, and they require lifelong follow-up evaluation.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 119

# Megaureter and Prune-Belly Syndrome

Mark C. Adams and W. Hardy Hendren III

## Megaureter

Megaureter describes a ureter that is abnormally dilated. The ureter can sometimes also be greatly elongated and tortuous. In general, the two principal pathologic types of megaureter are those that are obstructed and those with massive vesicoureteral reflux (Fig. 119-1). There may be both reflux and obstruction present, as in a megaureter ending ectopically in the bladder neck or urethra, which may be obstructed during the resting state but allow reflux during voiding when the bladder neck opens. In primary cases, the bladder is normal and the abnormality is located in the distal ureter. In other cases, megaureter may be secondary to bladder dysfunction. For example, impressive megaureters are seen in some males with high-grade urethral obstruction from posterior urethral valves. Ablating the valves can decrease intravesical voiding pressures and allow compensation of the ureters in time. Similarly, a neuropathic bladder secondary to meningomyelocele can cause physiologic obstruction of the bladder outlet with secondary megaureter. Occasionally, megaureters may represent a dysmorphic anomaly without obstruction or reflux despite the dilation (nonobstructive nonrefluxing megaureters). Megaureters may be classified on the basis of pathophysiology according to an international system proposed in 1977.[1]

When the abnormality is intrinsic in the lower ureter, the megaureter may be a unilateral problem, especially with a typical obstructive megaureter. These cases classically feature an abnormal terminal ureter with a variety of histologic and ultrastructural abnormalities.[2,3] Some have referred to this abnormality as an *adynamic segment,* but it is not comparable with the adynamic segment of lower colon in Hirschsprung disease or the lower esophagus in achalasia. The ureteral orifice often looks normal in obstructive megaureter, and true stenosis is rarely noted. Typically, a ureteral catheter can be passed through the segment without difficulty. The ureteral orifice of a refluxing megaureter is usually abnormally dilated. Indeed, an endoscope can often be passed readily up many such megaureters. In primary reflux, there exists an inadequate valvular mechanism related to the diameter of the ureter and the length of submucosal ureter within the bladder wall.

Ureterocele and ectopic ureter are commonly associated with megaureter, especially in the female infant with a duplex collecting system. Rarely, megaureter is the result of excessive urine flow, such as that seen in diabetes insipidus. The prune-belly syndrome features abnormal development of the entire urinary tract including the ureters, which are typically elongated and tortuous. Microscopic section of those ureters may show decreased musculature and excessive connective tissue in the ureteral wall, often affecting the lower ureter more than the mid or upper segments.

Megaureters are typically found in two patient populations. Newborns with the problem may be identified in follow-up of antenatally detected hydronephrosis. The relative incidence of megaureter compared with other congential upper tract anomalies is higher in this group than in older children presenting with clinical problems. The most common presentation in older children is urinary tract infection, although some children may have intermittent pain from obstruction. Infants may show failure to thrive.

Whenever megaureters are encountered during urologic evaluation, the entire urinary tract must be evaluated to determine whether they are a primary or secondary problem. The kidneys and ureters are often first visualized by ultrasonography. Intravenous pyelography may be useful; however, the diagnosis of obstruction is most often made by nuclear imaging with diuretic washout. The drainage curve after diuresis is informative, but care must be taken that the area of interest includes the entire upper system (ipsilateral kidney and ureter). Drainage of radionuclide out of the kidney into ureter and not bladder can lead to a false-negative examination. Particularly in newborns evaluated for antenatally detected hydronephrosis, the function of the kidney should be considered in interpreting nuclear renography, and significantly decreased relative function is generally considered an indication for surgical intervention in an otherwise asymptomatic child. Any decline in function (>10%) on serial renography is a strong indication for repair. Antegrade pyelography performed by inserting a needle into the kidney and infusing contrast medium is occasionally helpful in defining anatomy and demonstrating differential pressures between the upper tract and bladder (Whitaker test). Voiding cystourethrography is mandatory to determine if reflux is present and will demonstrate the ureteral anatomy if there is reflux. In addition, in males it

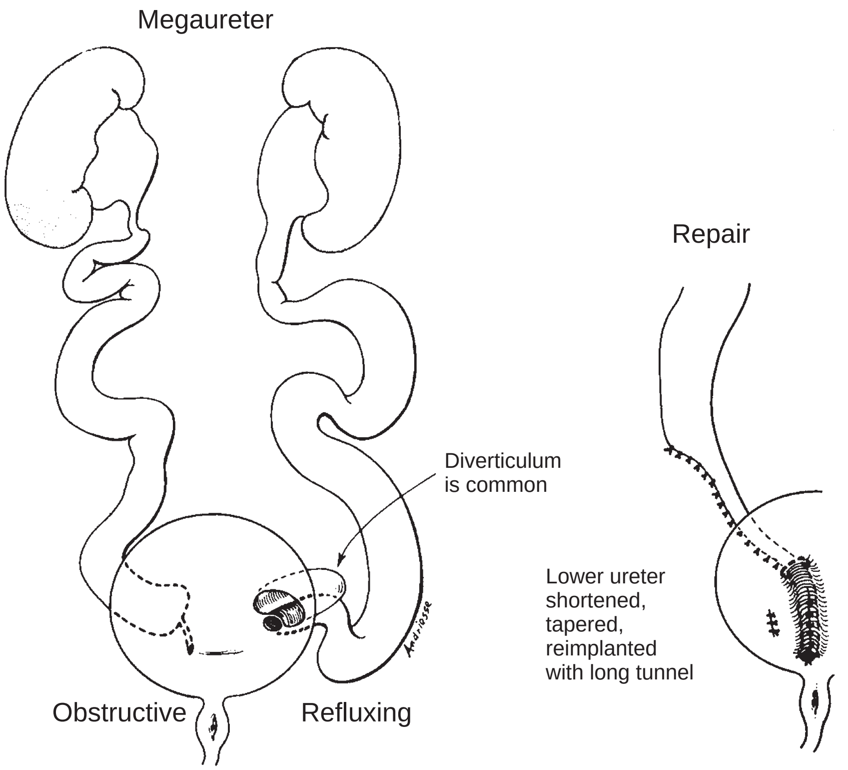


**FIGURE 119-1** Types of megaureter and scheme of lower repair.

will demonstrate any urethral pathology. Urodynamic study may be a valuable adjunct in assessing these cases if any bladder abnormality is suspected. Temporary placement of an indwelling urethral catheter may also differentiate between primary and secondary megaureter on serial imaging. Cystoscopy should define the appearance of the orifices but is generally only performed at the time of reconstructive surgery. As noted, the orifices in obstructive megaureter usually look normal; in refluxing megaureter, they are usually widely dilated with a "gopher hole" appearance.

The advent and widespread use of intrauterine ultrasonography has allowed early diagnosis of many cases of megaureter. Affected babies should have selective urologic investigation after birth. Obstructive megaureters without reflux may improve spontaneously. Thus in asymptomatic infants with mild or moderate obstructive megaureter and normal relative renal function, serial observation may be considered for a period of time to see whether spontaneous improvement occurs.[4,5] If improvement is not clear cut or if the patient develops symptoms, operative repair should be performed. Retrovesical ureteral diameter is a reasonable predictor of the likelihood of resolution of hydronephrosis or the necessity of surgical intervention in the absence of reflux. This is helpful in counseling parents.[6]

If the primary problem is a neuropathic bladder, anticholinergic therapy and intermittent catheterization may result in improvement in ureteral dilation. If the patient has severe urethral valves, fulgurating the valves may suffice. Valves occur in a spectrum of severity.[7] Thus treatment may be valve fulguration in some patients, valve fulguration followed by early megaureter repair in others, and, occasionally, valve ablation and immediate megaureter reconstruction.[8]

In summary, indications for repair of a primary megaureter vary with the etiology. In cases of primary obstructive megaureter, poor renal function ($\leq$35% to 40% of total function by renography), a severely scarred kidney, symptoms, or decreasing function on serial studies are generally considered as clear indications for intervention. Bilateral megaureters or one involving a solitary renal unit threaten total renal function and should be treated more aggressively. Finally, failure to improve after a reasonable period of observation may, at times, be an acceptable indication for surgical repair. Primary reflux into a megaureter, except in a newborn with normal renal function, is unlikely to resolve and usually will eventually require repair. Febrile urinary tract infection is another indication for surgical correction of primary megaureter whether reflux or obstruction is present. Secondary reflux may resolve with treatment of bladder outlet obstruction or bladder dysfunction. Intervention, when indicated, is virtually always open repair because the results are good even when dealing with large ureters in neonates. Endoscopic dilation followed by temporary internal stenting may result in temporary improvement in function or drainage but is unlikely to be lasting in effect.[9] Diversion by cutaneous ureterostomy has occasionally been used for an infected system or when renal function in a neonate is so poor that it is not clear whether repair or nephrectomy is more appropriate, or in premature infants who are symptomatic or have significantly compromised renal function. In those settings, temporary percutaneous nephrostomy drainage may be just as beneficial and less morbid. As such, cutaneous ureterostomy is rarely necessary.

## SURGICAL TECHNIQUE

In most cases, only the lower ureter requires repair.[10–14] Although the upper ureter may be tortuous, it often straightens out in time if the lower ureter is repaired and obstruction or reflux is relieved. This type of surgery requires gentle and

meticulous technique based on the principles of standard antireflux repair. The ureter should be handled minimally with forceps to avoid injury to its delicate wall. The ureter should be mobilized enough to taper and reimplant it into the bladder without angulation or tension. Its blood supply must be preserved. The ureter should enter into the bladder through the fixed posterior wall at a point at which it will not be obstructed or angulated when the bladder fills. The ratio of tunnel length to the diameter of the ureter must be high enough to prevent reflux, usually 4 or 5 to 1.

### Repair of the Lower Megaureter

The surgical steps are shown in Figure 119-2. A transverse suprapubic skin incision is usually made, and the midline fascia opened vertically. A vertical fascial incision may be preferable to give easy access not only to the bladder but also the middle and lower third of the ureter. Exposure or mobilization of the middle third of the ureter is rarely necessary in routine cases but may be accomplished by medial reflection of the colon. The Denis Browne universal retractor provides ideal exposure.

As shown in Figure 119-2, *A,* a catheter is sewn into the ureteral orifice for manipulation. After the orifice is circumscribed, ureteral mobilization begins intravesically and continues until mobilization is no longer easily accomplished through the bladder hiatus. Muscular and vascular attachments to the ureter within the intramural tunnel are divided and then cauterized on the bladder side but not the ureter. Shifting outside the bladder and dissecting up along the hypogastric vein, the lateral umbilical ligament is encountered and divided to allow upward and medial retraction of the peritoneum. After dissection cephalad along the anterior aspect of the ureter, it can be pulled through the hiatus and exposed in the gutter. Paravesical dissection, which can injure the bladder nerve supply, should be minimal. As the ureter is mobilized upward, all periureteral tissue should be swept toward the ureter to maintain its collateral blood supply (Fig. 119-2, *B*). In dissection of the ureter from peritoneum located medial to it, the peritoneum, not the ureter, should be skeletonized. In the male, the vas deferens should be identified where it lies on the peritoneum. Mobilization of the ureter is often easier if it is filled with saline.

After careful mobilization, periureteral tissue is undermined on the lateral aspect of the ureter and then opened to expose the wall to be tapered (Fig. 119-2, *C*). During the first 20 years of experience with repairing megaureters, which began in 1959, special megaureter clamps were used to exclude redundant circumference as an aid in tapering ureters. Some surgeons continue to find them useful. In more recent years, we have not used such clamps because the vascular periureteral tissue can be laid back, preserved, and then closed over the trimmed ureter more easily without clamps. The segment to be tapered is marked and trimmed appropriately (Fig. 119-2, *D*). Excision of redundant ureteral wall posteriorly places the eventual ureteral closure against the bladder muscle rather than next to mucosa and can usually be achieved. Occasionally, however, the dominant vessels in the ureteral adventitia are found there and should be avoided and preserved. It is important not to make the ureter too narrow, and it should be noted that closing the ureter uses 3 to 4 mm of ureteral circumference. Closure should be performed over a 10-Fr catheter except in infants, in whom 8-Fr may be more appropriate. Closure should never be tight over the catheter. The tapering should begin proximally enough that it begins well cephalad to the eventual bladder hiatus. The taper should begin gradually to avoid creation of an outpouching in the ureter that can behave as a diverticulum.

The ureter is closed with a running, locking suture (Fig. 119-2, *E*). It is helpful to interrupt the last few sutures in order to allow shortening, if necessary, during reimplantation. The periureteral tissue that had been saved is then closed to seal the primary suture line. Both layers should be closed with fine absorbable suture. It can be helpful to retain the distal tip of the ureter as a handle, trimming it off after placing the first anchoring sutures during reimplantation. The adynamic segment of an obstructed megaureter should be excised in this manner.

Selection of the new hiatus through which to bring the ureter (Fig. 119-2, *F*) is of prime importance. One mistake is to make the hiatus too lateral, which can result in angulation of the ureter and obstruction when the bladder fills. If the hiatus is located in the back wall of the bladder, it will not do so. The new hiatus must be large enough that it does not compress the ureter. Incising the lower rim of bladder muscle at the new hiatus helps create a smooth course for the ureter to enter the bladder. Care must be taken to avoid injury to the vas in males at this point in the repair.

After the ureteral hiatus has been prepared, the mucosa can be opened widely to prepare a bed in which to place the ureter (Fig. 119-2, *G*). Opening the mucosa is often more accurate than tunneling beneath intact mucosa. There is no disadvantage from this approach if the suture line in the ureter lies posteriorly against bladder muscle. In some bladders (such as in the prune-belly syndrome), elevating mucosa is difficult and requires a tedious sharp dissection. The old muscular hiatus is closed precisely. If a paraureteral diverticulum is present before surgery, the bladder mucosa must be dissected free from the original hiatus to eliminate the diverticulum and the muscular defect closed.

The ureter is then sutured in its bed (Fig. 119-2, *H*). The distal anchoring sutures at the orifice should include trigone muscle and mucosa and full thickness of ureter. The remainder of the orifice is completed with mucosal sutures. The tapered back wall of the ureter lies against the muscle of the bladder.

Figure 119-2, *I* shows the completed repair. The trigone mucosa is closed over the tapered ureter. A 5-Fr feeding catheter is passed through the opposite bladder wall and up the operated ureter to the kidney for 10 to 12 days of drainage after surgery. Alternatively, double J stents can be used, with the disadvantage of often requiring an additional anesthetic for removal. Nephrostomy drainage is generally not necessary. In patients with bilateral megaureters, we routinely repair both lower ureters simultaneously, although this involves a long operation. The technique of megaureter repair as described earlier is our preference for these cases. Some surgeons favor a cross-trigonal reimplantation technique, but it should only be considered if the bladder floor is wider than long so as to provide a long intramural tunnel. Refluxing megaureters have been repaired extravesically as well with the same success rates.[15,16] Likewise, primary megaureters have been repaired laparoscopically with and without robotic assistance[17] but should only be approached in that manner if the same surgical principles can be applied equally well.

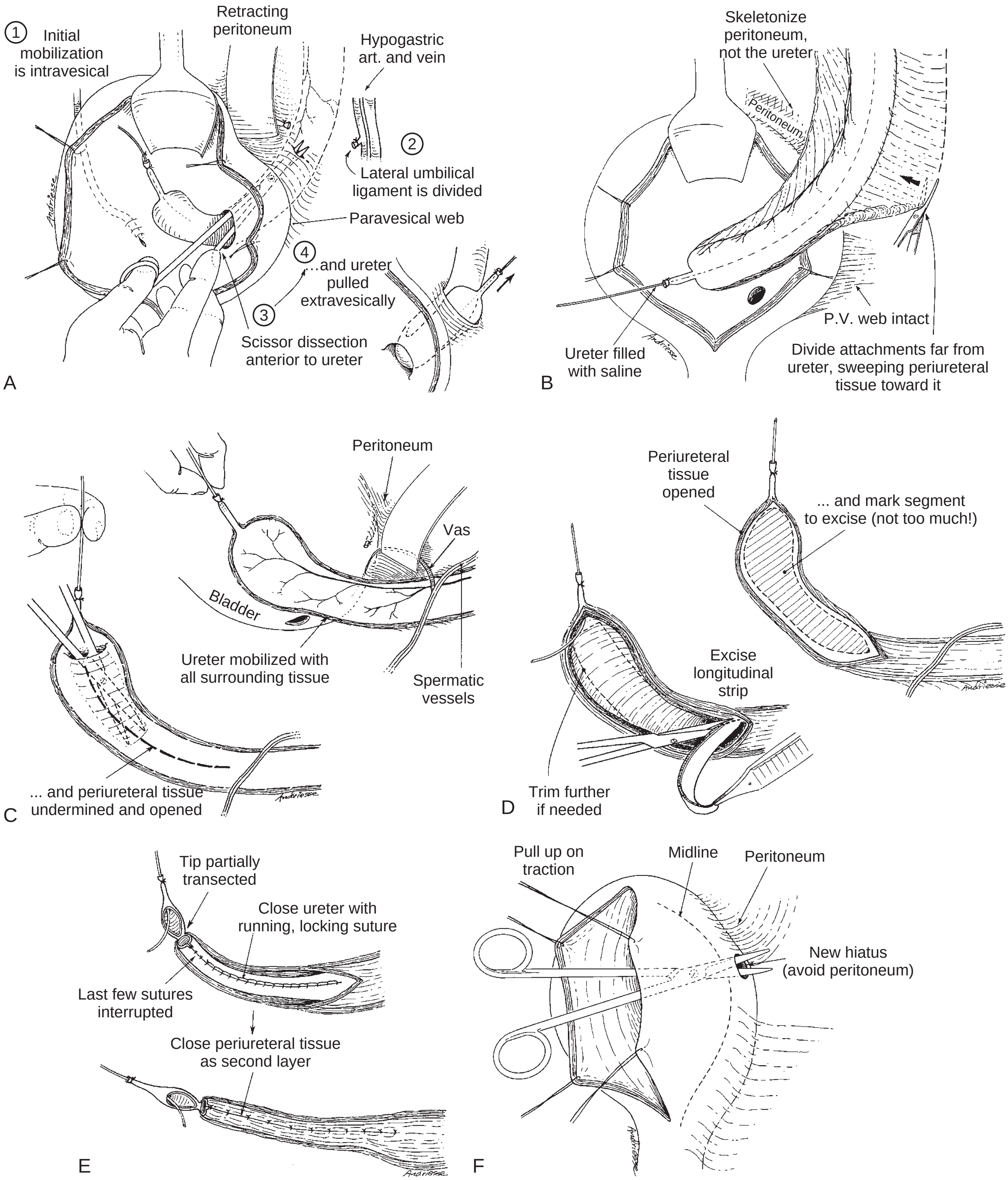


**FIGURE 119-2** Repair of the lower ureter. **A,** Initial intravesical mobilization. **B,** Extravesical mobilization. **C,** Opening periureteral tissue. **D,** Trimming of lower ureter. **E,** Closing lower ureter. **F,** Preparing new hiatus.

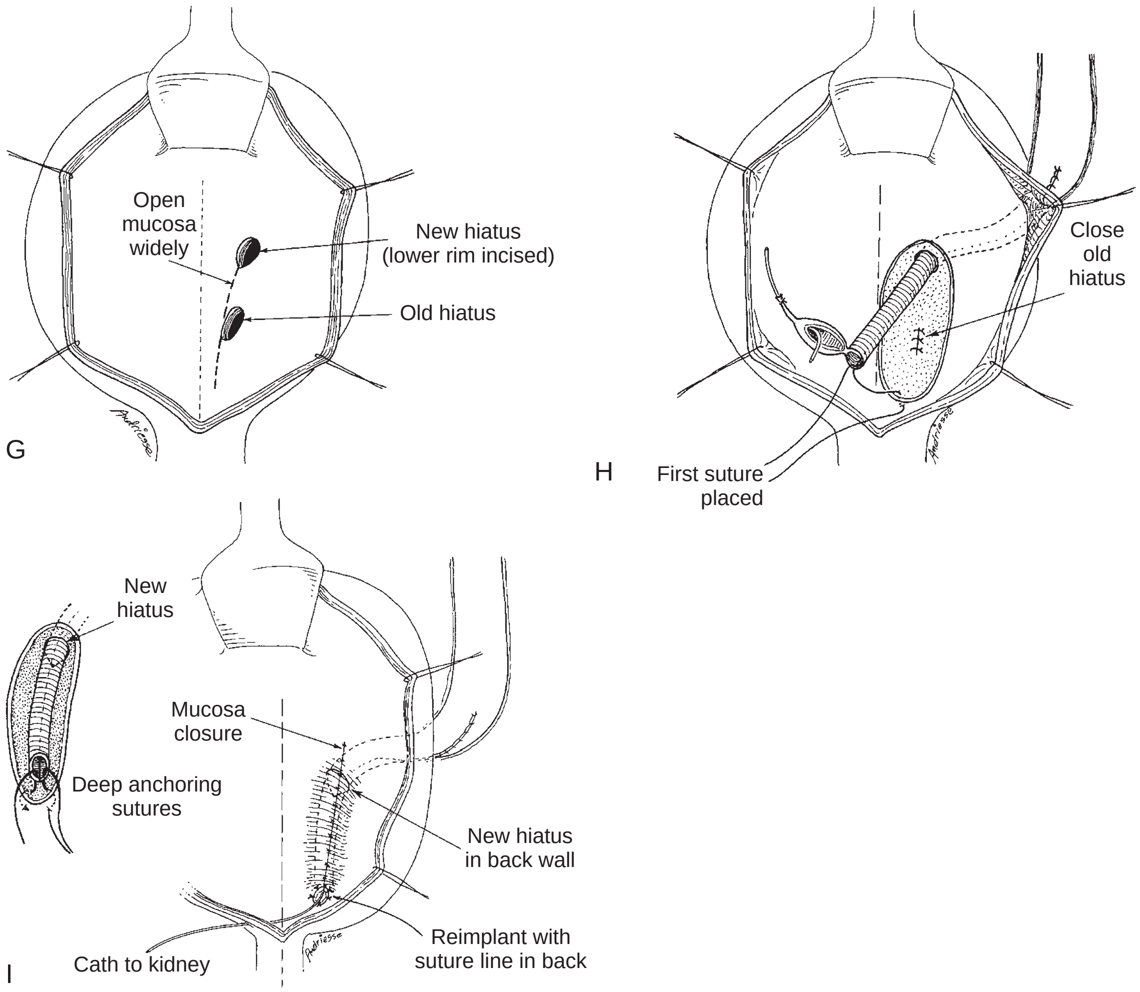


**FIGURE 119-2—CONT'D.** **G,** Creating bed for tapered reimplant. **H,** Suturing tapered ureter in its tunnel. **I,** Completed repair.

For bladder drainage after the repair, it is best to use a straight rather than Foley catheter through the urethra so that the balloon does not compress or irritate the ureteral repair. Only rarely is a suprapubic tube used, for example, in a patient undergoing incontinence surgery on the bladder outlet simultaneously. Ten to 12 days after surgery, contrast studies are performed by injecting the ureteral catheters. This testing rules out a leak, which should be rare. The catheters are then removed, one side at a time if both sides have been repaired. Measuring the urine output after each ureteral catheter is pulled indicates whether each kidney is draining.

## Imbrication

The classic description of megaureter repair involves excision of a part of the ureteral wall to reduce circumference, and this is our preference. Plication or folding may be considered for a moderately dilated ureter, although such techniques may create excessive bulk in the wall of the ureter when severely dilated or thickened. In either type of plication, atraumatic clamps are briefly placed onto the ureter to mark redundancy around an appropriately sized catheter. Again, the clamps should be placed to avoid major blood supply in the adventitia. After removal of the clamps, the ureteral wall is plicated by one of two techniques. Starr[18] described placement of Lembert sutures along the clamp marks (Fig. 119-3), which served to imbricate the ureteral wall and reduce lumen size. Kalicinski and colleagues[19] placed a running horizontal mattress suture, which excluded the redundant portion of lumen. A second running suture was then used to fold the accessory

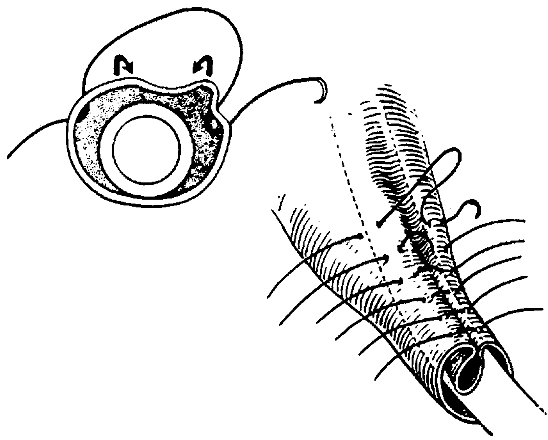

**FIGURE 119-3** Ureteral plication performed with small interrupted absorbable sutures placed in Lembert fashion. (From Keating MA, Retick AB: Management of failures of ureteroneocystostomy. In McDougal WS (ed): Difficult Problems in Urologic Surgery. Chicago, Year Book, 1989, p 131.)

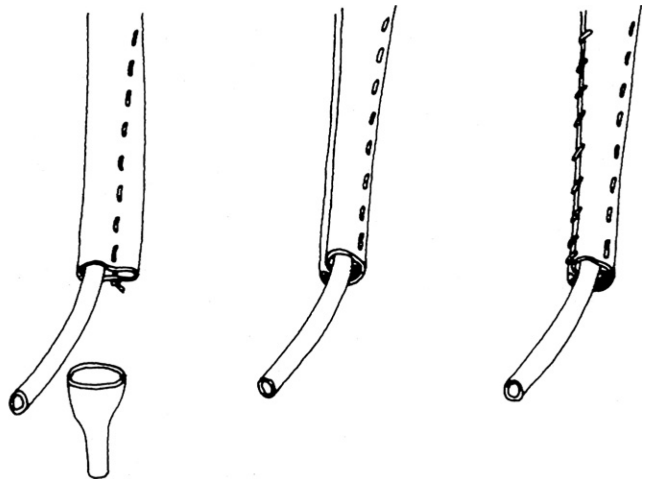

FIGURE 119-4 A running horizontal mattress suture isolates redundant lumen. The redundant portion is then folded and approximated to the main ureteral wall. (From Kalicinski ZH, Kansy J, Kotabinsia B, et al: Surgery of megaureters: Modification of Hendren's operation. J Pediatr Surg 1977;12:183.)

channel over against the wall of the ureter (Fig. 119-4). Histologic examination demonstrates that the folded segment undergoes progressive obliteration over months, although the second lumen remains patent.[20]

## Endoscopic Injection

Since early reports of subureteric injection for reflux using polytetrafluoroethylene (Teflon),[21] endoscopic treatment has been used for refluxing megaureters. The procedure is not indicated for obstructive megaureters. Higher grades of reflux have proven harder to stop endoscopically just as they are with open surgery. The success rate with a single injection for reflux may approach 60% to 80% with a normal-sized ureter. The failure rate increases significantly by as much as 20% or more when treating a refluxing megaureter, although success may increase with a second or third injection.[22] Recurrence rates are relatively low with long-term follow-up.[23] Alternative biocompatible, biodegradable materials have been evaluated with the most extensively used material being a dextranomer/hyaluronic acid copolymer (Deflux, Oceana Therapeutics, Inc., N.J.).[24] The material is easier to use and inject than Teflon and has been used with similar effect for all grades of reflux including megaureters.[25–28] Ureteral hydrodistention at the time of injection and use of an increased volume of injected material within the submucosal intraureteral space may result in more effective placement and less caudal migration of the bioimplant (Fig. 119-5).[26,29] Endoscopic injection has been used for complex patients with reflux including those with secondary reflux, duplication anomalies, and reflux after transurethral incision of ureterocele.[27,29] The least effective site for injection appears to be reflux into ectopic ureters. Open dissection of a ureter previously injected with any material may be more difficult if necessary. In general, the ureter with bioimplant should be mobilized together initially and the distal involved segment of ureter then excised.

Direct repair of megaureters has worked well for 45 years in our experience, and we continue to prefer it. The few cases in which we have used injection therapy with a dilated ureter are megaureters that have some residual reflux despite previous surgery and a long intramural tunnel.

## Repair of the Upper Ureter

If the primary pathophysiology was ureterovesical obstruction or severe reflux alone, upper ureteral obstruction after lower repair will be rare. Several points should be stressed regarding the upper ureter. First, tortuosity can considerably improve

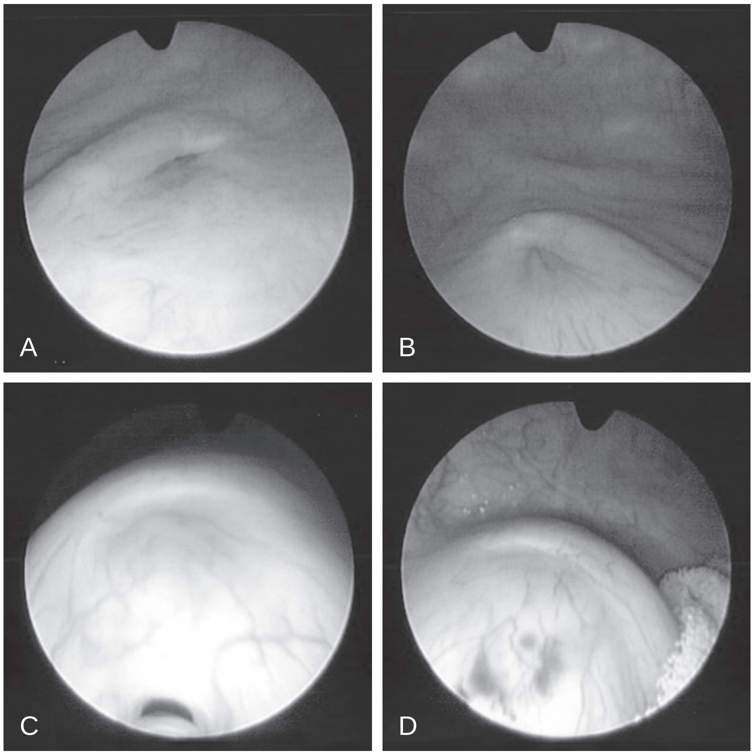


FIGURE 119-5 Endoscopic injection. **A** and **B** Orifice with hydrodistention. **C,** Needle for injection inserted in intraureteric submucosal space. **D,** Coaptation after injection. (Pictures courtesy Anthony Caldamone, MD.)

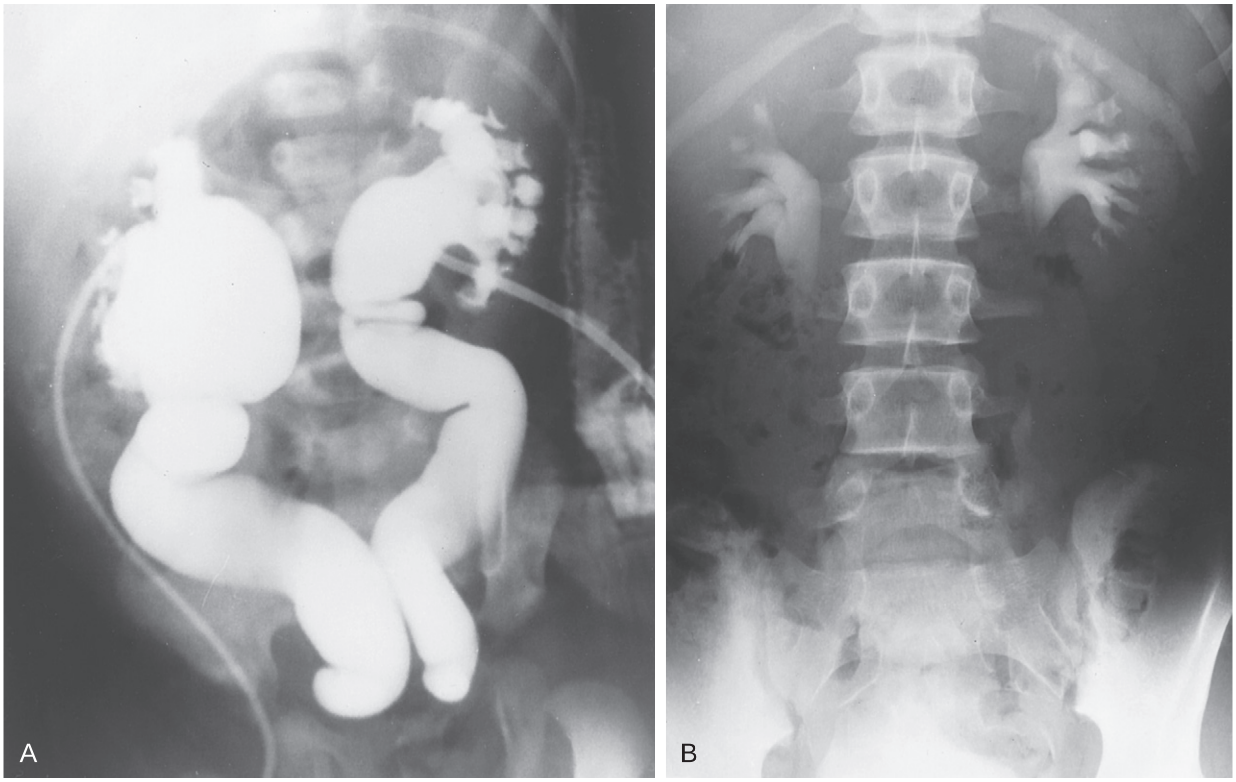


**FIGURE 119-6** Refluxing megaureters. **A,** Massive preoperative reflux at age 4 weeks. Previously placed nephrostomy tubes were unnecessary. **B,** Intravenous pyelogram 13 years after bilateral megaureter repair. Note proximal improvement after distal ureteral repair alone.

after successful repair of the lower ureter that was once obstructed or refluxing. Kinks can straighten, and dilation can recede (Fig. 119-6). If the patient is doing well clinically, it is best to wait for several months or longer to make any decision about proximal ureter. The upper ureter may be dilated immediately after repair of the lower end because of edema surrounding the reimplantation. Imaging studies of the kidney should be repeated to rule out a true obstruction. If the upper ureter remains persistently tortuous and dilated from documented obstruction, it should be tailored as shown in Figure 119-7. The tailoring sometimes merely resects a kink, which can cause poor drainage, particularly at the ureteropelvic junction. In extreme cases, tailoring includes reducing the caliber of the upper ureter. The ureter is incised longitudinally, in situ, and its width is trimmed appropriately. Clamps are not necessary to taper the upper ureter. Temporary urinary drainage with a nephrostomy catheter or indwelling ureteral stent should be used.

It is interesting to watch a dilated ureter fluoroscopically. If the walls of the ureter cannot coapt, active peristalsis may be present but ineffective. The urine churns back and forth with ureteral peristaltic waves instead of being passed effectively into the bladder. Figure 119-8 shows a ureteral peristaltic study in a dilated ureter. Before surgery, peristaltic waves could be seen at various levels of the ureter, but they were of low amplitude and ineffective. After surgery, peristaltic waves in the tapered lower 10 cm of ureter were excellent and effective but not in the persistently dilated ureteral segment 15 cm above the lower end of the ureter. In some cases, the upper ureter has been observed for a long time before being tapered because of continued dilation and poor emptying. In one case in which the upper ureter was repaired 8 years after the lower ureter was repaired, the upper tract hydronephrosis improved remarkably and creatinine clearance increased substantially.

## COMPLICATIONS

Surgical success without obstruction or reflux when reimplanting a normal-sized ureter into a normal bladder should approach 97%. The success rate of megaureter repair is not quite as high. Figure 119-9 shows the principal complications that can occur with repair of the megaureter.[30] When the orifice is too lateral, the tunnel too short, or the distal ureter too broad, reflux can result. A rare cause of reflux is a fistula at the top of the ureteral tunnel potentially caused by a stiff ureteral stent that can erode the ureter at the point at which it turns to exit the bladder. A soft No. 5 infant feeding tube should prevent this problem. The most common cause of persistent postoperative obstruction is by compression of the ureter at its new hiatus through the bladder wall often due to a hiatus that is located too far laterally on an unstable part of the bladder. This complication underscores the importance of having the new hiatus in the back wall of the bladder, not its side wall. In some cases, fixation of the bladder and hiatus with a psoas hitch is helpful to prevent this complication. A diverticulum is sometimes seen at the site of the new hiatus if it is left too large. The complication of fibrosis of the distal ureter can be avoided by meticulous handling and preservation of the blood supply to the ureter during mobilization, not making it too narrow when trimming it, and avoiding the temptation to taper so extensively that the blood supply to the lower ureter is jeopardized.

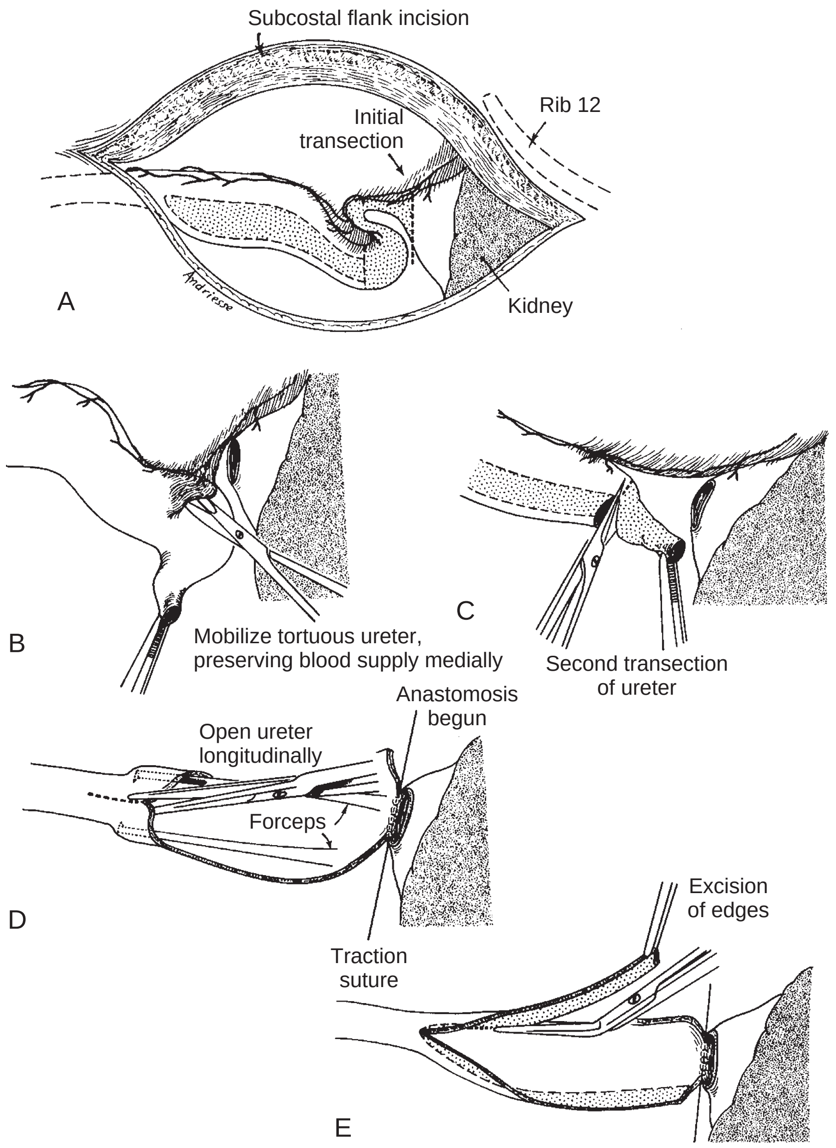


**FIGURE 119-7** Straightening and tapering of the upper part of the ureter. Trimming the upper ureter can improve its emptying and is performed in one quarter of cases in our experience, particularly those that remain tortuous and show evidence of obstruction, especially at the ureteropelvic junction. In some, the upper ureter remains dilated and does not empty well.

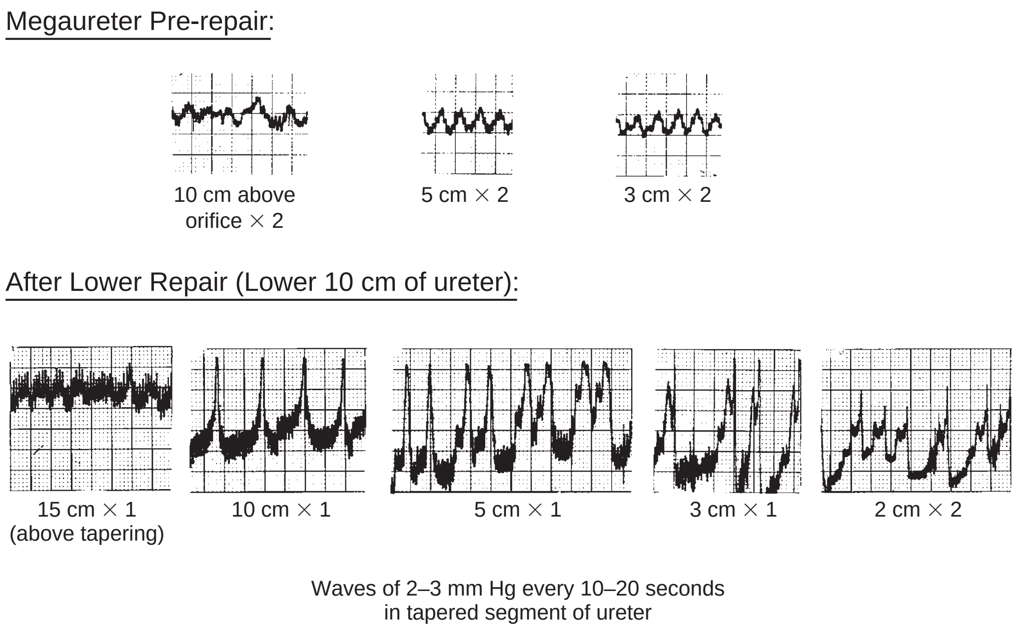


**FIGURE 119-8** Peristaltic study. Peristaltic waves in the lower ureter were ineffective before surgery but were excellent after the lower ureter was tapered. Peristalsis remained ineffective in the dilated upper ureter above the level of tapering at the time of this study.

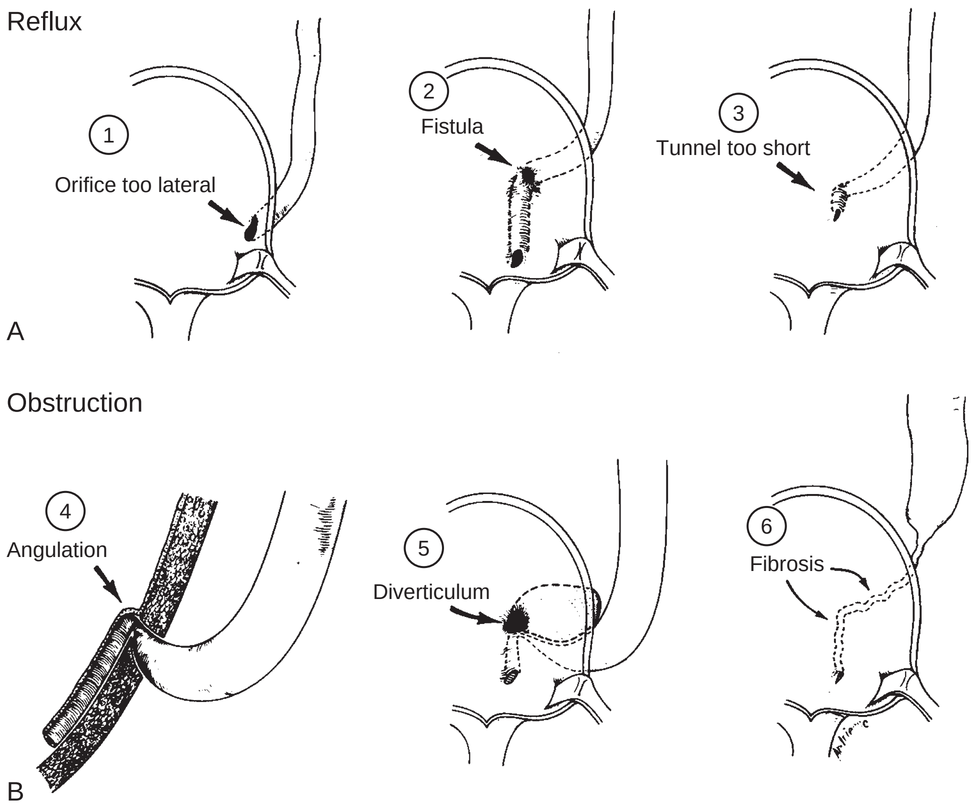


**FIGURE 119-9** The most common complications in failed surgery for megaureter.

In an experience with tapering 404 ureters in 294 patients (217 male and 77 female), which included 75 infants younger than 1 year of age, the success rate was 93% in obstructive megaureter but 83% when the problem was massive reflux. Success was higher with a normal bladder (130 patients) than with a markedly abnormal bladder (164 patients), such as in cases with urethral valves, neurogenic bladder, ureterocele, prune-belly syndrome, and exstrophy. Most patients who underwent a second operation on the ureter eventually achieved success (Fig. 119-10). Others have reported similar results,[12,19,31,32] and problems may occur whether excision or folding techniques are used. Consistently, problems with secondary reflux and obstruction have been noted more commonly after megaureter repair for reflux variants as compared with obstructive ones. Increased collagen deposition and abnormal collagen to muscle orientation have been noted in refluxing megaureters relative to obstructive ones above the distal adynamic segment.[33] Such intrinsic differences may be responsible for the difference in results for the two types.

## CONCLUSIONS

The function of the ureter is to transport urine from the kidney to the bladder at low pressure. It cannot do this effectively when the ureter is so dilated that its walls do not coapt with peristaltic waves. When ureters store urine rather than transport it, there is little question that stasis favors infection. This is particularly true if an inadequate ureterovesical junction allows reflux of urine. Megaureters may be repaired with consistent, good results. The large ureter should be handled minimally and mobilized carefully so as to preserve blood supply. The distal adynamic segment of ureter when obstructing should be completely excised. More proximal dilated ureter can then be tailored to normal size. We favor excisional tapering to achieve this, although folding techniques may be useful if the ureter is less dilated or thickened. The reconstructed ureter can then be reimplanted into bladder using the principles of standard antireflux surgery. The results of such repair are slightly more prone to complications of obstruction and, particularly, persistent reflux than are those done for reflux into a ureter that is not initially dilated. Those complications are also more likely to occur when repair is performed for reflux rather than obstruction. Longer follow-up and further experience at more centers should help define the role of endoscopic injection in the treatment of refluxing megaureters.[29]

# Prune-Belly Syndrome

Some of the most unusual and impressive megaureters are found in patients with the prune-belly syndrome, a term used by William Osler in 1901 to describe the appearance of the abdominal wall in patients with congenital deficiency of the abdominal wall musculature.[34] The skin usually has an irregularly wrinkled appearance similar to that of a prune. The condition has also been called the triad syndrome because there are three major features: deficiency of abdominal muscles, hydroureteronephrosis, and cryptorchidism.[35,36] Its cause is unknown. It has been suggested that early urinary tract obstruction[37] or urinary ascites[38] might be causative or that a primary mesodermal error might lead to the abdominal wall

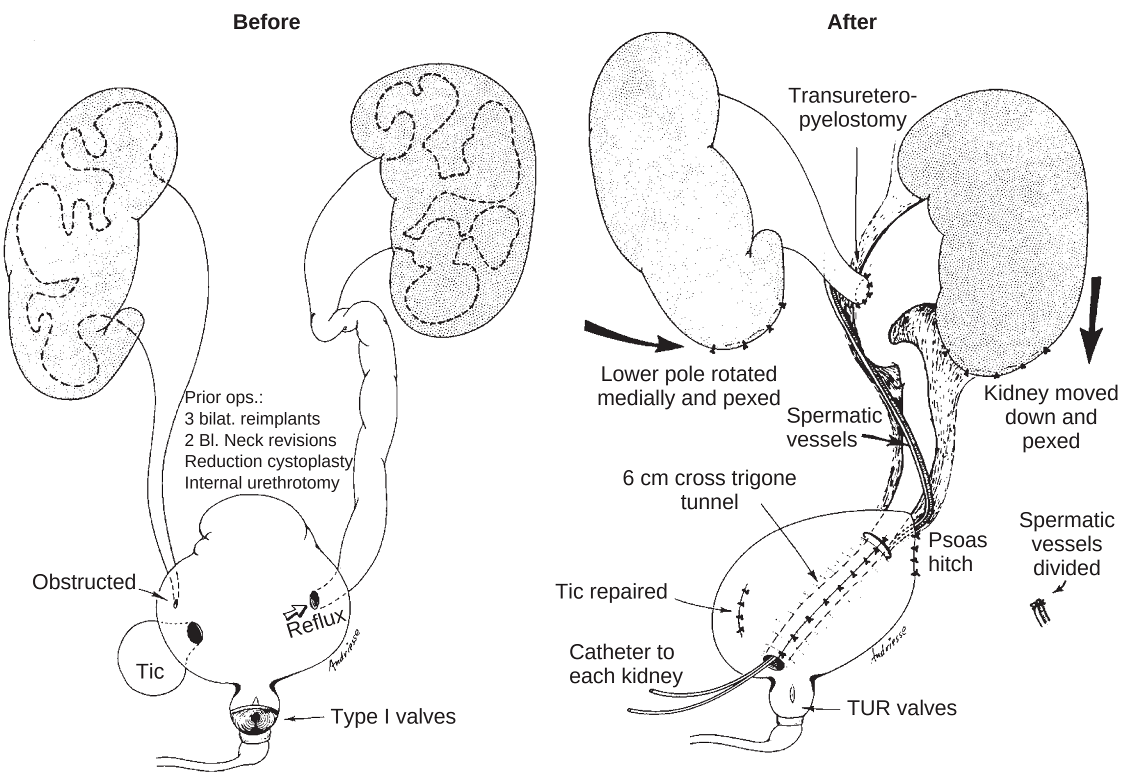


**FIGURE 119-10** A 14-year-old boy presented after three previous ureteral reimplantation operations but was left with a short obstructed megaureter on the right and massive reflux on the left. The left ureter was satisfactory for tapering and a fourth reimplant, and extra length was gained by sliding the kidney down and hitching the bladder upward.[81] Blood supply to that ureter was enhanced by maintaining the spermatic vessels with it. The right side was drained by transureteropyelostomy.

and genitourinary findings.[39] Almost all patients are male, but the condition has occurred in females.[40] We have cared for 48 patients with prune-belly syndrome since 1968, only 3 of whom were female. It has been described in a pair of twins,[41] one infant from a pair of twins, and in consecutive siblings with a mosaic chromosome abnormality.[42] Such cases suggest a genetic influence, but no clear pattern of inheritance has been identified. Like most pathologic entities, the prune-belly syndrome ranges from mild to severe in the degrees of both abdominal wall and urinary tract abnormality.

## ABDOMINAL WALL

The abdominal walls of four patients with the prune-belly syndrome are shown in Figure 119-11. In a typical case the abdominal wall is lax and protuberant, and close inspection shows coarse wrinkling of the skin. The abdominal wall may be so thin that loops of dilated ureter and intestine are easily visible and peristalsis can be seen or palpated. A protuberant abdomen and flaring rib margins are common, and the lower sternum is often depressed. As the child becomes older, the skin often becomes smoother; however, the lower abdomen may be remarkably protuberant in a potbellied appearance. Histologic examination of the abdominal wall has revealed both absence and hypoplasia of muscle, particularly in the lower, central area.[43] Normal relationships of muscle groups may be preserved, or they may be fused as a single fibrotic layer. Innervation does appear to be intact.[44] Poor support of the lower chest wall leads to an ineffective cough mechanism in many of these children and may make them more prone to respiratory infections. The lax abdominal wall may also contribute to poor bladder and bowel function. Interestingly, wound healing does not appear compromised and the appearance and function of the abdominal wall may be improved by surgical repair. The earliest and most simple techniques involved a midline incision and closure after trimming redundant skin and thinned abdominal wall from either side. Randolph and colleagues[45] described a nearly transverse incision extending from the tip of the lowest rib on either side to the symphysis pubis with central excision. Techniques reported by Ehrlich[46,47] and Monfort[48,49] (Fig. 119-12) preserve a central musculofascial strip, which is overlapped by better lateral fascia and skin. Both provide adequate exposure for orchiopexy or genitourinary reconstruction at the same time.

## KIDNEYS AND URETERS

Renal architecture and function vary widely in prune-belly syndrome. In some cases the kidneys are severely dysplastic and the infants die soon after birth of renal failure (Fig. 119-13).[50,51] At the other end of the spectrum are patients with relatively normal kidneys. Some element of renal dysplasia is found in more than half of patients with prune-belly syndrome,[51] and the severity is a major determinant of patient prognosis. The degree of dysplasia may vary greatly from side to side in the same patient. It tends to be worse in patients with bladder outlet obstruction (urethral atresia) and imperforate anus.[52]

This wide variability in severity is seen not only microscopically in the renal parenchyma but also in the collecting system

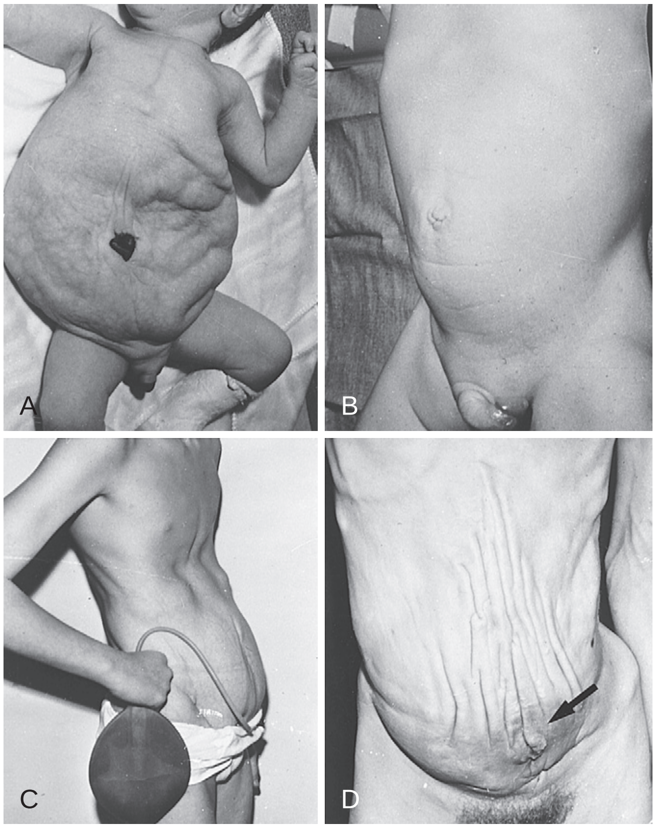


**FIGURE 119-11** Variable appearance of the abdominal wall in the prune-belly syndrome. **A,** Neonate with typical features of severe prune-belly syndrome. Note the sagging flanks and loops of bowel visible beneath extremely thin abdominal wall with deficient musculature. **B,** Mild case of prune-belly syndrome in an 8-week-old boy. Note the slight wrinkling of the skin of the lower abdomen and underlying distended bladder. The abdominal wall is lax but more developed than the patient shown in **A. C,** An 18-year-old patient with typical protuberant abdomen seen in prune-belly syndrome. Note inward protrusion of the lower sternum, which is common in these patients. A long-standing nephrostomy and cystostomy have been present since infancy. The urinary tract was subsequently reconstructed. **D,** A 16-year-old patient with severe wrinkling of the abdominal wall. The patient had long-standing end ureterostomies (*arrow*). Marked kyphoscoliosis is present. An undiversion operation was performed subsequently.

of the kidney, which can be dilated and have a peculiar dysmorphic appearance (Fig. 119-14). The ureters are characteristically dilated, elongated, and tortuous to a much greater degree than is seen in males with even high-grade obstruction from urethral valves. Some patients have scant muscle in the ureteral wall; others have well-developed muscle. In general, the upper ends of the ureters have better preserved architecture than do the lower ends.[53] Collagen is often increased and muscle mass decreased in the ureteral wall, especially when there is massive reflux.[54] In some patients the ureteropelvic junction is extremely tortuous but not obstructed. In others, ureteropelvic junction obstruction is present. Peristalsis is poor in some ureters and active but ineffective in others because the walls of the ureters cannot coapt. Repeat urinary infection can lead to inflammation and further fibrosis of the ureter, aggravating an already compromised situation. The hydronephrosis at the level of the kidney is often less remarkable than that of the distal ureter and bladder, and the parenchyma is sometimes better preserved than might be expected from the degree of distal dilation. Up to 85% of patients with prune-belly syndrome have vesicoureteral reflux.[55] The reflux may be difficult to grade because of the dysmorphism but often involves a massive volume of urine that may interfere with bladder dynamics and make the patient prone to urinary tract infection.

## BLADDER

In these patients the bladder usually has a large capacity. Most bladders feature a large diverticulum-like dome involving the area of the urachus (see Fig. 119-14). In those patients with urethral atresia, the dome may drain through a patent urachus at the umbilicus. Endoscopy shows that the wall of the bladder is usually smooth, not trabeculated. The ureteral orifices are often lateral and somewhat craniad. The orifices are often widely dilated, consistent with the massive reflux seen in most cases. The bladder neck is abnormally wide and funnels down into a dilated prostatic urethra. Grossly, the bladder wall is usually thick and quite vascular. The thickness of the bladder wall is not the result of hypertrophied muscle. Histologic examination reveals muscle and abundant collagen and fibrous tissue. The bladder will usually function as an adequate, if not enlarged, reservoir with good capacity and compliance, but it may not empty efficiently. Massive reflux, diminished detrusor contractility, decreased sensation of fullness, poor abdominal wall support, and diverticulum-like malformations at the dome all may serve to prevent normal emptying. Despite those problems, about half of such patients can void spontaneously.[56] Both spontaneous improvement and deterioration in the quality of voiding have been noted. Reducing the size of the bladder by excising the dome should be considered in some cases.[57,58] Domectomy can improve emptying and decrease postvoid residual urine in select cases.[80] Some children with prune-belly syndrome benefit from bladder emptying by intermittent catheterization.[56]

## URETHRA

In males with prune-belly syndrome, the dilation of the posterior urethra may be secondary to congenital deficiency of surrounding prostate tissue. The prostatic urethra appears heart shaped on voiding cystography. The external urethral sphincter is just below the apex. The narrowing of the prostatic urethra at the level of the external sphincter does not necessarily denote urethral obstruction, but some male patients have urethral atresia.[59] Those with urethral atresia who survive usually have a patent urachus that affords decompression of the urinary tract and allows for amniotic fluid needed for pulmonary development. Congenital urethral stenosis is also sometimes present. In the 45 males we have treated, true urethral valves were seen in 6; 20 had valvelike narrowing, usually at the level of a rudimentary verumontanum. Patients with poor bladder emptying may benefit from incision of such folds (Fig. 119-15). Besides atresia, the anterior urethra may be abnormal in the form of congenital megalourethra, the fusiform variant of which may distort development of all corpora in the phallus. Anterior urethral anomalies generally require surgical repair when present. Atresia may be repaired by open urethroplasty (Fig. 119-16), although progressive dilation may at times be effective.[60] Megalourethra is corrected by open tailoring of the urethral mucosa, which can be covered by the investing, periurethral tissue in several overlapping layers.

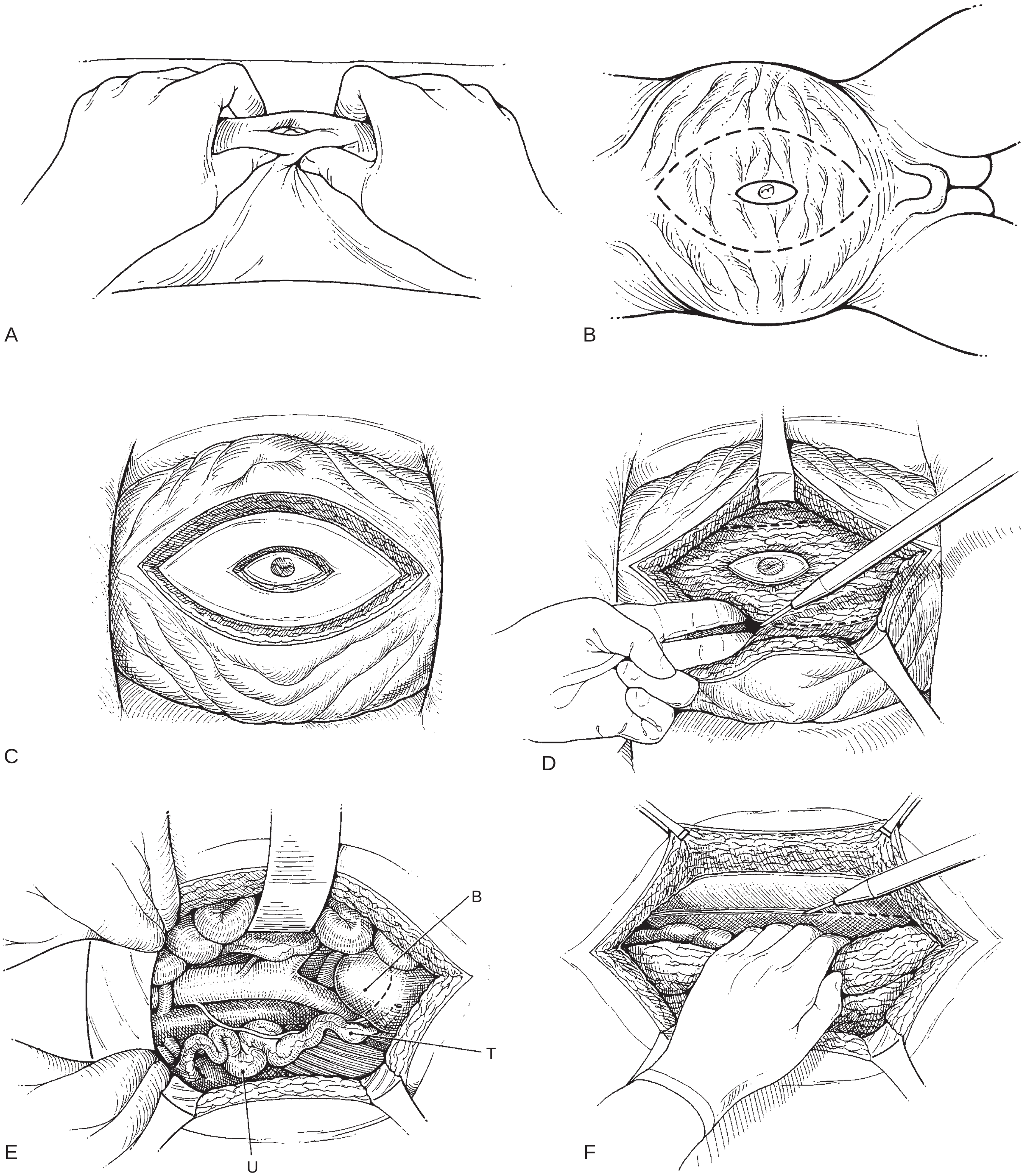


FIGURE 119-12 Surgical technique for Monfort abdominoplasty.[48,49] **A,** Delineation of redundancy by tenting up abdominal wall. **B,** Skin incisions are outlined with a separate circumscribing incision to isolate the umbilicus. **C,** Skin (epidermis and dermis only) is excised with electrocautery. **D,** Abdominal wall is incised at the lateral border of the rectus muscle on either side, creating a central musculofascial plate. **E,** Adequate exposure is provided for concomitant transperitoneal genitourinary procedures by retracting the central strip laterally. **F,** Completion of abdominoplasty by scoring of the parietal peritoneum underlying the lateral abdominal wall musculature with electrocautery.

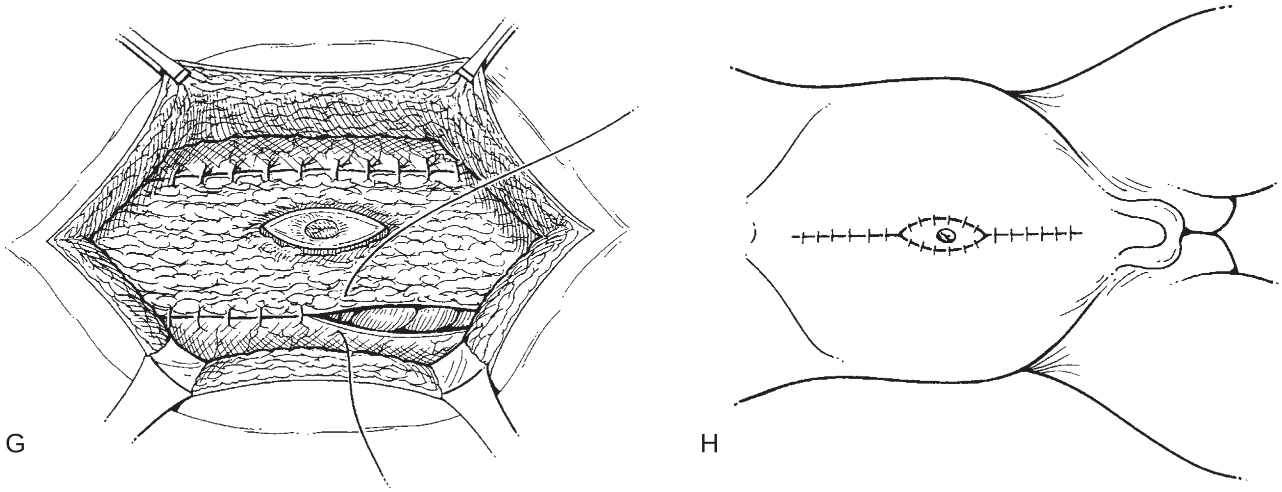


**FIGURE 119-12—CONT'D.** **G,** The edges of the central plate are sutured to the lateral abdominal wall musculature along the scored line. **H,** Lateral flaps are brought together in the midline, with closed suction drains placed between the lateral flaps and the central plate. Skin is brought together in the midline, enveloping the previously isolated umbilicus. (From Woodard JR, Perez LM: Prune-belly syndrome. In Marshall FF (ed): Operative Urology. Philadelphia, WB Saunders, 1996.)

## TESTES

Bilateral undescended testes lie in the abdomen in most males with prune-belly syndrome. The testes are usually smaller than normal and lie well inside the internal inguinal ring, much like ovaries in females. The spermatic vessels are shorter than normal, and there is often dysjunction of the epididymis from the testis. The vasa may be tortuous, and atresia of the vas is not uncommon. The pelvic peritoneum adjacent to the vas deferens usually has an abundant blood supply, which makes the Fowler-Stephens method of orchidopexy possible.[61] This technique involves dividing the spermatic vessels in the abdomen above the testis while mobilizing the testis with a broad strip of pelvic peritoneum and collateral blood supply surrounding the vas deferens. The goal of orchidopexy is to place the testes in the scrotum, where they can be monitored for development of malignancy and for psychologic reasons. Fertility has not been reported in these patients, although Leydig function leading to secondary sexual development with penile growth and libido is usually normal. Most surgeons have found that bringing a high testicle into the scrotum is easier in the young infant, in whom the relative distance is shorter.[62] Laparoscopic orchidopexy has been used for these patients[63] and may be particularly useful for a staged Fowler-Stephens technique. Access technique, insufflation pressure, and port stabilization may have to be modified because of the floppy abdominal wall.[64]

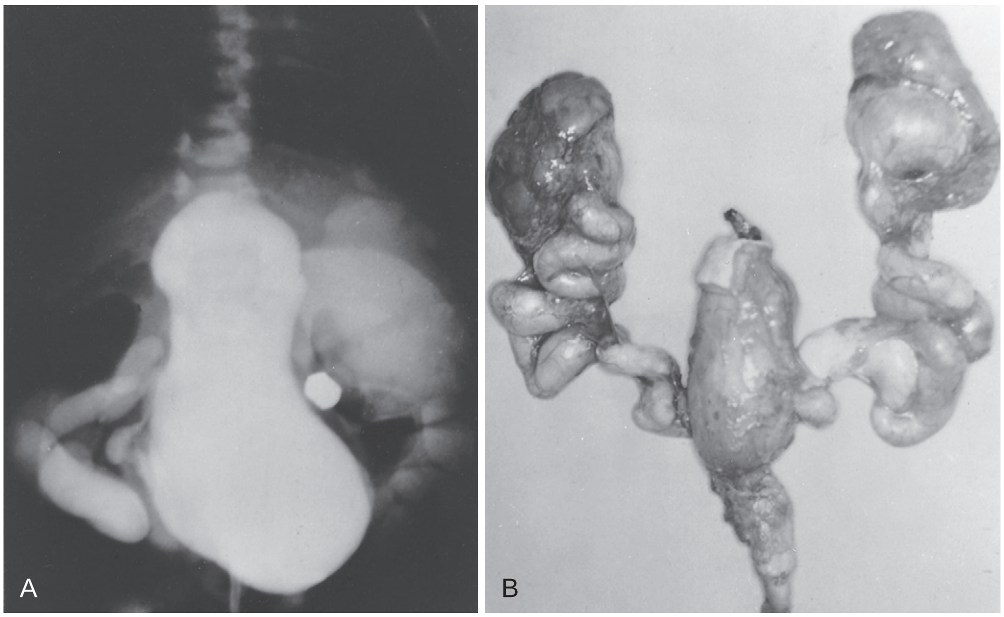


**FIGURE 119-13** Prune-belly syndrome in a neonate who died at 1 week of age with uremia. **A,** Cystogram showing large, elongated bladder with diverticulum-like dome, often seen in prune-belly syndrome. Massive reflux into dilated, convoluted ureters. **B,** Postmortem specimen of urinary tract. Note attachment of bladder to navel and cystic, dysplastic kidneys.

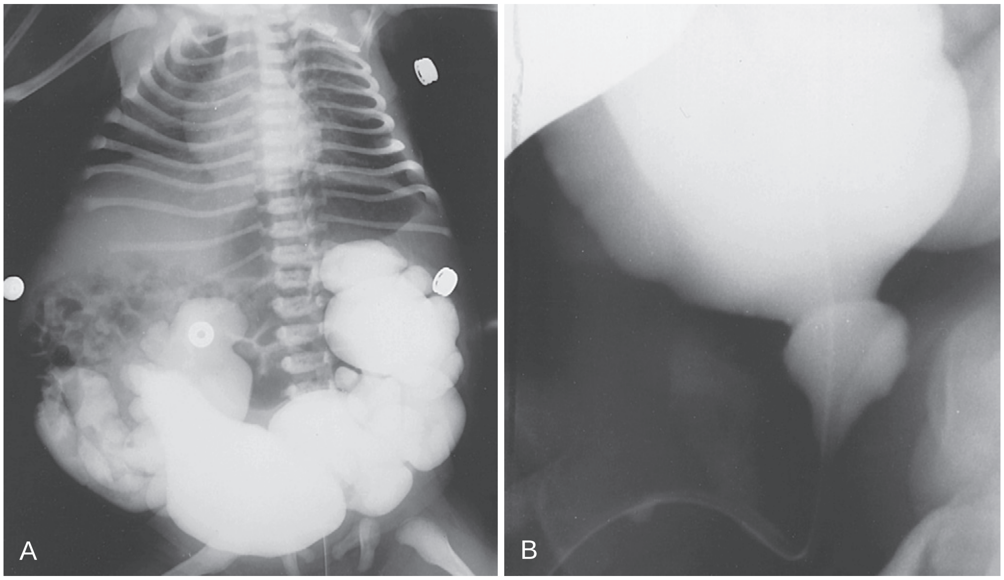


**FIGURE 119-14** Typical severe prune-belly case. **A,** Cystogram. Note large bladder, with appearance of an inverted light bulb and massive reflux into convoluted ureters. When straightened, the ureters were longer than the patient's legs. **B,** Cystourethrogram. Note smooth wall of bladder, open bladder neck, and heart-shaped urethra.

## OTHER ANOMALIES

Many patients with prune-belly syndrome have musculoskeletal or orthopedic abnormalities that require treatment.[65,66] Most of these patients have malrotation with nonfixation of the colon, but intestinal obstruction with midgut volvulus is extremely rare. Imperforate anus may be seen in prune-belly syndrome. All of the females we have treated for prune-belly syndrome have had cloacal malformations. Pulmonary hypoplasia is seen in some cases, and such severe cases are also prone to pulmonary infection. Pectus excavatum is common, and the abdominal wall musculature is weak. Various types of congenital heart disease may occur in association with prune-belly syndrome.

## CLINICAL MANAGEMENT

A newborn with prune-belly syndrome should be evaluated carefully because of the potential for sepsis. Any study that involves catheterization should be performed under cover of appropriate antibiotics and with meticulous aseptic technique. The dilated urinary tract, which may contain a large volume of urine and drain poorly, does not tolerate the introduction of bacteria. In some babies with poor renal function and dysplastic kidneys, early death from renal failure may be predestined due to associated pulmonary hypoplasia. Measurement of serum creatinine levels and, particularly, creatinine clearance identifies infants who have a reasonable measure of kidney function.

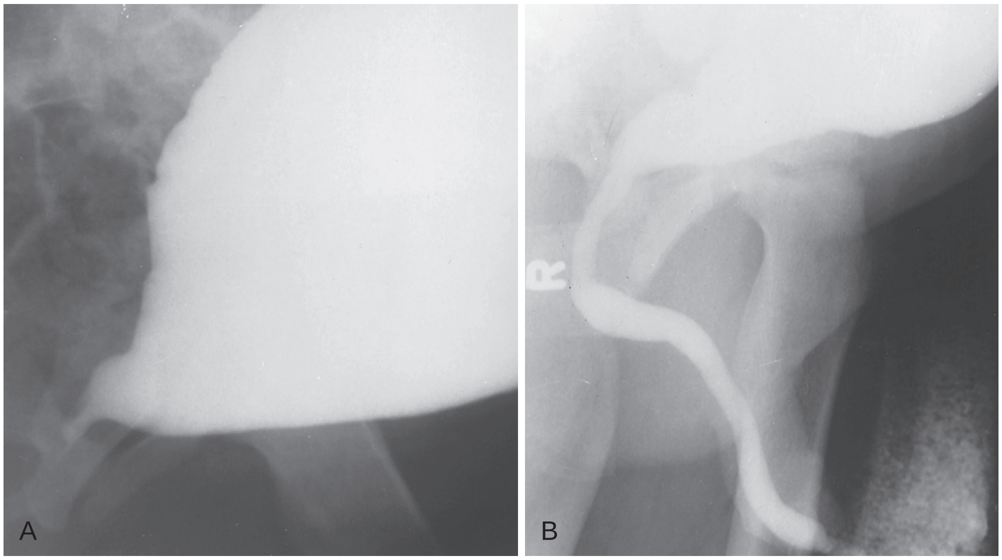


**FIGURE 119-15** Voiding urethrograms. **A,** Preoperative study showing typical dilated proximal urethra and wide bladder neck, with abrupt cutoff of contrast distal to rudimentary veru. There was a urethral valve. **B,** Postoperative study 7 months later showing free flow and normal caliber of the entire urethra.

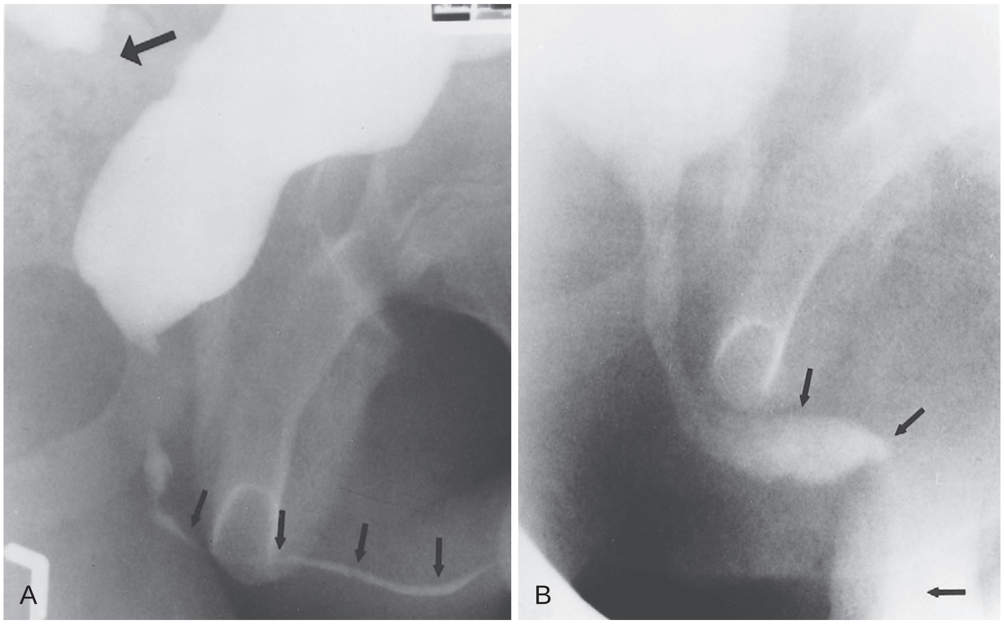


**FIGURE 119-16** Cystourethrograms. **A,** Preoperative. Note hypoplastic urethra (*small arrows*) and unusual obstruction of a megaureter by ureteral valve (*large arrow*). **B,** Postoperative study after long preputial patch graft to urethra.

Prune-belly syndrome in babies represents one of the most controversial conditions in pediatric urology. At one end of the therapeutic spectrum are those who advocate watchful waiting and minimal surgical intervention, citing a delicately balanced uropathy.[67–69] Others favor major reconstructive surgery when indicated.[8,57,70–76] It should be emphasized that reconstructive surgery in an infant with prune-belly syndrome should not be undertaken unless expert anesthesiology and medical support are available and the surgeon has extensive experience doing such surgery. Furthermore, a major reconstructive operation should not be considered unless the baby's overall status including pulmonary function and absence of established urinary tract infection is reasonable. Woodard and Zucker have suggested that an aggressive approach must be considered with caution because the surgery is difficult and the patients are vulnerable to pulmonary complications.[76]

Much of this controversy centers on the appropriate role for reconstruction of the urinary tract. There is little question that the intra-abdominal testes should be brought down by orchiopexy at an early age. Likewise, many patients and families will request reconstruction of the abdominal wall, for psychologic reasons if none other. It is our preference to perform such repairs at the same time as urinary tract reconstruction if necessary. If the patient will tolerate it from a pulmonary standpoint, we favor one longer reconstruction to repair everything rather than putting the same patient through multiple surgeries.

When initial evaluation demonstrates clear obstruction, correction should be performed whether it involves ureteropelvic junction, ureterovesical junction, or bladder outlet (Fig. 119-17). Most patients have some underlying renal dysplasia, and secondary insult from obstruction should not be allowed. It is our experience that most patients with this syndrome and vesicoureteral reflux eventually undergo repair. Classic grading systems for reflux may not apply to such patients; however, reflux in patients with prune-belly syndrome is often massive in volume. Early observation while the patient is on daily antibiotics to prevent infection may be appropriate and allow evaluation of bladder emptying or other issues. If reflux persists, correction is appropriate. When patients with reflux suffer breakthrough urinary tract infection or deterioration in renal function, repair of the reflux should be undertaken.

In considering the urinary system in patients with this syndrome, it may be useful to categorize them into three groups as described by Smith and Woodard.[77] The categories roughly correlate with the degree of renal dysplasia present. Group I patients usually have both severe renal dysplasia and pulmonary hypoplasia and do not survive. Urologic intervention will not rescue such patients. Group III patients generally have a mild or incomplete form of the syndrome and well-preserved renal function. Although some such patients may have impressive dilation of the urinary tract, little urologic intervention may be required if the patients do not suffer recurrent urinary tract infection. Definite indications for intervention in group II patients with intermediate degrees of dysplasia and renal dysfunction are less clear. These patients typically have full-blown features of the syndrome and a stagnant urinary system at best. Clearly, some such patients will progress to renal insufficiency with or without surgical intervention.[69,78] So many variables are present in patients with prune-belly syndrome that it remains difficult to predict the natural history for a given patient early in presentation. Careful surveillance is critical, and we favor surgical intervention in group II patients if they suffer from recurrent infection or deterioration of renal function. Those two problems often go hand in hand. We believe that correction of obstruction or reflux, optimizing bladder emptying, and avoidance of infection may prevent renal insufficiency in some patients with marginal function or, at least, prolong the time until they suffer insufficiency. It is clear that the scientific evidence to support such intervention, or argue against it, is largely anecdotal at this point.

We have performed reconstructive surgery on 40 patients with prune-belly syndrome; 12 were primary cases (Figs. 119-18 and 119-19), and 28 were secondary cases that had been previously treated with surgery elsewhere. Twenty-four of the latter 28 patients had undergone urinary diversion.[72,79] This illustrates how often urosepsis occurs in patients with prune-belly syndrome and has led to various types of surgery for diversion in the past (Fig. 119-20). We

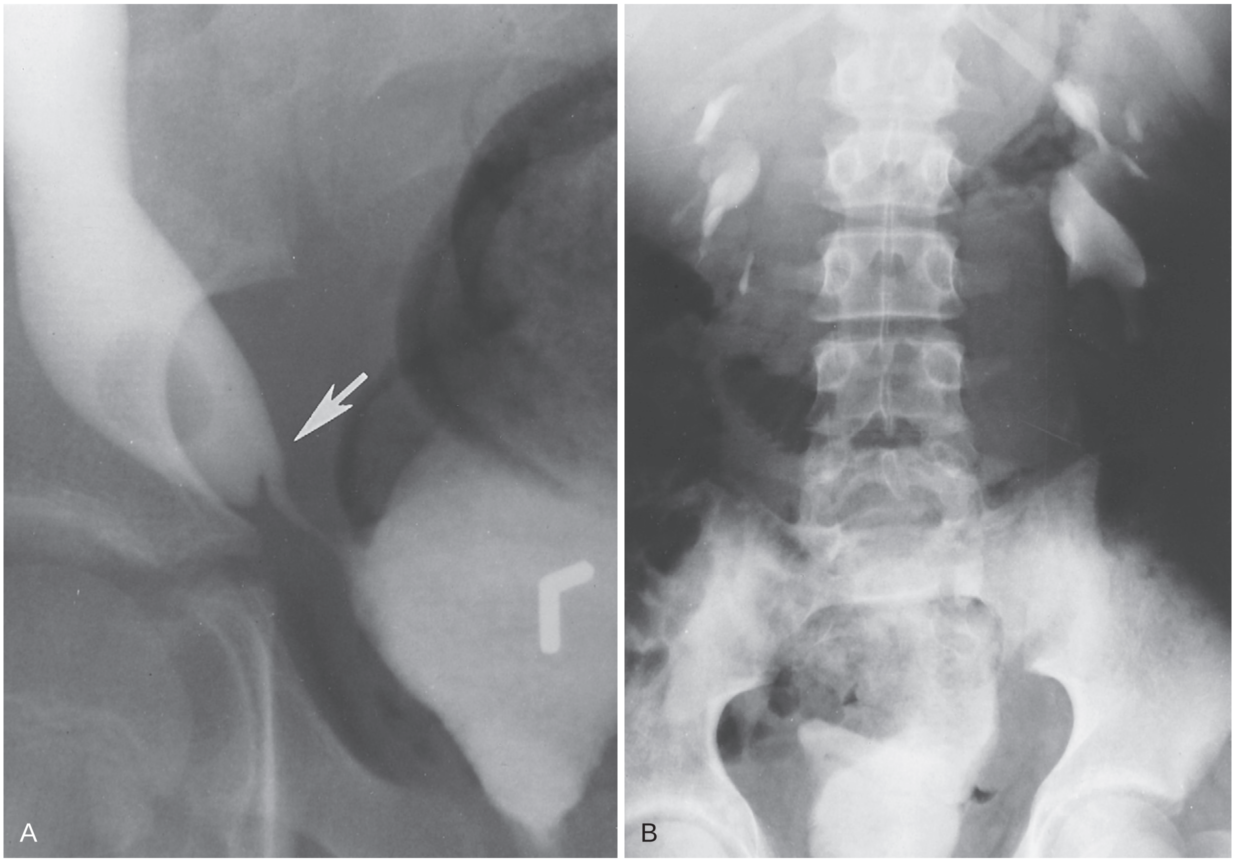


**FIGURE 119-17** Intravenous pyelograms from same patient shown in Figure 119-16. **A,** Ureteral valve in right megaureter (*arrow*). **B,** Intravenous pyelogram 3 years after extensive undiversion.

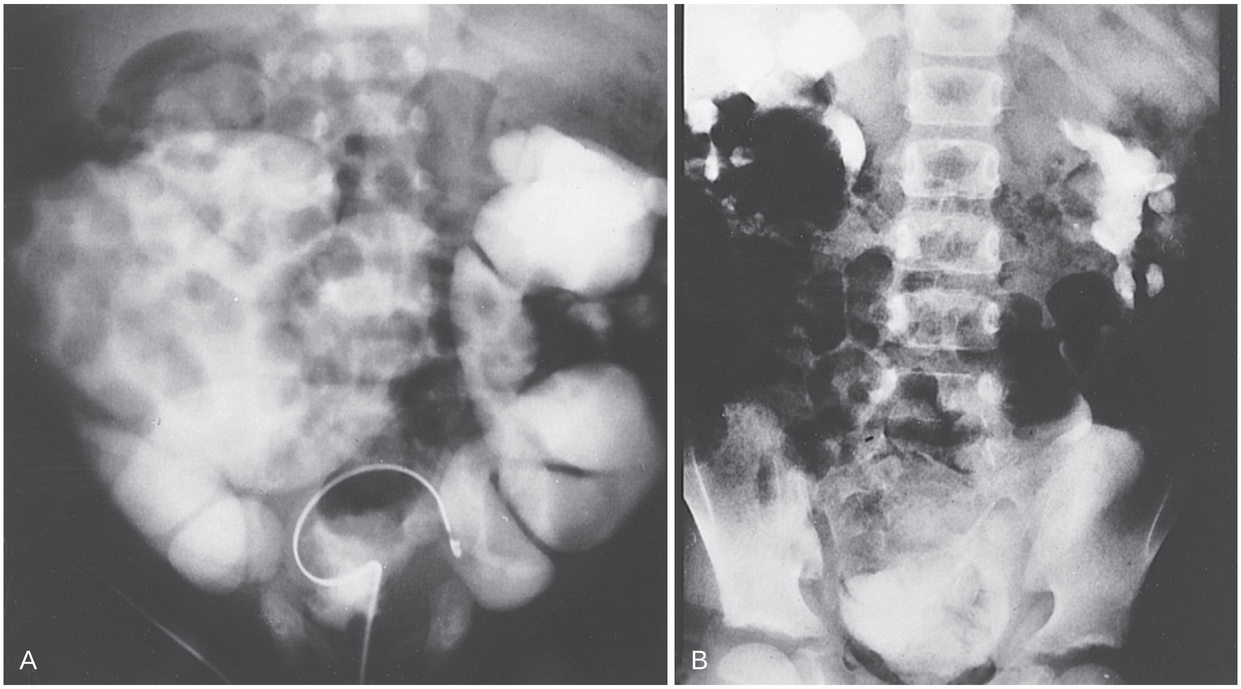


**FIGURE 119-18** Infant with prune-belly syndrome. **A,** Preoperative cystogram. There is massive bilateral reflux into elongated and tortuous ureters, especially on the right side. Note the dysmorphic collecting system of the left kidney. Total reconstruction was performed. **B,** Intravenous pyelogram at 7 years of age. The patient is well with no urinary tract symptoms. Note the contrast visible in the left ureter, which is of normal caliber. It is difficult to imagine that the great improvement in the appearance of the urinary tract does not equate with a better prognosis for the patient.

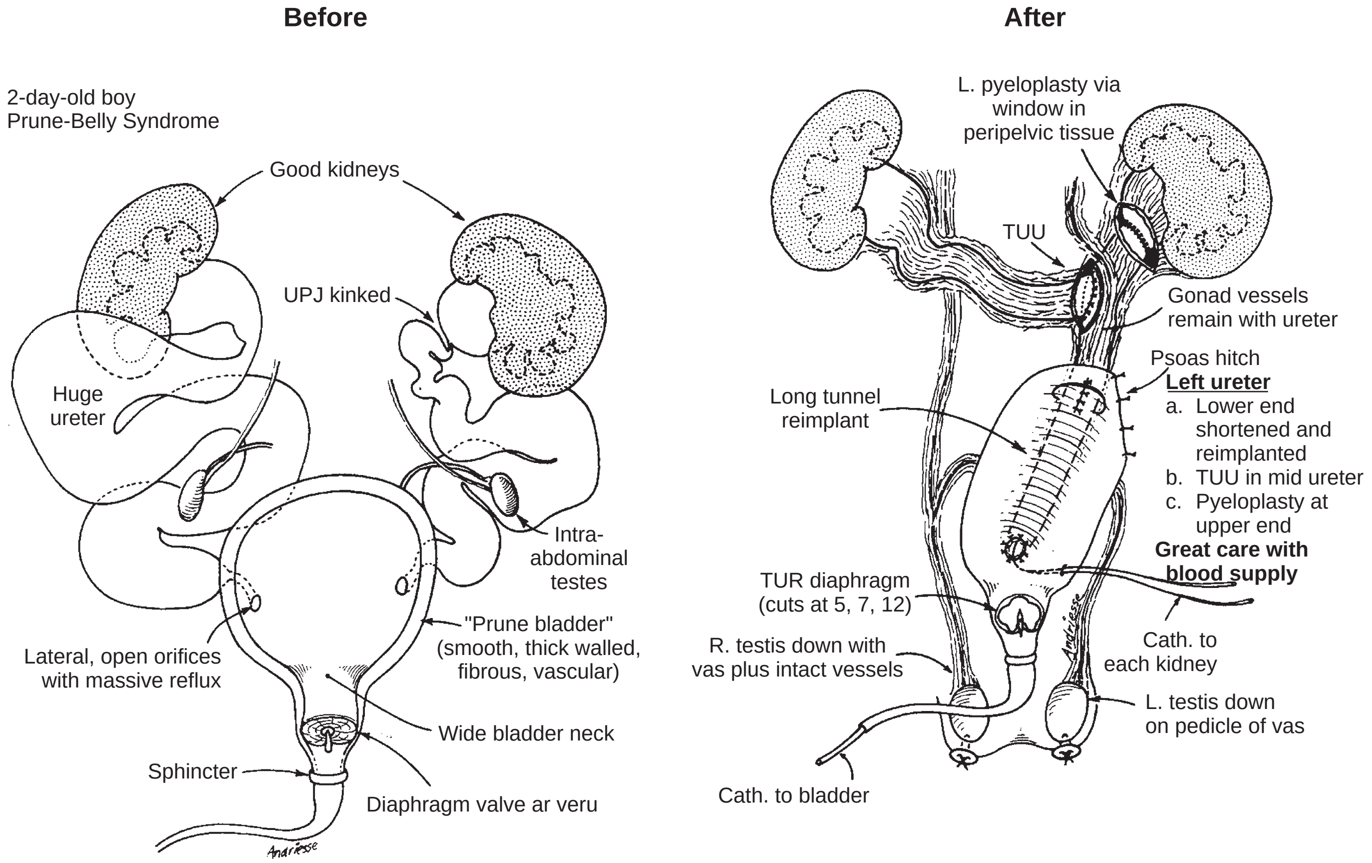


**FIGURE 119-19** Infant with prune-belly syndrome. Anatomy preoperatively and postoperatively.

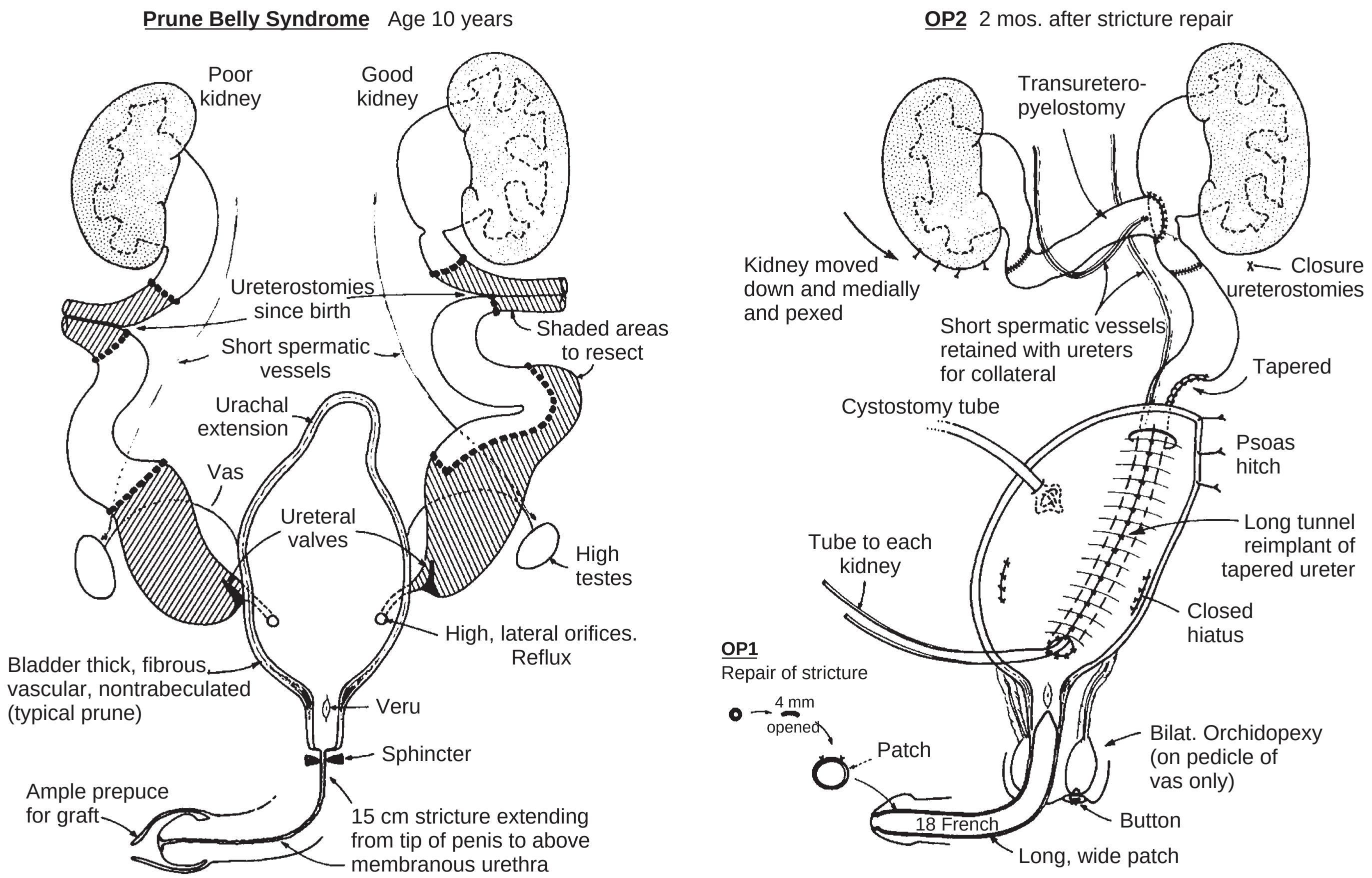


**FIGURE 119-20** 1-year-old boy with prune-belly syndrome, unusual anatomic findings, and long-standing ureterostomies. With operation 1, an extensive urethroplasty was performed with a long onlay of prepuce. Two months later, undiversion with urinary reconstruction and bilateral orchiopexies was performed. The patient voids normally and is continent. Renal function has been normal (serum creatinine 0.9 mg/dL and creatinine clearance 106 L/m$^2$ per day). Pyelograms are shown in Figure 119-17.

generally favor reconstruction over diversion in such patients as long as their general condition allows it. Twelve of these patients had only one kidney because of previous nephrectomy. Thirty-five of the 40 patients are alive (time since surgery, 1 to 27 years). Eight patients have had renal transplantation. Eight more will probably require renal transplantation, given their current renal function. Five patients have died. One infant died in the hospital because of blood loss secondary to hemophilia and inadequate monitoring. Another infant died at home 2 months after surgery of pulmonary aspiration. Three late deaths occurred: one 3 years after renal transplantation; another 10 years after successful transplantation, from an automobile accident; and one 11 years after reconstruction from septicemia during dialysis. It should be noted that this series is a select group and does not necessarily reflect rates of death from renal dysplasia in primary infants with prune-belly syndrome.

## Conclusions

Some of the most impressive megaureters are found in patients with prune-belly syndrome, and they are often then associated with other clinical problems. The philosophy of treating selective cases by aggressive surgical reconstruction is the opposite of the "watchful waiting" espoused by others. Surgical intervention is actually a conservative method in that it attempts to decrease stasis, urinary tract infection, and renal failure, the natural history of many patients with the syndrome. Reconstruction is demanding and technically difficult in these patients. It also requires extensive anesthesiology expertise to maintain metabolic hemostasis in a young child undergoing major reconstruction. This surgery should be performed in centers where surgeons concentrate on major reconstructive surgery and have access to all of the requisite back-up systems.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 120

# Bladder and Cloacal Exstrophy

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The authors would like to acknowledge Romano T. DeMarco and James A. O'Neill, Jr. for their previous contributions to this chapter.

## Bladder Exstrophy

Bladder exstrophy is a rare midline defect and exists as part of a larger spectrum of abdominal-pelvic fusion abnormalities, known collectively as the exstrophy-epispadias complex (EEC). Presentation of EEC can range from isolated glanular epispadias to cloacal exstrophy, in which several other organ systems may be affected. In the case of bladder exstrophy, the open bladder can be seen everting through a lower abdominal wall defect. This is accompanied by epispadias, a widened pubic diastasis, and an anus that is anteriorly displaced. Over the past 2 decades, continued improvements in the methods of functional bladder closure have dramatically increased reconstructive success rates; however, achieving the ultimate goals of adequate bladder capacity, urinary continence, and a good cosmetic outcome remain challenging.

### HISTORICAL PERSPECTIVES

The earliest account of bladder exstrophy can be found on Assyrian tablets, dating back to 2000 BC. Von Grafenberg first described the medical condition in 1597, and Mowat is credited with providing a complete description of bladder exstrophy in 1748. It was not until 1780, however, that Chaussier first coined the term "exstrophie."[1] Early management of bladder exstrophy included the application of an external urinary receptacle to the surface of the exposed bladder,[2] ureterosigmoidostomy,[3] transplantation of the bladder trigone into the rectum,[4] and coverage of the exposed bladder with lateral skin flaps.[5] These methods were fraught with continued urinary incontinence and/or urosepsis. Contributions by Coffey, Nesbitt, Leadbetter, and Clarke improved the technique of ureterosigmoidostomy; however, associated morbidities included infection, electrolyte abnormalities, and malignancy.[6] Complete urinary diversion into the colon or alternate conduit was preferentially used to provide continence and minimize infection, but the problems of anatomic reconstruction and sexual function persisted.

Paralleling efforts to develop improved methods of urinary diversion were attempts at successful bladder closure. Trendelenburg described bilateral sacroiliac osteotomies and the application of a pelvic sling to support bladder and abdominal wall closure in 1892.[7] The first case of successful closure and continence in a female patient with bladder exstrophy was not reported until 1942 by Young.[8] Michon subsequently reported successful reconstruction in a male patient 6 years later.[9] Despite these accounts of functional closure, a 1970 review of 329 cases by Marshall and Muecke concluded that only 19% of patients undergoing total reconstruction had fair-to-satisfactory results.[10] These unfavorable outcomes were reported by others, spurring efforts to improve methods of surgical repair.[11,12]

### EPIDEMIOLOGY

The incidence of bladder exstrophy is estimated at between 1 in 10,000 and 1 in 50,000 live births[13] with a higher male-to-female ratio of between 2.3:1 and 4:1.[14] Familial recurrence is approximately 1 in 100.[15] On the basis of a survey of 2500 indexed cases, familiar occurrence was found to be 1 in 275.[14] Multiple reports of bladder exstrophy among identical twins have demonstrated variability in involvement of one or both twins. Subsequent siblings and the offspring of individuals with bladder exstrophy may be at increased risk of being affected.[14,15] However, no clear pattern of inheritance has been characterized and no specific genetic or environmental factor that predisposes to bladder exstrophy has yet been identified.

### EMBRYOLOGY

The underlying embryologic defect shared by bladder exstrophy and other variants of the EEC is due to abnormal development of the cloacal membrane, a bilaminar structure composed of endoderm and ectoderm that overlies the cloacal cavity at the caudal end of the germinal disk.[16] In normal

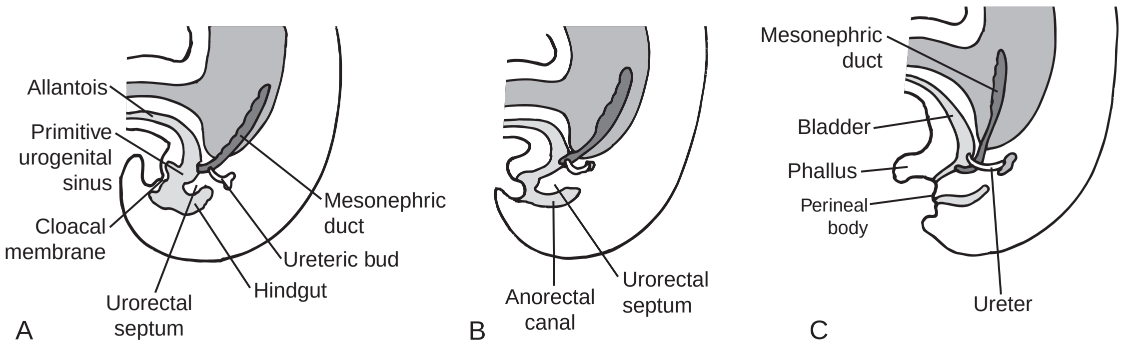


**FIGURE 120-1** Division of the cloaca in the urogenital sinus and rectum. **A,** At the end of the fifth week. **B,** At 7 weeks. **C,** At 8 weeks. (Modified from Sadler TW: Langman's Medical Embryology, 8th ed. Philadelphia, Lippincott Williams and Wilkins, 2000, p 316.)

development, lateral ingrowth of mesoderm occurs between the two layers of the cloacal membrane during the fourth and fifth weeks of gestation. This results in formation of the lower abdominal wall and pelvis. Subsequent caudal growth of the urorectal septum results in its fusion with the cloacal membrane, thus fully separating the cloaca into the bladder anteriorly and the rectum posteriorly (Fig. 120-1). The paired genital tubercles, which will give rise to the phallus, migrate medially to fuse in the midline. Normal perforation of the cloacal membrane occurs *after* fusion with the urorectal septum, at approximately the sixth week, resulting in formation of separate urogenital and anal openings.[17]

Migratory failure of the lateral mesodermal folds and abnormal overdevelopment of the cloacal membrane have both been proposed as potential causes of the prevention of normal mesodermal ingrowth to the cloacal membrane.[16,18] The lack of adequate mesodermal reinforcement is thought to result in *premature* rupture of the cloacal membrane, the timing of which determines the extent of the abdominal wall defect and degree/severity of urogenital tract involvement.[19] Rupture of the cloacal membrane after fusion with the urorectal septum results in bladder exstrophy, whereas rupture before fusion gives rise to the more severe presentation of cloacal exstrophy (see later discussion).

## CLINICAL PRESENTATION

In general infants with bladder exstrophy are born full term, without coexisting anatomic anomalies. At birth, an everted posterior bladder plate of varying size is seen in the midline of the lower abdomen. The mucosa of the exposed bladder in the newborn is typically smooth and pink. The umbilical cord exits from the superior-most border of the bladder plate, and a small umbilical hernia may be present (Fig. 120-2). In addition, there is significant widening of the pubic symphysis and the anus is anteriorly displaced. The levator ani complex is also divergent, leading to an inherent weakness in the pelvic floor and a tendency toward rectal prolapse and varying degrees of fecal incontinence. Associated inguinal hernias are common and have been reported in 82% of boys and 10% of girls.[20] The upper urinary tract is usually normal, though renal anomalies including ectopic, horseshoe, hypoplastic, dysplastic kidneys, and megaureters may be observed.[21] Vesicoureteral reflux occurs in the vast majority of children after bladder closure, secondary to an exaggerated lateral course of the ureters within the pelvis and lack of adequate submucosal tunnel in the bladder wall.[22] With continued exposure and chronic inflammation, the exstrophied bladder becomes thickened and polypoid (Fig. 120-3). Long-term exposure may eventually result in a fibrotic, rigid bladder plate that is ultimately unsuitable for closure.

## GENITAL DEFECTS—MALE

In the male infant, the open and everted urethral plate can be seen joining the exposed bladder. The penis is characteristically short with a flattened, everted glans. The prepuce is located on the penile ventrum (Fig. 120-4). The ejaculatory ducts are typically normal and exit at the exposed verumontanum in the posterior urethra. The base of the penis and scrotum are widely separated, with lateral displacement of the corporal bodies and neurovascular bundles. Historically it was believed that the individual corpora were of normal caliber and appeared shortened because of their attachment to the widened pubic diastasis and associated dorsal chordee.

**FIGURE 120-2** Typical findings of classic bladder exstrophy in a newborn male. The bladder plate is small, and a small hernia is evident at its superior border. The penis is foreshortened, with widely splayed corporal bodies and glanular separation. The urethral plate is short and located on the anterior surface of the split phallus.

FIGURE 120-3 When the bladder has been exposed for at least 1 week after birth and the mucosa is subjected to continued exposure and inflammation, polypoid excrescences typically appear, as in this female infant.

More recently, an MRI-based study by Silver and colleagues of adult men with exstrophy and age-matched controls found that although the length of the posterior corporal bodies was the same between groups, anterior corporal length in men with exstrophy was nearly 50% shorter than that of controls.[23] Therefore the penis appears shortened not only secondary to corporal divergence, dorsal chordee, and abnormal crural attachments to the corpora cavernosa but also because of an inherent deficiency of corporal tissue (Fig. 120-5). The testes may appear to be undescended, but in most cases they are actually retractile and will eventually reside in the scrotum without the need for formal orchiopexy. Should it be required, orchiopexy is performed in conjunction with inguinal hernia repair.

## GENITAL DEFECTS—FEMALE

The clitoris is bifid, with divergence of the mons pubis, labia, and clitoral halves (Fig. 120-6). The urethra and vagina are shortened, and the introitus is anteriorly displaced. The vaginal orifice is often stenotic. The uterus and adnexa are typically normal, though vaginal and uterine duplication have been reported.[24,25] Uterine prolapse occurs commonly in female patients, secondary to the inherent weakness in pelvic floor support.

## PELVIC DEFECTS

Some degree of widening of the pubic symphysis is present in all cases of bladder exstrophy and contributes to outward rotation and eversion of the pubic rami at their junctions with the ischial and iliac bones (Fig. 120-7). Using computed tomography (CT), Sponseller and colleagues further characterized the pelvic anatomy of a large group of exstrophy patients, noting a significantly increased distance between the triradiate cartilages (31%), external rotation of the anterior pelvis (18%), and 30% shortening of the pubic rami.[26] On the basis of three-dimensional models generated by CT, Stec and colleagues observed that among children with exstrophy, the levator ani muscles were more posteriorly positioned and outwardly rotated. Furthermore, the puborectal sling had a more flattened configuration and supported twice the body cavity area in exstrophy patients.[27] As mentioned previously, these pelvic floor defects predispose to pelvic organ and rectal prolapse in this patient population.

## PRENATAL DIAGNOSIS

The use of prenatal ultrasound (US) and MRI has improved the antenatal diagnosis of bladder exstrophy, allowing for appropriate parental counseling and planning of postnatal management. The prenatal diagnosis of bladder exstrophy may be suggested on US by failure to visualize the bladder in the presence of normal kidneys and amniotic fluid.[28–30] In a review of prenatal US studies from 25 women who delivered infants

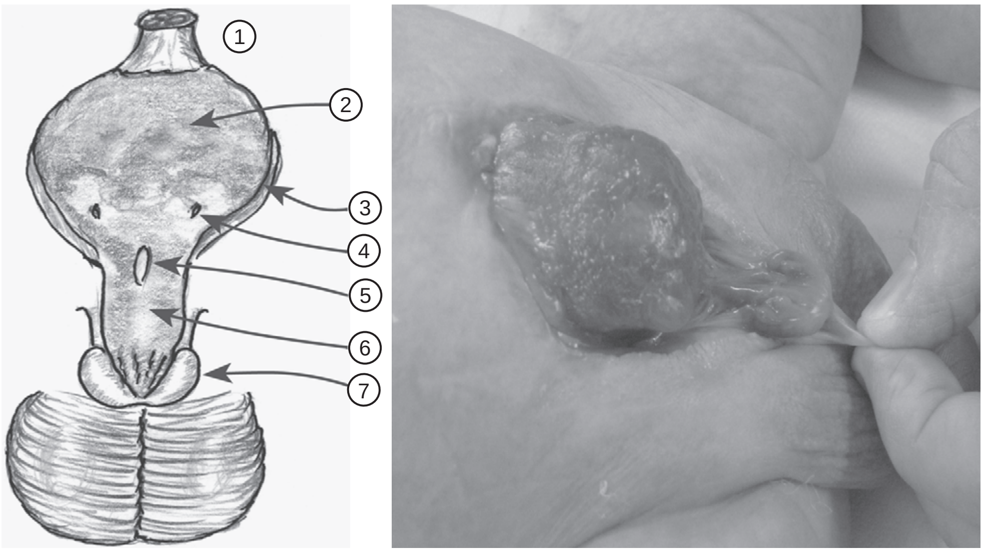


FIGURE 120-4 Classic exstrophy in the male. The penis is pulled downward to expose the dorsal aspect, revealing the urethral plate leading to the exposed bladder. *1,* umbilical cord; *2,* bladder mucosa; *3,* paraexstrophy tissues; *4,* left ureteric orifice; *5,* verumontanum; *6,* urethral plate; *7,* glans penis.

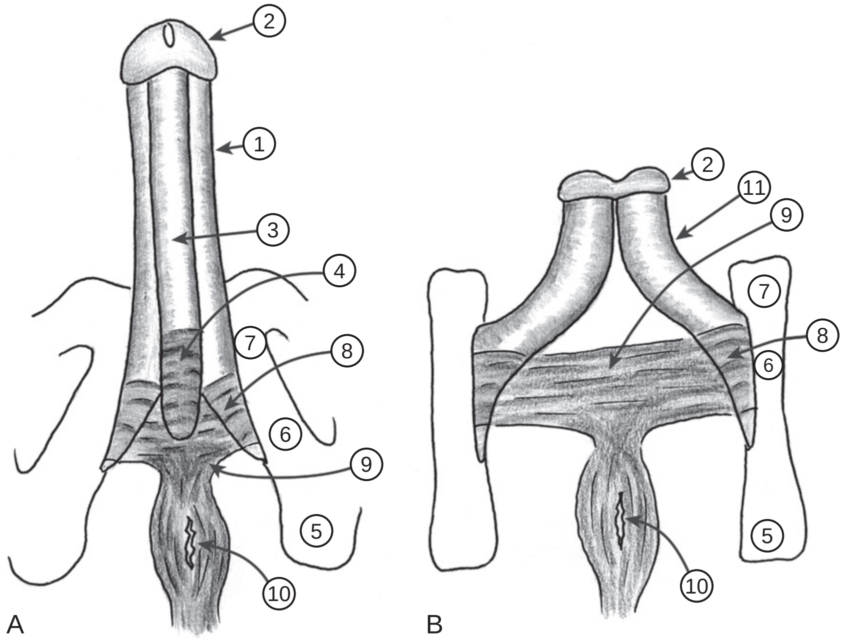


**FIGURE 120-5** Penile configuration in classic bladder exstrophy. Normal male perineum **(A)** and with bladder exstrophy **(B).** Note the loss of the normal triangular shape of the perineum and widening of the pubic symphysis. In the setting of exstrophy, the corpora cavernosa are widely separated and are intrinsically shorter. *1,* corpus cavernosum of the penis; *2,* glans penis; *3,* corpus spongiosum; *4,* bulbospongiosus muscle; *5,* ischium; *6,* ischiopubic ramus; *7,* pubis; *8,* ischio-cavernosus muscle and crus of penis; *9,* urogenital diaphragm; *10,* anus and external anal sphincter.

with exstrophy, Gearhart and colleagues observed the following features: absent bladder (71%), lower abdominal bulge (47%) and anteriorly displaced scrotum with small phallus in male fetuses (57%), low-set umbilical cord (29%), and abnormal widening of the iliac crest (18%).[31]

## SURGICAL RECONSTRUCTION

Surgical management of classic bladder exstrophy consists of functional closure of the native bladder, closure of the epispadic urethra and genitalia, and creation of a continence mechanism to allow for proper urine storage. Reconstruction may be accomplished in a multi- or single-stage (complete) repair. Multiple contemporary approaches including the modern staged reconstruction of exstrophy (MSRE) and complete primary reconstruction of exstrophy (CPRE) along with Warsaw,[32] Erlangen,[24] Mainz,[33] and Kelly[34] techniques have been published; however, for the purposes of this review, only the major principles of MRSE and CPRE are discussed.

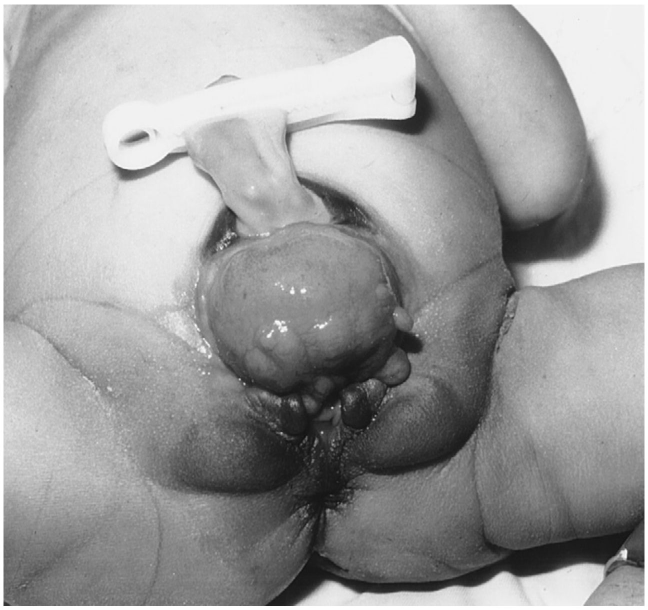

**FIGURE 120-6** Typical appearance of classic bladder exstrophy in a female. Note the widely divergent labia and anterior displacement of the vaginal introitus and anus.

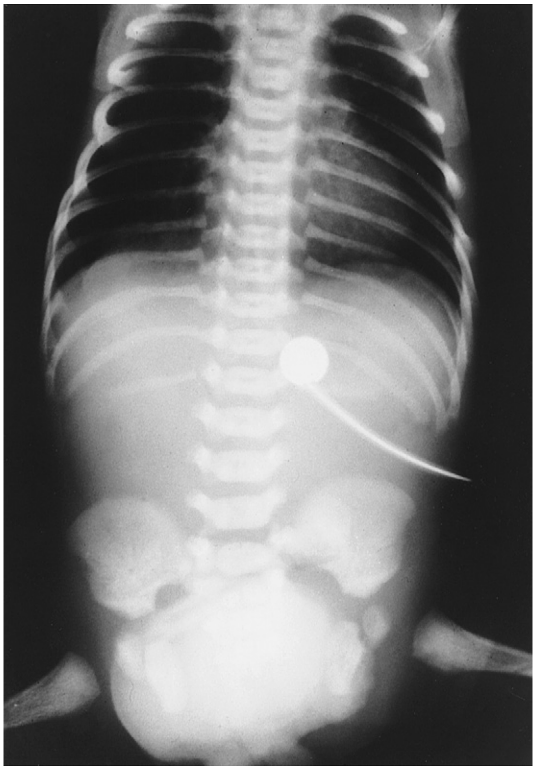

**FIGURE 120-7** Plain radiograph of a neonate with bladder exstrophy demonstrates the soft tissue mass effect of the exposed bladder, the wide diastasis of the symphysis pubis, and the posterior rotation of the acetabula.

## INITIAL MANAGEMENT

At birth, the umbilical cord should be ligated with a silk suture to avoid irritation of the bladder surface from the traditional plastic clip. The exposed bladder mucosa should be moistened with saline and protected with a nonadherent sheet of plastic wrap (e.g., Saran Wrap). A complete physical examination is performed to rule out associated anomalies and to assess the size of the bladder plate and extent of the genital defect. Renal US may be obtained to exclude hydronephrosis and/or other upper tract abnormalities. Prophylactic antibiotics should be administered.

## MODERN STAGED RECONSTRUCTION OF BLADDER EXSTROPHY

A three-stage approach for the treatment of bladder exstrophy was first pioneered by Jeffs and Cendron in the 1970s,[35,36] and continued improvements in technique have contributed to increased success of the procedure.[37–39] Stage 1 is performed at birth to protect the upper urinary tracts and assist later continent reconstruction. It consists of early closure of the bladder, posterior urethra, and abdominal wall with or without osteotomy. The primary objective of functional closure is to convert the bladder exstrophy into a complete epispadias.[40] Stage 2 is performed in later infancy and involves repair of the epispadias, with the goal of optimizing genital function and appearance, as well as increasing outlet resistance to promote bladder growth. Stage 3 is undertaken before school age and consists of bladder neck repair for continence and ureteral reimplantation for vesicoureteral reflux.

Primary functional closure is generally undertaken in the neonatal period, which offers several potential advantages. The pliability of the pelvic ring, in infants younger than 72 hours old, may obviate the need for osteotomy; early closure prevents further exposure and scarring of the bladder plate; there is theoretically less opportunity for bacterial colonization of the plate with decreased risk of postoperative infection. Alternatively, delayed closure in combination with pelvic osteotomy may be performed, allowing for patient growth and a period of time out of the hospital before reconstruction.

### Stage 1: Functional Closure

At the time of surgery, the patient should be prepped widely including the entire body anteriorly and posteriorly below the nipple line so that intraoperative turning is easier. Cardiopulmonary monitoring and adequate intravenous access are critical. Intraoperative and postoperative analgesia may be afforded by means of an epidural catheter. The most common technique of functional closure is based on descriptions by Jeffs and colleagues[36,41,42] and Duckett and Caldamone.[43] Figure 120-8 depicts the initial incisional template for bladder closure in the female infant, and Figure 120-9 details the complete sequence of stage 1 closure in the male. Traction sutures are placed into the glans penis, and ureteral catheters are secured in each ureteral orifice. An incision is made around the periphery of the exstrophic bladder plate, and a plane of dissection is established between the rectus fascia and bladder. The umbilical cord is excised, and umbilicoplasty may be performed during or after the initial procedure. Dissection is continued toward the pubis, and the incision is then extended

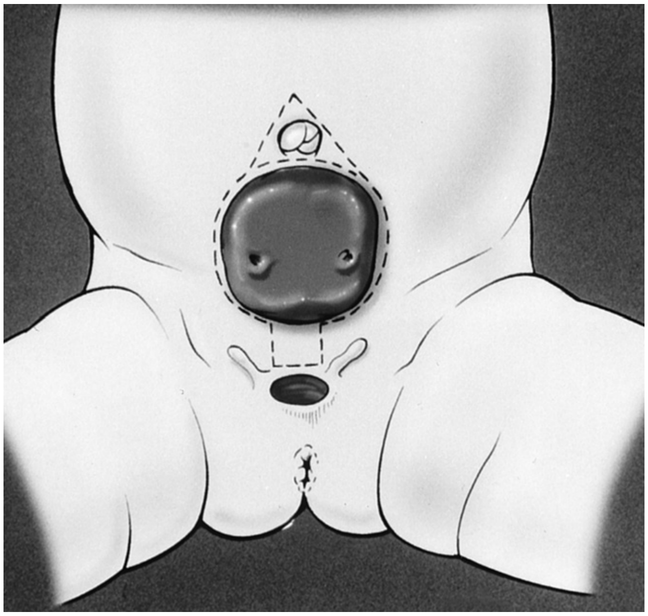

FIGURE 120-8 Typical findings of classic bladder exstrophy in a female and the incision template used for repair.

distally to the verumontanum on both sides of the prostatic urethra, leaving a wide strip of bladder neck and urethral plate.

A major objective of primary closure in the male patient is to place the bladder and prostate deep within the pelvis to achieve a more normal anatomic position.[44,45] In some boys, this maneuver results in inadequate length of the urethral plate for subsequent penile reconstruction. Duckett therefore proposed transection of the urethral plate, distal to the verumontanum, with the development of lateral paraexstrophic skin flaps, which could be then rotated medially to bridge the gap between the transected edges of the urethra.[46] Although this technique allows for better mobilization of the bladder, Gearhart and colleagues[41,47] reported a 40% complication rate associated with the use of paraexstrophy flaps. Urethral stricture is the most common complication and may be secondary to local tissue ischemia. The routine use of such flaps appears to be decreasing, though their application remains a viable option when a short urethral plate prohibits adequate bladder mobilization.[48]

If the urethral plate is left intact, it should be mobilized to the level of the prostate to create as much urethral length as possible. Following complete mobilization of the bladder, the corpora cavernosa are dissected off the inferior pubic rami bilaterally, taking care to preserve the neurovascular bundles and avoid penile devascularization. This maneuver aids in penile lengthening, primarily through release of dorsal chordee.[23] After placement of a Malecot suprapubic tube and exteriorization of the ureteral catheters, the bladder is closed anteriorly in the midline and the urethra tubularized over a 10- to 12-Fr sound. The first-stage repair thus results in an isolated penopubic epispadias, which is generally incontinent.

Closure of the pelvic ring is required to assist in abdominal wall closure. Pubic approximation without ancillary osteotomy may be possible in the immediate newborn period, when the bones are still malleable; however, osteotomy is generally required after 3 days of age. Although multiple techniques are

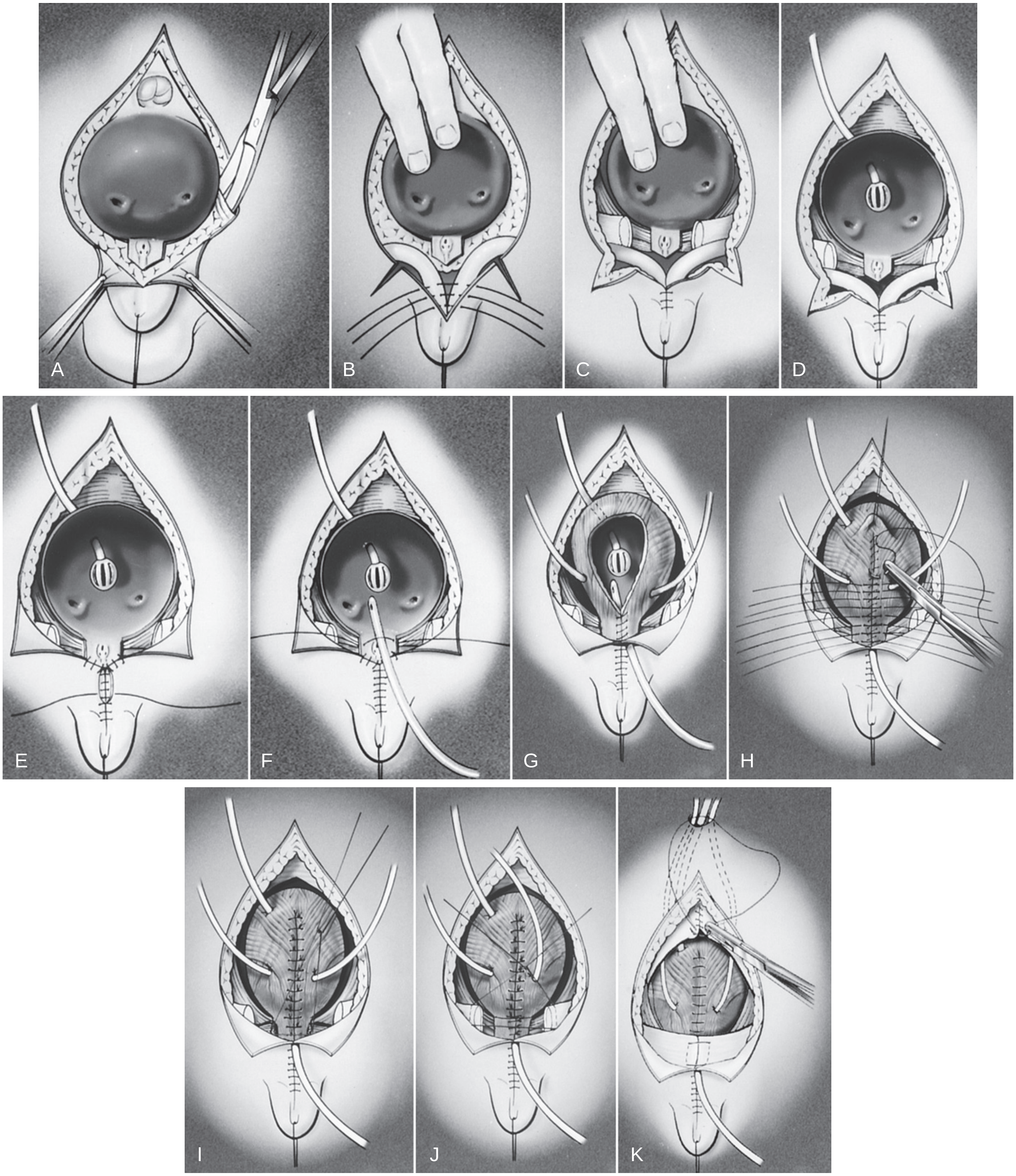


**FIGURE 120-9** Sequence of repair of bladder exstrophy in a male. **A**, Completion of the dissection around the periphery of the bladder and the urethral plate. **B**, Inversion of the bladder plate and approximation of the corpora as a first stage in epispadias repair. Also note the inferior paraexstrophy incisions. **C**, Further closure of the skin over the corpora and their partial freeing from the pubis. **D**, Placement of a suprapubic drainage tube. **E**, Further closure of the skin inferiorly, with approximation to the urethral plate. Creation of the paraexstrophy flaps is now evident. **F**, The urethral plate is prepared for tubularization over a catheter. **G**, The urethral plate is now tubularized, and ureteral catheters are placed bilaterally and brought out on each side of the bladder. The bladder is also in the process of being tubularized. **H**, Completion of tubularization of the bladder and urethra, and location of the various drainage tubes. **I**, After two-layer closure of the bladder and urethral plate, the bladder is reduced into the pelvis and fixed with sutures. **J**, Sutures are placed to encourage approximation of the pubic halves. **K**, Drainage tubes are brought out superiorly, and fascia, subcutaneous tissue, and skin are approximated. Approximation of the pubis helps protect the bladder closure and the abdominal wall closure.

described, combined bilateral anterior innominate and vertical iliac osteotomy is most frequently used to assist symphyseal approximation and medial rotation of the pelvic bones.[49] Fixator pins are then placed into the iliac wings and lower osteotomized segments. Our group generally used bilateral anterior iliac osteotomies (Fig. 120-10). Closure of the pelvic ring is performed using a large-sized, monofilament suture, taking care to place the knot anteriorly to avoid erosion into the soft tissue below. The newly closed bladder and urethra can now be covered by reapproximation of the rectus fascia and skin, with externalization of tubes and drains. External fixators are applied to the pins to hold the pelvis in the correct configuration. Lower extremity traction is applied to keep the legs still and prevent destabilization of the pelvis (Fig. 120-11). The external fixator remains in place for 4 to 6 weeks after surgery, allowing for callus formation at the osteotomy sites. As an alternative to external fixation, immobilization may also be accomplished through the application of a spica cast, which envelops the hips and lower extremities. The cast remains in place for 4 to 6 weeks.

The technique for initial closure in a female patient is similar to that described previously. The traction suture is initially placed anterior to the vagina, which is fully mobilized, as the neourethra is tubularized. The vagina is then repositioned to create a more caudal angle of entry.

Postoperatively, the patient is maintained on antibiotic prophylaxis. Parenteral nutrition may be used initially in order to avoid abdominal distension. Close attention must be given to patient positioning and fixator pin sites to minimize the risk of skin ulceration and nerve injury.

### Stage 2: Epispadias Repair

The second stage of repair is generally undertaken between 6 and 12 months of age. It centers on reconstruction of the phallus, with repair of epispadias and urethroplasty. This may further optimize bladder capacity, through an increase in outlet resistance.[50] Although many techniques have been used, the method described by Cantwell and later modified by Ransley has been shown effective in accomplishing urethral relocation to the penile ventrum, correction of chordee, and a

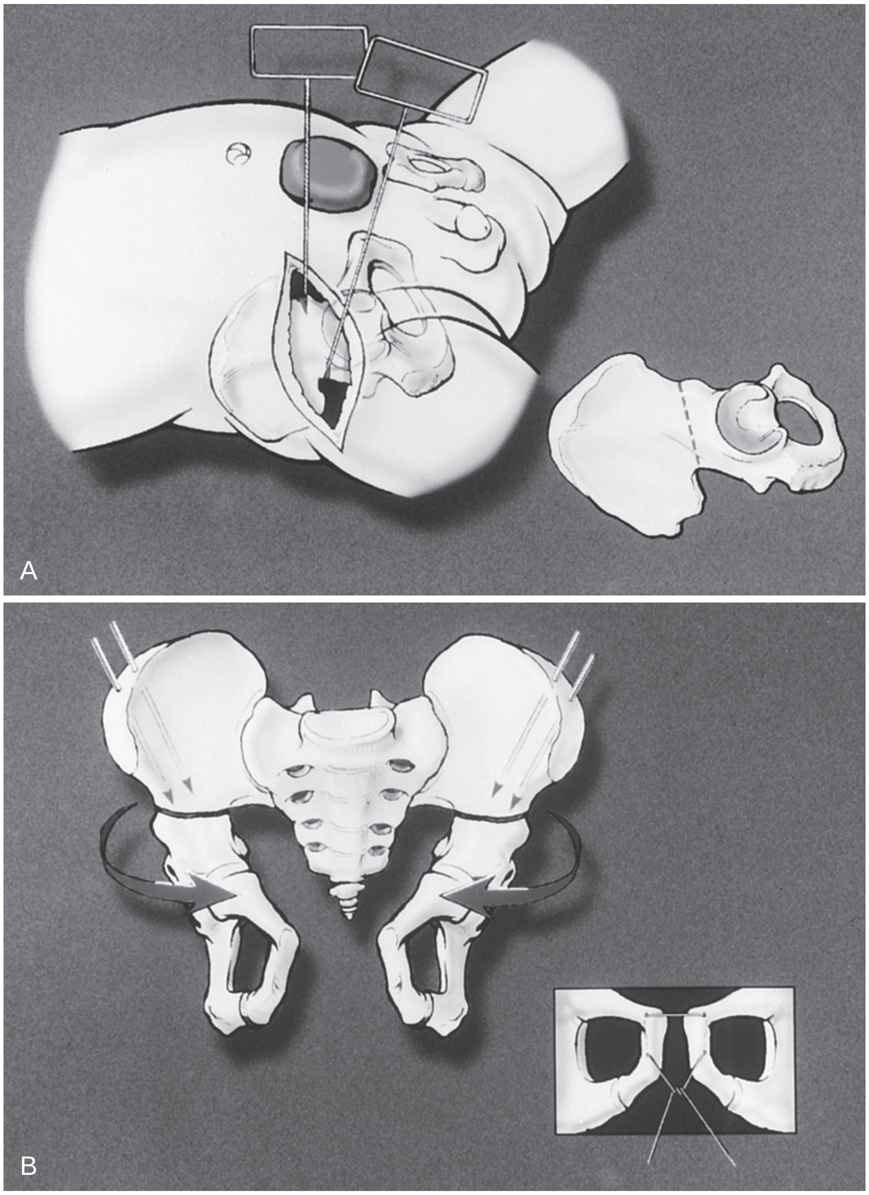


**FIGURE 120-10** **A,** If the pubis cannot be approximated in a newborn or if the procedure is undertaken later, when the pelvis is less flexible, pelvic osteotomy is required. The location of an anterior iliac osteotomy is shown. **B,** External fixator pins are used to hold the pelvis, and the pubic halves are brought together in the midline.

**FIGURE 120-11** An infant in Bryant's traction. The patient must remain immobilized for 4 to 6 weeks postoperatively.

low fistula rate (Fig. 120-12).[51,52] This technique involves full mobilization of the corpora and dorsal urethral plate, which is dissected free and tubularized. Correction of dorsal chordee is achieved by incising each corpora transversely, creating diamond-shaped defects and anastomosing their dorsal medial aspects over the tubularized urethra. A ventral meatotomy is then performed at the tip of the glans to produce a more anatomically normal meatal position.[53] Other described modifications of the Cantwell-Ransley technique include full detachment of the urethral plate from the corporal bodies, leaving only the distal-most 1 cm of urethra attached to the glans tip. The urethra is then tubularized, the corpora are incised transversely at the point of maximum dorsal curvature, and the corporocavernostomy defects sutured together, thus covering neourethra. This maneuver places the urethra ventrally between the corporal bodies, causes downward deflection of the penis, and also provides extra length. If chordee is correctable by simple corporal rotation, bilateral corporotomies are not required. The glansplasty is completed in two layers, resulting in a ventrally placed neourethra.[54] Further modifications to the technique of epispadias repair include the use of full penile disassembly described by Mitchell and Bagli (Fig. 120-13).[55]

### Stage 3: Bladder Neck Reconstruction and Ureteroneocystostomy

The final stage of exstrophy repair involves the construction of a urinary continence mechanism and is generally undertaken around 4 years of age.[56] During this interval, the patient is monitored periodically with renal US to evaluate the adequacy of upper tract drainage. Bladder capacity is also assessed before bladder neck surgery. Jeffs and colleagues[57] reported that a bladder capacity of greater than 60 mL typically allows for adequate functional storage capacity without the need for concomitant bladder augmentation, although others have reported median capacities of greater than 85 mL to be more predictive of achieving continence.[58] Regardless, it is generally agreed that continence is highly dependent on the size of the original bladder plate, successful initial bladder closure, and an adequate preoperative bladder capacity.

The Young-Dees-Leadbetter technique of bladder neck repair remains the most common approach to bladder neck reconstruction (Fig. 120-14). After opening the bladder, the ureters are first mobilized and reimplanted into a more cephalad position by either cross-trigonal or cephalotrigonal ureteroneocystotomy.[22,59] This procedure not only corrects vesicoureteral reflux, which occurs in virtually all cases of closed bladder exstrophy, but also allows for creation of posterior bladder plate flaps for the bladder neck reconstruction. A recent report by Braga and colleagues also describes

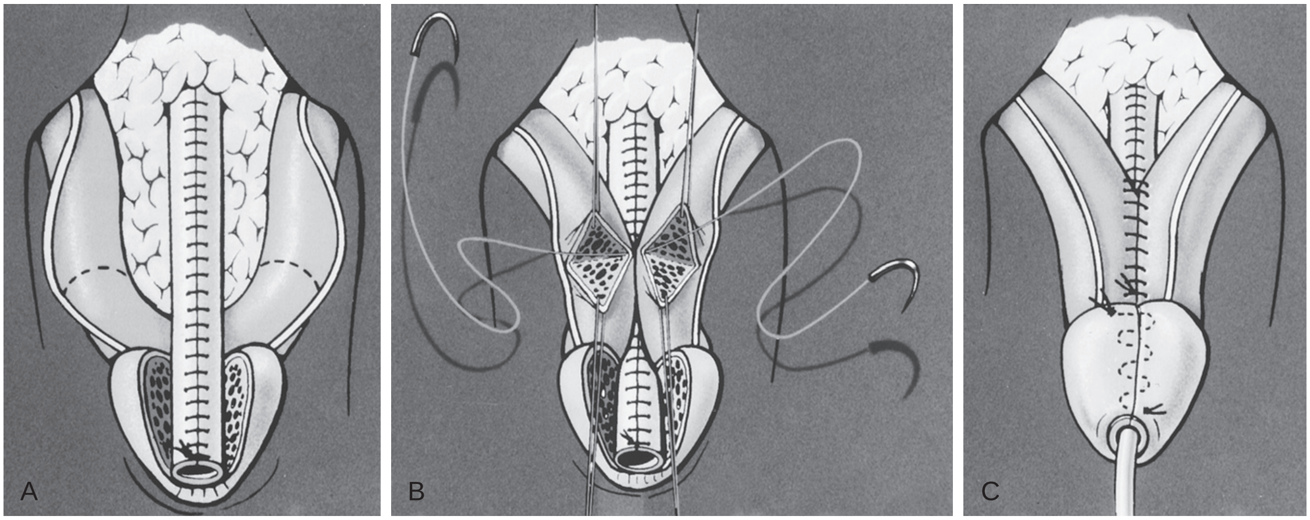


**FIGURE 120-12** Steps in the Cantwell-Ransley epispadias repair. **A,** The urethral plate is dissected from the corpora and is tubularized, taking care to preserve the lateral blood supply of the urethra and the neurovascular bundles**. B,** Corporotomies are created at the midphallus, and the urethra is transposed to the ventral surface. **C,** The corpora cavernosa are rotated medially and reapproximated at the corporotomy sites, pulling the corporal bodies inward and providing coverage of the neourethra. This procedure permits further urethral lengthening, approximation of the corpora with preservation of the blood supply, and full coverage of the urethra.

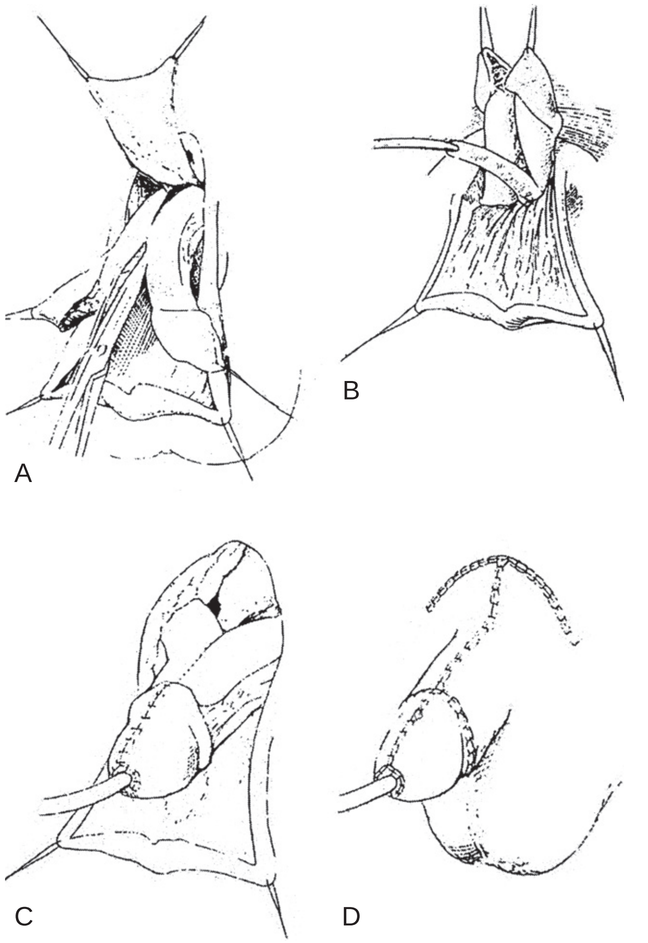


**FIGURE 120-13** Complete penile disassembly technique. **A,** The corporal bodies and the hemiglans are separated. **B,** The urethra is tubularized and moved ventrally. **C,** The corpora are reapproximated dorsally. **D,** Glans closure is performed distally to complete the repair. (Modified from Mitchell ME, Bagli DK: Complete penile disassembly for epispadias repair: The Mitchell technique. J Urol 1996;155:300.)

successful bilateral ureteral reimplantation at the time of primary bladder closure.[33]

A strip of posterior bladder plate 2 cm × 4 cm is marked off, and the triangles of bladder laterally are demucosalized. The strip of bladder is tubularized, and the triangles of denuded muscle are mobilized laterally to provide coverage of the neourethra. If prior urodynamic evaluation has demonstrated inadequate bladder capacity, augmentation cystoplasty with a bowel segment may be performed at this setting.

## SINGLE-STAGE RECONSTRUCTION: COMPLETE PRIMARY REPAIR OF EXSTROPHY

Recently, Mitchell and Grady minimized the number of required operations by combining bladder closure with epispadias repair at birth in a technique known as *complete primary repair.*[60] Major potential benefits of this approach include the earlier creation of bladder outlet resistance, theoretically leading to normal cycling and improved bladder capacity and functionality as the patient grows. Major principles of CPRE include total penile disassembly and division of the intersymphyseal band, which enables posterior positioning of the bladder, bladder neck, and urethra. As described by Grady and Mitchell,[60] CPRE begins with intubation of each ureteral orifice with ureteral catheters. Traction sutures are placed into each hemiglans, the bladder plate is circumscribed, and dissection is continued inferiorly along the ventral aspect of the penis. The urethral plate is mobilized off the penis, which is fully disassembled into separate right and left corporal bodies and the spongiosum-containing urethra. The intersymphyseal band is incised (Fig 120-15), which allows the bladder unit to be positioned deep within the pelvis. A suprapubic tube is left in place, the ureteral catheters are externalized, and the bladder is closed. Similar to the staged approach, pelvic osteotomy may be required for abdominal closure. The pubic symphysis is approximated using PDS sutures, and the abdominal wall is closed. The urethral plate is tubularized and transposed to the penile ventrum, and the corporal bodies are rotated medially and reapproximated (Fig. 120-16). Because of the new posterior positioning of the bladder unit, urethral length is often inadequate to reach the glans, and a hypospadiac meatus is left for future reconstruction (Fig. 120-17). Penile shaft coverage is achieved through the use of ventral rotational penile skin flaps. Postoperatively, the patient remains immobilized as previously described in the technique of staged closure. Additional procedures to correct for residual hypospadias, vesicoureteral reflux, and incontinence may be required as the child grows.

## URINARY DIVERSION

Urinary diversion, in the form of a bowel conduit or reservoir, may ultimately be required for patients with insufficient bladder plate or after reconstructive efforts have been unsuccessful and is discussed in Chapter 118.

## OUTCOMES AND COMPLICATIONS

The most devastating complication of bladder closure is dehiscence. Major contributing factors include wound infection, abdominal distension, bladder prolapse, and loss of ureteral and/or suprapubic catheters within 6 days of closure.[61] Urinary diversion, reclosure of the bladder as a urethral tube for later augmentation, or delayed repair of the bladder may be performed. If not performed in the initial setting, pelvic osteotomy is frequently necessary for successful reclosure.

Urinary incontinence remains a significant problem for up to 30% of bladder exstrophy patients. In the case of bladder neck incompetence, injectable bulking agents, bladder neck sling or artificial urinary sphincter have all been applied. Bladder neck reconstruction or formal closure of the bladder neck, with the creation of a catheterizable channel, can also be performed. In cases where incontinence is secondary to insufficient bladder capacity, augmentation cystoplasty remains the most viable treatment option.

Following epispadias repair, the most common complication is urethrocutaneous fistula, which ranges from 2% to 26% in modern series.[51,54,62]

The incidence of adenocarcinoma of the bladder in adults with bladder exstrophy has been estimated to be 250 times that of the normal population and is likely due to chronic inflammation, infection, and metaplasia of an exposed bladder plate.[63] A series by Woodhouse and colleagues, however, recently documented an 800-fold risk in the incidence of bladder

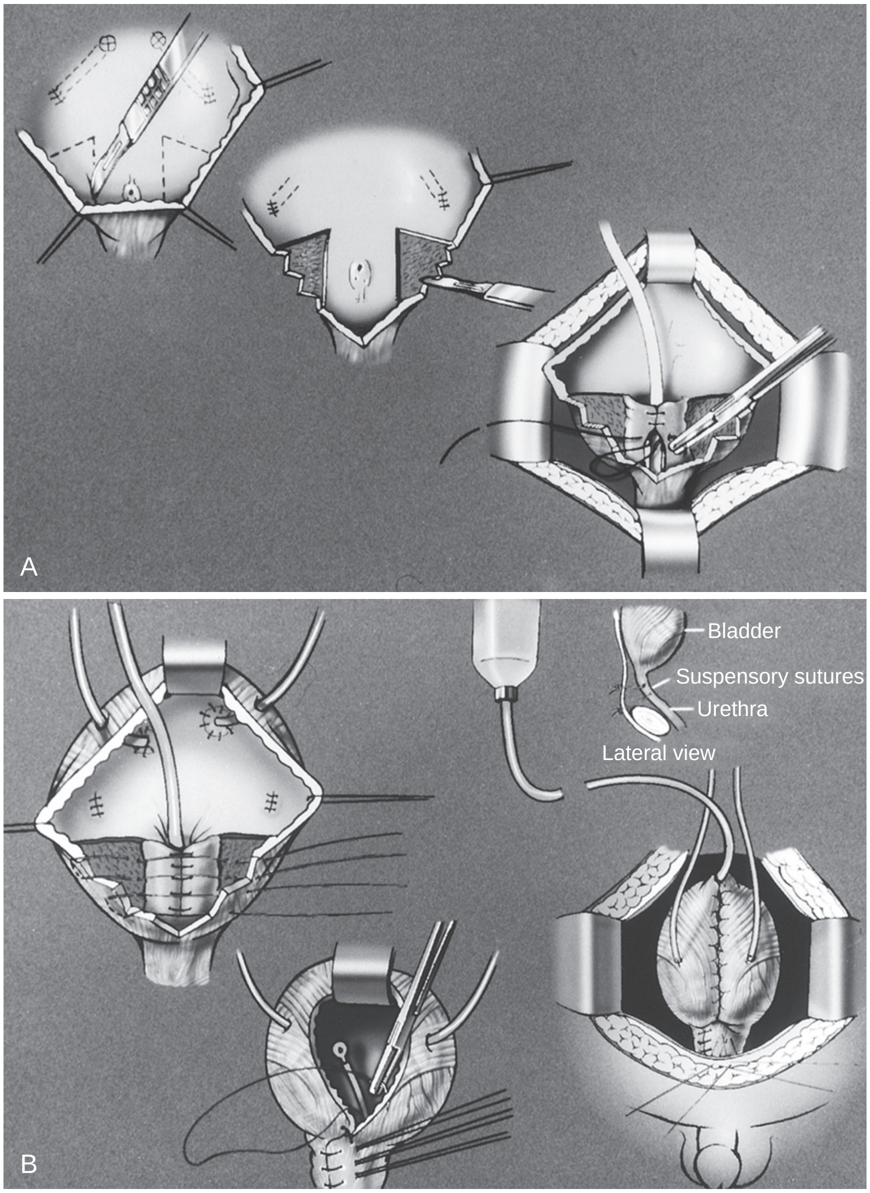


**FIGURE 120-14** Young-Dees-Leadbetter procedure for bladder exstrophy repair. **A,** The ureters are appropriately reimplanted to avoid reflux. Triangular areas at the bladder base are then denuded, and the remaining muscle is tubularized over a catheter. This serves to lengthen the urethra and provides sufficient pressure to encourage the development of improved bladder capacity without causing urethral obstruction. **B,** The bladder is reclosed, and the bladder neck is further supported by sutures, which secure it to the pubis anteriorly.

malignancy among those with a history of bladder exstrophy by age 40.[64] The development of adenocarcinoma and transitional cell carcinoma of the bladder is also a potential risk in those patients who have undergone augmentation cystoplasty.[65,66]

Fertility in patients with bladder exstrophy and epispadias was studied by Shapiro and colleagues,[14] who surveyed 2500 patients. Among these, 38 men had successfully fathered children and 131 women had given birth. Diminished fertility rates among males may be secondary to retrograde ejaculation, though libido and erectile function appear to be normal according to a report by Woodhouse and colleagues.[67] Female patients face a significant risk of uterine prolapse.

### CONCLUSION

Contemporary reconstructive techniques for the repair of bladder exstrophy have resulted in acceptable function and cosmesis for the majority of patients with classic bladder exstrophy. Overall continence rates range from 70% to 80%. Bladder augmentation is preferred in patients without adequate bladder capacity, and bladder neck closure with creation of a continent catheterizable stoma may be performed when other continence procedures have failed.

## Cloacal Exstrophy

Cloacal exstrophy is a rare condition occurring in 1 of 200,000 to 400,000 live births[68] and comprises the most severe deformation along the EEC spectrum, which includes both epispadias and classic bladder exstrophy. Cloacal exstrophy is also referred to as the *OEIS complex* (omphalocele, exstrophy, imperforate anus, and spinal defect) when other malformations of the urogenital, gastrointestinal, skeletal, and neurospinal axis are present.

Although first described by Littre in 1709, historic survival rates were dismal secondary to sepsis or fluid, electrolyte, and nutritional derangements from short gut syndrome or

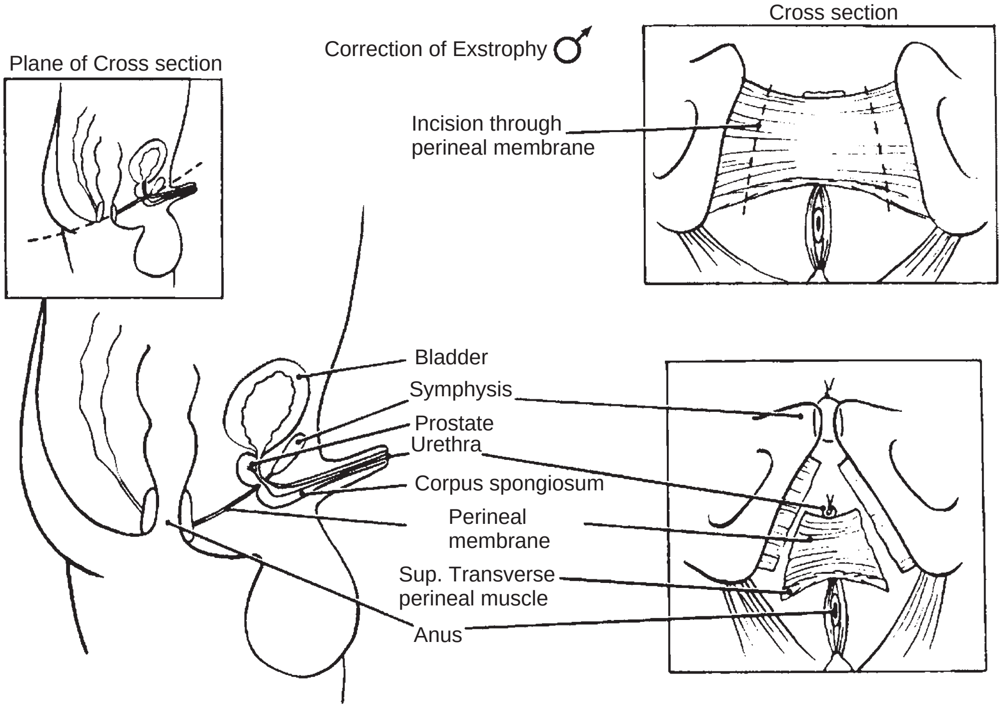


**FIGURE 120-15** Pelvic view of male exstrophy repair as described by Grady and Mitchell. Aggressive dissection along each side of the urethra and division of the intersymphyseal band allow posterior positioning of the bladder in the pelvis. (Modified from Grady RW, Mitchell ME: Complete primary repair of exstrophy. J Urol 1999;162:1416.)

intestinal obstruction.[69] The first successful repair was reported in 1960 by Rickham, who recommended staged surgeries for reconstruction.[70] Advances in neonatal care and surgical technique have resulted in present-day survival rates that exceed 90%, and principle goals of treatment are now directed toward improving quality of life in these patients.[68,71–75]

## EMBRYOLOGY AND GENETICS

The underlying defect in cloacal exstrophy is thought to be related to abnormal development and premature rupture of the cloacal membrane, as described earlier in the bladder exstrophy section. In the setting of cloacal exstrophy, it has been postulated that membrane rupture occurs within the first 8 weeks of gestation. Confirmation of this theory is difficult, however, given no embryologic stage similar to cloacal exstrophy exists in normal development.[76] Disruption of the cloacal membrane, as the principle underlying abnormality, has been supported by surgically induced exstrophy in animal models.[19,77] The prevailing developmental theories are further clouded by several recent reports documenting rupture as late as 26 weeks.[78,79] Rupture at 5 weeks gestation, as traditionally postulated, would cause anterior herniation of the bladder and small bowel, which would prevent normal midline fusion of the hindgut, bladder plate, genital tubercles, and müllerian ducts, thus resulting in the typical anatomic presentation of two open bladder halves separated by a strip of exstrophied cecum, hemiphallic halves with a widely separated pubic diastasis, an underdeveloped and blind-ending distal hindgut with imperforate anus, and an omphalocele of varying size (Fig. 120-18).

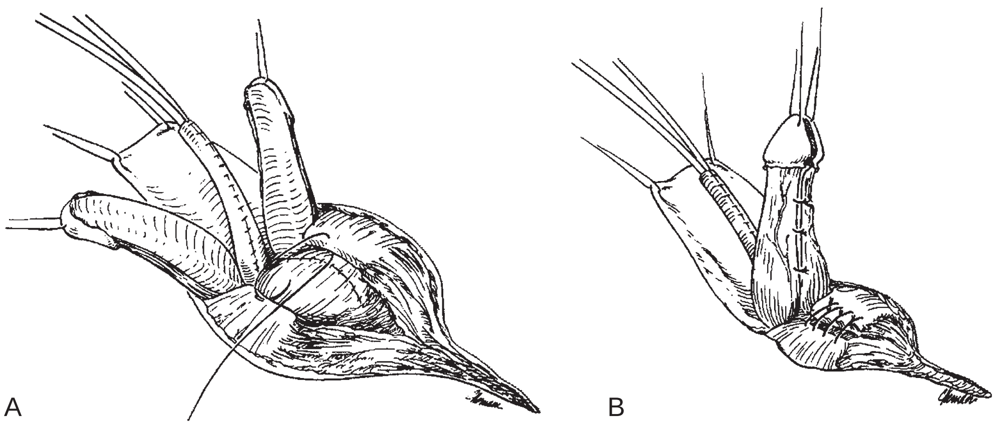


**FIGURE 120-16** **A,** Closure of the urethral plate and bladder as a continuous unit. **B,** Placement of the urethra ventral to the corporal bodies by positioning the bladder, bladder neck, and urethra posteriorly in the pelvis. (Modified from Grady RW, Mitchell ME: Complete primary repair of exstrophy. J Urol 1999;162:1417.)

FIGURE 120-17 At completion of complete primary closure, placement of the bladder and urethral units deeper within the pelvis along with ventral transposition of the urethra may result in a hypospadiac meatus, which can later be reconstructed with formal urethroplasty.

No single environmental exposure or consistent genetic defect in the etiology of cloacal exstrophy has yet been identified. Thauvin-Robinet and colleagues recently identified an unbalanced translocation between chromosomes 9q and Yq, and other studies have implicated mutations in homeobox genes such as HLXB9 and HOX, which are involved in the development of embryonic mesoderm.[80–82] Although there have been multiple reports of cloacal exstrophy among members of the same family, these are generally anecdotal and have involved multigenerational relatives or nontwin siblings.[83–85] Multiple instances of affected monozygotic twins have been reported, however, which lends support to an underlying genetic cause.[76,86–88]

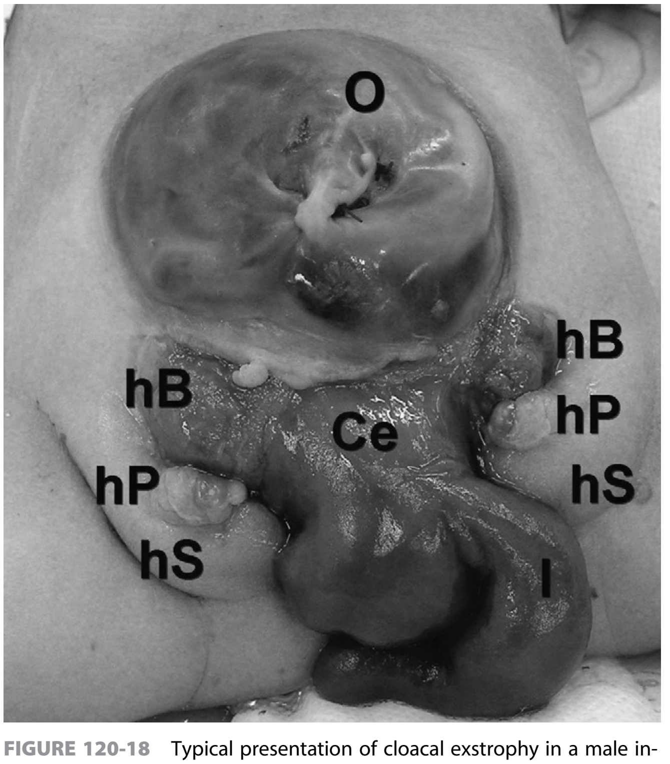


FIGURE 120-18 Typical presentation of cloacal exstrophy in a male infant. O, omphalocele; hB, hemibladder; Ce, exstrophied cecum; hP, hemiphallus; hS, hemiscrotum; I, prolapsed ileal segment.

## ASSOCIATED ANOMALIES

Unlike classic bladder exstrophy, cloacal exstrophy is typically associated with a variety of other anatomic defects (Table 120-1).

## GASTROINTESTINAL

Ileocecal exstrophy with an associated omphalocele, hindgut remnant, and imperforate anus is the most common clinical presentation.[54] Omphaloceles are present in 88% to 100% of infants and generally contain portions of small bowel and/or liver.[54,89] Other findings include intestinal duplication anomalies, gastroschisis, ectopic anus, colonic exstrophy, and malrotation.[90,91] Short gut syndrome may be a significant source of morbidity among patients with cloacal exstrophy and is observed in 25% of cases.[71] The risk of short gut syndrome is markedly increased in patients subjected to ileostomy placement as the initial intestinal diversion procedure.[92,93] Furthermore, the phenomenon may occur even in the presence of normal bowel length, implicating an inherent absorptive abnormality of the intestine.[71,72,90]

## GENITOURINARY

Abnormalities of the upper urinary tract have been reported in 41% to 66% of cases.[72,89] Unilateral renal agenesis, pelvic kidney, and/or hydronephrosis were observed in up to 33% in Diamond's 1990 series.[89] Less commonly reported findings include horseshoe kidney, fusion anomalies, and ureteral abnormalities.[72,89,90] Complete separation or even absence of the phallic/clitoral halves may be observed, and the scrotum/labia are widely separated. Male infants frequently have undescended testes with associated bilateral inguinal hernias, whereas failure of müllerian duct fusion in females results in varying degrees of uterine and vaginal duplication anomalies in the majority of patients.[72,89]

**TABLE 120-1**
**Anomalies Associated with Cloacal Exstrophy**

| |
|---|
| **Gastrointestinal** |
| Omphalocele |
| Imperforate anus, anal atresia/stenosis |
| Short gut syndrome |
| Intestinal malrotation |
| Intestinal duplication |
| **Genitourinary** |
| Unilateral renal agenesis |
| Pelvic kidney |
| Ureteral duplication |
| Hydronephrosis |
| Bilateral cryptorchidism, inguinal hernias |
| Uterine duplication |
| Vaginal duplication |
| **Central Nervous System** |
| Spinal dysraphism |
| **Skeletal** |
| Vertebral (absent, extra, hemi) |
| Club foot |
| Other lower limb (absence, shortening) |
| Hip subluxation |

## CENTRAL NERVOUS SYSTEM

Some form of spinal dysraphism including tethered cord, myelomeningocele, or lipomyelomeningocele is present in nearly all patients, with recent reports ranging from 64% to 100%.[74,84,91,94] Neurologic impairment is variable and may affect bladder function, urinary continence, lower extremity movement, and erectile function. Detailed postmortem microdissection studies have demonstrated both aberrant origin and vascular supply of the pelvic autonomic nerves,[95] and these nerves are at additional risk of iatrogenic injury during operative repair. Other reported abnormalities include periventricular leukomalacia, hydrocephalus, hypoplastic cerebellum, and Chiari malformation.[84]

## SKELETAL

Abnormalities of the spine, pelvis, and limbs have all been observed in the setting of cloacal exstrophy. Spinal anomalies, excluding myelodysplasia, have been reported in 22% to 60% and consist mainly of absent or extra vertebrae, scoliosis, and kyphosis.[90,96,97] The pelvic deformity is similar to that of classic bladder exstrophy but typically more severe with significant widening of the pubic diastasis, external angling of the posterior and anterior segments, and external rotation and abduction of the iliac wings.[70] A review by Jain and Weaver found a 17% to 26% incidence of associated lower limb abnormalities.[98] Certain limb malformations like club foot and equinovarus deformities can be seen in association with myelomeningocele, which often accompanies cloacal exstrophy; however, a variety of true limb malformations including hypoplasia, absence, split foot, and ectopic or additional digits have also been observed.[98]

## PRENATAL DIAGNOSIS

Early prenatal diagnosis allows time for thorough parental counseling and allows for consideration of pregnancy termination. Prenatal diagnosis was first reported by Meizner and Bar-Ziv in 1985,[99] and since then, several authors have proposed criteria for the prenatal diagnosis of cloacal exstrophy. Principle findings include failure to visualize the urinary bladder along with a large midline anterior abdominal wall defect and/or lumbosacral myelomeningocele.[87,100–102] The prolapsed ileal segment, which may appear as an "elephant trunk–like" mass on US, has also been reported as a pathognomonic finding.[103] From a review of 22 cases, Austin and colleagues[102] developed a list of major and minor criteria for prenatal US diagnosis on the basis of the frequency with which abnormalities were observed. Major criteria were those seen in greater than 50% of cases and included nonvisualization of the bladder (91%); a large, midline, infraumbilical anterior abdominal wall defect or cystic anterior abdominal wall structure (82%); omphalocele (77%); and myelomeningocele (68%). Minor criteria were observed in less than 50% and consisted of lower extremity defects (23%), renal anomalies (23%), ascites (41%), widened pubic arches (18%), narrow thorax (9%), hydrocephalus (9%), and single umbilical artery (9%).[102]

## SURGICAL REPAIR

### Immediate Postnatal Management

After delivery and stabilization of the newborn, exposed organs and mucosal surfaces including the omphalocele, bladder, intestine, and myelomeningocele should be protected by enclosing the infant's lower torso in a bowel bag or by first moistening surfaces with saline and covering with sterile plastic wrapping.[90] Urologic examination should attempt to note genetic sex and size of hemibladder plates. Baseline renal function, electrolyte, and hematologic status should be determined. Karyotyping can be performed if gender has not been previously determined or is not obvious on examination. Initial imaging should include plain films of the chest and spine along with head, abdominal, renal, and spinal US. In the absence of obvious spinal dysraphism, magnetic resonance imaging (MRI) may be advisable for detection of occult lesions. Consultation should also be made to general surgery, neurosurgery, and orthopedics for operative planning. Once the initial evaluation has been completed, discussion may be had with the parents regarding gender assignment, surgical reconstruction, potential functional deficits, and overall expected quality of life.

### Principles of Repair

The surgical management of cloacal exstrophy is typically undertaken in the newborn period (48 to 72 hours) as a combined effort between pediatric surgery and urology. In the setting of associated spinal dysraphism, neurosurgical consultation and closure should be undertaken as soon as the infant is medically stable. Early operation minimizes bacterial colonization of exposed viscera and may decrease the need for pelvic osteotomy.[68,104] The traditional approach of staged repair has been thoroughly described by Gearhart and Jeffs.[40,94] Complete primary repair has also been reported by Howell and colleagues,[68] Zderic and colleagues,[105] Hendren,[106] and most recently by Mitchell and Plaire.[75] It is generally agreed that an individualized approach toward reconstruction, whether in a single-staged or multistaged procedure, results in the best long-term outcomes.[107] The main goals of reconstruction include secure abdominal wall and bladder closure, preservation of renal function, prevention of short gut syndrome, creation of functionally and cosmetically acceptable genitalia, and attainment of urinary and fecal continence.[73,94]

Although various operative algorithms have been published, all approaches begin with initial separation of the intervening cecal plate from the two bladder halves, closure of the omphalocele, and hindgut preservation (Fig. 120-19).[68,71,72,75,107] In the past, the bowel was initially diverted through the creation of loop or end-ileostomies, and the hindgut segment was uniformly discarded. This practice has since fallen out of favor in order to maximize the absorptive capabilities of the intestinal tract.[72,74] Currently, after tubularization of the exstrophied cecum, it is recommended that the hindgut segment be brought out as an end-colostomy.[92] In the rare instance when the hindgut remnant is not used, it may be left as a mucous fistula for use in future urologic or vaginal reconstruction.[90]

The omphalocele is reduced to assist abdominal wall closure; however, in cases of large omphaloceles, complete initial reduction may not be possible. In this setting, a silo device

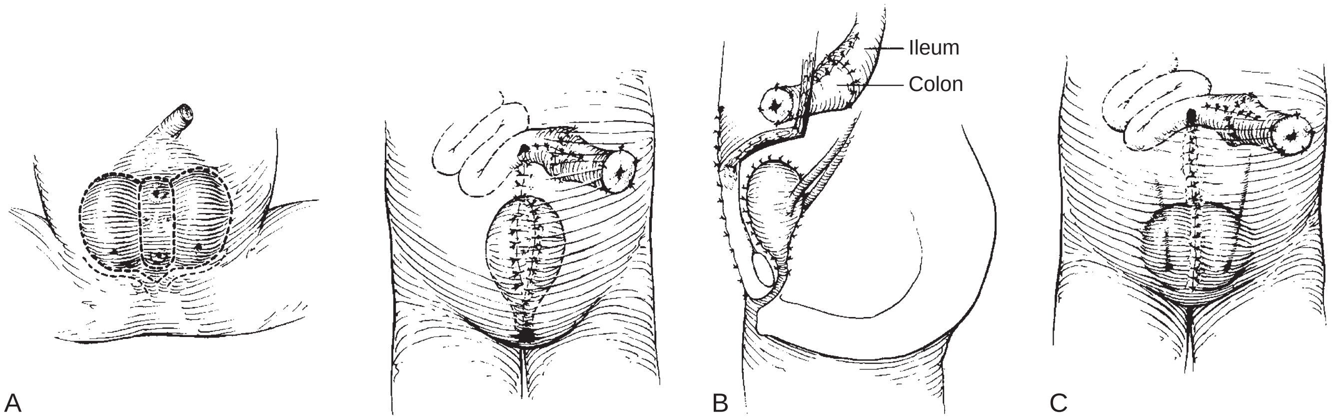


**FIGURE 120-19** Repair of cloacal exstrophy. **A** and **B,** The bowel and bladder mucosa are separated, and the ileocecal junction is tubularized and brought out as an end-colostomy. The bladder halves are turned in, as in a complete exstrophy repair, with approximation of the pubic rami. **C,** Alternatively, the bladder halves are approximated in the midline and left open for staged repair if tubularization is not possible. The omphalocele is also closed.

may be used or the omphalocele may be allowed to re-epithelialize, converting it to a ventral hernia, which may be repaired at a later time (Fig. 120-20).[94]

The hemibladders are dissected and then reapproximated in the midline. In infants with few other associated malformations and who are medically stable, complete closure of the abdominal wall, bladder, and phallic halves may be undertaken at this point in a single-stage procedure with or without pelvic osteotomy. If this is not possible at the initial setting, the two bladder halves can first be joined in the midline, recapitulating the appearance of classic bladder exstrophy, which can then be repaired in a staged fashion as described in the previous section.

Genital reconstruction consists of bringing the phallic halves together to create an appearance congruent with the assigned gender. In the male infant with cloacal exstrophy, the phallic halves are characteristically diminutive, widely separated, and asymmetric. Historically, genetically male infants were routinely assigned to female gender at the time of initial closure, undergoing orchiectomy and feminizing genitoplasty.[108] Recent data regarding gender identity outcomes in gender-reassigned cloacal exstrophy patients has suggested an inherent preference toward male behaviors and sexual identities in these patients.[75,105,109] It remains a topic of continued study and debate. Gender reassignment has since been largely abandoned in the current management of cloacal exstrophy, though functional and aesthetic phallic reconstruction remains challenging. Vaginal reconstruction is necessary in females and in gender-reassigned males and is accomplished through the use of bowel or skin grafts.

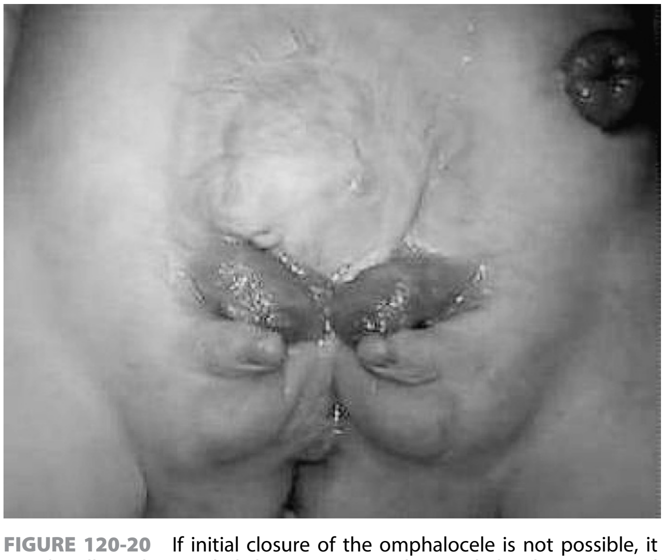

**FIGURE 120-20** If initial closure of the omphalocele is not possible, it may be allowed to epithelialize, converting the omphalocele to a ventral hernia, which can be repaired at a later time.

Gastrointestinal reconstruction, in the form of a pull-through procedure, may be performed in select patients, some time after initial diversion and abdominal closure. The decision is based on the potential for fecal continence and may be influenced by colonic length, ability to form solid stool, and the presence of anal stenosis versus imperforate anus.

Like those with classic bladder exstrophy, these patients will also require the creation of antireflux and urinary continence mechanisms. The presence of myelodysplasia in these patients usually necessitates augmentation cystoplasty with a bowel segment and intermittent catheterization in order to achieve continence. Continence procedures include creation of a neourethra, construction of a catheterizable abdominal stoma with concomitant bladder augmentation, and/or bladder neck closure, the selection of which is influenced by the presence of short gut syndrome, manual dexterity, degree of mobility, and patient motivation.[94]

## POSTOPERATIVE CONSIDERATIONS

Given the high incidence of short gut syndrome, fluid and nutritional status must be carefully monitored and the initial use of total parenteral nutrition (TPN) is advocated.[110] The keys to postoperative success are similar to those for repair of classic bladder exstrophy. Patients are immobilized in some type of traction device. In the setting of pelvic osteotomy, an external fixator is left for 4 to 6 weeks postoperatively. Broad-spectrum antibiotics are administered to minimize risk of wound infection and urosepsis. In contrast to patients with classic bladder exstrophy, the presence of associated myelodysplasia in cloacal exstrophy generally precludes use of an epidural catheter. Pain control in cloacal exstrophy patients can be challenging, and the involvement of the pediatric pain service is recommended. Finally, the importance of limiting abdominal distension to ensure successful abdominal closure and

adequate drainage of both ureteral and bladder catheters cannot be understated.[61,111,112] Following repair, close monitoring of the upper tracts by US is mandatory to observe for adequate renal growth and to detect evidence of obstruction or VUR, which has been reported in 50% to 60% of cloacal exstrophy patients after staged or complete primary repair.[60,107]

## CONCLUSION

For the past 20 years, survival among patients with cloacal exstrophy has exceeded 90%.[68,72,74,105] Death is typically related to complications related to extreme prematurity, renal agenesis, or other complex malformations that are incompatible with life. It is interesting to note that cardiovascular anomalies are rarely observed in the setting of cloacal exstrophy. The various complications related to the management of patients with cloacal exstrophy are similar to those of patients with classic bladder exstrophy, as described in the previous section. Compared with those with classic exstrophy, however, cloacal exstrophy patients face additional challenges of achieving bowel and bladder continence secondary to the need for anal reconstruction and the associated defect of spinal dysraphism. It must be stressed that multiple operations are the rule, and these patients will likely face significant medical, psychologic, and social challenges throughout their lives. Advancements in medical and surgical management continue to improve functional and quality of life outcomes in these patients, but it is important that these individuals remain under the care of a multidisciplinary team of providers who can offer medical care, psychologic support, and lifelong follow-up.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 121

# Hypospadias

Laurence S. Baskin

Hypospadias is one of the most common congenital anomalies, occurring in approximately 1 in 250 newborns, or roughly 1 in 125 live male births.[1,2] Hypospadias can be defined as an arrest in normal development of the urethra, foreskin, and ventral aspect of the penis.[3] This results in a wide range of abnormalities; the urethral opening can be anywhere along the ventral shaft of the penis, within the scrotum, or even in the perineum (Fig. 121-1). Hypospadias is also associated with a ventral curvature of the penis, or chordee. Left uncorrected, patients with severe hypospadias may need to sit down to void and tend to shun intimate relationships because of fears related to abnormal sexuality. Babies born with severe hypospadias and penile curvature may have "ambiguous genitalia" in the newborn period, making an immediate and accurate sex assignment difficult.

Hypospadias is classified by the location of the urethral meatus (Fig. 121-2). Mild (distal) hypospadias may be glanular (meatus on the ventral surface of the glans penis), coronal (meatus in the balanopenile furrow), or distal (in the distal third of the penile shaft). Moderate hypospadias is along the middle third of the penile shaft. Severe (posterior) hypospadias extends through the proximal third of the penile shaft to the perineum and may be described as posterior penile (at the base of the shaft), penoscrotal (at the base of the shaft in front of the scrotum), scrotal (on the scrotum or between the genital swellings), or perineal (behind the scrotum or behind the genital swellings). Classifying hypospadias is not necessarily useful in determining surgical approach, and these classifications do not take into account the associated penile curvature (Fig. 121-3). A patient with severe curvature and an anterior urethral meatus may require more extensive surgery to correct both anomalies.

## Historical Notes

Throughout Greek culture, there was high appreciation for the goddess Hermaphrodite, who was half man and half woman. Many statues reflect hypospadiac genitalia, perhaps indicative of admiration for this condition. It is, therefore, understandable why it was not until the first and second centuries AD that the Alexandrian surgeons Heliodorus and Antyllus attempted to correct this anomaly by amputation of the distal curved portion.[4] Sexually, the dystopia of the meatus may cause impotentia generandi. Henry II of France was known to have hypospadias, as recorded by his physician Fernal. Henry's marriage with Catherine de Medici was infertile until Fernal "advised his patient that in such cases *coitus more ferarum* permitted him to overcome the difficulty."[5] Henry II went on to sire three kings of France, along with seven other children.

## Embryology

Formation of the external male genitalia is a complex developmental process involving genetic programming, cell differentiation, hormonal signaling, enzyme activity, and tissue remodeling.[6,7] By the end of the first month of gestation, the hindgut and future urogenital system reach the ventral surface of the embryo at the cloacal membrane.[8] The urorectal septum divides the cloacal membrane into a posterior, or anal, half and an anterior half, the urogenital membrane. Three protuberances appear around the latter. The most cephalad is the genital tubercle. The other two, the genital swellings, flank the urogenital membrane on each side. Up to this point, the male and female genitalia are essentially indistinguishable. Under the influence of testosterone and dihydrotestosterone in response to a surge of luteinizing hormone from the pituitary, masculinization of the external genitalia takes place (Fig. 121-4). One of the first signs of masculinization is an increase in the distance between the anus and the genital structures, followed by elongation of the phallus, formation of the penile urethra from the urethral groove, and development of the prepuce.[9,10]

At 8 weeks' gestation, the external genitalia remain in the indifferent stage (see Fig. 121-4). The urethral groove on the ventral surface of the phallus lies between the paired urethral folds (Fig. 121-5). The penile urethra forms as a result of fusion of the medial edges of the endodermal urethral folds. The ectodermal edges of the urethral groove fuse to form the median raphe. By 12 weeks, the coronal sulcus separates the glans from the shaft of the penis. The urethral folds have completely fused in the midline on the ventrum of the penile shaft. During the 16th week of gestation, the glanular urethra appears. Two possible explanations for formation of the glanular urethra have been proposed (see Fig. 121-5): (1) endodermal cellular differentiation or (2) primary intrusion of ectodermal tissue from the glans (Fig. 121-6).

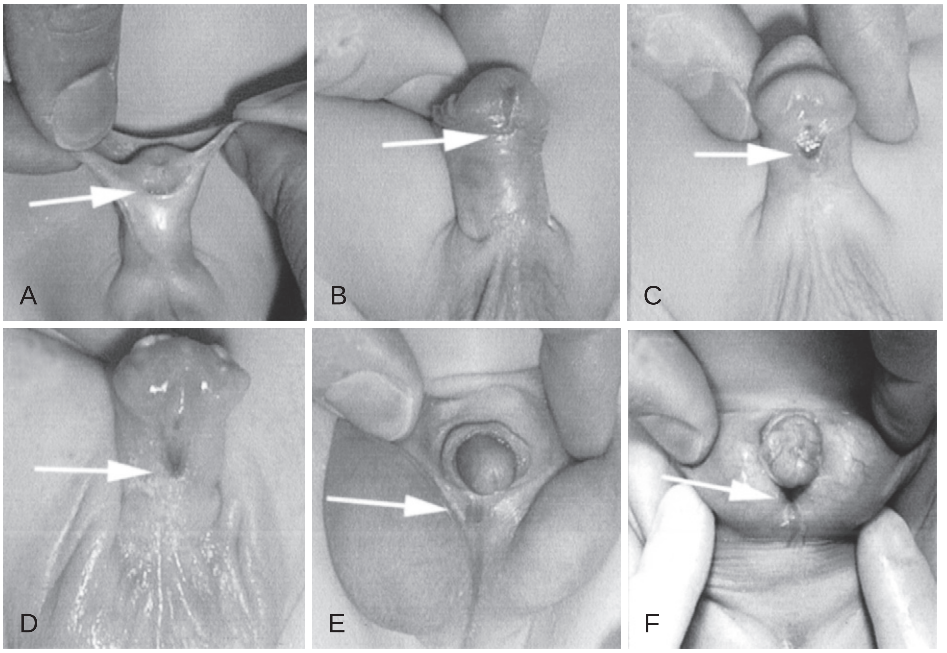


FIGURE 121-1 Mild to severe hypospadias. **A,** Mild hypospadias with the urethral opening on the glans. **B,** Mild hypospadias with the urethral opening at the coronal margin. **C,** Moderate hypospadias with the urethral opening on the distal penile shaft. **D,** Moderate hypospadias with the urethral opening on the midpenile shaft. **E,** Severe hypospadias with the urethral opening at the penoscrotal junction. **F,** Severe hypospadias with the urethral opening in the scrotum (the *arrows* indicate the opening of the hypospadiac urethral meatus). Note that the foreskin is absent on the ventral surface of the penis and excessive on the dorsal aspect. The more severe forms of hypospadias are associated with penile curvature. (From Baskin LS: Hypospadias and urethral development. J Urol 2000;163:951-956.)

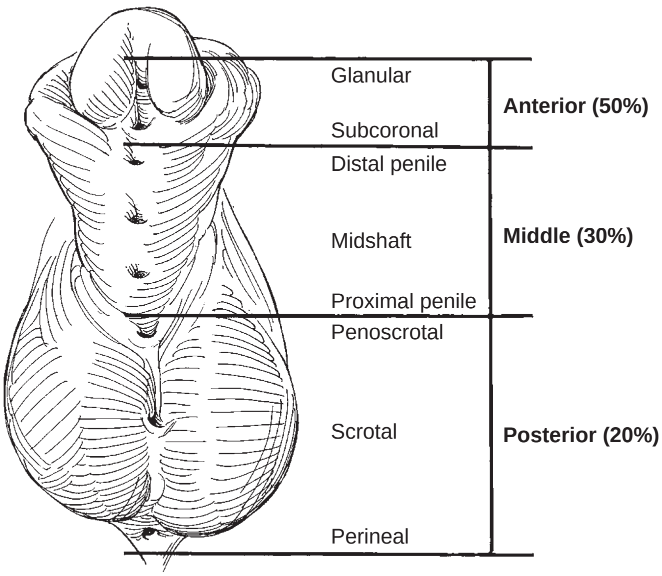


FIGURE 121-2 Classification and incidence of hypospadias: distal (anterior), moderate (middle), and posterior.

Anatomic and immunohistochemical studies advocate the theory of endodermal differentiation on the basis of evidence that the epithelium of the entire urethra is of urogenital sinus origin.[11] The entire male urethra including the glanular urethra is formed by dorsal growth of the urethral plate into the genital tubercle and ventral growth and fusion of the urethral folds. Under proper mesenchymal induction, urothelium has the ability to differentiate into a stratified squamous phenotype with characteristic keratin staining, thereby explaining the cell type of the glans penis.[12] There is no evidence of ectodermal ingrowth, as proposed under the second theory.[13]

The future prepuce is forming at the same time as the urethra and is dependent on normal urethral development. At about 8 weeks' gestation, low preputial folds appear on both sides of the penile shaft, which join dorsally to form a flat ridge at the proximal edge of the corona. The ridge does not entirely encircle the glans because it is blocked on the ventrum by incomplete development of the glanular urethra (see Fig. 121-5, *A*). Thus the preputial fold is transported distally by active growth of the mesenchyma between it and the glanular lamella. The process continues until the preputial fold (foreskin) covers all of the glans (see Fig. 121-5, *C*). The fusion is usually present at birth, but subsequent desquamation of the epithelial fusion allows the prepuce to retract. If the genital folds fail to fuse, the preputial tissues do not form ventrally; consequently, in hypospadias, preputial tissue is absent on the ventrum and is excessive dorsally (see Fig. 121-1).

At the molecular level, testosterone must be converted to $5\alpha$-dihydrotestosterone (DHT) by the microsomal enzyme type 2 $5\alpha$-reductase for complete differentiation of the penis with a male-type urethra and glans.[14–16]

## Incidence

Several European countries including Norway, Sweden, England, Wales, Hungary, Denmark, Finland, Italy, France, and the United States published independent reports of increasing rates of hypospadias during the 1960s, 1970s, and 1980s.[2,17] More recently, data from the International

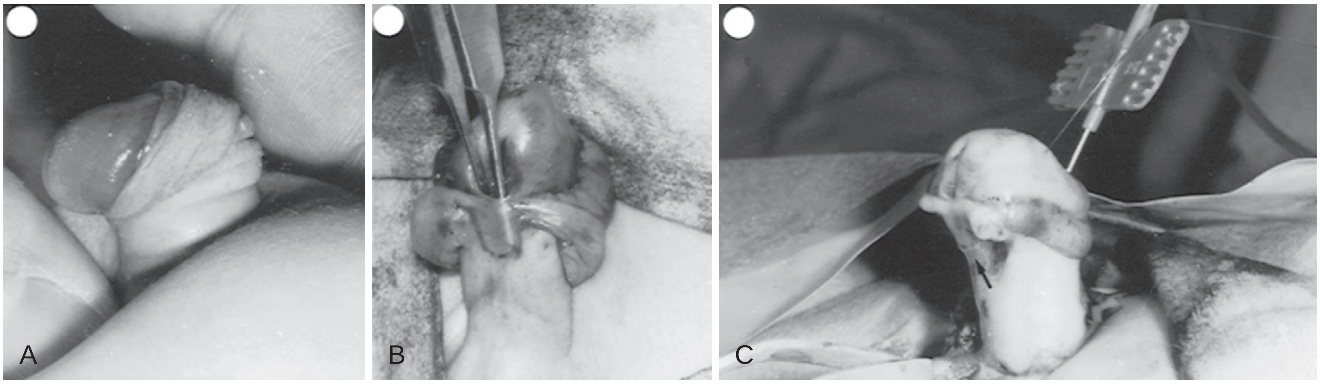


FIGURE 121-3 **A,** Coronal hypospadias with penile curvature. **B,** The thin ventral skin is not suitable for a parameatal-type procedure. **C,** After release of the skin and dartos fascia (straightening the penis), the meatus (*arrow*) is cut back to remove thin urethral skin in preparation for an onlay island flap urethroplasty. (From Baskin LS, Duckett JW, Ueoka K, et al: Changing concepts of hypospadias curvature lead to more onlay island flap procedures. J Urol 1994;151:191.)

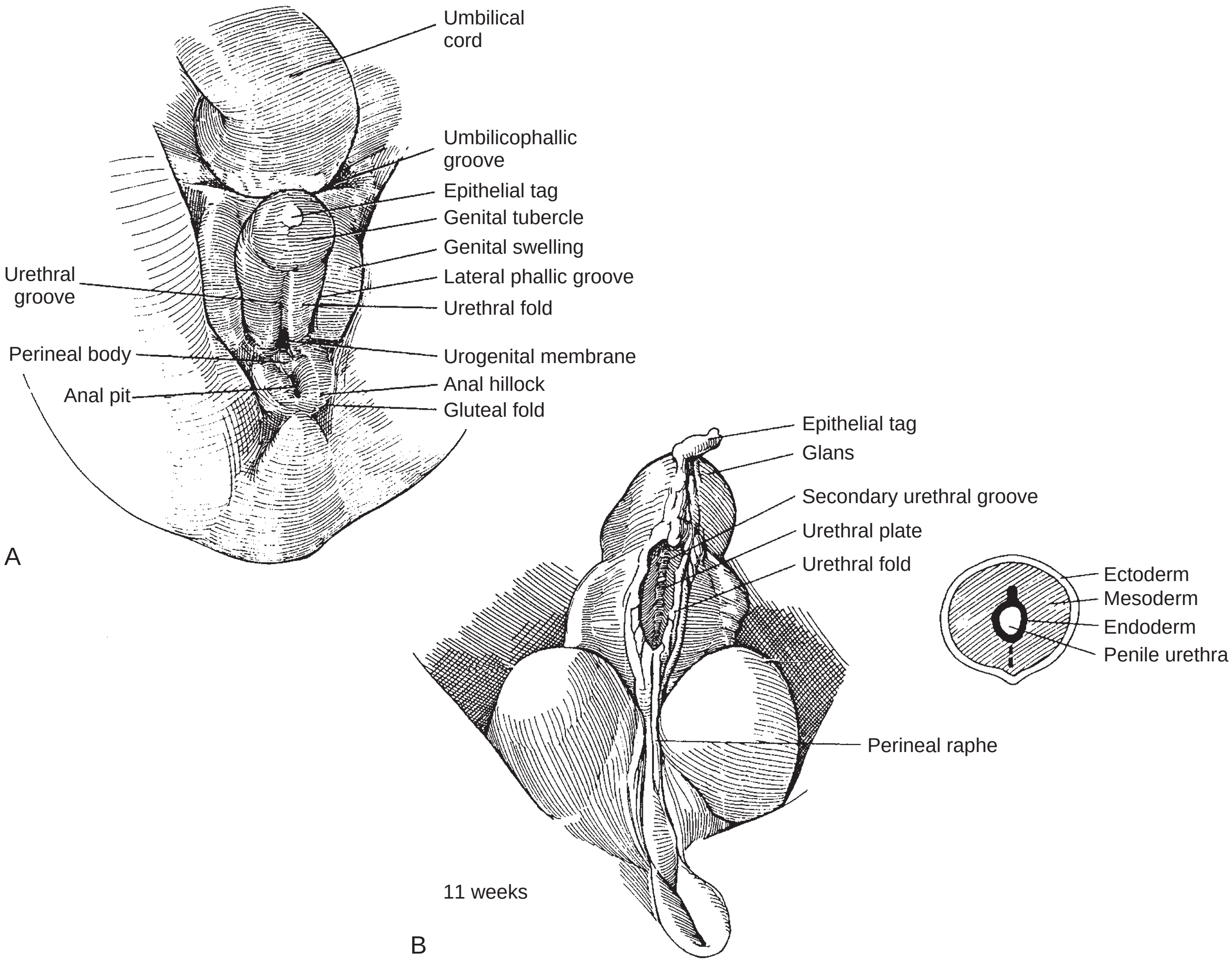


FIGURE 121-4 Development of the penis and urethra. **A,** Indifferent stage at about 8 weeks. Note that the primitive urethral groove forms on the caudal slope of the genital tubercle. Paired genital (labioscrotal) swellings arise on either side of the urogenital membrane above the anal pit and the perineal body. **B,** Enclosure of the urethra at 11 weeks. Beginning near the anus, the adjacent ectodermal urethral folds fuse over the urethral plate to form the penile urethra, with the distal urethra at the coronal sulcus being the last to close.

*Continued*

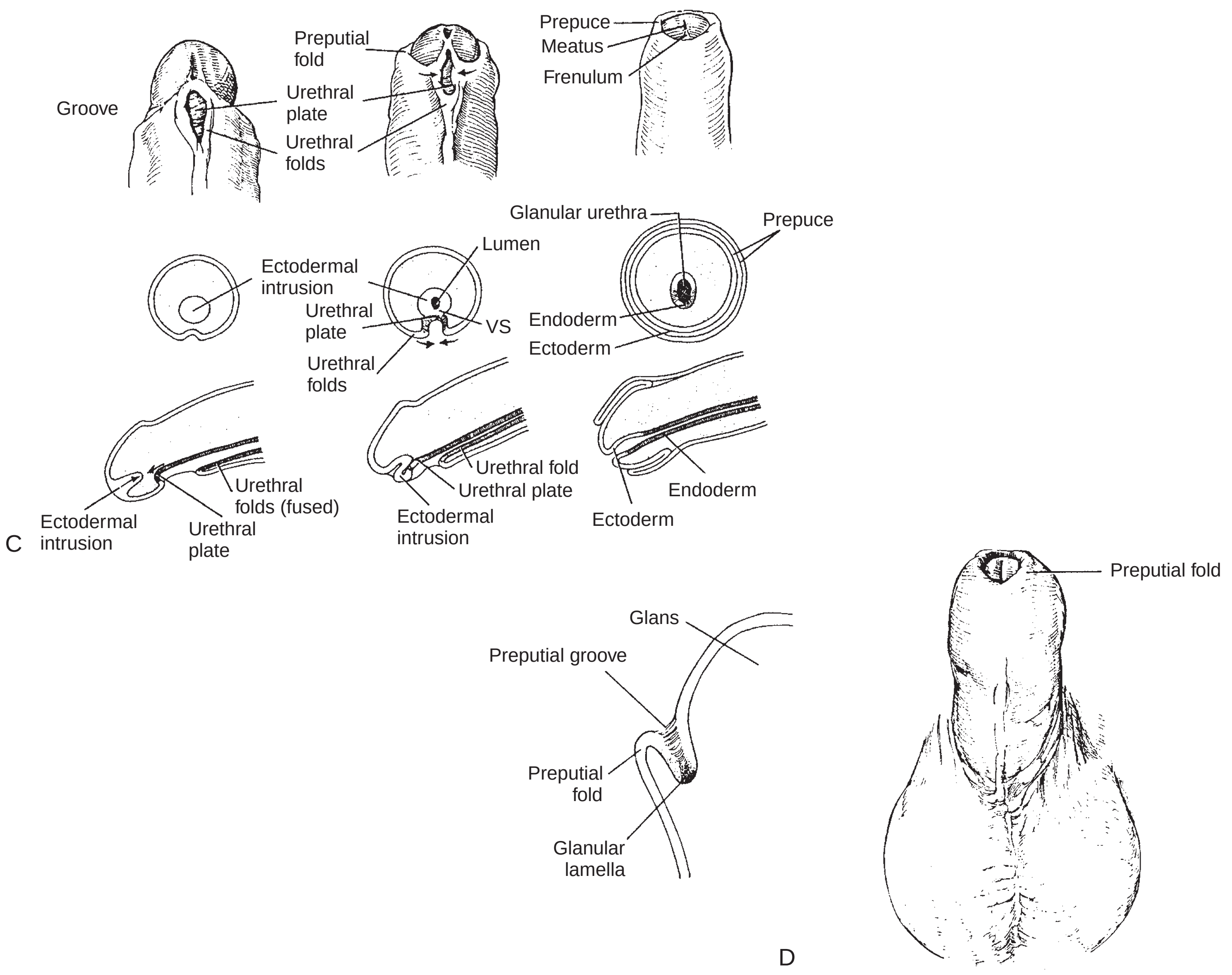


**FIGURE 121-4—CONT'D** **C,** Formation of the glanular urethra and fossa navicularis occurs late in gestation. A plug of ectoderm from the tip of the glans invades the mesenchyma as an ectodermal intrusion. The floor of the ectodermal intrusion makes contact with the end of the urethral plate that forms the roof of the advancing urethra, and the intervening double wall breaks down. **D,** The prepuce forms by the differentiation of the epithelial cells of the glanular lamella, which forms a groove between the preputial folds and the glans. (From Hinman F Jr: Surgical Anatomy of the Genitourinary Tract. Philadelphia, WB Saunders, 1994, pp 418-470.)

Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) were analyzed to determine whether these increases were worldwide and continuing and whether they had any geographic pattern.[2] The ICBDMS data suggested that the increased incidence of hypospadias was not a worldwide trend; it was most notable in the United States, Norway, and Denmark. Also, it was determined that the incidence was not increasing in the less affluent and less industrialized nations (on the basis of gross domestic product) for which data were available. Increasing trends in England, Canada, and northern Netherlands appear to have leveled off since 1985.

Data from the Metropolitan Atlanta Congenital Defects Program showed that the incidence of severe hypospadias increased between 1968 and 1990.[1] The Birth Defects Monitoring Program (BDMP), which gathers diagnoses recorded on newborn discharge summaries from hospitals nationwide, also reported an increase in hypospadias. However, more recent studies in the New York area question whether the incidence is actually changing.[18]

## Associated Anomalies

Undescended testis and inguinal hernia are the most common anomalies associated with hypospadias. In one series, 9.3% of hypospadias patients had an undescended testis; the incidence was 32% with posterior hypospadias, 6% for moderate, and 5% with distal.[19] The same investigators found the overall incidence of inguinal hernia to be 9%, with 17% of those cases associated with posterior hypospadias. A utriculus masculinus (utricle) is more often found in cases of severe hypospadias.[20,21] Combining two large studies in severe hypospadias, there was an 11% incidence of a utricle. Usually, the only complications caused by the presence of a utricle are difficulty passing a catheter and rarely infection.[22]

It is not surprising that urinary tract anomalies are infrequent because the external genitalia are formed after the supravesical portion of the urinary tract. McArdle and Lebowitz found only 6 genitourinary anomalies among

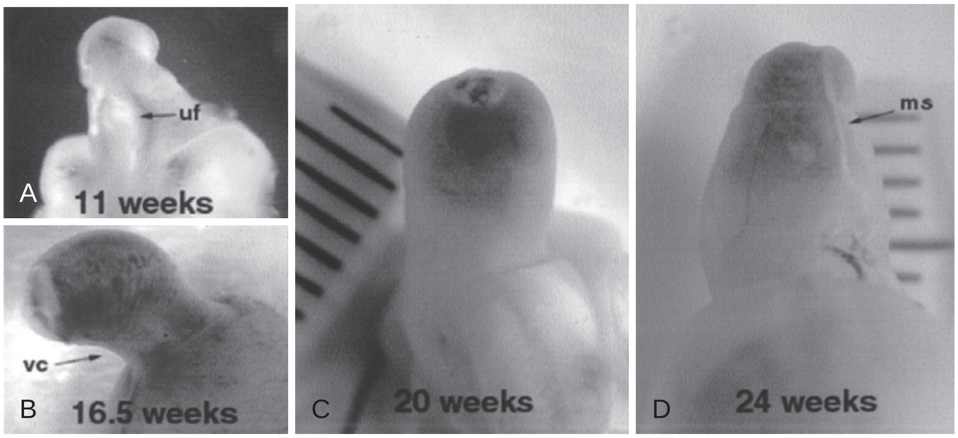


**FIGURE 121-5** Normal human male genitalia development at 11, 16.5, 20, and 24 weeks' gestation. **A,** Note the open urethra and prominent urethral folds (*uf*). **B,** Note the natural phase of penile curvature that occurs during development. **C,** The foreskin is completely formed, and the curvature has resolved. **D,** Continued growth with visualization of the midline skin seam (*ms*).

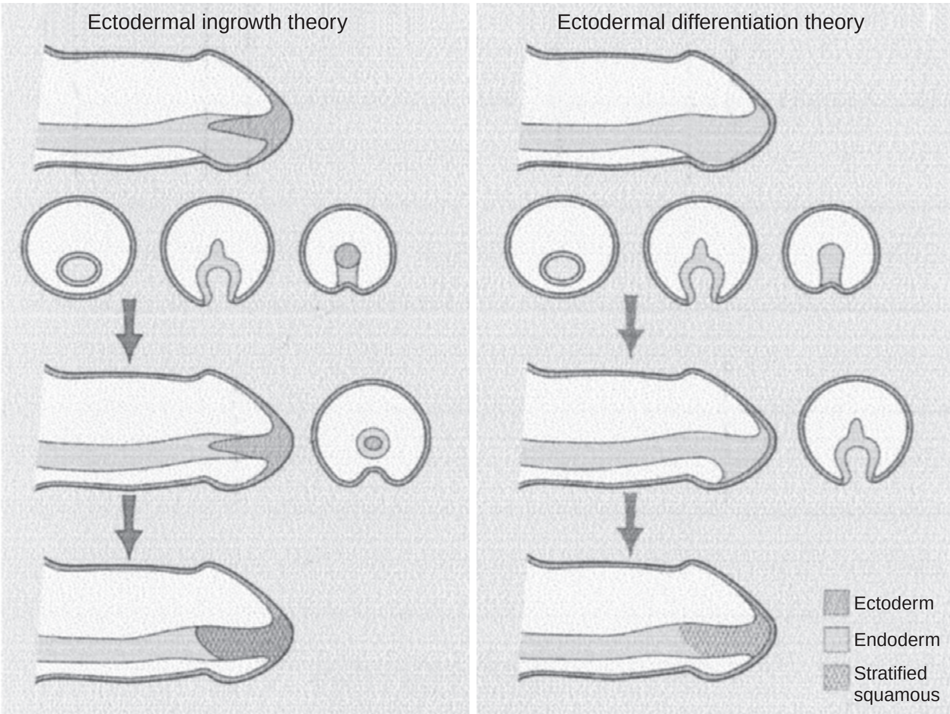


**FIGURE 121-6** Two theories of urethral development: the older theory of ectodermal intrusion and the newer theory of endodermal differentiation. (From Kurzrock EL, Baskin LS, Cunha GR: Ontogeny of the male urethra: Theory of endodermal differentiation. Differentiation 1999;64:115-122.)

200 patients with hypospadias (3%).[23] Cerasaro and colleagues[24] found that 1.7% of patients (4 of 233) had significant anomalies. On the basis of a review of 169 patients, Shelton and Noe[25] did not recommend routine urinary tract evaluation. Khuri and colleagues,[19] in a review of 1076 patients, did not find any significant associated urinary tract anomalies. They concluded that patients with hypospadias and an associated inguinal hernia or undescended testis did not require further urinary tract evaluation; however, patients with hypospadias and other organ system anomalies found on physical examination should undergo upper urinary tract screening with abdominal ultrasonography.

## Cause

In the majority of patients the etiology of hypospadias remains unknown.[3] For example, 33 patients with severe hypospadias were evaluated with a range of diagnostic techniques including clinical assessment, ultrasonography, karyotyping, endocrine evaluation, and molecular genetic analysis of the androgen receptor (AR) and 5α-reductase genes to classify and determine the cause of hypospadias. Diagnoses were determined in only 12 patients (36%); the remaining 64% of patients were classified as having hypospadias of unknown etiology.[26]

## HORMONE RECEPTOR IMPAIRMENT

Many investigators have also attempted to link abnormalities in androgen metabolism or the AR to hypospadias. For example, Gearhart and colleagues[27] found no deficiencies in either AR levels or 5α-reductase in their study of preputial skin from boys with hypospadias. Allera and colleagues[28] analyzed nine patients with severe hypospadias and found a defect in the open-reading frame of the AR in only one patient. Sutherland and colleagues[29] also concluded that mutations in the AR gene are rarely associated with hypospadias. Molecular biology techniques have demonstrated that defects in the AR gene are definitely associated with isolated hypospadias. However, these genetic defects account for an extremely small subset of cases, implying that other factors are responsible for hypospadias.

## GENETIC IMPAIRMENT

Increasingly, researchers are examining the role of cellular signals other than testosterone and DHT in the morphogenesis of the phallus and the cause of hypospadias. Normal embryogenesis of the urogenital system depends on epithelial-mesenchymal interactions, and it has been hypothesized that aberrant signaling between the epithelium and mesenchyma could lead to hypospadias.[12] For example, prostate development requires testosterone-dependent Sonic hedgehog (Shh) expression in the epithelium of the urogenital sinus.[30] In mice null for Shh, penile development is inhibited and cloacal defects exist.[31,32] Mice null for fibroblast growth factor 10 have a proximal urethral opening and a flattened glans, consistent with the hypospadias defect.[32] It is likely that researchers will find similar genetic signaling molecules involved in epithelial-mesenchymal interactions in the phallus that play a role in its development.

Another area of investigation with respect to the cause of hypospadias is the expression and regulation of homeobox (Hox) genes. These genes are transcriptional regulators that play an essential role in directing embryonic development. Genes of the *Hox A* and *Hox D* clusters are expressed in regionalized domains along the axis of the urogenital tract. Transgenic mice with loss of function of single *Hox A* or *Hox D* genes exhibit homeotic transformations and impaired morphogenesis of the urogenital tract.[30,33–35] Human males with hand-foot-genital syndrome, an autosomal dominant disorder characterized by a mutation in *Hox A13,* exhibit hypospadias of variable severity, suggesting that *Hox A13* may be important in the normal patterning of the penis.[36–38] Furthermore, research has shown that the embryonic expression of certain Hox genes is regulated by hormonal factors.[39] Estrogen and the synthetic estrogen DES, for example, inhibit *Hox A9, Hox A10, Hox A11,* and *Hox A13* genes in mice. Thus in addition to defects in Hox genes, it is possible that improper regulation or expression of hormonal factors during embryogenesis could disrupt normal expression of Hox genes and lead to reproductive tract anomalies. More recently, *ATF3* and *MAMLD1 (Cxorf6)* are new candidate genes that are associated with hypospadias.[40] *ATF3* is an estrogen-responsive gene whose expression is increased in hypospadiac boys.[41,42] MAMLD1, which is expressed in the gonad during sex differentiation and interacts with steroidogenic factor 1 (SF1), a transcription factor expressed in the mammalian sex-determining pathway, has also been shown to be mutated in patients with isolated hypospadias.[43]

## ENZYME IMPAIRMENT

Despite the central role that testosterone plays, attempts to ascribe all hypospadias to an underlying genetic defect in this pathway have only rarely been successful. Holmes and colleagues[44] determined the incidence of defects in three major enzymes in the biosynthetic pathway of testosterone: 3α-hydroxysteroid dehydrogenase, 17α-hydroxylase, and 17,20-lyase. Forty-eight boys with fully descended testes and various degrees of hypospadias were compared with age-matched controls who were undergoing circumcision. Morning fasting serum samples of pregnenolone, progesterone, 11-deoxycorticosterone, 17-OH pregnenolone, 17-OH progesterone, 11-deoxycortisol, cortisol, dehydroepiandrosterone, androstenedione, androstenediol, testosterone, and dihydrotestosterone were obtained. To focus on the proximal steps in androgen biosynthesis, 12 individuals with hypospadias underwent standard adrenocorticotropic hormone (ACTH) stimulation. No significant differences in the androgen precursors and metabolites were found between the controls and the individuals with hypospadias. The response to ACTH was variable, with no significant difference between patients with different degrees of hypospadias and controls. These data indicate that enzymatic defects in the steroidogenic steps from cholesterol to dihydrotestosterone are not a common cause of hypospadias.

## ENVIRONMENTAL FACTORS AND ENDOCRINE DISRUPTERS

In the past, environmental factors were generally ruled out as causes of hypospadias.[45,46] More recently, multicausality models have included environmental contaminants to determine the risk of developing a given phenotype. For example, familial clustering of hypospadias among first-degree relatives has been perceived as being under the influence of a strong genetic and heritable component, but there have been many exceptions in which genetics was ruled out. It has thus been suggested that environmental influences should be considered as well, given that families share similar exposures. In particular, in cases in which the effects are profound, genetic predisposition exacerbated by environmental exposure should be considered.[47–49]

Attempts to determine risk factors for hypospadias have yielded a number of maternal and paternal risk factors. Among traditional studies of maternal risk factors for congenital anomalies, maternal age and primiparity are significantly associated with hypospadias, although some studies have contested the maternal age effect.[45] Paternal risk factors associated with hypospadias include abnormalities of the scrotum or testes and low spermatozoa motility and abnormal sperm morphology.[48,50] It has been suggested that the recent increase in hypospadias reflects the improvement in fertility treatments, contributing to more subfertile men fathering children. As Fritz and Czeizel state, this “relaxed-selection hypothesis, which states that there is a redistribution in the number of children born to fertile and infertile (subfertile) couples, may account for the increasing number of other defects and cancers of male genitalia observed today and the fall in sperm counts.”[48,51]

In addition to parental risk factors, there is strong consensus in the literature that boys with hypospadias have lower

birth weights.[52] Fredell and colleagues[52] examined hypospadias in discordant monozygotic twins and found that the twin with hypospadias weighed 78% of the twin without hypospadias. The birth weight difference was still significant in healthy monozygotic twins. Another study found that boys with hypospadias had a lower placental weight than control boys did.[46]

A 1995 meta-analysis of first-trimester exposure to progestins and oral contraceptives did not indicate an increased risk of hypospadias.[53] Exposure to DES was excluded in that study. However, a number of other studies did list gestational exposure to progestins as a causal agent. Another recent study linked a maternal vegetarian diet during pregnancy to an increase in the incidence of hypospadias.[54] This study looked at 51 boys with hypospadias from a group of 7928 boys born to mothers taking part in the Avon Longitudinal Study of Pregnancy and Childhood. The authors hypothesized that vegetarians have a greater exposure to phytoestrogens than omnivores do. The phytoestrogens may come in the form of soy, which is high in isoflavones, or may be related to endocrine disrupters in pesticides and fertilizers.[55]

Although these risk factors may not be direct causes of hypospadias, they provide additional information that may reveal a common developmental pathway and inform future research. For example, there is growing evidence that androgens play a central role in the lower birth weight of girls compared with boys.[56] Androgens are also crucial to the development of the male reproductive tract. Thus exposure to an agent that compromises the weight-gaining advantage of androgen during gestation could play a role in the development of hypospadias and low birth weight.

Increasing rates of hypospadias have paralleled reports of other untoward end points related to male reproductive health including increases in testicular cancer, an increased incidence of cryptorchidism, and decreased semen and sperm quality.[57,58] The increasing incidence of such anomalies over the past 50 years concomitant with the increased production and use of synthetic chemicals has raised concerns that environmental factors may play a role in these problems.[17,47] It is now well documented from wildlife studies and accompanying laboratory data that a number of synthetic and natural chemicals commonly found in the environment can mimic or antagonize hormones or otherwise interfere with the development and function of the endocrine and reproductive systems.[59,60] The offspring of pregnant mice exposed in utero to both estrogen and prednisone have been shown to develop hypospadias.[61] Whether endocrine disrupters are having an impact on human male reproductive health and on hypospadias in particular is difficult to determine.[62] Regardless, public health agencies worldwide are increasingly concerned about endocrine disruption and it remains an active area of research.[63–65]

## Normal and Hypospadiac Penile Anatomy

Surgical repair of hypospadias requires an expert understanding of the normal anatomy of the penis, as well as an understanding of the anatomy of the hypospadiac penis. The human penis consists of paired corpora cavernosa covered by a thick, elastic tunica albuginea, with a midline septum (Fig. 121-7).[9,66–69] The urethral spongiosum lies in a ventral position, intimately engaged between the two corporal bodies. The Buck fascia surrounds the corpora cavernosa and splits to contain the corpus spongiosum in a separate compartment. The neurovascular bundle lies deep to the Buck fascia, and where the two crural bodies join to form the corporal bodies, the neurovascular bundle completely fans out around the corpora cavernosa, all the way to the junction of the corpus spongiosum (see Figs. 121-6 and 121-7).[68,70] This concept disagrees with the classic dogma that the neurovascular bundle lies in the 11 o'clock and 1 o'clock positions. Superficial to the Buck fascia is the dartos fascia, which lies immediately beneath the skin. This fascia contains the blood supply to the prepuce. The prepuce is supplied by two branches of the inferior external pudendal arteries, the superficial penile arteries.[71] These arteries divide into the anterolateral and posterolateral branches. In hypospadias surgery, the island flap is typically based on the anterolateral superficial vessels. The onlay island flap, tubularized island flap, and de-epithelialized pedicle flap are dependent on careful preservation of these blood vessels. The outer skin survives from the intrinsic subcutaneous vessels.

Compared with the normal penis, the anatomy of the hypospadiac penis is no different in terms of neuronal innervation, corpora cavernosa and tunica albuginea architecture, and blood supply, except at the region of the abnormal urethral spongiosum and glans (Figs. 121-8 and 121-9).[66,72] The nerves in both the normal and the hypospadiac penis start as two well-defined bundles superior and slightly lateral to the urethra. As the two crural bodies converge into the bodies of the corpora cavernosa, the nerves diverge, spreading around the cavernosal bodies up to the junction with the urethral spongiosum, not limiting themselves to the 11 and 1 o'clock positions (see Figs. 121-7 and 121-8). The 12 o'clock position in a hypospadiac penis is spared of neuronal structures, just as in a normal penis. At the hilum of penis where the bodies of the corpora start to separate, the cavernous nerve sends nNOS-positive fibers to join the dorsal nerve of the penis, thereby changing the functional characteristics of the distal penile dorsal nerve (see Fig. 121-8). Similarly, the nNOS-negative, ventrally located perineal nerve originating from the pudendal nerve becomes nNOS reactive at the cavernosa-spongiosum junction. The redundant wiring in the penis may be important in the preservation of erectile function.[68]

The most striking difference between the normal penis and the hypospadiac penis is a difference in vascularity (see Fig. 121-9). The hypospadiac penis has large endothelium-lined vascular channels filled with red blood cells on the abnormal ventral shaft. In contrast, the normal penis has well-defined, small capillaries around the urethra, fanning into the glans. Anatomic studies of the urethral plate show no evidence of fibrosis or scarring.[73] The urethral plate is well vascularized, has a rich nerve supply, and has an extensive muscular and connective tissue backing (Fig. 121-10). These features may explain the success of incorporating the urethral plate or abortive spongiosum into hypospadias reconstruction.[74,75]

Hypospadias repair requires attention to three major anatomic defects: (1) abnormal urethral meatus, (2) penile curvature, and (3) foreskin defect and, in more severe cases, scrotal anomalies.

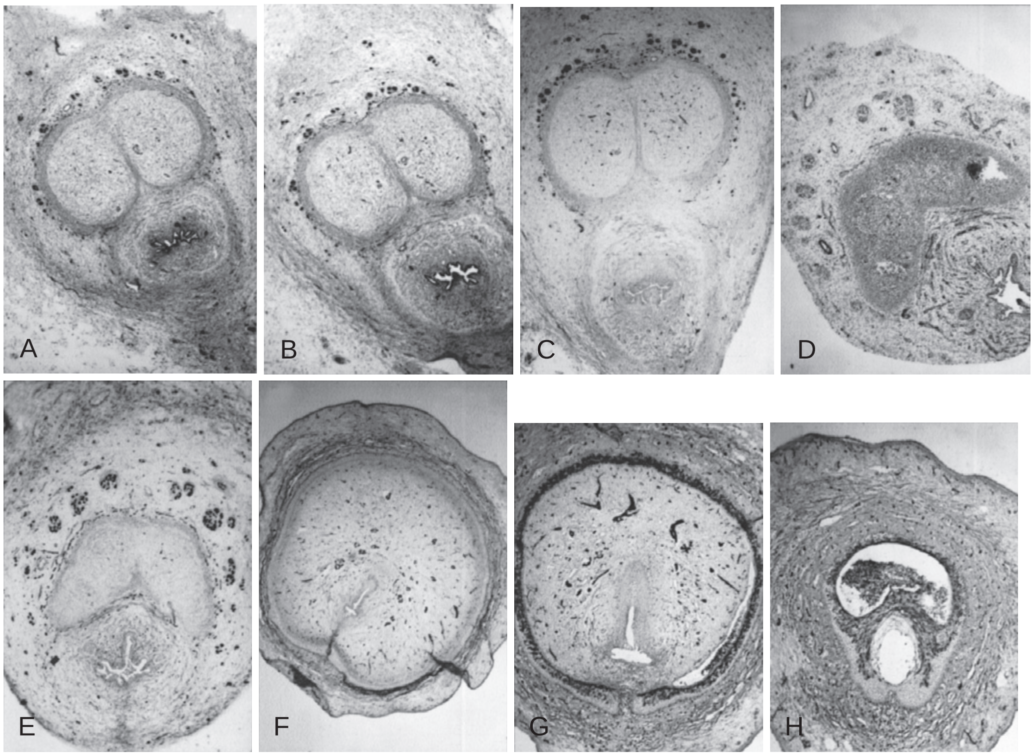


**FIGURE 121-7** Normal human fetal penis at 25 weeks' gestation. **A** to **H,** Transverse sections, distal to proximal, immunostained with neuronal marker S-100 (25×). Note localization of the S-100 nerve marker in brown, completely surrounding the cavernous bodies up to the junction with the urethral spongiosum along the penile shaft, except at the 12 o'clock position (**A** to **D**). On the proximal penis at the point where the corporal bodies split into two **(E)** and continue in a lateral fashion inferior and adjacent to the pubic rami, the nerves localize to an imaginary triangular area at the 11 and 1 o'clock positions. At this point **(E),** the nerves reach their farthest vertical distance from the corporal body (about half the diameter of the corporal body) and continue **(F, G)** in a tighter formation at the 11 and 1 o'clock positions, well away from the urethra. (From Baskin LS, Erol A, Li YW, Cunha GR: Anatomical studies of hypospadias. J Urol 1998;160:1108-1115.)

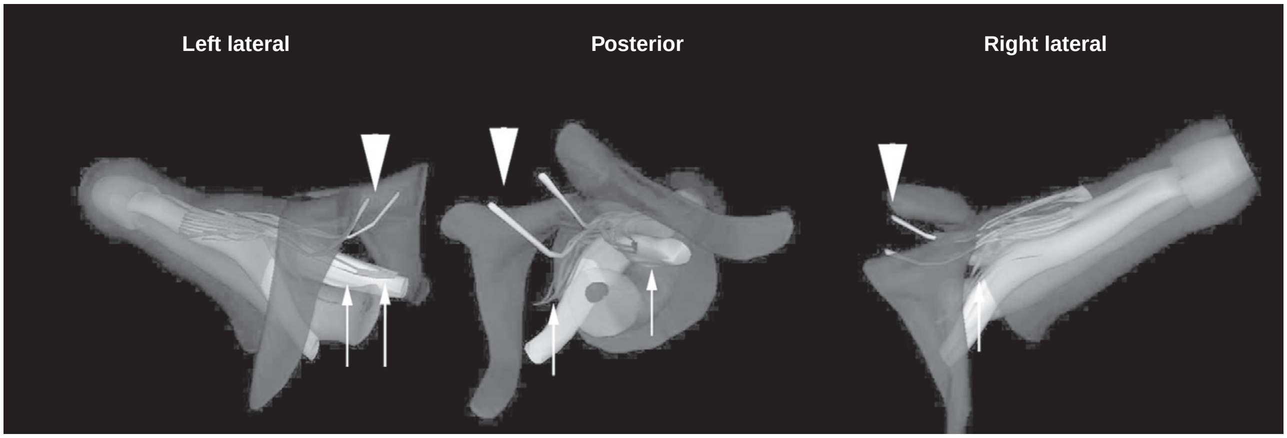


**FIGURE 121-8** Computer-generated three-dimensional reconstruction of the normal human fetal penis at 27 weeks' gestation. Note that the pathway of the cavernosal nerves (*white arrows*) and dorsal nerves (*arrowheads*) is away from the origin of the crural bodies (*white*), which is along the ischial tuberosity. The cavernosal nerves follow a more direct pathway to reach the penile hilum, where they penetrate the corporal bodies under the pubic arch. As the cavernosal nerves travel close to the penile hilum, they send interconnecting fibers to the dorsal nerves, with subsequent positive immunostaining for nNOS. nNOS-positive dorsal nerves travel on the corporal bodies (*gray*) to the glans. As the dorsal nerves of the penis change from nNOS-negative immunostaining character into nNOS positive, the proximal nNOS-negative perineal nerves turn into nNOS-immunoreactive nerves.

## MEATAL ABNORMALITIES

Hypospadias is characterized primarily by location and configuration abnormalities of the urethral meatus. The urethral meatus may be located only slightly ventrally, just below a blind dimple at the normal meatal opening on the glans, or it may be so far back in the perineum that it appears as "vaginal hypospadias."[76] Most patients present with the meatus in one of the many transitional forms. The meatus is encountered in a variety of configurations in terms of form, diameter, elasticity, and rigidity. It can be fissured in both transverse and longitudinal directions, or it can be covered with delicate skin. In the

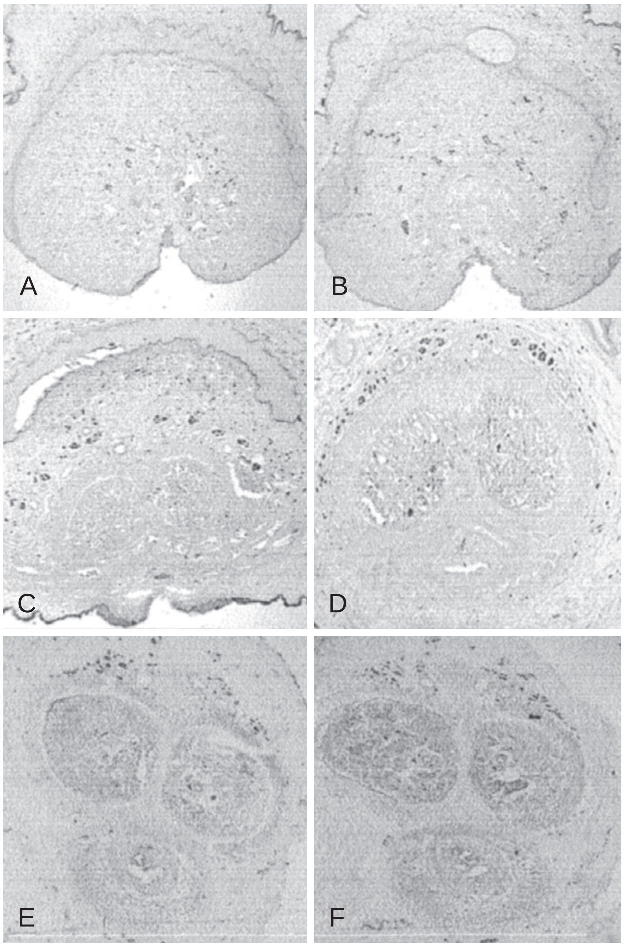


**FIGURE 121-9** Hypospadiac penis at 33 weeks' gestation. **A** to **F,** Transverse sections, distal to proximal, immunostained with neuronal marker (dark staining) S-100 (20×). Note that the anatomy of the hypospadiac penis is the same as the normal penis, except for the abnormal formation of the distal urethra and glans (**A** to **C**). (From Baskin LS, Erol A, Li YW, Cunha GR: Anatomical studies of hypospadias. J Urol 1998;160:1108-1115.)

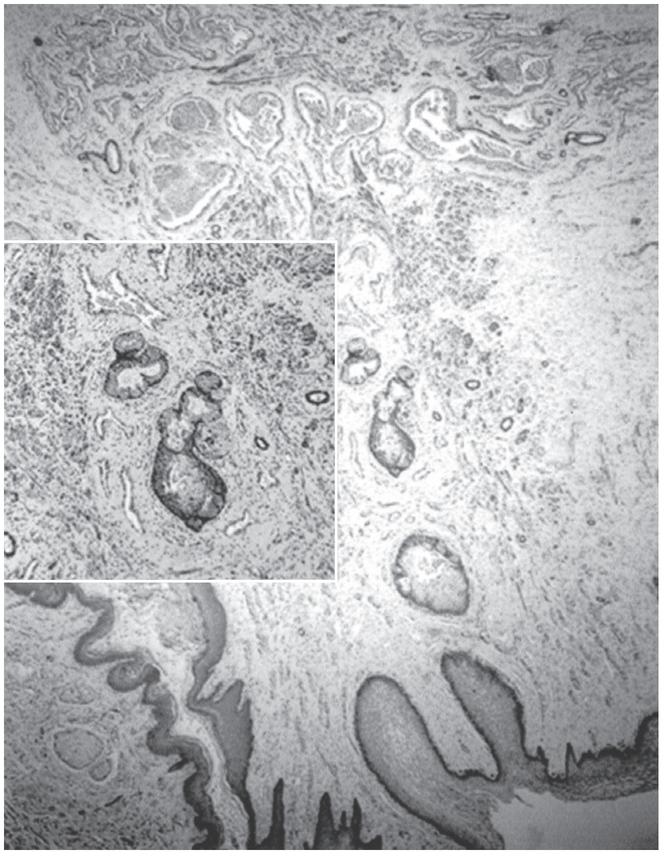

**FIGURE 121-10** Urethral plate in a newborn human penis with proximal hypospadias (smooth muscle alpha actin immunostaining, 25×). The urethral plate is well vascularized, without any evidence of fibrosis or scarring. Epithelial nest or an abortive attempt at the formation of the urethra is seen within the plate (*inset*).

case of the megameatus intact prepuce variant, the distal urethra is enlarged, tapering to a normal caliber in the penile shaft.[77] Often, there is an orifice of a periurethral duct located distal to the meatus that courses dorsal to the urethral channel for a short distance. It has a blind ending and does not communicate in any way with the urinary stream. The periurethral duct corresponds with the Guérin sinus or Morgagni lacunae.[78] Unless these ducts are inadvertently closed, leading to a blind-ending epithelial pouch, they are of no clinical consequence.

## PENILE CURVATURE

The curvature of the penis is caused by a deficiency of the normal structures on the ventral side of the penis. The causes of penile curvature are diverse: a skin deficiency, a dartos fascial deficiency, a true fibrous chordee with tethering of the ventral shaft, or deficiency of the corpora cavernosa on the concave (ventral) side of the penis.

Occasionally other penile anomalies, which represent variations of the embryologic defect causing hypospadias, are reported. They can be characterized as a defect in the course of the urethra (congenital urethral fistula) and a group of defects characterized by curvature of the penis (chordee) without hypospadias.[80,81]

## SKIN AND SCROTAL ABNORMALITIES

The skin of the penis is radically changed as a result of the disturbance in the formation of the urethra. Distal to the meatus, there is often a paucity of ventral skin, which may contribute to penile curvature. The frenulum is always absent in hypospadias. Vestiges of a frenulum are sometimes found inserting on either side of the open navicular fossa.

The skin proximal to the urethral meatus may be extremely thin, to the extent that a catheter or probe passed proximally may be readily apparent through the tissue-paper thickness of skin. The urethral plate extending from the meatus to the glanular groove may be well developed. Even with a meatus located quite proximal on the shaft, this normal urethral plate is elastic and typically nontethering. Artificial erection demonstrates no ventral curvature in these situations. A normal urethral plate may be incorporated into the surgical repair. However, if the urethral plate is underdeveloped, it will act as a tethering fibrous band that bends the penis ventrally during artificial erection. When this fibrous tissue is divided, the penis frequently straightens.

Normally, the genital tubercle should develop in a cranial position above the two genital swellings. The penis may be caught between the two scrotal halves and become engulfed with fusion of the penoscrotal area. The boundary between the penis and scrotum may be formed by two oblique raphes that extend from the proximal meatus to the dorsal side of the penis.

## TREATMENT

The object of therapy is to reconstruct a straight penis with a meatus as close as possible to the normal site (ventrum of the terminal aspect of the glans) to allow a forward-directed urine stream and normal coitus. There are five basic phases for a successful hypospadias outcome: (1) orthoplasty (straightening), (2) urethroplasty, (3) meatoplasty and glanuloplasty, (4) scrotoplasty, and (5) skin cover. These elements can be applied sequentially or in various combinations to achieve surgical success (Fig. 121-11). They are described in conjunction with a number of specific surgical techniques in this section.

## DISTAL OR ANTERIOR HYPOSPADIAS

The treatment of distal hypospadias is dependent on the cultural preference of the child's family. Many patients with distal hypospadias do not have a functional defect, lack significant penile curvature, and will be able to stand and void with a straight stream. Therefore the goal of placing the meatus in its normal position within the glans is essentially cosmetic. The outcome needs to be as close to perfect as possible. The present standard is outpatient surgery. The technique chosen depends on the anatomy of the hypospadiac penis.

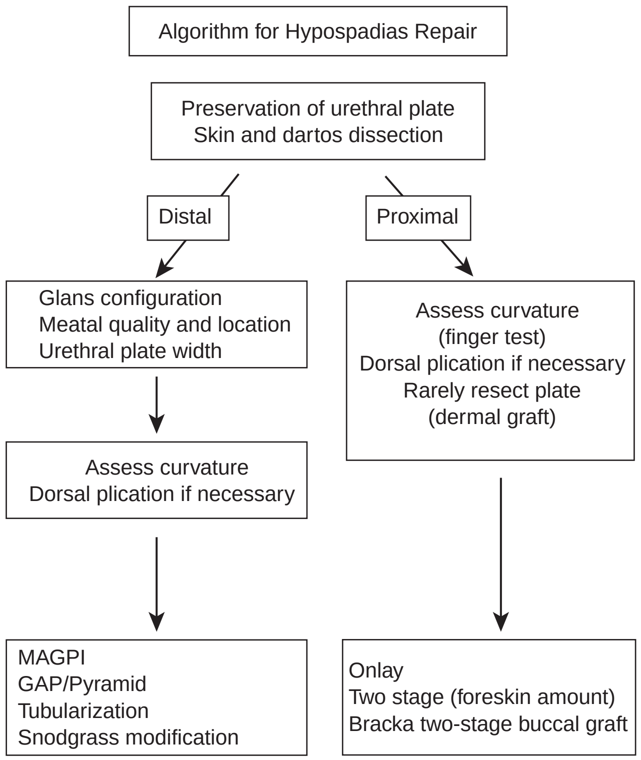


**FIGURE 121-11** Algorithm for hypospadias repair. *GAP,* Glans approximation procedure; *MAGPI,* meatal advancement glansplasty.

The most common procedures performed presently are the meatal advancement with glansplasty incorporated (MAGPI), the glans approximation procedure (GAP), primary tubularization, the Mathieu or flip-flap, and the Duplay or primary tubularization with the incision of the urethral plate (Snodgrass modification) when the plate is too small for primary closure.[75,82–86]

### MAGPI Technique

The MAGPI technique was devised by Duckett in 1981. This technique provides outstanding results in appropriately selected patients. The hypospadiac penis that is amenable to the MAGPI technique is characterized by a dorsal web of tissue within the glans that deflects the urine from either a coronal or a slightly subcoronal meatus. The urethra itself must have a normal ventral wall, without any thin or atretic urethral spongiosum. The urethra must also be mobile so that it can be advanced into the glans (Fig. 121-12).

A circumferential incision is made around the corona proximal to the meatus on the ventrum and 5 mm below the coronal margin to create a Firlit collar on the dorsum (see Fig. 121-12, *A*). The meatal advancement of the dorsal urethral wall is accomplished by a Heineke-Mikulicz vertical incision and horizontal closure (see Fig. 121-12, *B*). More commonly, a wedge of glanular tissue that includes the glanular meatal wall is removed. The horizontal closure flattens out the glanular bridge and permits the dorsal urethra to be advanced out onto the glans tissue to the apex of the glanular groove, where it is sutured with interrupted 7-0 Vicryl (see Fig. 121-12, *C*). This flattens the deflecting ridge of glans and permits the stream to be directed forward.

The glansplasty is made by reconfiguring the flattened glans into a conical shape (see Fig. 121-12, *D*). By rotating the lateral wings around to the midline proximal to the meatus, a proper conical glans shape can be recreated. The deep glanular tissue is brought together with interrupted 6-0 Vicryl, and the superficial epithelial edges are closed with 7-0 chromic suture (see Fig. 121-12, *E*). In this way, mesenchymal glans tissue heals to glans tissue between the epithelial layers of the urethra and the outer epithelium of the glans; this prevents meatal retraction. The rotation of the glans wings reconfigures a nearly normal glanular appearance. When there is ventral skin deficiency, dorsal preputial skin can be transposed in a Byar flap fashion to the ventrum (see Fig. 121-12, *E*). No stents or catheters are required for diversion in children younger than 12 months. Preservation of the foreskin is possible with the MAGPI procedure as long as penile curvature is minimal.[46,87] Polus and Lotte,[122] Gilpin,[66] and Snodgrass[88] demonstrated foreskin preservation in anterior hypospadias repair without chordee (Fig. 121-13).[88–90]

### GAP Procedure

The GAP procedure is applicable in a small subset of patients with distal hypospadias who have wide and deep glanular grooves.[86] These patients do not have a bridge of glanular tissue that typically deflects the urine stream, as seen in patients who would be more appropriately treated with the MAGPI procedure. In the GAP procedure the wide-mouthed urethra is tubularized primarily, over a stent (Fig. 121-14). Ventral glanular tilt, meatal retraction, and splaying of the urine stream can result from the inappropriate use of the MAGPI technique in these circumstances.

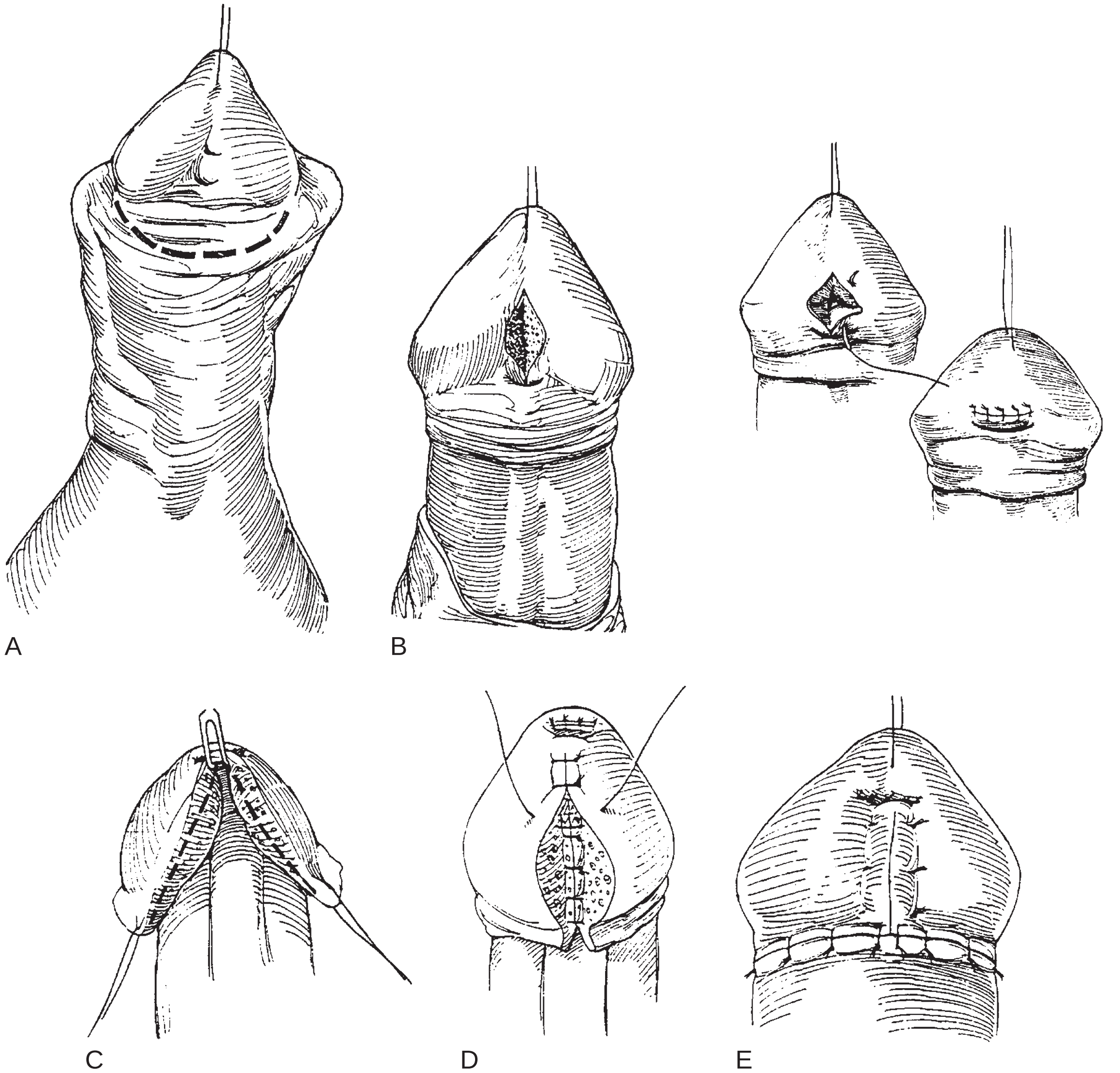


**FIGURE 121-12** MAGPI hypospadias technique. **A,** Initial circumferential subcoronal incision. **B,** Heineke-Mikulicz closure of the dorsal meatus after excision of the dorsal web skin bridge. **C,** Exposure of the glans mesenchyme, the most critical step, is accomplished by trimming the excess skin (*dashed lines*) and advancing the mobile urethra with the use of a 6-0 chromic suture or a skin hook. **D,** Two-layer closure of the glans mesenchyme over the advanced urethra, allowing for a normal-appearing glans with excellent support of the urethra. **E,** Skin closure with a sleeve approximation of the penile shaft skin. If there is ventral skin deficiency, a Byar flap rearrangement with a standard midline seam is appropriate. (From Hinman F Jr: Atlas of Pediatric Urologic Surgery. Philadelphia, WB Saunders, 1994, pp 575-578.)

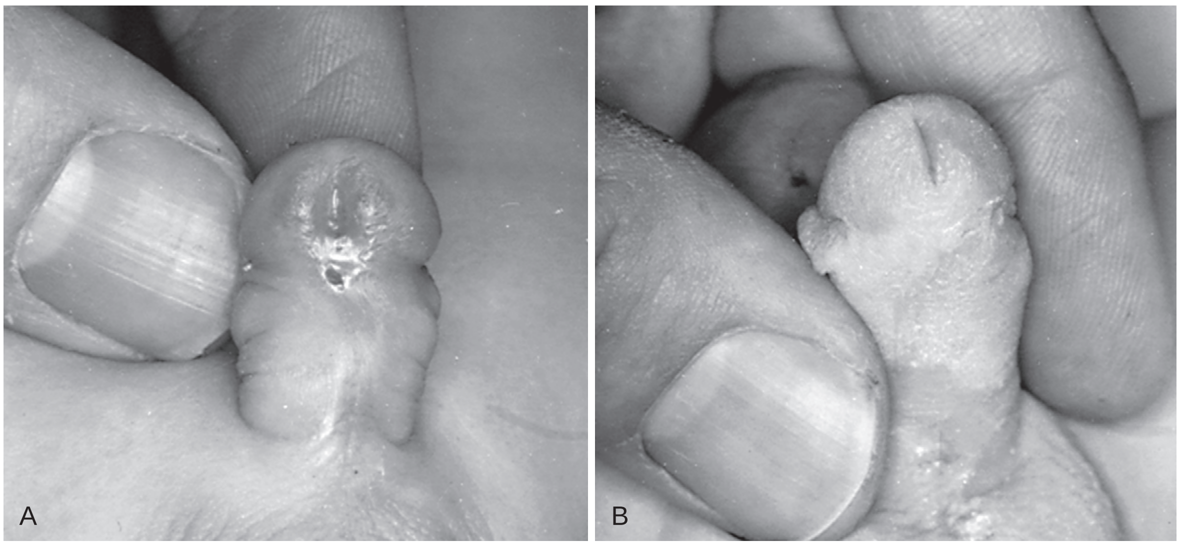


**FIGURE 121-13** **A,** Preoperative patient with anterior hypospadias amenable to the MAGPI procedure. Note the dorsal web of tissue. **B,** Postoperative result of the MAGPI procedure. (From Duckett JW, Baskin LA: Hypospadias. In Gillenwater J, Grayhack JT, Howards SS, Duckett JW (eds): Adult and Pediatric Urology, 3rd ed. St Louis, Mosby-Year Book, 1996.)

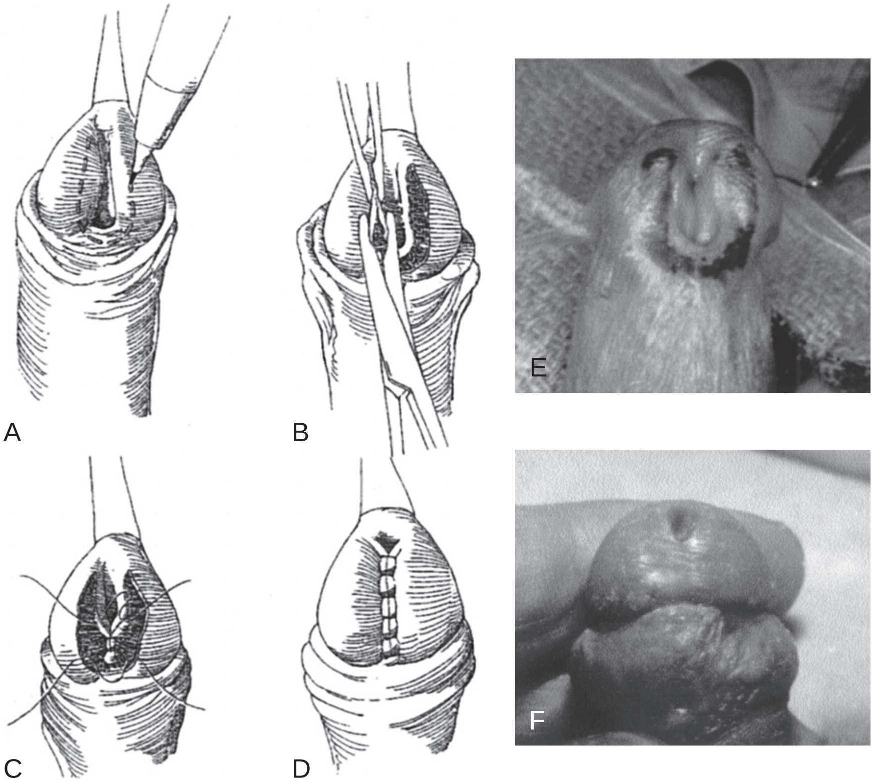


**FIGURE 121-14** GAP hypospadias technique. **A,** Initial incision. **B,** Exposure of the glans mesenchyme by de-epithelialization of tissue. This is critical for a two-layer glans closure and provides good support of the urethroplasty. **C,** Tubularization of the neourethra, followed by glans closure. **D,** Completed repair. **E,** Anterior hypospadias with a patulous fish-mouth urethra amenable to the GAP procedure. **F,** Postoperative outcome.

## Urethral Mobilization

Another method of dealing with a subcoronal meatus is urethral mobilization. Reported as far back as 1917 by Beck,[91] urethral mobilization was revived by Koff and de Sy.[92–94] This technique offers little advantage over the other distal techniques and requires a more extensive procedure to mobilize the penile urethra potential compromising the urethra's vascular supply. The meatal stenosis rate is significant.

## Pyramid Procedure

In 6% of those with distal hypospadias, the prepuce is intact and a megameatus exists under the normal foreskin, with a wide glanular defect and no penile curvature (Fig. 121-15).[77] These anomalies may be recognized only after circumcision is performed, potentially making correction more complex. Duckett and Keating designed the "pyramid" technique to repair the megameatus variant.[77] The enormous distal urethra is carefully dissected down the shaft of the glans and distal penis by way of a four-quadrant exposure (hence the pyramid designation). The urethra is tapered and buried in the glans, similar to an epispadias repair (see Fig. 121-15, *C*).

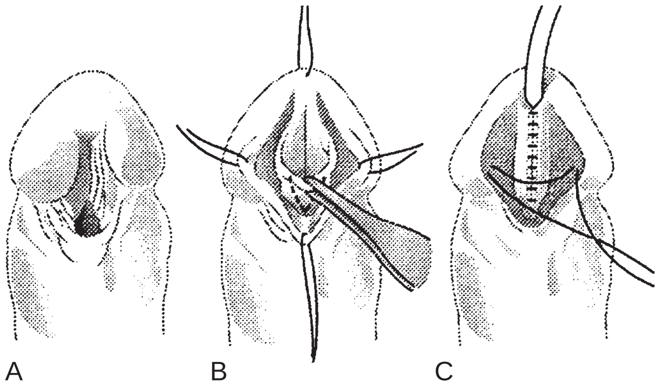


**FIGURE 121-15** Megameatus hypospadias repaired by the pyramid procedure. **A,** Patients with a megameatus have a wide glanular defect and no penile curvature. Calibration reveals that the meatus is 22 to 24 Fr in a newborn baby, compared with the normal caliber of 12 to 14 Fr. Often this anomaly is recognized only after circumcision. Correction, however, is the same as if the foreskin were intact. **B,** The technique involves careful periurethral dissection, exposing the urethra and glans tissue and then removing a wedge of the abnormally enlarged urethra. **C,** The exposed glans tissue is closed over the newly closed neourethra. Technically, this procedure involves careful dissection down the shaft and distal penis by way of a four-quadrant exposure, hence its designation as the *pyramid technique.* Tapering the urethra and burying it into the glans are similar to the technique used for epispadias.

## Mathieu or Perimeatal-Based Flap Procedure

When the meatus is too proximal on the shaft to perform a MAGPI procedure, or when there is no deep glanular groove appropriate for a GAP or in situ tubularization technique (see later), the meatus is advanced onto the glans using the technique described in 1932 by the French surgeon Mathieu.[84] This technique involves the use of a perimeatal skin flap, based on the intrinsic blood supply. To ensure viability, the length-to-width ratio of the skin flap should not exceed 2:1. The flap has also been used essentially as a free skin graft, with no attempt made to preserve any of the subcutaneous tissue. A pedicle of foreskin is brought around, as in a vascularized flap technique, and used as a recipient bed. When designing a Mathieu repair (Fig. 121-16), the ventral skin must be able to be advanced to its new location on the glans. Some modifications of the Mathieu procedure involve a second layer as a subcutaneous pedicle.

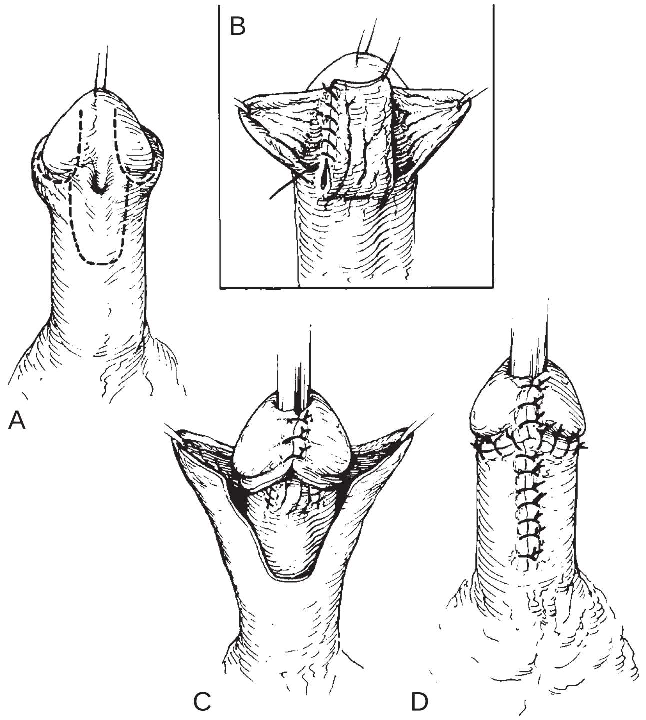


**FIGURE 121-16** Mathieu procedure. **A,** *Dotted lines* outline the skin flaps. **B,** The proximal flap is rotated, and the lateral glans flaps are developed. **C,** The glans flaps cover the neourethra, and preputial skin is moved, if necessary. **D,** Completed repair. (From Duckett JW: Hypospadias. In Walsh PC, Gittes RF, Perlmutter AD, et al [eds]: Campbell's Urology, 5th ed. Philadelphia, WB Saunders, 1986, pp 1969-1999.)

Redman[95] revived the Barcat[96] modification of the Mathieu procedure by mobilizing a glans flap in addition to the perimeatal-based flap and splitting the glans dorsally to bury the urethral extension farther toward the apex of the glans. Koff and colleagues[93] have extensive experience with this technique and have reported excellent results.

### Tubularized Plate Urethroplasty with and Without Snodgrass Modification

Historically, if the urethral groove was not wide enough for tubularization in situ, an alternative approach such as the Mathieu technique or, for more severe hypospadias, a vascularized pedicle flap was taken. More recently, the concept of incising the urethral plate, with subsequent tubularization and secondary healing, was introduced by Snodgrass (Fig. 121-17).[75] Short-term results have been excellent, and this procedure is enjoying extensive popularity.[85] One appealing aspect is the slitlike meatus, which is created with a dorsal midline incision. This technique has also been applied to more posterior forms of hypospadias.[97] Theoretically, one concern is the possibility of meatal stenosis from scarring, as occurs in patients with urethral stricture disease; in the latter, direct-vision internal urethrotomy often leads to recurrent stricture. However, reports of meatal stenosis have been rare.[98] In hypospadias, the native virgin tissue, with its excellent blood supply and large vascular sinuses, seems to respond to primary incision and secondary healing without scarring.

The tubularized incised plate urethroplasty is conducive to preservation of the foreskin (Fig. 121-18).[88] To preserve the foreskin, the incision is made only on the ventrum; therefore

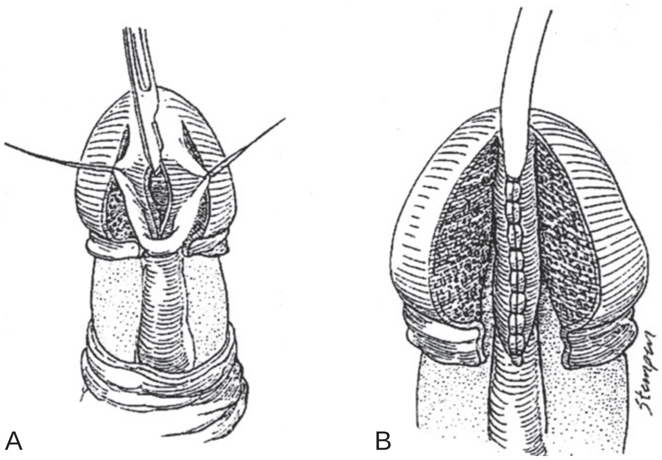


**FIGURE 121-17** Tubularized plate urethroplasty. **A,** Deep incision in the urethral plate down to corporal tissue. **B,** Tubularization of the neourethra, with subsequent glansplasty.

patients with significant penile curvature are not candidates for this procedure. A three-layer closure of the prepuce prevents foreskin fistula. The fact that the foreskin cannot be used as a de-epithelialized flap theoretically increases the possibility of urethral fistula.

## POSTERIOR HYPOSPADIAS

### Urethral Plate Preservation

Duckett popularized the concept of preserving the urethral plate, which is now standard practice for the repair of almost all hypospadias cases.[83,99] The urethral plate serves as the dorsal urethral wall, and the ventral urethra is created by a vascular onlay flap of tissue from the inner prepuce. Extensive experience has shown that the urethral plate is rarely the cause of penile curvature (Fig. 121-19). This knowledge was gained by repetitive resection of the urethral plate and subsequent artificial erection, which showed no improvement in correction of the penile curvature (see Fig. 121-19).[99] Further efforts and experience have shown that the urethral plate is typically supple and pliable and that ancillary penile strengthening procedures such as midline dorsal plication (see later), with preservation of the urethral plate, have led to fewer complications such as fistula and stenosis at the proximal anastomosis.[99,100]

The concept of preserving the urethral plate but undermining it[108,110] and exposing the corporal bodies—with the goal of releasing the chordee tissue—has been advocated.[101,102] Careful anatomic studies have shown that there is an extensive network of blood vessels supplying the urethral plate in the hypospadiac penis, and lifting the urethral plate defeats the purpose of preservation by violating this intricate blood supply.[66] Historically, posterior hypospadias was approached by complete resection of the abnormal urethra and all tissue down to normal corporal bodies. The urethra was replaced by a tubularized vascular preputial flap from either the inner or outer prepuce.[103–105] Presently, in the majority of posterior hypospadias cases including perineal hypospadias, the urethral plate can be preserved and a vascularized flap used in an onlay fashion. In the rare case in which the urethral plate needs to be resected, a two-stage technique can be used (see later).

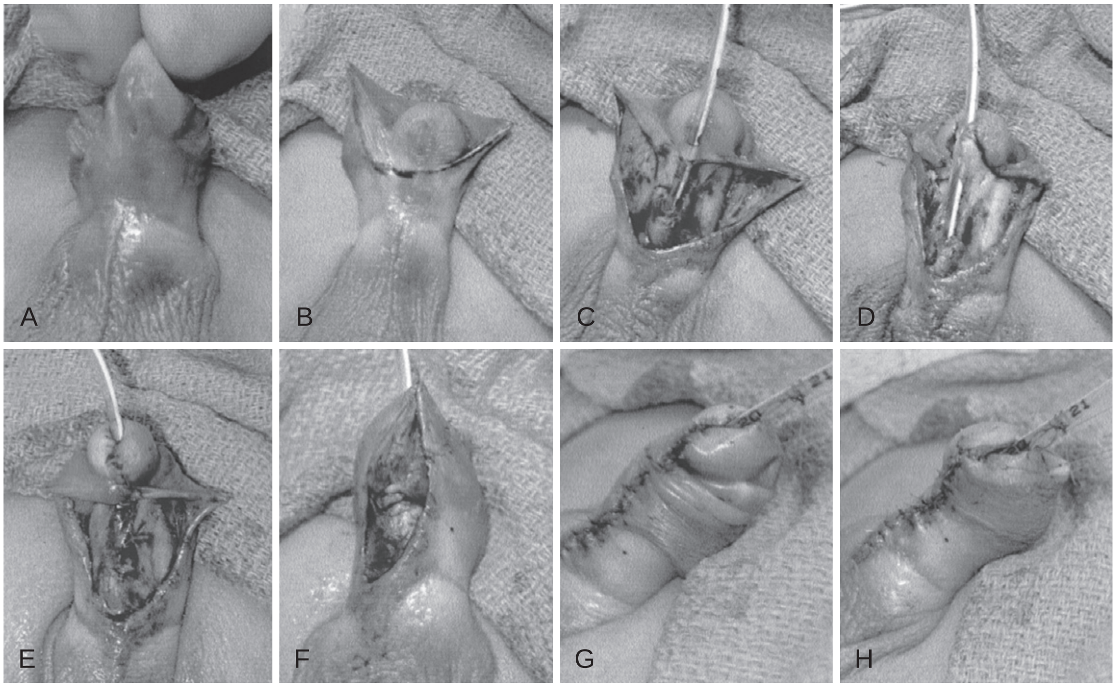


**FIGURE 121-18** Foreskin preservation technique for distal hypospadias. **A,** Distal hypospadias. **B,** The incision is marked for foreskin preservation. **C,** Dissection of ventral skin. Note the thin spongiosum with the distal urethra exposed. **D,** Glans wings have been mobilized, and the distal urethroplasty is completed by the Snodgrass technique. **E,** Two-layer glansplasty. **F,** Three-layer foreskin reconstruction: (1) inner prepuce, (2) subcutaneous tissue to prevent foreskin fistulas, and (3) outer foreskin. **G,** Completed repair with foreskin retracted. **H,** Completed repair.

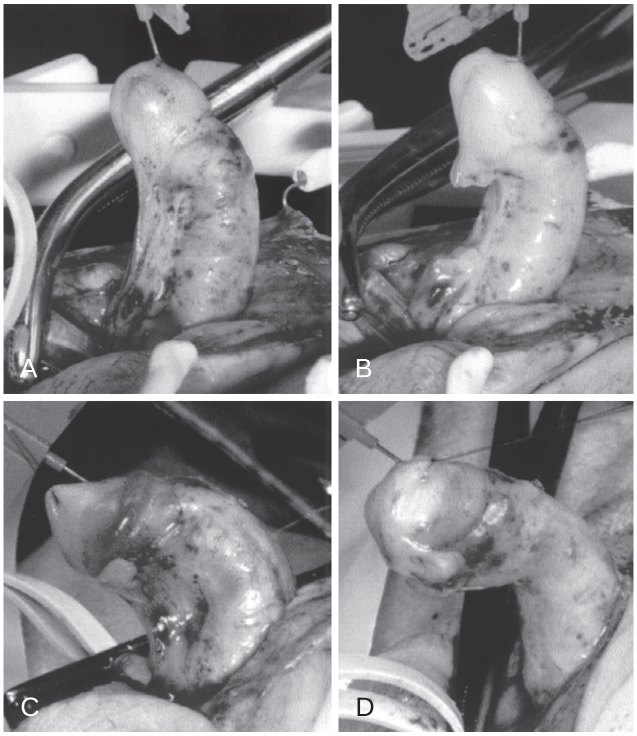


**FIGURE 121-19** **A,** Penile curvature with preservation of the urethral plate. **B,** Resection of the urethral plate with continued severe curvature. **C,** Penile curvature with preservation of the urethral plate. **D,** Resection of the urethral plate with continued severe curvature. Extensive experience has shown that the urethral plate is rarely the cause of penile curvature.

## Onlay Island Flap

The blood supply to the hypospadiac preputial tissue is reliable and easily delineated (see Fig. 121-18).[71,106] The abundance of cutaneous tissue on the dorsum of the penis is vascularized in a longitudinal fashion.[107] This tissue may be dissected from the penile skin, creating an island flap from the inner layer of the prepuce. The blood supply to the dorsal skin of the foreskin and the penile skin comes from its broad base and is not dependent on the subcutaneous tissues, except at the remote edges of the dorsal preputial skin. The tips of the distal portion of the penile skin flaps can be excised and not used in the repair.

All cases of posterior hypospadias (i.e., with or without penile curvature) are approached by initially leaving the urethral plate intact. This technique can be applied to the penile shaft, as well as scrotal and perineal hypospadias. The intact dorsal plate essentially avoids the complication of proximal stricture, and the excellent blood supply has decreased the fistula rate to approximately 15% for all cases of onlay island flap hypospadias repair (Fig. 121-20).[99] For shorter repairs, the flap may be dissected from half the prepuce, as described by Rushton and Belman,[108] leaving the remaining half of the foreskin available for a second layer of coverage. Long-term results with the onlay island flap have been durable.[101,109,110] For severe hypospadias, the prepuce can be designed in a horseshoe style to bridge extensive gaps (see Fig. 121-20, *K*).

## Transverse Tubularized Island Flap

The technique of using the transverse tubularized island flap was used extensively before the concept of preserving the urethral plate (Fig. 121-21). It is still successful in severe

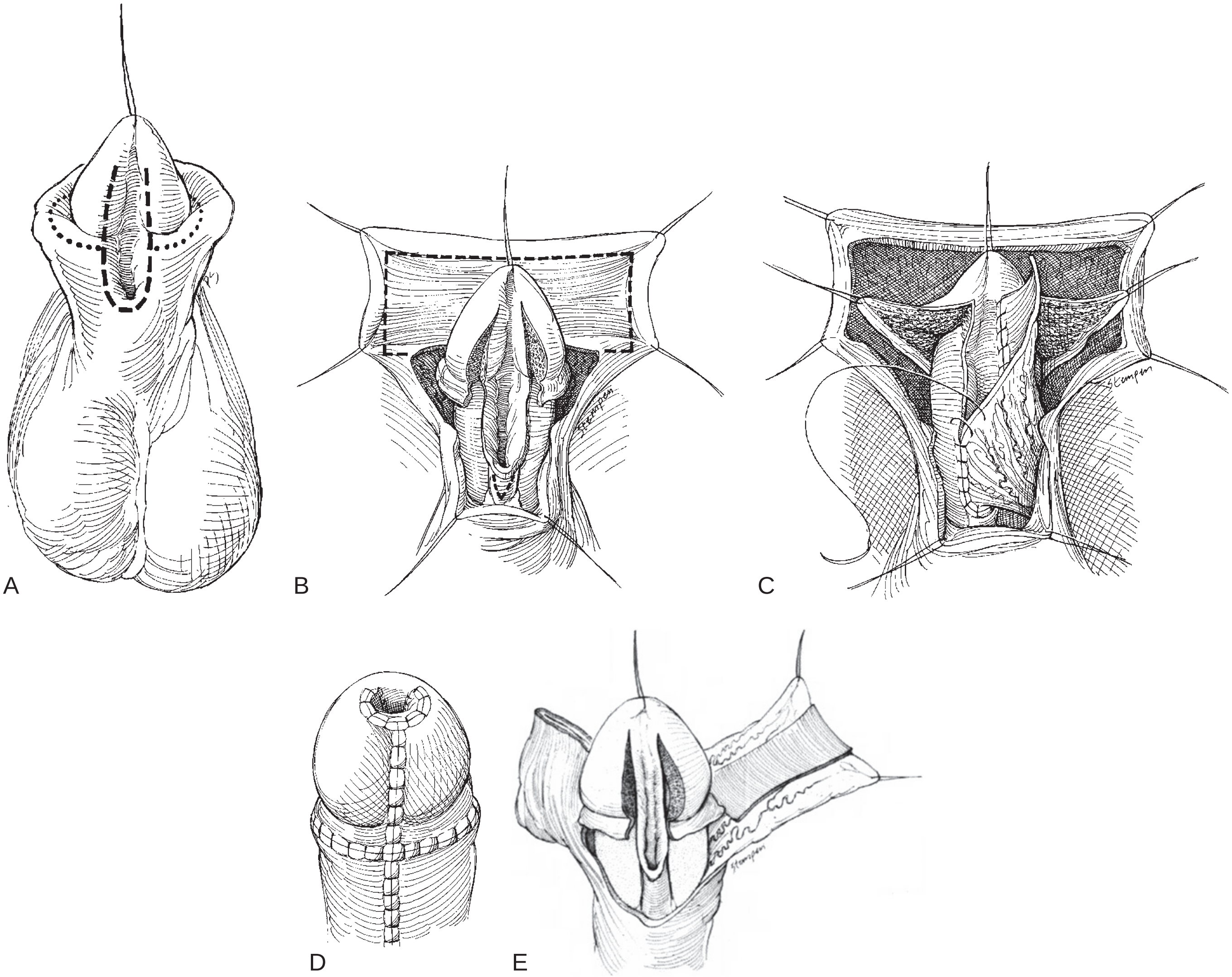


**FIGURE 121-20** Onlay island flap hypospadias repair. **A,** A U-shaped incision is made around the urethral plate, preserving a dorsal urethral strip approximately 8 mm wide. **B,** Takedown of the skin and subcutaneous tissue and outlining of the inner prepuce for the onlay island flap. Glans wings are mobilized along the plane of the corporal body and the glans mesenchyme. **C,** Preservation of the urethral plate with penile curvature in a case of penoscrotal hypospadias. **D,** Suturing of the onlay flap to the urethral plate with running 7-0 sutures. The flap is trimmed to obtain a 12-Fr bougie in a 1-year-old child to prevent the complication of urethral diverticulum, which results from leaving excess tissue. The glans wings are approximated over the new urethra after maturing the meatus. The skin is then closed by a classic Byar flap rearrangement. **E,** The split prepuce in situ technique for dissection of a short vascularized onlay island flap. This method is useful for shorter onlays, leaving the remaining half of the foreskin available for a second layer of coverage.

*Continued*

cases when the urethral plate needs to be resected, although long-term problems with diverticulum have resulted in a high reoperation rate. Technical nuances involve an oblique proximal anastomosis with interrupted sutures to avoid stenosis; fixation of the neourethra to the corporal bodies to prevent diverticulum and improve ease of catheterization; and a wide glans channel made underneath the glans cap, against the corporal bodies to avoid meatal stenosis.[104]

### Two-Stage Hypospadias Repair

An alternative approach for severe hypospadias is to transfer the dorsal prepuce to the ventrum after correcting the penile curvature (Fig. 121-22). In severe cases the urethral plate may need to be resected to correct chordee. Dermal grafting may be required, and performing a urethroplasty on top of the healing graft is not suggested. Instead, Byar flaps can be rotated from the dorsum, setting up ventral coverage for subsequent urethroplasty.[111] Occasionally the chordee can be corrected without resection of the urethral plate. In this case the dorsal skin can be sutured to each side of the preserved urethral plate (see Fig. 121-22, *D*). The second stage is performed at least 6 months after the first stage. To assist the urethroplasty within the glans, dorsal skin can be tucked within the glans wings during the first stage. Subcutaneous secondary coverage of the reconstructed urethra is performed to prevent fistula. In cases where local tissue is not readily available, a tunica vaginalis flap from the testicle can be mobilized and used to cover the urethroplasty.[112–114] Long-term results documented through puberty have been durable.[115]

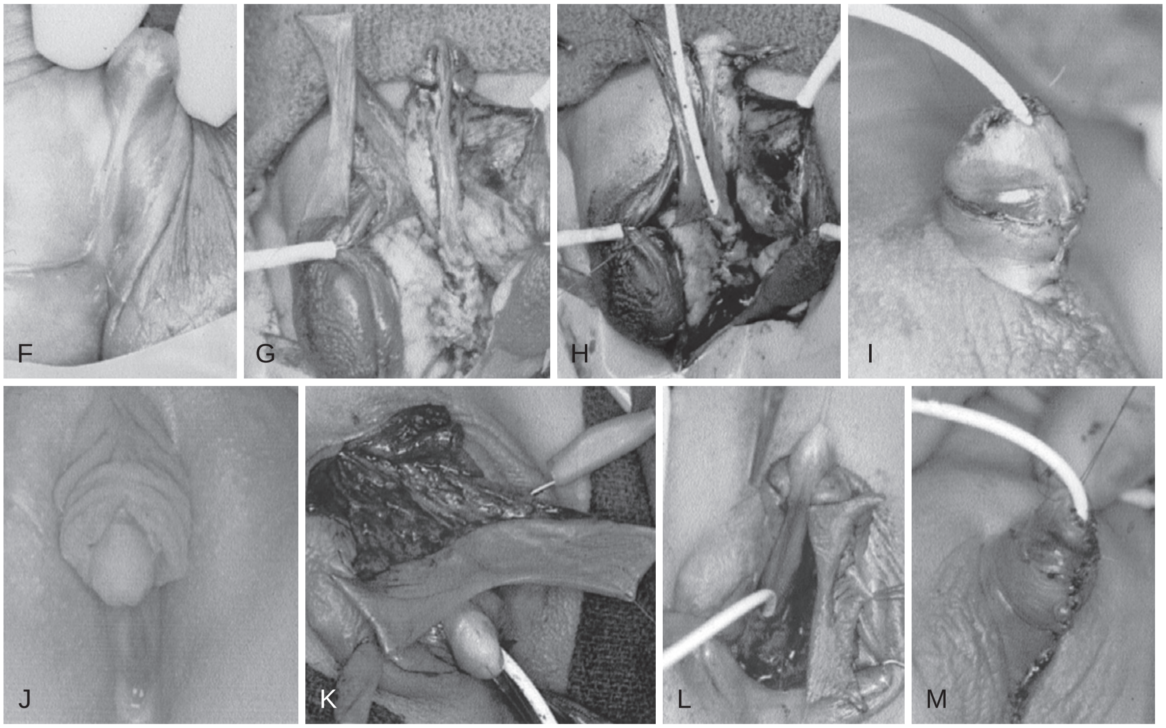


**FIGURE 121-20—CONT'D** **F,** Penoscrotal hypospadias amenable to the onlay island flap technique. **G,** Preservation of the urethral plate and flap dissection. **H,** Suturing of the onlay to the urethral plate. **I,** Completed repair. **J,** Perineal hypospadias. **K,** Horseshoe vascularized onlay island flap to bridge a long urethral deficit. **L,** Onlay flap rotated to bridge the urethral defect. **M,** Completed repair.

### Bracka Two-Stage Buccal Graft Repair

For patients with prior surgery or with severe hypospadias, Bracka described a two-stage buccal graft repair.[116–118] In the first stage the penis is straightened, and the scarred urethra is discarded (Figs. 121-23 and 121-24). Buccal mucosa is harvested from either the cheek or the lip and grafted to the prepared bed.[119] Extensive quilting of the graft is performed to prevent hematoma from lifting off the buccal mucosa. During the first stage, glans wings are mobilized in preparation for the creation of a slitlike meatus during the second stage. The second-stage urethroplasty is undertaken at least 6 months after the first stage. In the second stage, excess buccal mucosa is trimmed off the glans, setting up a two-layer glans closure (see Figs. 121-23 and 121-24). The buccal mucosa is rolled into the new urethra, and subcutaneous tissue is used for secondary coverage.

## PENILE CURVATURE

Correction of penile curvature has evolved along with the concept of preserving the urethral plate. Artificial erection, introduced by Gittes and McLaughlin in 1974, provides a mechanism to check for penile curvature and the success of correction at the time of surgery.[120] A tourniquet is placed at the base of the penis, and a corpus cavernosum is injected with saline. Both corporal bodies fill, so it is possible to determine the extent of curvature and the success after correction. The assurance of complete correction is essential before proceeding to urethroplasty and one-stage repair. There have been no reports of damage to the cavernous tissue with this technique, as long as care is taken to ensure that injectable saline is used.

In reality, all penises have penile curvature during development (Fig. 121-25). The majority of penile curvature resolves when the penile skin is dissected to the penoscrotal junction—hence the term "skin chordee."[121] Curvature may also result from differential growth of the dorsal and ventral aspects of the corpora body.[122] Finally, in rare cases the urethra itself may be short or atretic, requiring resection to correct curvature and subsequent augmentation.

Historically, chordee was corrected by a modification of Nesbit's dorsal plication, taking out wedges of tunica albuginea in an ellipse and closing this with permanent suture.[123] This technique was first described by Syng Physick, the "father of American surgery," in the early nineteenth century. Physick treated chordee by shortening the dorsal tunica albuginea.[124] When the arc of maximal curvature is identified during artificial erection, wedges of tunica albuginea are excised in a stepwise fashion. These diamond wedges are closed transversely with permanent suture until the penis is straight. Nesbit's technique has been modified into dorsal tunica albuginea plication for the correction of penile curvature in the setting of corporal disproportion, as well as hypospadias.[100] On the basis of anatomic studies of the human fetal penis, a simpler approach—placing dorsal midline plication sutures in the nerve-free zone at the 12 o'clock position—is now advocated.[66] Midline dorsal plication avoids the need for mobilization of the neurovascular bundle (Fig. 121-26).[72] Midline plication can be applied to mild to moderate degrees of curvature (Fig. 121-27).[125] If more than two rows of plication sutures or more than four permanent sutures are

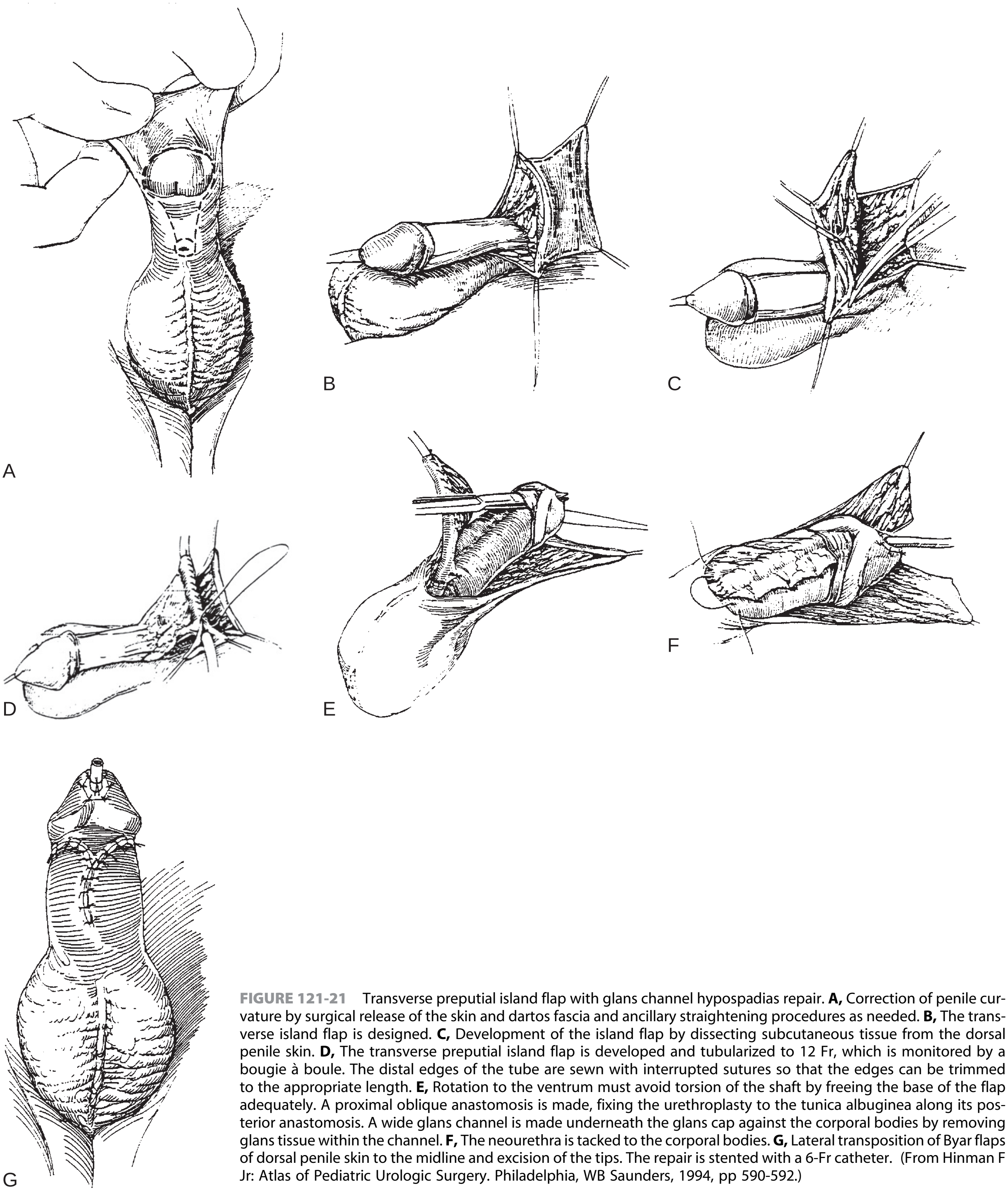


**FIGURE 121-21** Transverse preputial island flap with glans channel hypospadias repair. **A,** Correction of penile curvature by surgical release of the skin and dartos fascia and ancillary straightening procedures as needed. **B,** The transverse island flap is designed. **C,** Development of the island flap by dissecting subcutaneous tissue from the dorsal penile skin. **D,** The transverse preputial island flap is developed and tubularized to 12 Fr, which is monitored by a bougie à boule. The distal edges of the tube are sewn with interrupted sutures so that the edges can be trimmed to the appropriate length. **E,** Rotation to the ventrum must avoid torsion of the shaft by freeing the base of the flap adequately. A proximal oblique anastomosis is made, fixing the urethroplasty to the tunica albuginea along its posterior anastomosis. A wide glans channel is made underneath the glans cap against the corporal bodies by removing glans tissue within the channel. **F,** The neourethra is tacked to the corporal bodies. **G,** Lateral transposition of Byar flaps of dorsal penile skin to the midline and excision of the tips. The repair is stented with a 6-Fr catheter. (From Hinman F Jr: Atlas of Pediatric Urologic Surgery. Philadelphia, WB Saunders, 1994, pp 590-592.)

necessary, however, an alternative approach such as complete resection of the urethral plate and dermal grafting should be considered. Midline dorsal plication has also been effective for recurrent curvature.[126] During artificial erection, if the curvature cannot be corrected with the surgeon's finger, midline dorsal plication is not advised. A glans tilt may also be repaired by permanent sutures on the dorsum, but care must be taken to avoid the neurovascular structures supplying the glans.[18]

In rare cases the tunica albuginea is so deficient on the ventrum that excision of the tunica is required, with replacement

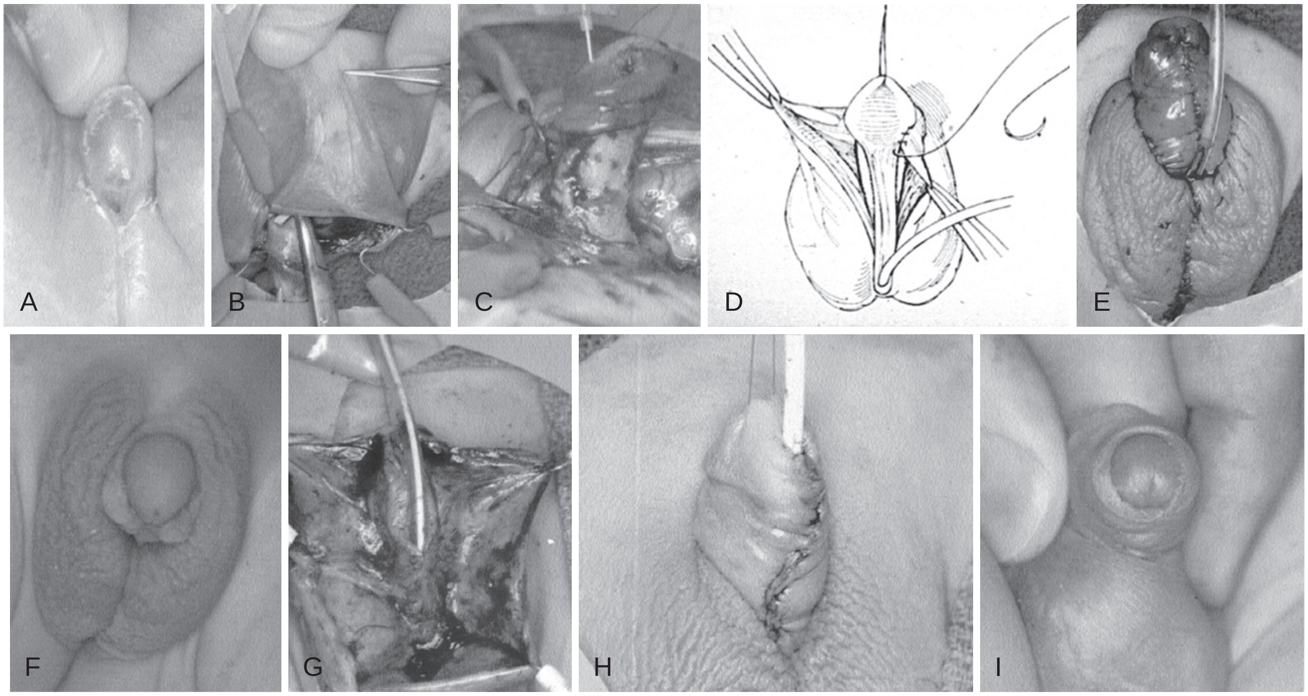


FIGURE 121-22 Two-stage hypospadias repair. The first stage includes correction of penile chordee and transfer of dorsal foreskin to the ventral aspect of the penis. **A,** Scrotal hypospadias with chordee and penoscrotal transposition. **B,** Foreskin attached to the scrotal skin. **C,** Penile straightening with removal of the ventral tethering urethral plate. **D,** In select cases, the urethral plate can be preserved and the dorsal skin split and wrapped to the ventrum. **E,** First stage complete. **F,** Second-stage urethroplasty is done 6 months after the first-stage surgery. **G,** Urethroplasty. **H,** Completed repair. **I,** Six-month follow-up.

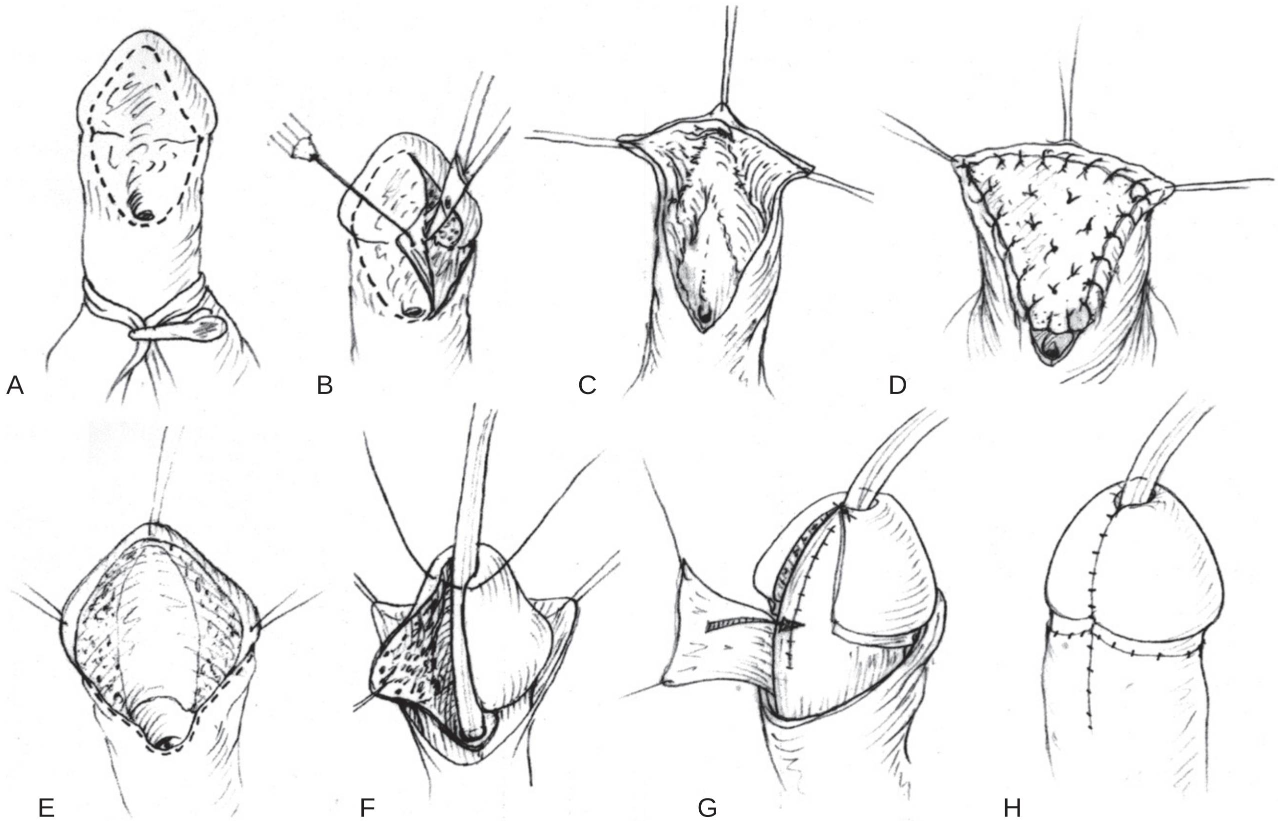


FIGURE 121-23 Two-stage Bracka buccal hypospadias repair. First stage: **A,** Patient with midshaft hypospadias and a paucity of available skin after multiple previous hypospadias repairs. **B,** Resection of scar tissue. **C,** Mobilization of glans wings. **D,** Buccal free graft quilted into the resected scar. The second stage is done after 6 months of healing. **E,** Exposure of the glans mesenchyme, and trimming of the buccal graft for subsequent urethroplasty. **F,** Meatal stitch for start of urethroplasty. **G,** Secondary de-epithelialized pedicle coverage of the urethroplasty. **H,** Two-layer glansplasty and completed repair.

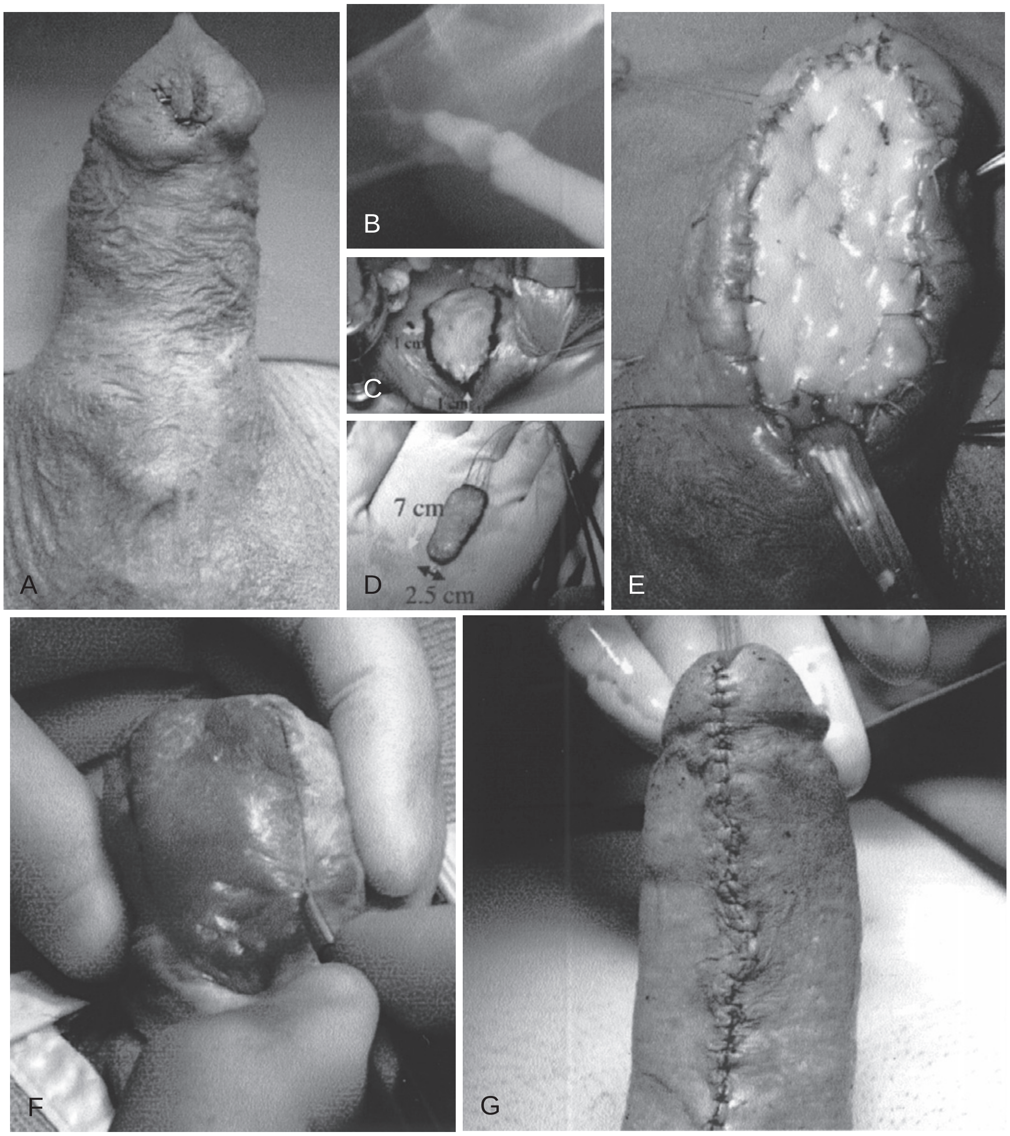


**FIGURE 121-24** **A,** Patient with a distal urethral stricture after multiple previous hypospadias repairs. **B,** Urethrogram. **C,** Outline of buccal mucosa graft harvest. **D,** Free buccal harvest prepared for grafting. **E,** Quilted buccal mucosa graft applied to the ventral penis after resection of scar tissue. **F,** Healed buccal mucosa 6 months after grafting. **G,** Completed repair.

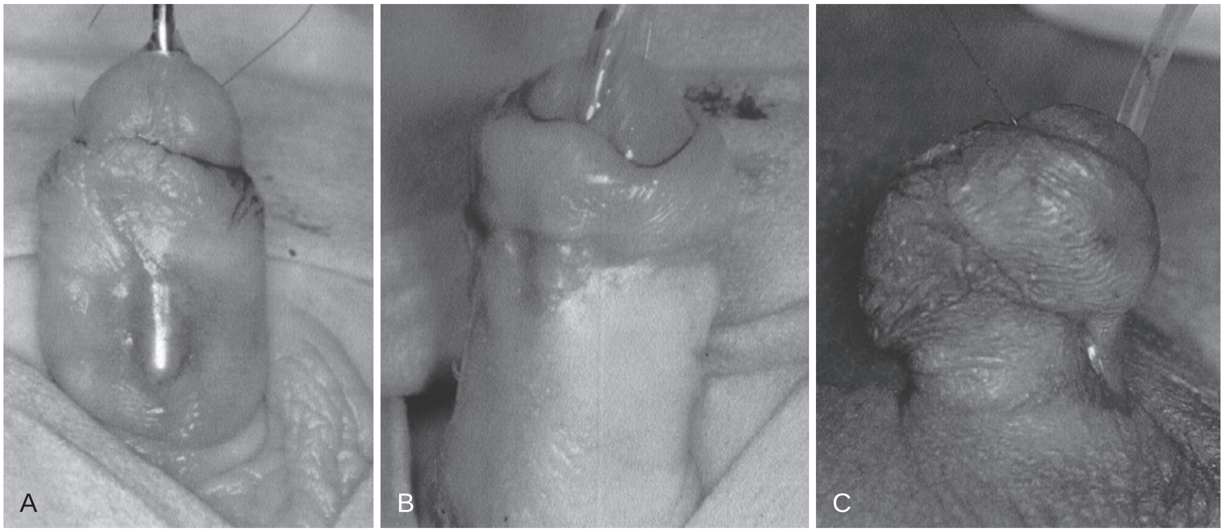


**FIGURE 121-25** **A,** Congenital fistula. **B** and **C,** Chordee without hypospadias. Abnormal development of the urethral spongiosum necessitates urethroplasty and causes penile curvature.

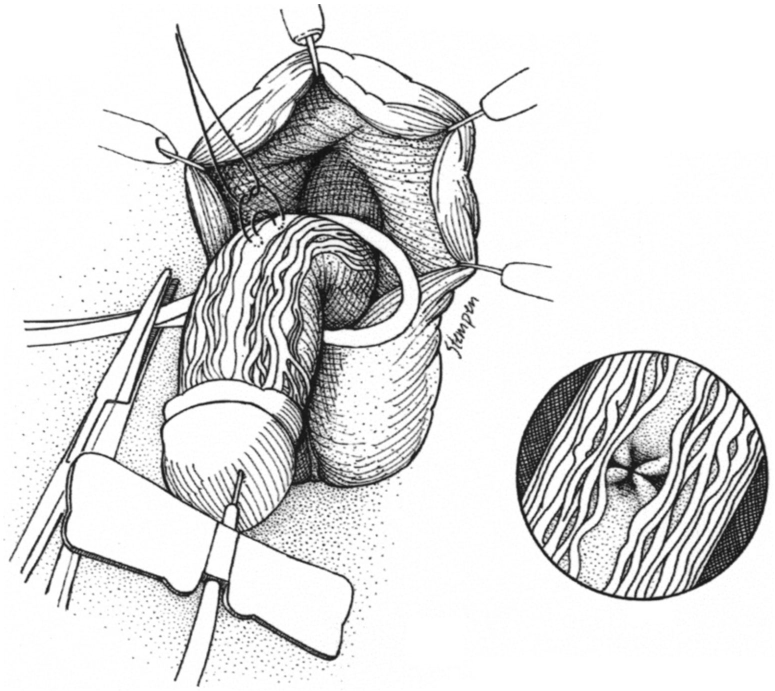

**FIGURE 121-26** Midline dorsal plication technique. In this technique, parallel plication sutures are placed in the tunica albuginea in the 12 o'clock position, which is free of both nerves and vascular structures. This technique requires a minimal amount of manipulation of the penis. It is not necessary to incise into the corporal body or extensively mobilize Buck fascia. If the curvature is severe, a maximum of two rows of parallel plications can be placed for correction.

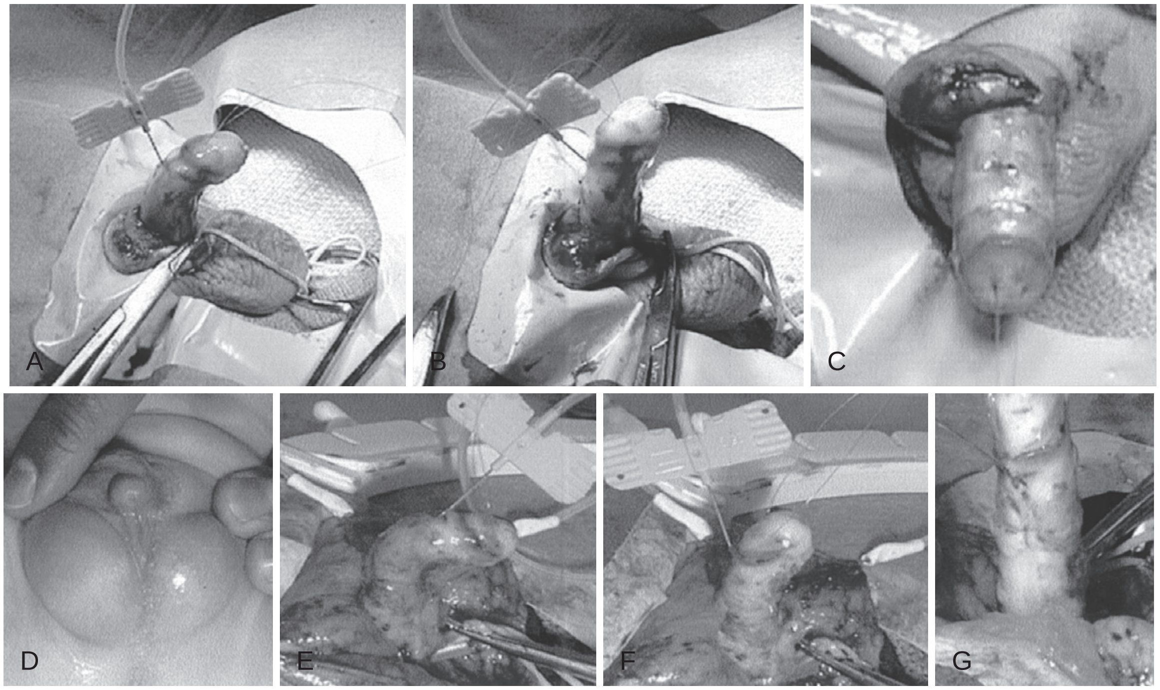


**FIGURE 121-27** Midline dorsal plication technique. **A** to **C,** Correction of mild curvature. **D** to **G,** Correction of moderate to severe curvature. Note the two permanent 5-0 Prolene plication sutures in the midline nerve-free zone.

by an elastic graft. I prefer the use of dermis, as described by Horton and Devine,[80] which has withstood the test of time (Fig. 121-28).[127]

About 5% of patients need ancillary penile straightening procedures after the release of skin curvature by aggressive dissection to the penoscrotal junction.[3,99,128] Of those requiring ancillary procedures, most (>90%) can be corrected by dorsal midline plication without the need for resection of the urethral plate. This leaves a small minority of severe cases requiring resection of the urethral plate, dermal grafting, or both.

## PATIENTS WITH MULTIPLE FAILURES

Some patients undergo multiple hypospadias repairs that fail; this unfortunate outcome can occur even in skilled hands.[129] In such patients, it is often necessary to discard the previously

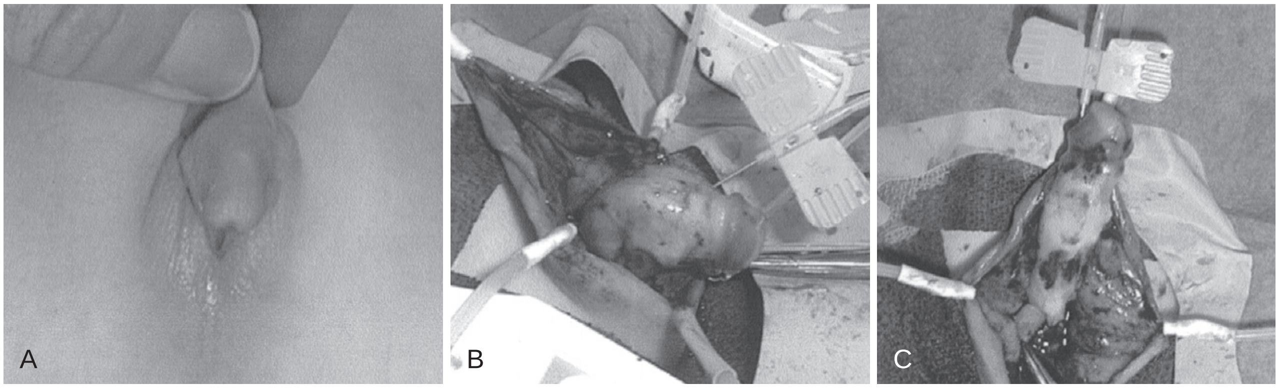


**FIGURE 121-28** Dermal graft for severe ventral penile curvature. **A,** Scrotal hypospadias. **B,** Severe right-angle curvature after aggressive skin and subcutaneous dissection. **C,** Ventral incisions for placement of dermal graft. (From Hinman F Jr: Atlas of Urologic Surgery. Philadelphia, WB Saunders, 1989, pp 91-92.)

created problem-plagued urethra and start anew. The penis may be further straightened, if necessary. In some cases it may be appropriate to place a meshed split-thickness skin graft and go back later for tubularization[130,131] or to place a free graft of buccal mucosa or skin where the scarred urethra was resected.[117] In patients with a paucity of penile skin, a full-thickness skin graft can provide adequate skin coverage.[132] I prefer harvesting the skin from the patient's buttock so that the scar from the graft site will be well hidden. A wound vac for 5 days postoperatively has ensured excellent graft take. Rarely, tissue expanders have been useful to stretch local genital skin.[133] In the past, bladder mucosa was used for the neourethra[134,135] because the long-term results with free skin grafts were not as good as previously reported.[136] Unfortunately, bladder mucosa grafts were complicated by eversion at the meatus in up to 30% of patients.[134] Meatal dilatation on a daily basis could not avoid this problem. More recently, buccal mucosa grafts have been used for urethral replacement in these difficult patients.[134,137,138] I presently advocate the two-stage approach of Bracka (see Fig. 121-23).[118,139]

In the future it may be possible to treat difficult cases of hypospadias with autologous grafts of cultured urethral epithelium.[140,141] Finding the ideal support matrix to scaffold the urothelial cells may make this technique widely applicable.

## Technical Considerations

The principles of hypospadiology have been enhanced over the years by the precise, delicate tissue handling taught by plastic surgeons and the use of optical magnification. Sharp-pointed iris scissors and delicate-toothed forceps are the principal tools. Castroviejo needle holders and 0.5-mm forceps are useful for delicate maneuvers with 7-0 sutures. Bougie à boule probes are useful as the procedure progresses for calibrating the sizes of tubes and the anastomosis, as well as the meatus. Fine lacrimal duct probes are useful for identifying fistulas and periurethral ducts.

### HEMOSTASIS

Control of bleeding from the vascular penis and glans can be achieved in a number of ways. Placing a tourniquet at the base of the penis is simplest.[142,143] Recommended tourniquet times vary from 20 minutes to 1 hour. I prefer the injection of 1:100,000 epinephrine in 1% lidocaine (Xylocaine) using a 29-gauge needle. Infiltration around the urethra and into the glans is helpful for developing glans wings. Usually, only 1 to 1.5 mL are required. There is a wide margin of safety before epinephrine sensitizes the myocardium to arrhythmias with the use of inhalational anesthetics.[144] A safe dose is 1 mL/kg of a 1:100,000 solution. I do not believe that epinephrine compromises the vascularity of the flaps. Various methods of coagulation have been recommended; I prefer a low-current electrocautery (Bovie) applied to the 0.5-mm forceps.

### ANALGESIA

In anticipation of postoperative discomfort, the anesthesia team places a long-acting caudal nerve block before the procedure.[145,146] If the repair takes longer than 2 hours, the block can be repeated at the completion of the procedure. Evidence suggests that the caudal block also reduces the amount of bleeding.[147] Alternatively, a supplemental local block with 3 mL of 0.5% bupivacaine (Marcaine) is placed just beneath the symphysis to infiltrate the dorsal penile nerve bundle.[148] Penile blocks also reduce the general anesthetic needs and prevent erections, which can be bothersome and cause extra bleeding.

### DRESSING

For distal hypospadias repair performed without urinary diversion, I currently use a Tegaderm wrap.[3] The parents remove the dressing at home in 24 to 48 hours. For hypospadias repair with urinary diversion, a "sandwich" dressing allows the application of more diffuse pressure by placing the penis onto the abdominal wall. A layer of Telfa followed by a 4- by 4-inch gauze folded three times on the ventrum of the penis is secured with a medium Tegaderm sheet of sticky plastic. The dressing is typically removed at home after 48 hours. I encourage bathing twice a day with the stent in place after 48 hours to allow the dressing to soak off. Warm bathwater allows the repair to remain clean and assists healing.

### DIVERSION

Bladder spasms caused by irritation of the trigone with a catheter can be an aggravating problem. Oral oxybutynin chloride may be of help. Another problem relates to

connections between tubing and a drainage bag. I avoid a Foley catheter, except in teenagers and adults, and prefer a "dripping stent" in infants aged 6 to 18 months. Kendall manufactures a prepackaged 6-Fr hypospadias catheter; alternatively, 5- and 8-Fr feeding tubes are effective. Urethral diversions are used for 3 to 10 days. If the diversion is used for 5 days or less, the family is advised to allow the stent to fall out when the dressing comes off. If used for more than 5 days, the temporary stents can be sutured to the glans with 5-0 polypropylene on a noncutting needle. I have had good success with this technique, which allows the overwhelming majority of hypospadias repairs to be done on an outpatient basis. Patients are followed at 6 months to 1 year after surgery, after toilet training, and after puberty. The urethra is not instrumented during follow-up visits. After toilet training the child urinary stream is observed to assess for occult fistula, diverticulum, and urethral stricture.

### AGE FOR REPAIR

Hypospadias repair is being performed at progressively younger ages. Schultz and colleagues[149] pointed out that an ideal age might be 6 to 18 months to minimize the emotional effect of this traumatic experience. The consensus statement on the timing of genital surgery from the American Academy of Pediatrics also supports early surgery before 18 months of age.[150] Gender identity does not seem to be defined until after 18 months. I now prefer to operate when patients are between 4 and 9 months old; at that age, the penis is of sufficient size to achieve success comparable with that obtained by waiting until age 2 to 5 years, which was previously popular. For many reasons (medical and social), however, surgery may be delayed. Kaplan and colleagues[151–154] studied 69 boys aged 6 to 10 years who had had hypospadias repair in infancy and found no increase in significant psychopathology during childhood, although more recent studies suggest that before age 5 is the most ideal for both functional and psychosocial outcomes.

### TESTOSTERONE STIMULATION

Enlargement of the infant penis is possible by testosterone stimulation. The recommended dose is 25 to 50 mg of testosterone propionate (2 mg/kg) intramuscularly given at 3-week intervals for up to three preoperative doses.[14,155] In Europe dihydrotestosterone transdermal gel has also proven to be effective.[156] I have not found the routine use of testosterone stimulation to be beneficial. In severe cases when the penis is small such as partial androgen insensitivity syndrome or for diagnostic purposes, testosterone is helpful. A patient with a small glans may benefit from presurgical testosterone stimulation. There is a suggestion in animal models that testosterone stimulation may be detrimental to the later maturation of prostatic tissue and penile growth.[157,158] To date, clinical practice has not documented any untoward effects in humans.[159]

## Complications

### MEATAL STENOSIS

Meatal stenosis is caused by technical errors in operative design or poor vascularization of the urethroplasty or glansplasty.[160] Postoperative dilatation is seldom therapeutic and often traumatic for the patient and family. Internal urethrotomy also has poor long-term results. Often the glansplasty will have to be taken apart and reperformed. In some cases a two-stage approach (Bracka) is necessary.[117,118]

### URETHROCUTANEOUS FISTULA

Urethrocutaneous fistulas are the most common late complication of hypospadias repair, and their incidence has been used to evaluate the effectiveness of the surgical procedure.[160,161] The expected fistula rate is between 10% and 20% for most one-stage hypospadias surgery. Often, distal obstruction is related to persistent fistulas. The principles of repairing urethrocutaneous fistulas require wide mobilization, adjacent skin flaps, and multilayered closure.[162–164] I recommend using magnification and delicate instruments for fistula repair. Dissection is carried down to the urethra, and a 7-0 suture is used to close the urethral edges in an inverting fashion. Watertight closure is ensured by irrigating the urethra with proximal compression. Irrigating the urethra will also confirm the absence of an additional fistula. In straightforward fistulas no urinary diversion is used. The patient is allowed to void through his urethra and goes home on the same day.

It is extremely important to recognize a concomitant urethral stricture or diverticulum at the time of fistula closure. These should be repaired to ensure the success of the fistula closure. Occasionally, a meatoplasty may be necessary at the time of fistula repair. A fistula near the glans is best repaired by opening the bridge between the meatus and fistula, mobilizing the inner urethral edges, and closing in two layers with good glans approximation (Fig. 121-29).

### STRICTURE

Strictures result from technical problems during the initial hypospadias repair. Proximal anastomotic strictures may result from either a luminal calibration miscalculation, resulting in a narrow neourethra, or an anastomotic overlap. A meatal stricture may result from chronic balanitis xerotica obliterans. This reaction is located at the meatus or may extend into the more proximal urethroplasty. This may be caused by a poorly vascularized meatoplasty, especially the Mathieu procedure.

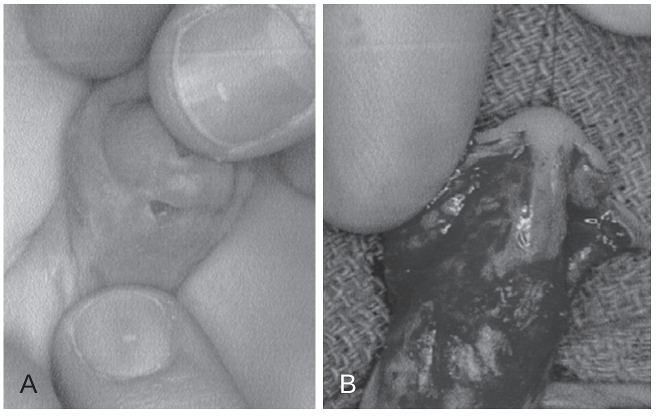


**FIGURE 121-29** Hypospadias fistula. **A,** Coronal fistula requiring redo glansplasty. **B,** Preservation of the urethral plate with eccentric vascularized onlay flap preparation.

The most likely cause of meatal stenosis is vascular compromise of the urethra at the apex of the meatus. It may be secondary to an inadequate glans channel that compresses the vascularity of the pedicle. Once a stricture has developed, it can be repaired by excision and reanastomosis, a vascularized pedicle graft, or a two-stage buccal graft using the technique of Bracka.[117,165] Of note, there has been little success treating strictures secondary to hypospadias surgery with optical internal urethrotomy.[165]

### DIVERTICULUM

A fusiform urethral diverticulum may form because the neourethra was made too wide and meatal stenosis allowed ballooning of the proximal urethra.[1] Reduction of a diverticulum may be necessary and should be done in a longitudinal fashion.[166] Most often, a circumcising incision is used and the penile skin is dropped to the penoscrotal junction, which allows for longitudinal repair of the diverticulum without overlying suture lines. Care must be taken to evaluate the neourethra for an associated fistula. A discrete diverticulum may develop from urinary extravasation into the tissues adjacent to the anastomosis.

## Results

Long-term follow-up reflects the older age at which repair was undertaken and the difficulties of hypospadias surgery in the past.[167–170] Today's results are much better both cosmetically and functionally than those in the past.[171–174,175] The use of one-stage hypospadias repair at an early age with a low complication rate encourages our current positive outlook for patients with this condition. Curvature correction with the aid of an artificial erection is extremely important for ensuring satisfactory sexual function. With the placement of the urinary meatus at the tip of the glans, the fertility potential has been improved, unless the patient has other coexisting testicular problems. Evidence shows that the neourethra grows with the child. Early hypospadias repair with minimal hospitalization helps avoid separation anxiety and castration fears. We can now counsel parents confidently that there is an excellent chance of a good cosmetic, functional, and emotional result in boys with all degrees of hypospadias.

## Summary

1. Hypospadias should be repaired within the first year of life, preferably at 4 to 6 months of age. Pain and catheters seem to be better tolerated at this age, and the baby's lack of mobility simplifies postoperative care.
2. A terminal slitlike meatus should be the goal, with or without preservation of the foreskin in distal hypospadias, depending on parental preference.
3. Preservation of the urethral plate provides the best possible chance of recreating normal urethral anatomy by incorporating the abortive spongiosum into the repair.
4. Midline dorsal plication is safe and effective for the correction of penile curvature in the majority of patients. (Placing more than two rows of sutures is a sign that another technique such as dermal grafting is indicated.)
5. In the small percentage of patients who require resection of the urethral plate, a two-stage approach is generally warranted.
6. Vascularized pedicle onlay flaps are successful in primary and redo hypospadias surgery.
7. De-epithelialized vascular flaps should be used as a second layer for all urethroplasties.
8. Patients with a paucity of skin are best managed with the Bracka two-stage buccal repair.
9. Coronal fistulas require a redo glansplasty.

*The complete reference list is available online at www.expertconsult.com.*

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# CHAPTER 122

# Abnormalities of the Urethra, Penis, and Scrotum

J. Patrick Murphy and John M. Gatti

The evaluation of abnormalities of the urethra, penis, and scrotum now begins before birth. Prenatal ultrasound (US) has become standard of care, and with it has come the early diagnosis of many congenital anomalies of the genitourinary tract. Virtually every hydronephrotic or obstructive lesion has been documented prenatally, but new controversies have been generated regarding the efficacy and appropriateness of prenatal therapy. In no area is this more apparent than in the diagnosis of posterior urethral valves (PUVs). Interventions in the way of vesicoamniotic shunting and fetoscopic urethral valve ablation have been described and used, but a benefit in outcome has yet to be confirmed.[1–3]

## Posterior Urethral Valves

PUVs are the most common obstructive anomaly of the urethra. The incidence is between 1 in 5000 and 1 in 8000 male births.[4,5] Hugh Hampton Young is credited with the first description and classification of PUVs.[6] He described three types. Type II PUVs are now generally considered to be nonobstructive and are of historical interest only. Type I represents 95% of PUVs. They are membranes that originate at the verumontanum and travel distally to insert in the anterior proximal membranous urethra with an opening present posteriorly at the verumontanum. The etiology is probably a result of the mesonephric ducts entering the cloaca more anteriorly than normal and fusing in the midline.[7] Type III PUVs represent the other 5% and consist of a ring-type membrane distal to the verumontanum with a perforation present centrally. The membrane may occasionally migrate distally, forming a windsock appearance.[8] The cause of these PUVs is an incomplete dissolution of the urogenital membrane.

Presently, most cases of PUVs are detected prenatally by US showing hydronephrosis and/or a distended thick-walled bladder. Postnatally, the US will show a thickened bladder wall and classically a dilated and elongated posterior urethra. Hydronephrosis will vary in degree and may be unilateral or bilateral. Physical examination may exhibit a distended, firm bladder, weak urinary stream, abdominal distention, and, possibly, urinary ascites. If the fetus has been subjected to oligohydramnios, there may be respiratory distress and the stigmata of Potter syndrome may be present. Older boys may present with urinary tract infection (UTI) and voiding dysfunction, particularly daytime urge incontinence. The voiding cystourethrogram (VCUG) is usually diagnostic with a dilated and often elongated posterior urethra and abrupt transition to a narrower distal urethra; a thickened bladder wall, trabeculation, bladder diverticulum, and vesicoureteral reflux (VUR) may also be seen (Fig. 122-1).

Fetal intervention for PUVs is controversial. The diagnostic accuracy of prenatal US has improved significantly over the past 10 years, but nonobstructive disorders such as prune-belly syndrome and high-grade VUR may be difficult to differentiate from PUVs. Fetal intervention may involve early delivery, vesicoamniotic shunting,[3,9] amnioinfusion,[10] percutaneous fetal cystoscopy,[11–13] or open fetal surgery.[14] All of these have significant risks to the fetus and mother including preterm labor, bleeding, and infection. Therefore the consideration of fetal intervention should be limited to centers with experienced personnel in both the diagnostic and technical skills involved. Renal dysplasia (RD) may occur early in fetal development before the time of consideration for fetal manipulation. Intervention to relieve obstruction will not reverse RD. Therefore most clinicians agree that a fetus with signs of severe RD is not a candidate for prenatal treatment. Several parameters are used for determining the severity of RD. Increased echodensity of the renal parenchyma, cystic changes of the parenchyma, and early moderate or severe oligohydramnios are all US signs of severe RD. The character of percutaneously sampled fetal urine also predicts the degree of RD.[1,2,15,16] Normal fetal urine is hypotonic and low in sodium. Fetal urine sodium greater than 100 mEq/L, osmolality greater than 210 mOsm, protein greater than 20 mg/dL, and $\beta_2$-microglobulin greater than 4 mg/L[17] are suggestive of significant RD. Improvement in these parameters on serial bladder taps is encouraging, but a fetus with these radiographic and urine parameters probably would not benefit from prenatal manipulation. Prenatal intervention has not been shown to improve the overall long-term renal function when compared with conventional postnatal therapy.[3,9] However, the patients who are treated prenatally likely represent the more severe degree of obstruction, and it could be argued that these

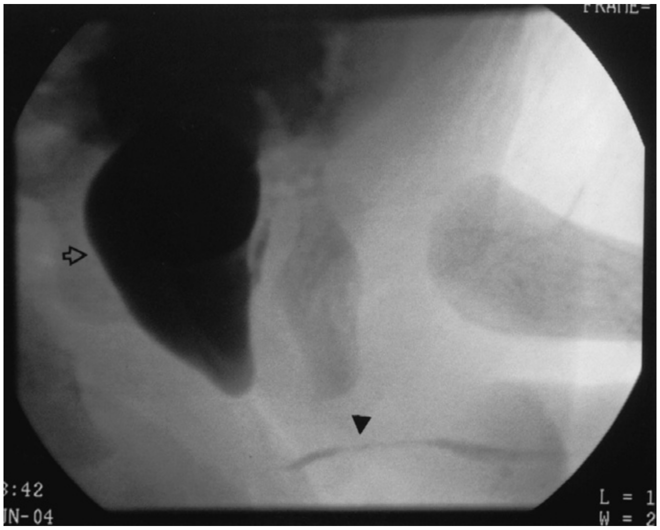

**FIGURE 122-1** Voiding cystourethrogram showing posterior urethral valves with dilated posterior urethra (*open arrow*) and abrupt transition to narrower anterior urethra (*solid arrow*). The trabeculated bladder is above the posterior urethra.

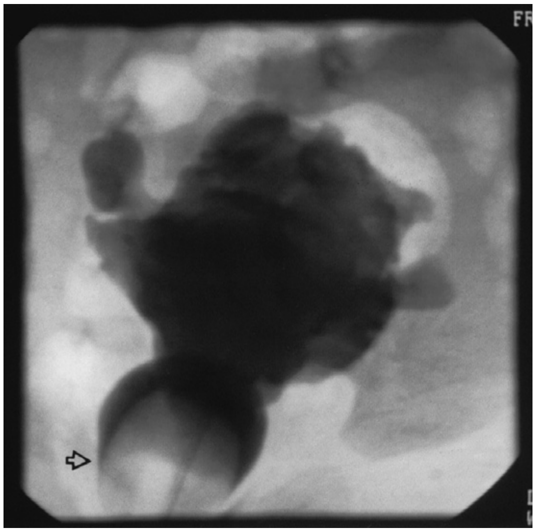

**FIGURE 122-2** Voiding cystourethrogram with posterior urethral valves and heavily trabeculated bladder and Foley balloon inflated in dilated posterior urethra (*arrow*).

patients should be predicted to have worse outcomes than those treated postnatally. Therefore prenatal treatment may have had a beneficial effect in these higher-risk patients. The ultimate role of fetal intervention for PUVs is still evolving; newer technology allowing safer and earlier treatment may improve outcomes.[2,18]

Postnatal management of PUVs initially involves obtaining bladder drainage. Usually this can be accomplished with a small, soft 5- or 8-Fr feeding tube passed per urethra. Care must be taken to ensure it does not coil in the dilated posterior urethra. Bladder US can help confirm proper placement. Generally, Foley catheters should be avoided for initial drainage because the balloon may cause bladder spasm in the thick-walled bladder and affect urine drainage, or the balloon may slip into the dilated posterior urethra (Fig. 122-2). In the rare case that the urethra cannot be cannulated, percutaneous suprapubic access can be used. Fluid and electrolyte management is critical in the first 24 to 48 hours. Postobstructive diuresis may occur, and both water and solute may be rapidly depleted, requiring aggressive fluid and electrolyte replacement. Acid-base balance is also important and is more of a problem in severe renal insufficiency. Serum creatinine is monitored closely, realizing that for the first few days of life the value reflects the maternal renal function. Historically, when the creatinine stayed elevated beyond several days, supravesical diversion was considered. However, a number of studies suggest this is not necessary and subsequent renal function was not improved when supravesical diversion was compared with treatment with standard postnatal valve ablation or vesicostomy.[19–21] Antibiotic prophylaxis is indicated, especially in those patients presenting with hydronephrosis or VUR.

When fluid electrolyte status is stable, most patients can be treated with endoscopic valve ablation. With advanced fiberoptic technology, cystoscopes of 7-Fr size are now available, allowing urethral access in all but the smallest premature infants. A Bugbee or angled wire electrode with cutting current or a small-caliber laser fiber[22] can be used to incise the valves at the 5, 7, and 12 o'clock positions in a retrograde transurethral fashion. In the older child, a small resectoscope can be used. Some have advocated a percutaneous antegrade approach to fulgurate PUVs.[23] In the rare case in which the valves cannot be fulgurated endoscopically, cutaneous vesicostomy is used. The Blocksom technique is favored, bringing the bladder dome to the skin to decrease the chance of bladder prolapse.[24,25] When the child has grown and stabilized medically, the valves may then be ablated endoscopically and the vesicostomy closed. Vesicostomy probably does not decrease long-term bladder capacity or function.[5,26,27]

The long-term prognosis for patients with PUVs has improved over the decades and is affected mostly by three factors: (1) degree of RD; (2) incidence of UTI with or without VUR; and (3) bladder function. The overall infant mortality rate has improved from about 50% to 1% to 3% in the past 3 decades.[28,29] Improved neonatal critical care, along with careful attention to the treatment of these factors, are responsible for this improvement. RD is irreversible, but attention to the other issues of UTI and bladder dysfunction can decrease or delay ongoing renal deterioration. Renal failure occurs in as high as 40% of patients treated for PUVs.[19,20] Renal transplantation has improved in this group of patients owing to improved medical care and modern immunosuppressive therapy. The graft survival is comparable with patients without significant urologic pathology.[30,31] Attention to bladder dysfunction and treating these higher pressure bladders for urge incontinence with anticholinergic therapy and frequent voiding are all important to delay renal deterioration or to protect the transplanted kidneys. In bladders that have progressed to myogenic failure and incomplete emptying, clean intermittent catheterization and/or overnight bladder drainage may be necessary. Urodynamics are helpful in directing this type of bladder therapy. In rare cases, bladder augmentation may be necessary.[20,32–34] VUR occurs in up to half of patients with PUVs.[4,5,35] The high incidence is probably related to the high-pressure bladder, but anatomic studies suggest primary VUR related to ureteral position is frequent.[36] The VUR is more often bilateral, and resolution after valve fulguration occurs in one third to one half of patients.[4,35] Unilateral VUR is sometimes associated with a dilated, dysplastic, poorly functioning

kidney. It has been suggested that this vesicoureteral reflux-renal dysplasia (VURD) syndrome may have a protective effect on the bladder and the opposite kidney, much like other "popoff" mechanisms such as a large bladder diverticulum or urinary ascites secondary to a ruptured renal fornix.[37–39]

Traditionally, it has been advocated that removal of this dilated dysplastic kidney and ureter would improve voiding efficiency and decrease potential for UTI.[38] More recent evidence suggests that retaining this dysplastic unit does not affect UTI or function, and these units may be left in place.[40] These dilated ureters also have the potential for use as a ureterocystoplasty to augment the bladder in those rare cases of high-pressure bladder refractory to standard therapy.[41]

The presence of VUR should not change the initial overall treatment of PUVs.[42] Ureteral reimplantation is generally indicated only in those patients with recurrent UTI despite appropriate chemoprophylaxis and after appropriate therapy to treat bladder dysfunction. The presence of VUR probably does not change long-term prognosis unless recurrent UTI is an issue.[35,43] Over time, with appropriate bladder therapy, the dilation of the ureters may decrease and bladder wall thickness improves, making surgery technically easier with improved results if reimplantation is ultimately necessary.

# Anterior Urethral Valves in Boys

Anterior urethral valves occur much less frequently than PUVs, but their overall presentation and impact on the urinary tract are quite similar. They can occur anywhere along the anterior urethra, with a slight predominance in the bulbar urethra.[44] The etiology is most likely to be the development of a ventral urethral diverticulum. With antegrade flow of urine during voiding, the diverticulum undermines the distal urethra with the common wall becoming an obstructive flap.[45] Others postulate that this lesion develops from a primary weakness in the spongiosum or an abortive attempt at urethral duplication.[46] The diagnosis is made radiographically, with a VCUG revealing a dilated proximal anterior urethra, a narrow distal anterior urethra, and often a subtle flap of tissue. These valves are treated with endoscopic incision and are best visualized with minimal irrigation to prevent flattening of the valve with forceful retrograde flow. Hydronephrosis and VUR are commonly associated and are generally managed in the same manner as PUVs.[47]

A similar lesion is the lacuna magna, or valve of Guérin, a dorsal urethral diverticulum located in the fossa navicularis. This is a rare entity and may require incision as described previously. The lesion can be difficult to diagnose owing to its proximity to the tip of the penis, but voiding images of the VCUG that include the glans reveal the distal lesion.[48]

# Urethral Diverticulum in Girls

Urethral diverticula are rare lesions in children. They can present as dysuria, hematuria, or symptoms of obstruction. Their diagnosis can be extremely difficult because of problems of imaging the short length of the female urethra. Cystoscopy may be required for diagnosis and treatment by excision, or, if small, incision of the distal lip endoscopically may be warranted.[49]

# Urethral Stricture

Urethral strictures are more common in boys than girls. They are classified as congenital, inflammatory, iatrogenic, or traumatic.[50] Congenital strictures are rare, but urethral hypoplasia can occur. Inflammatory strictures are uncommon in children and are more likely associated with gonococcal or chlamydial urethritis in sexually active adolescents. Inflammatory strictures related to chronic indwelling catheters are rare in the modern era. Iatrogenic strictures are encountered after urethral surgery or instrumentation.

Traumatic strictures of the anterior urethra are seen after straddle injuries in which the urethra is compressed against the pubic bone, such as falling on the crossbar of a bicycle. Posterior urethral strictures are generally seen associated with displaced fractures of the pelvis. Blood at the tip of the meatus, a high-riding bladder or prostate on abdominal and rectal examination, or a suspected pelvic fracture should all merit a retrograde urethrogram (RUG) before catheter placement to avoid converting a partial urethral disruption into a complete one. A partial injury is generally treated with endoscopic or fluoroscopic catheter placement of an indwelling catheter until the injury has healed and no extravasation of contrast agent is seen on the RUG done alongside the indwelling catheter. Controversy exists on initial management of the complete disruption. Suprapubic tube placement or vesicostomy and delayed reconstruction approximately 6 months later is generally accepted, but some advocate primary realignment of the urethra using retrograde urethroscopy and antegrade cystoscopy to place a catheter across the defect.[51]

The location and length of the stricture determine therapy. Most clinicians use antegrade cystography with RUG to define these parameters, but others report more accurate assessments using intraoperative US.[52] Short, filmy strictures can generally be incised or dilated with reasonable results.[53] Some authors have been quite successful with progressive urethral dilation in the setting of urethral hypoplasia.[54] Longer strictures or recurrent strictures of the bulbar urethra are generally treated by excision of the stricture and spatulated reapproximation in an end-to-end fashion. This may require an inferior pubectomy or corporal rerouting to cover a long distance.[55] The navicular and pendulous urethra are less forgiving because excision and reapproximation can result in ventral chordee. Longer strictures in these locations are generally treated with patch grafts or flaps using prepuce, penile shaft skin, or buccal mucosa.[56] These patients require long-term follow-up, although most strictures that recur do so during the first year.

# Urethral Atresia

Urethral atresia is incompatible with renal development unless an alternative communication with the bladder such as a patent urachus exists. Prenatal intervention with vesicoamniotic shunting may aid in getting the fetus to delivery, but there is often significant RD. There is a strong association with prune-belly syndrome.[57] The associated perinatal problems associated with obstructive infravesical uropathy must be dealt with initially. Further reconstruction is individualized to the degree of urethral development, but some will require continent diversion ultimately.

## Urethral Stenosis in Girls

It was once believed that irritative or obstructive voiding symptoms or recurring urinary tract infections in girls could be related to urethral stenosis. The diagnosis was supported by the narrowed urethra at the level of the genitourinary diaphragm and sphincter on VCUG. It is now realized that the radiographic and clinical findings represent voiding dysfunction and its associated inappropriate sphincter activity during voiding. Although some short-term benefit of incapacitating the external sphincter muscle with dilation may be seen, urethral dilation has been largely abandoned, owing to its long-term ineffectiveness and potential for creating a true urethral stricture after overly vigorous dilation.

## Urethral Mass in Girls

Multiple lesions may present as a urethral mass in young girls. Careful attention to the lesion can often make the diagnosis by inspection. Lesions of the urethral meatus include urethral prolapse, prolapsing ureterocele, urethral cyst, or sarcoma. Lesions of the vagina may be mistaken for having a urethral origin and include Gartner duct cysts, imperforate hymen, and sarcoma.

Urethral prolapse has classically been described in prepubertal African American girls, but Caucasian girls can also be affected.[58,59] The chief complaint is blood spotting in the underwear and painful urination. On physical examination, the markedly edematous urethra protrudes circumferentially at the level of the meatus and is often seen as a friable rosette that is bright red or cyanotic with a central dimple (the urethral meatus). A trial of sitz baths, estrogen cream, or a mild corticosteroid cream is reasonable, but if this is ineffective, the redundant tissue is excised and the urethral mucosa is anastomosed to the adjacent introital epithelium in the operating room.[60] Complications are rare but can include bleeding, recurrence, or urethral stricture.

A prolapsing ureterocele can also be quite edematous, but it can usually be discerned because it is not connected to the surrounding urethral meatus. The presentation may include blood spotting in the underwear, painful urination, or urinary retention. The diagnosis is confirmed by findings of hydroureteronephrosis associated with the ectopic moiety on US. If the ureterocele cannot be manually reduced, it can be reduced and unroofed cystoscopically with definitive excision/reconstruction performed in staged fashion.

Rhabdomyosarcoma is the most common primary malignant tumor involving the uterus, vagina, or bladder in infants and children and can present in similar fashion. The botryoid type lesion is usually exophytic and commonly emanates from the vagina or urethrovaginal septum. It generally presents before 2 years of age. The urethral margins are at least partially discrete, which differentiates it from urethral prolapse. It is classically a grapelike clustered mass that extrudes through the introitus and presents as bleeding. Radiographic imaging is warranted to fully evaluate the mass and rule out metastases to the lungs, liver, or bone marrow. After tissue diagnosis, multimodal therapy including chemotherapy, radiation, and surgical excision is usually used.[61,62]

Imperforate hymen may present as hydrocolpos or hydrometrocolpos as a bulging introital mass often with palpable distended abdominal uterus or vagina. The urethra is discretely visualized anterior to the mass. Treatment is incision and drainage.

Various cysts including epithelial inclusion cysts, Skene's duct cysts, müllerian duct cysts, and wolffian or Gartner duct cysts (GDC) can occur in this area, which can be incised and drained or excised if they recur. GDCs, which line the vaginal wall adjacent to the bladder, are worth elaboration because of their embryologic origins from the wolffian or mesonephric duct. As a result, ectopic ureters may end in a GDC, and rupture into the vagina results in chronic drip incontinence. Although GDCs are unusual in infants, they are the most common benign cause of vaginal swelling in children. They are generally asymptomatic, but when large they can protrude from the vagina and can be associated with urinary retention or dyspareunia in sexually active adolescents.[63] These are usually treated with marsupialization, but those associated with ectopic ureters require more proximal reconstruction involving ureteral reimplant or nephrectomy.

Urethral polyps are rare but present as intermittent bleeding or obstruction and are treated with excision.[64] Anterior vaginal wall or retention cysts are commonly seen in newborn females and lie between the posterior urethral wall and the anterior vaginal wall. These most commonly resolve spontaneously with a few days after birth.

## Labial Adhesions

Labial adhesions, or fusion of the labia minora, are believed to occur as a result of chronic inflammation related to vulvovaginitis or chronic dampness resulting from urinary incontinence. The labia may fuse near completely, causing obstructive-type symptoms or incontinence with trapping of urine. More commonly they present as postvoid drip incontinence as small volumes of urine pool above this shelf of tissue while seated to void, and they drip into the underwear when the child stands. This chronic dampness can also cause irritative symptoms of itching or dysuria, and an aseptic urine specimen is difficult to obtain owing to the impediment of preparing this adhesed area for culture acquisition.

Treatment of labial adhesions is not warranted in the absence of urinary tract infection, dysuria, obstruction, or drip incontinence because these adhesions commonly resolve with the physiologic estrogen surge at puberty.[65] If the adhesions warrant treatment, a trial of topical estrogen cream (0.01%) applied twice daily for 2 to 4 weeks may be attempted but can be unsuccessful in up to half of patients.[66] Estrogens also carry the risk of vulvar pigmentation, development of breast buds, or breast tenderness in prepubertal patients with prolonged use. The effects reverse with the withdrawal of treatment. An effective alternative is the use of betamethasone cream (0.05%) topically twice daily for 1 month.[67]

If the adhesions are persistent or thick and well developed, surgical lysis can generally be performed in the office setting using eutectic mixture of local anesthetics (EMLA) cream. A cotton-tipped applicator or hemostat can then be used to bluntly push the adhesions apart in an anterior to posterior direction. It is imperative that the excoriated labia minora

be dressed with a lubricating or antibiotic ointment to prevent the recurrence of adhesions until healed and an ointment be applied regularly for a period of time after lysis to ensure re-epithelialization of the lysed edges.

## Cowper Gland Anomalies

Cowper glands are paired urethral glands that sit in the urogenital diaphragm and drain into the bulbar urethra. When the ducts draining these glands become obstructed, cysts termed *syringoceles* can form.[68] They may be seen on a urethrogram as a filling defect in the bulbar urethra or found on cystoscopy for another reason in which they appear as a blue-domed cyst on the floor of the bulbar urethra. Most cysts are asymptomatic; some may present with terminal hematuria, blood spotting from the urethra, urinary tract infection, or obstructive symptoms. These are generally treated with endoscopic unroofing, incising the leading lip to prevent obstruction. Open resection perineally is reserved for large cysts.[69]

## Urethral Polyps

Urethral polyps are fibromuscular epithelial structures with transitional epithelium covering the surface.[70] They may occur either in the posterior or anterior urethra.[71,72] In either position, they may cause hematuria, urgency, or obstructive symptoms. Bladder ultrasound may show the polyps in the posterior urethra (Fig. 122-3), but VCUG and cystoscopy are diagnostic and excision through the cystoscope is usually curative.[73] Polyps can present as congenital obstructing lesions with all of the characteristics of bladder outlet obstruction.

## Prostatic Utricle

Prostatic utricles are müllerian duct remnants, which are common in patients with ambiguous genitalia or proximal hypospadias. Enlarged utricles can cause urinary tract infection, dysuria, urgency, hematuria, or epididymitis.[74] Diagnosis is usually made by VCUG or RUG. However, US may detect the larger remnants.[75] Surgical treatment is reserved for those that are associated with recurrent symptoms. The surgical approach may be transabdominal, transvesical, perineal, posterior sagittal (transrectal or perirectal), or laparoscopic depending on the experience of the surgeon.[74,76–80]

## Urethral Duplication

Urethral duplication is rare but more common in males. Although embryologic explanations for the defect have been proposed, the multiple variants of the anomaly suggest that there is probably not a common etiology for all forms. Duplication of the urethra can occur along with bladder and genital duplication. In males the duplications usually occur in the same sagittal plane on a single phallus.[81] Less often, the urethras may be side by side on the glans with either a widened or duplicate phallus (Fig. 122-4). With the sagittal-type duplications, the ventral urethra is almost always the more normal one and passes through the prostate and sphincteric mechanism. It may end anywhere from the tip of the glans to the perianal area.

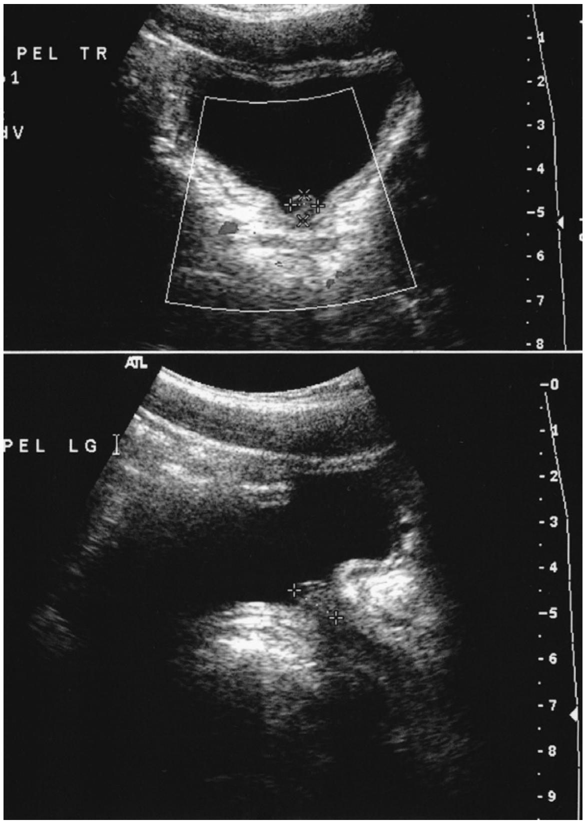


**FIGURE 122-3** Posterior urethral polyp seen on ultrasound of bladder. Top view shows transverse image of bladder with polyp arising from urethra (*cursors*). Bottom view shows longitudinal view of bladder with polyp seen at entry to posterior urethra (*cursors*).

**FIGURE 122-4** Duplicate urethra with a meatus on each side of glans and counterclockwise penile torsion.

The dorsal urethra may open anywhere on the shaft from an epispadiac location on the glans to the penopubic area. Dorsal chordee may be present, and a widened symphysis pubis may be present, suggesting possible association with the exstrophy complex.[82–85] This dorsal urethra may communicate with the bladder or ventral urethra (Fig. 122-5) but can end blindly beneath the symphysis pubis. If it does communicate, incontinence can be an issue because it often does not traverse the sphincter. Treatment in the symptomatic patient involves excision of the dorsal accessory urethra and correction of the chordee. Urethroplasty may be necessary to bring the ventral urethra to the glans. In the rare case of a dominant dorsal urethra and an accessory ventral one, the excision of the ventral tract cures the incontinence. The treatment of the even more rare side-by-side type requires an individualized approach depending on the varied anatomy. Full urinary tract evaluation radiographically is required in all forms of urethral duplication.

Female duplication may have complete bladder and genital duplication and may be associated with colonic atresia and/or cloacal anomalies.[86] A dorsal accessory urethra may occur in the pubic area and has been reported to communicate with a urachal remnant.[87] Treatment again is individualized to the particular anatomy involved, with attempts to preserve bladder tissue and maintain continence.

**FIGURE 122-5** Urethral duplication with dorsal urethral duplication (*arrow*) exiting in suprapubic area.

## Megalourethra

Megalourethra is a rare syndrome of urethral dilation. There are two types: scaphoid and fusiform. The scaphoid form is associated with abnormal development of the corpus spongiosum, and anterior bulging of the urethra is seen with voiding. In the more severe fusiform type (Fig. 122-6), the corpora cavernosa are also involved, which may have an impact on long-term potency, and the dilation during voiding is circumferential.[88] The lesion is generally discovered at birth but has also been diagnosed on prenatal US.[89]

The etiology is unclear, but it is thought to be a defect of mesodermal development, especially given its association with prune-belly syndrome.[90] A renal-bladder US is indicated to rule out other congenital anomalies. The dilation is nonobstructive, and urethroplasty with excision of the redundant tissue and tapering of the urethra is generally undertaken for cosmetic reasons.

## Congenital Urethral Fistula

Congenital urethral fistula is rare and usually occurs in the subcoronal area of the penis. Associated hypospadias and chordee occur, suggesting this may be a form of the hypospadias anomaly. The fistula generally has a well-formed urethra distally, but it may be thinned with poor glans formation. Repair involves the techniques used in hypospadias surgery and may involve simple multilayer closure of the fistula or more complex reconstruction of the distal urethra and glans.[91,92]

**FIGURE 122-6** Megalourethra, fusiform type.

# Phimosis

Phimosis is defined as the inability to retract the foreskin. At birth, physiologic phimosis is present as adhesions between the prepuce and glans preclude retracting the foreskin. As the child grows, the two layers begin to separate as sloughed epithelial debris, or smegma, accumulates between them, defining this plane. This smegma is commonly referred to as "foreskin pearls" and can be mistaken for infection or purulence by the uneducated parent. With spontaneous erections and natural manipulation, more than 90% of foreskin becomes retractable by age 3 to 4 years.[93]

Forceful retraction is not required for this to occur and may initiate the vicious cycle of tearing and scarring, which can lead to pathologic phimosis. In children older than 4 years who are unable to retract the foreskin and are symptomatic with episodes of posthitis or balanoposthitis or ballooning of the foreskin with voiding, a trial of betamethasone cream (0.05%) two times per day for 1 to 2 months allows the foreskin to retract in up to 90% of boys.[94] For those refractory to corticosteroid treatment, a temporizing dorsal slit, preputioplasty (surgical enlargement of the phimotic ring), or circumcision is indicated.

# Circumcision

Circumcision remains one of the most controversial topics in urology. The American Academy of Pediatrics issued a policy guideline in 1975 stating that there is no absolute medical indication for routine circumcision of the newborn.[95] In 1999 the Academy offered the opinion that there are some medical benefits of the procedure but not enough to warrant routine circumcision.[96]

Circumcision advocates argue that circumcised boys have lower urinary tract infection rates, lower incidence of zipper injury or paraphimosis, and lower rates of sexually transmitted disease and penile cancer as adults.[96–100] Circumcision opponents argue the procedure is nonphysiologic and may be unnecessary or even harmful. Some more extremist groups argue that circumcised males have decreased penile sensation, less satisfaction with intercourse, and possibly even higher divorce rates.[101] Unfortunately, this issue tends to be emotionally charged and a large body of "supportive research" is highly subjective. In a cost utility analysis of circumcision, Ganiats and colleagues determined that financial and medical advantages and disadvantages of routine neonatal circumcision cancel out one another and that personal cultural or religious views rather than cost or health outcomes should be the basis of decision making.[102]

Despite the controversy, circumcision is still one of the most common elective procedures in the United States and is usually done for cosmetic and cultural reasons.

The risk of circumcision is generally low in larger series (<1%) and includes bleeding, infection, skin separation, adhesions, too much or too little skin removed, and meatal stenosis.[103,104] The two major techniques used in neonates are the Plastibell and the Gomco clamp. Similar complication rates are noted with both, the Plastibell having more problems with infection and the Gomco clamp more problems with separation.[105] The Mogan clamp carries the additional risk of glans injury, and this technique should be limited to those adequately trained in its use.

## TECHNIQUE

Newborn circumcisions can be carried out at the bedside or in the office safely to 2 or 3 months of age. The authors advocate the use of local anesthetic, either topically or subcutaneously before the procedure. With the foreskin in an unstretched position, the palpable coronal margin is marked on the overlying shaft skin to indicate the appropriate position of the clamp device. A hemostat is used to develop the plane between the glans and adherent prepuce. In the dorsal midline, the tissue is clamped with a straight hemostat and then incised with scissors to allow placement of the device. All adhesions should be taken down and smegma débrided. The appropriate size of clamp device should be chosen. The conical portion of the clamp should cover the majority of the glans. Once this portion is in position, the excess foreskin is reduced back over the clamp device and the clamp is engaged (Gomco) or the suture is tied (Plastibell) at the previously marked site. Care should be taken to draw the foreskin over the clamp at its leading edge to avoid the foreskin intussuscepting over the clamp and giving a mismatch of inner prepuce and proximal shaft skin engaged in the clamp. The amount of inner prepuce and shaft skin excised should be equal to avoid the risk of recurrent phimosis creating a hidden or buried penis due to an inappropriately large amount of residual inner prepuce. Hemostasis is usually excellent with these techniques. Electrocautery should never be applied to the metal clamp because the penis can be completely devascularized (Fig. 122-7).

In older children, the procedure is performed under a general anesthetic when the risk of anesthetic is minimized (after 60 weeks' gestation). Because the clamp devices become less reliable in older children and have a less-tailored fit, a freehand surgical technique is used at our institution. The proximal and distal incisions are carefully marked before cutting sharply, with the proximal mark overlying the coronal margin when any prominent prepubic fat pad is reduced. The excess shaft skin is excised at the level of the dartos pedicle with electrocautery. Hemostasis is attained by electrocautery as indicated, and larger vessels can be ligated. The edges are reapproximated with fine chromic suture in an interrupted subcuticular technique to avoid the formation of epithelialized suture sinuses. A minimal dressing of antibiotic ointment and gauze is placed with the expectation of it falling off spontaneously or being removed the following day. The authors also advocate early bathing on postoperative day 1 and have the family apply the ointment to the area at least three times daily for the next few weeks. A caudal block or dorsal penile nerve and ring block is usually given at the end of the procedure to help with postoperative pain management.

# Meatal Stenosis

Meatal stenosis occurs in approximately 10% of circumcised boys.[106] It is virtually nonexistent in uncircumcised boys, with the exception of those with balanitis xerotica obliterans. It is thought to be related to subclinical chronic inflammation of the meatus in the circumcised phallus related to exposure to

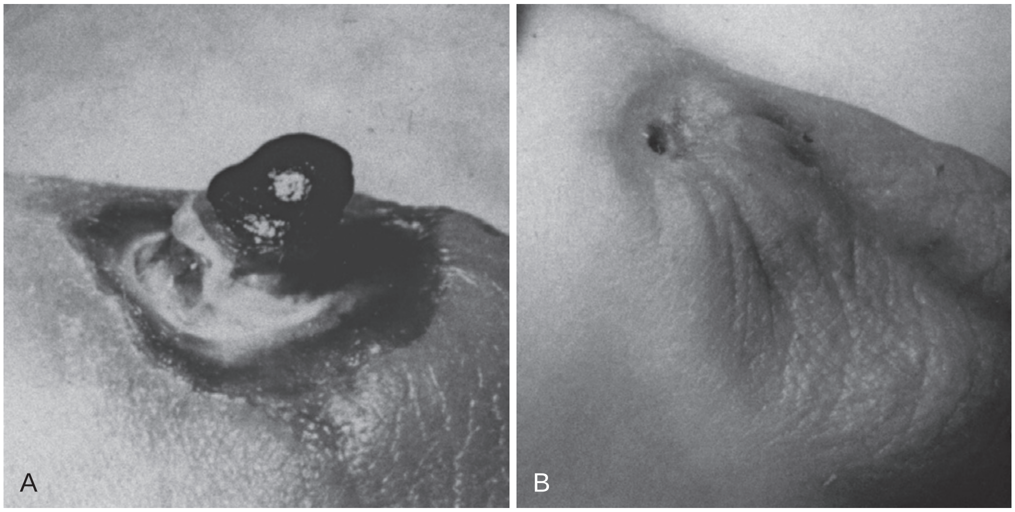


**FIGURE 122-7** Neonatal circumcision injury after applying electrocautery to metal clamp. **A,** Immediate postoperative appearance. **B,** End result 3 months after surgery.

urine (ammoniacal dermatitis) or to relative ischemia caused by compromising the vasculature to the meatus when the frenular artery is taken during circumcision. The classic history is that of a fine-caliber urinary stream with dorsal deflection, often greater than 90 degrees. The meatus is pinpoint and tight with 6- or 8-Fr calibration. It may or may not be associated with pain or blood spotting in the underwear. The disorder is commonly overdiagnosed, and those with painful urination who lack these physical findings often have voiding dysfunction and its associated inappropriate sphincter activity during voiding.

The treatment of meatal stenosis is a meatotomy in which the ventral parameatal tissue is engaged in a clamp or hemostat (the authors prefer a nontoothed bowel clamp), then incised roughly half the distance to the coronal margin. The edges are dressed with antibiotic ointment, and the family is encouraged to continue this application three times daily for at least a week to avoid recurrence, which is uncommon. This procedure can be performed safely in the office with local anesthetic or in the operating room setting.[107]

## Penile Agenesis

Congenital aphallia is extremely rare, with an incidence of 1 in 10 million to 30 million.[108,109] It is a result of partial or complete developmental failure of the genital tubercle. The karyotype is almost always 46,XY, and the urethra usually opens into the anal verge or rectum.[108,109] Common associated anomalies can include cryptorchidism, renal anomalies, VUR, anal anomalies, and cardiac anomalies.[108–110] The more proximal the urethral communication, the higher the incidence of associated anomalies and of neonatal mortality.[109] Female gender reassignment with orchiectomy, along with urinary tract and genital reconstruction, has traditionally been recommended for this anomaly.[108,111] However, recent evidence that persistence of male gender identity may occur despite female gender reassignment makes it imperative that careful consideration by a team dedicated to disorders of sexual differentiation including urology, endocrinology, and psychiatry be done before full informed consent is obtained from the family.[112] Discussion of maintaining male gender assignment with later construction of a neophallus along with the cosmetic and functional limitations of this approach should be included in the informed consent.[112]

## Diphallia

Penile duplication has a frequency of 1 in 5 million births.[113,114] The extent of the duplication varies, and the etiology is suggested to be a failure of mesodermal banding or mesoderm encountering two urethral anlages.[115] Presentation may range from a small accessory penis to complete duplication of urethra, glans, and corporal bodies (Fig. 122-8). There is often size discrepancy, and orientation is most commonly side by side. Associated abnormalities include

**FIGURE 122-8** Diphallia, side-by-side configuration.

hypospadias, scrotal anomalies, duplicate bladder, renal anomalies, exstrophy defects, and anal and cardiac anomalies. Complete imaging of the urinary tract should be performed, and US or magnetic resonance imaging may be helpful in assessment of penile anatomic development.[116] Surgical treatment must be individualized to the extent of the defect and may range from simple resection of the accessory penis to complex reconstruction.[113]

## Penile Torsion

Torsion of the penis is a rotational defect of the phallus, which is usually counterclockwise in direction and may be associated with hypospadias, chordee, and hooded dorsal foreskin. The median raphe generally courses obliquely around the shaft to the left. Rotation of less than 90 degrees often is not symptomatic and will not require correction. Surgical treatment involves degloving the penis and releasing any fibrous, dysgenic bands all the way to the base of the penis, allowing the phallus to reorient to the appropriate position.[117] In rare cases, fixation of the base of the corporal bodies to the symphysis pubis or creation of a dartos flap to rotate the corpora may be necessary to maintain proper orientation.[118]

## Penoscrotal Transposition and Scrotal Ectopia

The scrotum forms by migration of the labioscrotal folds inferomedial to the genital tubercle. Failure of migration possibly related to a gubernacular defect results in scrotal anomalies such as penoscrotal transposition, bifid scrotum, or scrotal ectopia.[119] Association with hypospadias and chordee is common. The more significant the scrotal defect, the more likely other anomalies are to occur including caudal regression, VATER syndrome, cryptorchidism, and other urinary tract abnormalities.[119–121]

Repair of significant forms of penoscrotal transposition require various advancement flap techniques. When associated with severe hypospadias, which requires preputial island flap type repairs, correction of penoscrotal transposition is usually done at a second stage to avoid the possibility of devascularizing the preputial flap.[122,123] Others propose combined repair of the hypospadias and scrotal transposition in one stage, but complications tend to be higher.[124–126] In cases of scrotal ectopia associated with cryptorchidism, scrotoplasty and orchiopexy can usually be accomplished at the same time.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 123

# Disorders of Sexual Development

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## Nomenclature

"Disorders of Sex Development" (DSD) and "Disorders of sexual differentiation" (DSD)[1] are more inclusive terms than "ambiguous genitalia" or "intersex." They include a broad clinical spectrum of hormonal, metabolic, and chromosomal abnormalities resulting in abnormal genital development.[2,3]

## Developmental Biology of Mammalian Sexual Differentiation

Phenotypic males and females develop as a result of a precise cascade of sequential morphologic, genetic, and molecular events, many of which have recently been elucidated. The intermediate mesoderm situated between the ectoderm and the endoderm is the site that gives rise to the urogenital ridge in the early embryo (Fig. 123-1).[2] The urogenital ridge, which develops from a thickening of the ventromedial aspect of the intermediate mesoderm, contains the undifferentiated gonad and the mesonephros, wherein both the reproductive wolffian and müllerian ducts reside. Formation of the ridge depends on the expression of a number of important genes including the Wilms' tumor gene *(WT1)* and steroidogenesis factor *(SF-1)* genes; in their absence, the gonad and adjacent structures fail to form. For example, mutations in *WT1* in mice result in absence of the gonad and kidney[4] and abnormalities of the urogenital system, heart, and thorax. Mutations in Wilms' tumor 1 (WT1) cause Denys-Drash syndrome, Frasier syndrome, and Wilms' tumor associated with aniridia, genitourinary (GU) malformations, and mental retardation (WAGR) in human patients.[5] Mutations in *SF-1* in mice result in absence of gonads and adrenal glands[6] (see Fig. 123-1) and produce similar phenotypes in humans.[7] Other genes such as *LIM1, LHX9, EMX2,*[8,9] and *GATA-4* that are essential for development during this early process are shown in Figure 123-1.

Simultaneously, genes important for wolffian and müllerian duct development are expressed. The wolffian duct requires the action of *PAX2* and possibly *PAX8,* which are paired genes important in *Drosophila* development. Müllerian duct formation requires the activity of a series of secreted factors whose expression is directed by the WNT family of proteins.[10] During formation of the urogenital ridge, primordial germ cells, the progenitors of the oocytes and spermatocytes, must migrate from outside the embryo in the epiblast.[11] During this time they undergo proliferation and imprint erasure imposed by DNA methylation and complex histone modification to reset epigenetic memory in germ cells as elucidated during mouse development,[12–14] where, under the influence of Blimp-1,[15] expression of BMP 2, 4, and 8b and Fragilis expands this alkaline phosphatase and Stella-expressing population[16,17] at 3 weeks' gestation in the human.[11] These germ cells migrate through the ectodermal layer of the embryo, the primitive streak, the base of the allantois, the wall of the hindgut, and then to the urogenital ridge, where they take up residence in the as yet undifferentiated gonad. Fragilis induces *Stella,* which in turn induces the pluripotency genes *OCT/4, SOX 2,* and *Nanog*. The migratory phenotype, controlled by integrins[18] and cKit signaling,[19] is characterized by extensive mitosis (170-fold in mice).[20] After entering the mesonephros, female germ cells enter meiosis in an anterior to posterior wave under the influence of retinoic acid–mediated *STRA8* (Fig. 123-2). Because the testes degrade retinoic acid with the enzyme CYP26b1, *STRA8* is unavailable to initiate meiosis, so male germ cells remain arrested in Go.[21,22] Further ovarian development of the urogenital ridge requires the presence of germ cells. Oocyte development also requires residence in the urogenital ridge,[23] as ectopic germ cells either fail to develop or form tumors outside the confines of the urogenital ridge.[8,24]

Differentiation of the gonads commences as an indifferent blastema of mesenchymal cells covered by coelomic epithelium. The testes are directed by the expression of small transcription factors such as *SRY,* a master switch gene present on the short arm of the Y chromosome, and an *SRY*-related autosomal gene called *SOX 9* from chromosome 17q. The fact that testicular differentiation requires a signal from the Y chromosome became evident in 1959, when the 45,X Turner phenotype was first recognized.[25] Subsequent cytogenetic studies progressively localized the male differentiation region to the short arm of the Y chromosome.[26] Much later, Page and colleagues[27] defined a critical region for testis determination near the pseudoautosomal region of the short arm of the Y chromosome by comparing chromosomal deletions and

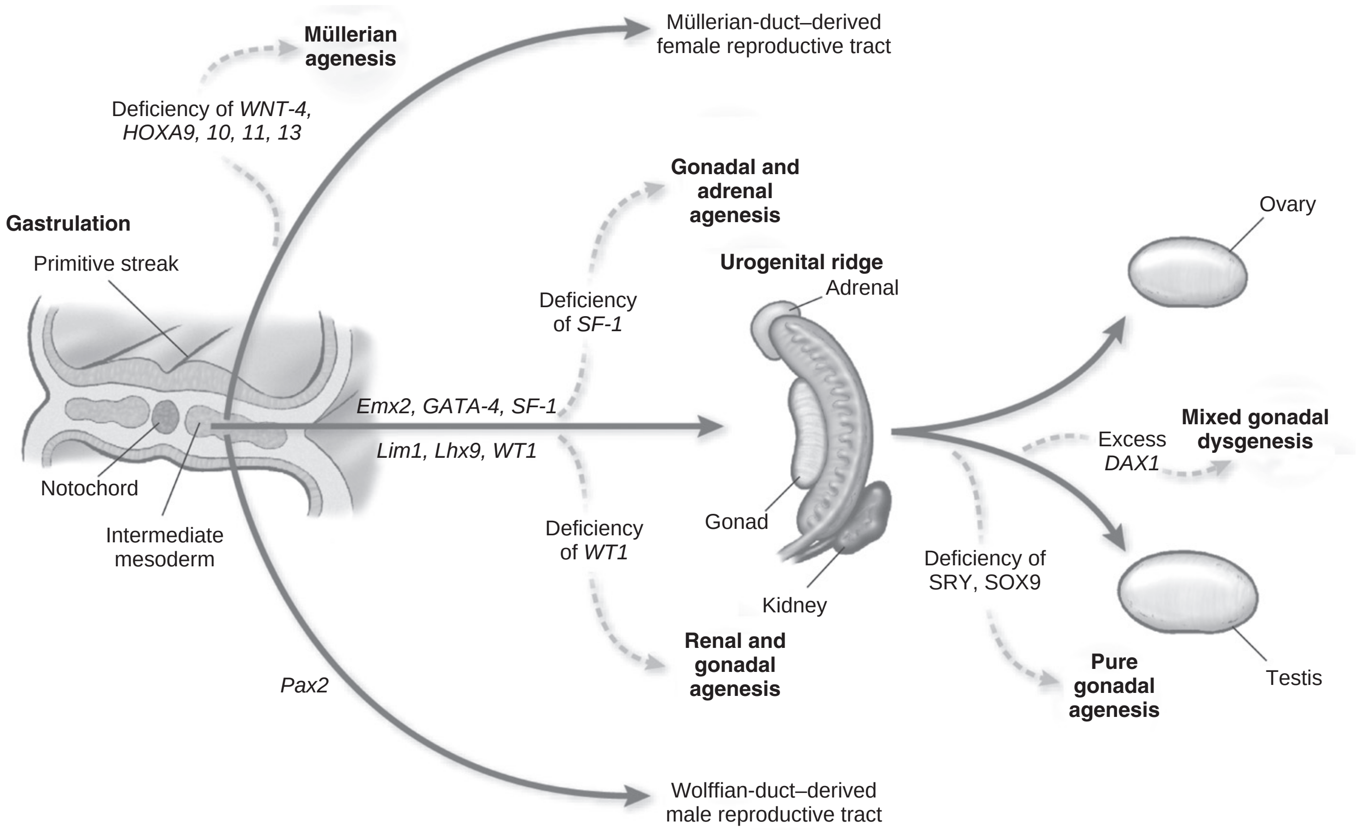


**FIGURE 123-1** Mutations in a number of genes can lead to a variety of syndromes of dysgenesis involving the müllerian or wolffian ducts, gonads, kidneys, and adrenal glands as a result of a deficiency or excess of the proteins shown. *DAX1,* Tgene duplicated in congenital adrenal hypoplasia on the X chromosome; *Emx2,* the empty spiracles homeobox gene; *GATA-4,* the gene encoding a protein that binds to a GATA DNA sequence; *HOXA,* homeobox protein; *Lhx9,* a LIM homeobox family member; *Lim1,* a homeobox gene important for limb development; *Pax2,* a paired box homeotic gene; *SF-1,* the gene for steroidogenic factor 1; *SRY,* the sex-determining region of the Y chromosome; *SOX9,* SRY homeobox 9; *WNT-4,* a protein that induces development of the müllerian mesenchyma; and *WT1,* Wilms' tumor suppressor gene 1. (From MacLaughlin DT, Donahoe PK: Sex determination and differentiation. N Engl J Med 2004;350:367-378.)

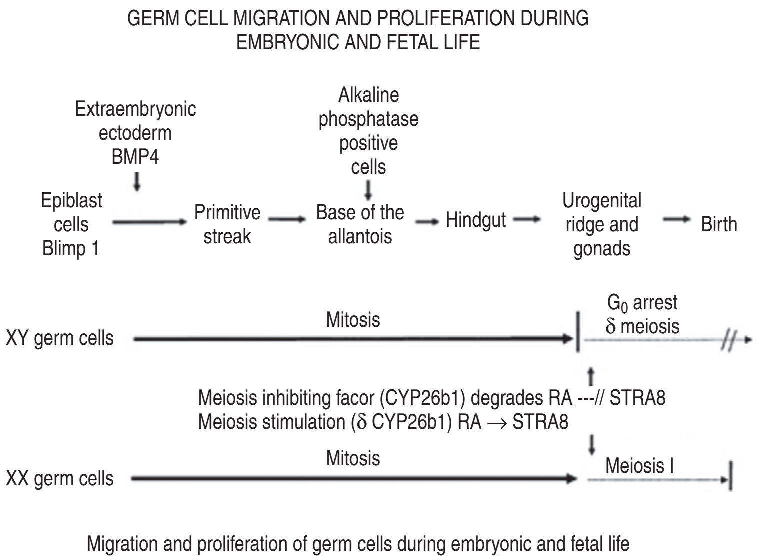


**FIGURE 123-2** Migration and proliferation of germ cells during embryonic and fetal life.[2,133]

translocations in a series of XY phenotypic females. Later, Sinclair and colleagues[28] defined a single-copy gene called the *sex-determining region of the Y chromosome (SRY)* that encodes a DNA binding protein, which is expressed in the gonadal ridge immediately before testis differentiation.[29] When the *SRY* gene, which expresses a protein homologous to the high mobility group (HMG) class of nuclear proteins, was transfected into XX female mouse embryos, a substantial proportion of these transgenic animals developed testes and assumed anatomic and functional male phenotypes.[30,29]

In addition to the Y chromosome, autosomal and X factors contribute to sex differentiation. For example, mutations on the long arm of chromosome 17q, found in cases of camptomelic dysplasia associated with sex reversal,[31–33] caused a defect in the *SRY*-related gene product, SOX 9, which contributes to sex differentiation. In addition, analysis of 46,XY sex-reversed females with intact *SRY* led to the discovery of the dosage-sensitive sex (DSS) reversal locus on the short arm of the X chromosome, duplication of which is required for female differentiation.[34] This region, which contains the gene *DAX-1,* was then assumed to have a negative influence on testis differentiation because a double dose of the X chromosome is associated with dysgenesis of the testis. However, knockout of *DAX-1* resulted in normal female gonadal development,[35] which undermines the hypothesis that *DAX-1* is responsible for ovarian differentiation. The only abnormality seen as a result of null mutation in *DAX-1* occurs, counterintuitively, in the male, which displays abnormalities in spermatogenesis and spermatogenic cord formation.[36] Defects in the distal end of the short arm of chromosome 9p[37] and the distal end of the long arm of chromosome 10q[38] are also associated with sex reversal.

The genes responsible for ovarian development are relatively obscure; in fact, the conventional wisdom has been that the ovaries developed passively as a result of the absence of testicular determining genes. Of the few genes studied in the mouse, it is clear that *WNT-4* is associated with ovarian development, as homozygous females have masculinized gonads and absence of the müllerian ducts.[39] Furthermore, *WNT-4* activation was recently shown to be regulated by *Respondin-1,* which regulates canonical-β-catenin, cytoplasmic stabilization of which in the XY gonad causes male-to-female sex reversal[9,40]; *FOXL2,* a forkhead transcription factor, was identified as another gene that represses the male development, allowing for normal ovarian development.[41–43] It is important to note, moreover, that prenatal ovarian development appears to be independent of steroid hormone action.[44] Taken together, it now seems reasonable to assume that ovarian differentiation is not merely a default pathway resulting from improper testis differentiation.

Thus the embryo must have the appropriate chromosomal endowment (i.e., 46,XX for females and 46,XY for males). Germ cells must then accurately migrate to the hindgut and subsequently take up residence in the retroperitoneum, where they condense in the urogenital ridge to become either a testis or an ovary. Germ cell migration into the urogenital ridge coincides with and probably induces the morphologic formation of a sex-specific gonad, which in turn produces steroid hormones and proteins. Receptors in local and more distant sites subsequently respond to the secreted extracellular hormones and proteins to activate intracellular signaling pathways and somatic gene responses, which lead to morphologic and biochemical changes resulting in the appropriate male or female phenotype.[45]

Male and female primordial reproductive ducts coexist for a short period in all mammalian embryos. Müllerian ducts, the anlage of the uterus, Fallopian tubes, and upper third of the vagina, develop autonomously in the female in the absence of the testis. Wolffian ducts, the anlage of the epididymis, vas deferens, and seminal vesicles, require testosterone to develop. The müllerian duct first forms by invagination of the coelomic epithelium, which tubularizes under the influence of *WNT-4* and then elongates, as the epithelial cells migrate in close approximation to the wolffian duct.[46] The wolffian duct provides no cells, but its presence is essential for full elongation of the müllerian duct to the urogenital sinus.[47] Wnt9b[47] and a functional PI3K/AKT pathway are essential for this final tubularization of the müllerian duct.[48]

The fetal testis, after morphogenesis into seminiferous tubules with Sertoli cells surrounding germ cells and interstitial differentiation to Leydig cells, produces two products required for further male differentiation, müllerian inhibiting substance (MIS), which inhibits differentiation of the müllerian duct, and testosterone, which stimulates wolffian structures.[49] The external genital primordia develop autonomously into clitoris, labia minora, and labia majora. Complete differentiation of the external genitalia to phallus and scrotum requires reduction of testosterone to dihydrotestosterone by 5α-reductase.[50] The interaction of dihydrotestosterone and an intracytoplasmic androgen receptor results in lengthening of the phallus into a penis, the urogenital folds fuse to form the penile urethra, and the labioscrotal swellings fuse in the midline to form the scrotum. The influence of testosterone is discussed in more detail later in the chapter. Autonomous female development can occur in the absence of ovaries.

The existence of a müllerian inhibitor was proposed by Jost,[49] who showed that testicular implants in female rabbit embryos stimulated the wolffian duct but also caused regression of müllerian ducts. This regression is characterized morphologically by programmed cell death. Because of the importance of these events, MIS was purified[51,52] and then used to clone the MIS gene.[53,54] The bioactive C-terminal domain of MIS is homologous to a group of evolutionary conserved proteins, referred to as the *transforming growth factor*-β (TGF-β) family, which is composed of TGF-β, MIS, activin, inhibin, bone morphogenesis factor, *Drosophila* decapentaplagia, *Xenopus* Vg1, and a number of growth and differentiation factors (GDFs).[54] The MIS ligand binds to a heterologous receptor composed of at least two serine-threonine kinase transmembrane units, the type II receptor,[55] which phosphorylates or activates the type I receptor,[56] which signals downstream via SMAD1/5/8 to begin the series of molecular events that results in regression of the müllerian ducts. This substance has been developed as an antiproliferative agent for tumors of müllerian duct origin and ovarian,[57,58] endometrial,[59] cervical,[60] breast,[61–63] and prostate[61] cancers. Abnormalities of the *MIS* gene itself can result in the retained müllerian duct syndrome, in which otherwise normal males, usually with undescended testes, have persistent müllerian structures that have not undergone normal regression.[64,65]

# Pathophysiology of Disorders of Sexual Differentiation

Three major categories of developmental aberrations are responsible for the most common forms of DSD in newborns (Table 123-1). In the first category, genetic females are masculinized by an overabundance of androgenic steroid production, causing a genital abnormality that requires highly specialized medical or surgical management (or both). In the second category, DSD occur because of deficient

**TABLE 123-1**
**Disorders of Sex Development Diagnosis and Treatment**

| *Disease* | *Diagnostic Features* | *Physical Examination Phenotype* | *Gender Assignment* | *Medical Therapy* | *Surgical Therapy* |
|---|---|---|---|---|---|
| 46,XX DSD (Overandrogenized Female)<br>Congenital adrenal hyperplasia (adrenogenital syndrome) | Karyotype 46,XX<br>Electrolytes: K high, Na low<br>Androgen high<br>17-hydroxyprogesterone high<br>MIS 0<br>Sequence CYP21<br>Chromosomal FISH | Symmetric gonads<br>Clitoral hypertrophy<br>Sinogram: UG sinus defect<br>Enlarged labioscrotum | F | Hydrocortisone or cortisone acetate + Florinef<br>Embryo selection from the blastocyst<br>Steroid replacement in utero from 6 wk gestation | Perioperative stress steroids<br>Clitoral reduction<br>Vaginal exteriorization<br>Labioscrotal reduction |
| 46,XY DSD (Underandrogenized Male)<br>Testosterone deficiency | Karyotype 46,XY<br>Testosterone low<br>Sequence enzyme genes:<br>17-KS OH, P450scc, 3β-HSD, CYP17<br>FISH | Symmetric, undescended, small testis<br>Severe hypospadias<br>No müllerian structures | If M | Presurgical testosterone stimulation<br>Testosterone at adolescence | Hypospadias repair<br>Prepenile scrotal repair<br>Orchiopexy |
| | | Predominant female phenotype if adolescence | If F | Estrogen/ progesterone at adolescence | Gonadectomy |
| Androgen receptor deficiency<br>Testicular feminization (complete androgen insensitivity) | Karyotype 46,XY<br>Testosterone high<br>MIS high<br>Sequence androgen receptor gene<br>FISH | Female phenotype<br>No müllerian structures<br>Normal testes<br>Narrow male pelvic structures<br>Sparse axillary and pubic hair | F | Estrogen/ progesterone at adolescence | Infancy: gonadectomy,<br>Adolescence: vaginal replacement |
| Reifenstein syndrome (incomplete androgen insensitivity) | Karyotype 46,XY<br>Testosterone normal<br>MIS slightly elevated | As for testosterone if deficiency | If F | Estrogen/ progesterone at adolescence | Infancy: gonadectomy, clitoral reduction, labioscrotal reduction<br>Adolescence: vaginal replacement |
| | Sequence androgen receptor gene<br>FISH<br>CGH | | If M | As for testosterone deficiency (above) | AS for testosterone deficiency (above) |
| 5α-Reductase deficiency | Karyotype 46,XY<br>Testosterone high<br>DHT low<br>MIS high<br>Sequence 5α-reductase type 2 gene<br>FISH | Severe hypospadias<br>Symmetrical, undescended, normal testes<br>Prepenile scrotum | M | Presurgical testosterone stimulation<br>DHT replacement | Hypospadias repair<br>Prepenile scrotal repair<br>Prostatic and utrical opening |
| Chromosomal Abnormalities | | | | | |
| 46,XY (complete gonadal dysgenesis) | Karyotype 46,XY<br>Sequence candidate genes: SRY, SOX 9, DAX-1<br>Testosterone absent<br>MIS absent<br>FISH<br>CGH | Phenotypic female<br>Vagina present<br>No gonads<br>Symmetric | F | Estrogen/ progesterone at adolescence | Gonadectomy |
| 45,X/46,XY (Ovotesticular DSD; MGD (mixed gonadial dysgenesis) | Karyotype 45,X/46,XY or 46,XY<br>Testosterone low<br>MIS low<br>Sequence DAX-1<br>FISH<br>CGH | Asymmetry of gonads: streak ovary and dysgenetic testis<br>UG sinus<br>Clitoral hypertrophy | If F | Estrogen/ progesterone at adolescence | Clitoral recession<br>Vaginal exteriorization<br>Labioscrotal reduction<br>Gonadectomy |
| | | | If M | Presurgical testosterone stimulation<br>Testosterone at adolescence | |

**TABLE 123-1**
**Disorders of Sex Development Diagnosis and Treatment—Cont'd**

| *Disease* | *Diagnostic Features* | *Physical Examination Phenotype* | *Gender Assignment* | *Medical Therapy* | *Surgical Therapy* |
|---|---|---|---|---|---|
| 46XY (90%)<br>Ovotesticular DSD<br>True hermaphrodite | Karyotype 46,XX<br>Testosterone normal or low<br>MIS normal or low<br>CGH | Asymmetric testis, ovary, or ovotestes<br>UG sinus defect<br>Clitoral hypertrophy | If F | Estrogen/ progesterone at adolescence | Clitoral recession<br>Vaginal exteriorization<br>Labioscrotal reduction<br>Preserve normal ovary or polar ovarian tissue |
| | | | If M | Presurgical testosterone stimulation<br>Testosterone at adolescence | Staged hypospadias repair<br>Prepenile scrotal repair<br>Removal of müllerian structures<br>Preserve vas and normal testis or central testicular tissue<br>Orchiopexy?<br>Prosthesis? |

*CGH,* Comparative genomic hybridization; *DHT,* dihydrotestosterone; *F,* female; *FISH,* fluorescent in situ hybridization; *M,* male; *MIS,* müllerian inhibiting substance; *PCR,* polymerase chain reaction; *UG,* urogenital.

androgen production or action in genetic males. The third category of abnormalities results from mutations leading to absent, incomplete, or asymmetric gonadal differentiation.[45] It is essential to understand the pathophysiology underlying these disorders in order to make a timely and accurate diagnosis and to plan optimal treatment strategies.

**TABLE 123-2**
**Steroid Biosynthetic Enzyme Nomenclature**

| *Old* | *New-Protein* | *New-Gene* |
|---|---|---|
| Testis | | |
| 20,22-desmolase | P450scc (side chain cleavage) | CYP11A |
| 17-hydroxylase | P450c17 | CYP17 |
| 17-lyase | P450c17 | CYP17 |
| 3β-hydroxysteroid dehydrogenase (3β-HSD) | Same | Same |
| 17-ketosteroid reductase | Same | Same |
| Adrenal | | |
| 21-hydroxylase | P450c21 | CYP21 |
| 11-hydroxylase | P450c11 | CYP11B1 |
| 18-hydroxylase | P450c11 | CYP11B2 |

## 46,XX DSD (OVERANDROGENIZATION OF 46,XX GENETIC FEMALES)

The most common cause of overandrogenization or virilization is a defect in the P450 (heme pigment 450 oxidases, which metabolize multiple substrates) adrenal enzymes responsible for the conversion of progesterones to glucocorticoids and mineralocorticoids, resulting in the syndrome of congenital adrenal hyperplasia (CAH) or adrenogenital syndrome, which is now known as 46,XX DSD (overandrogenization).[66] This syndrome affects both males and females but causes ambiguous genitalia only in females. Adrenal differentiation occurs in the human fetus at 11 weeks' gestational age, after differentiation of the gonads and reproductive tract. Therefore the excess androgen most severely affects the developing external genitalia, the genital tubercle, and the urogenital folds, which develop after 11 weeks. When exposed to excess androgens, the genital tubercle, instead of forming a clitoris, is stimulated to develop as a penile structure. The urogenital folds, rather than developing as labia, acquire a bifid infused or fused scrotal appearance. Important to the differential diagnosis, ovaries remain in their normal intra-abdominal position above the inguinal canal.

Mutations in the *P450c21,* or 21-hydroxylase gene, now known as *CYP21* (Table 123-2), cause 90% of cases of CAH. The mutated gene, which resides on chromosome 6p in the HLA locus, results from recombination between the functional CYP21B and the nonfunctional pseudogene *CYP21A.* Incorporation of deletions from this pseudogene act to disable the functional gene.[67–70] The remainder of CAH cases are distributed among deficiencies of P450c11, 3β-hydroxysteroid dehydrogenase, CYP17, or steroid acute regulatory protein (StAR), depending on the ethnic origin of the patient.[45,71,72] Rarely, 46,XX DSD can result from exposure to exogenous androgens such as those given in the past to prevent loss of pregnancy. In case of classical CAH, deficient glucocorticoids and mineralocorticoids result in negative feedback on the pituitary, which then leads to excessive production of adrenocorticotropic hormone. This, in turn, results in hyperplasia of the fasciculata and granulosa layers of the adrenal gland and preferential production of androgenic steroids from the reticulata layer. 17-hydroxyprogesterone accumulates proximal to the P450c21 block, resulting in overproduction of pregnenolone and progesterone and their 17-hydroxylated derivatives, leading to the overproduction of testosterone and ultimately its reduced derivative, dihydrotestosterone (see Fig. 123-2). Elevations in 17-hydroxyprogesterone can be detected from a spot serum sample.[73] Polymerase chain reaction (PCR), sequencing of known genes, or fluorescent in situ hybridization (FISH) can now be used to make this diagnosis in utero.[45]

The molecular defect in these 46,XX genetic females with adrenogenital syndrome resides in the adrenal glands. The condition presents in a wide clinical spectrum. The ovaries, uterus, and Fallopian tubes are normal. The vagina, however, is foreshortened as a result of having failed to migrate to the perineum. It joins the urethra either at the position of the prostate, if masculinization is severe, or at a more distal position, if masculinization is less severe. The external genitalia are

characterized by variable clitoral enlargement, ranging from trivial to severe; some patients form an almost normal phallus. The labia can be masculinized to form either labioscrotal folds or, in the most severe cases, complete scrotal fusion. Because the ovaries are normal, the gonads never descend into these labioscrotal folds or fused scrotum.[74] Therefore an infant with bilateral nonpalpable testes should have a spot test for 17-hydroxyprogesterone and a karyotype determination to identify the presence or absence of the Y chromosome. All the enzymatic defects result in deficient cortisol biosynthesis. Failure of feedback results in increased corticotropin production, which continues to stimulate the adrenal gland and leads to hyperplasia, elevated production of products proximal to the enzymatic defect, and preferential overproduction of androgenic steroids. Concomitant production of melanocyte-stimulating hormone can also darken the genitalia and breast areolae.

## 46,XY DISORDERS OF SEX DEVELOPMENT, UNDERVIRILIZATION OF THE MALE (46,XY)

Insufficient masculinization of a 46,XY genetic male can occur due to insufficient testosterone production, an androgen receptor deficiency, or an inability to convert testosterone to dihydrotestosterone resulting in 46,XY DSD (formerly known as *male pseudohermaphroditism*).[75] Deficiency of androgen production (Fig. 123-3) occurs because of genetic enzymatic defects including steroid acute regulatory protein (StAR), resulting in lipoid adrenal hyperplasia (formerly thought to represent defects in cholesterol desmolase, P450scc, or CYP11A1). CYP11A1 (20,22 desmolase), CYP17 (17-hydroxylase or lyase), 3β-hydroxysteroid dehydrogenase (3β-HSD), and 17β-hydroxysteroid dehydrogenase (17β-HSD), formerly known as 17-ketosteroid reductase, together and sequentially are responsible for the cascade of metabolism from cholesterol to testosterone.[71] In these patients, stimulation by chorionic gonadotropin produces little or no testosterone; in contrast, MIS levels are normal or high for age. The testes may be undescended, small, or both. Under the influence of normal MIS, there should be no müllerian structures. Because of testosterone deficiency, the penis may be small and hypospadiac.[70]

Androgen insensitivity can occur because of receptor deficiency. Most abnormalities are caused by point mutations in the androgen receptor gene,[76,77] which can now be detected by PCR and DNA sequencing. Only rarely have large deletions been found. The phenotype can be mild or severe; the complete androgen insensitivity syndrome (CAIS) manifestation was often referred to as *testicular feminization,* in which the patient has an almost complete female phenotype. Serum levels of testosterone may be high; MIS may be normal or,

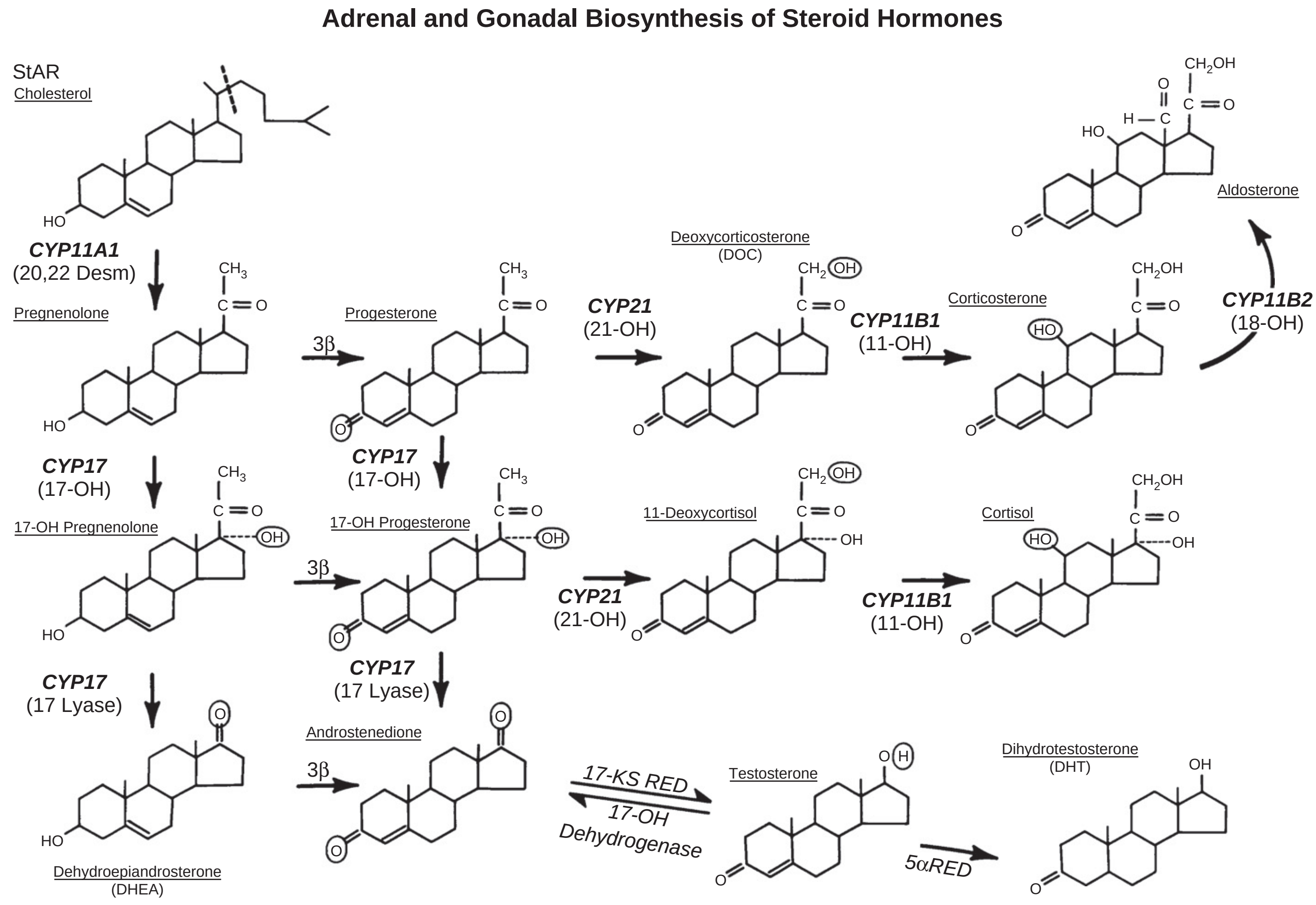


**FIGURE 123-3** Pathways of steroid hormone biosynthesis from cholesterol. New enzyme nomenclature is in bold lettering; old nomenclature is in parentheses. Enzymatic defects of CYP21, CYP11, or 3β-hydroxysteroid dehydrogenase can lead to congenital adrenal hyperplasia. Deficiencies in testosterone production leading to a form of male pseudohermaphroditism can result from defects in $CYP11A_1$, CYP17, 3β-hydroxysteroid dehydrogenase, and 17-ketosteroid reductase.

in some cases, considerably elevated; and müllerian structures are normally regressed. The gonads are symmetric and may be intra-abdominal or descended. However, not all patients with the 46,XY karyotype and the characteristics of 46,XY DSD have a detectable molecular defect in the coding region of the androgen receptor. It is possible that the noncoding promoter, the 3′ untranslated region, or other transcription factors or their cofactors are the cause of 46,XY DSD in the large subset of patients in which the molecular defect has not yet been defined.

3β-HSD acts by reducing the 3β-hydroxyl group to a 3-ketone, and by isomerizing the C5-6 double bond to the C4-5 position in the conversion of pregnenolone to progesterone, or 17-hydroxypregnenolone to 17-hydroxyprogesterone. All these steps are essential for the production of glucocorticoids and mineralocorticoids. The activity is also important in the testis for the conversion of dehydroepiandrosterone (DHEA) to androstenedione. Various isoforms of this enzyme have also been found in the placenta, but their functions have not been as carefully detailed. Another non-P450 enzyme in the pathway is 17β-HSD, which converts androstenedione to testosterone.

Mutations in the 5α-reductase type 2 genes cause another form of 46,XY DSD. Because of this deficiency, testosterone is not converted to dihydrotestosterone in peripheral, particularly genital, target tissues.[50,78] This non-P450 enzyme depends on the reduced form of NADPH (nicotinamide-adenine dinucleotide phosphate). Action in the genital area results in elongation and ventral closing of the penile raphe, which encloses the urethra and displaces the urethral orifice from the perineum to the tip of the penis.[75] The labioscrotal folds are also fused in a posterior direction to create scrotal sacs. This autosomal recessive form of severe hypospadias is associated with undescended testis, prepenile scrotum, and enlarged prostatic utricle. The enzyme has binding sites for both testosterone and the NADPH cofactor, where point mutations have been associated with the defective phenotype. Two known isoforms exist; however, type 2, located on chromosome 19, is the one expressed predominantly in the external genitalia. The paradoxical virilization that occurs at puberty and results in a change of sexual identity is caused by increased activity of the 5α-reductase type 1 isoform in a multitude of other tissues in these genetic males.

### ABNORMALITIES OF GONADAL DEVELOPMENT AND DIFFERENTIATION

Abnormalities of the sex chromosomes usually manifest as failed, incomplete, or asymmetric gonadal differentiation. Patients with these disorders have either bilateral streak gonads, as in 46,XY pure gonadal dysgenesis, or asymmetric gonadal development, as in mixed gonadal dysgenesis (MGD) or ovotesticular DSD (formerly termed *true hermaphroditism*). Patients with pure gonadal dysgenesis and a 46,XY karyotype may have a defective Y chromosome, with either deletion in the 1A1 pseudoautosomal region[27] or a point mutation in the *SRY* gene.[79] Mutations associated with camptomelic dysplasia, a severe disorder occurring in patients with a translocation in the distal arm of chromosome 9p near the *SRY*-related *SOX 9* gene,[31,33] or mutations in *WT1* associated with Frasier syndrome[37] also result in pure gonadal dysgenesis. These streak gonads fail to develop bilaterally, producing little or no end products of testosterone or MIS; gonadotropin levels are compensatorily high. Müllerian ducts are preserved, and the phenotype is female.

MGD (also known as *asymmetric gonadal dysgenesis*) with a 45,X/46,XY karyotype is by far the most common of the chromosomal abnormalities.[45,80] The gonads are asymmetric, most often with a small dysgenetic testis on one side and a streak gonad on the other.[81] Most patients with this defect have retained müllerian ducts. The small testis can produce enough testosterone to cause masculinization and hypertrophy of the clitoris. The vagina fails to migrate to the perineum and enters the urethra as a urogenital sinus defect more distal to the bladder neck than seen in severe cases of CAH. It is important to note that 40% of patients with MGD can have a 46,XY karyotype, and some have bilateral testes or streak ovaries. The absence of the second X chromosome is in some way related to the early ovarian dysgenesis. The mosaicism of MGD results from the presence of at least two gonadal (chimeric) germ cell lines, and the degree of testicular differentiation is determined by the percentage of cells expressing the XY genotype, which may also influence the degree of asymmetry. Loss of the Y chromosome can occur because of nondisjunction, the failure of paired chromosomes to migrate to opposite poles during cell division.[2,25,82,83] Because prenatal genetic testing has become more common, the 45,X/46,XY karyotype is now being detected in a small percentage of amniotic cells in phenotypically normal males.

True ovotesticular DSD (true hermaphrodites) are rare, except among the Bantu in Southern Africa; the cause of this anomaly remains elusive.[84,85] More than 90% of these patients have a 46,XX karyotype. Asymmetry characterizes many of these patients, who have simultaneous ovarian and testicular differentiation without the dysgenesis characteristic of MGD. The testicular and ovarian tissue can be separated on both sides or combined in one or both gonads as an ovotestis. When ovarian tissue and testicular tissue coexist in the same gonad, the testis is always central and the ovarian tissue is polar.[86] Although the molecular cause of this disorder has not been elucidated, translocation of a fragment containing the *SRY* gene to a cryptic site on the X chromosome has been observed.[87] Otherwise, *SRY* has not been detected in these patients. Although early testicular differentiation occurs, spermatogenesis is not evident,[84] which may reflect the absence of other necessary Y-directed functions. The müllerian structures are regressed on the side of the testicular tissue but retained on the side of the ovarian tissue and in the midline as well, with the vagina entering the distal urethra as a urogenital sinus defect. The asymmetry associated with this disorder remains an enigma.

## Diagnosis

A baby born with DSD must have an expeditious and thoughtful evaluation to determine whether gender assignment can be made. It is important to minimize the emotional trauma to the family and later to the child. Referral to a well-organized team of endocrinologists, geneticists, psychologists, and pediatric surgeons/urologists experienced with the complexity of these disorders is absolutely necessary. Although many syndromes can affect later sexual development, only four result in DSD at birth: 46,XX DSD (formerly known as *female pseudohermaphroditism*), ovotesticular DSD (true hermaphroditism);

46,XY DSD (previously termed *male pseudohermaphroditism, undervirilization of an XY male,* and *undermasculinization of an XY male*); and MGD 45,X/46,XY. A child with pure gonadal dysgenesis, although having a 46,XY karyotype, is phenotypically female. It is critical that the sex of rearing not be biased by the skills of the surgeons, who must be equally capable at reconstructing the infant as male or female. Two screening criteria can be used to diagnose the infant as having one of the four disorders: symmetry and the presence of a Y chromosome (Table 123-3). The diagnostic evaluation of patients with ambiguous genitalia is outlined in Table 123-1.

The first criterion is the physical finding of gonadal symmetry or asymmetry, and the second is a rapid analysis of the sex chromosomes. Probes for *SRY* can now be used to detect the distal end of Yp, the short arm of the Y chromosome, by PCR or FISH. Direct sequencing of the *SRY* gene is now available. Symmetry of the gonads is determined by the position of one gonad relative to the other, either above or below the external inguinal ring. Both gonads lie either above or below the external inguinal ring when a diffuse biochemical cause underlies the abnormality. For example, in 46,XX DSD or 46,XY DSD, a biochemical defect influences both gonads equally. Asymmetry occurs in chromosomal abnormalities such as MGD or ovotesticular DSD (true hermaphroditism), in which a predominant testis descends and a predominant ovary remains above the external ring. In cases of 46,XX DSD (female pseudohermaphroditism with adrenogenital syndrome) and in most cases of ovotesticular DSD (true hermaphroditism), the karyotype is 46,XX. Patients with 46,XY DSD (male pseudohermaphroditism) or MGD have a Y chromosome in their karyotype.

After this initial evaluation, rapid analysis for 17-hydroxyprogesterone to detect CYP21 disorders should be done emergently in patients with 46,XX with symmetric undescended gonads. This screening test is done in some states' laboratories on all newborns. A detailed history and physical examination can be coupled with PCR, FISH, or direct sequencing to detect mutations or deletions known to cause defects in the four major categories (Table 123-4) and to define these disorders more fully and guide sex assignment. Subsequently, ultrasonography, magnetic resonance imaging, contrast radiography, and later panendoscopy, coupled with accurate laboratory analysis for disorders of enzymes affecting testosterone synthesis, should provide a definitive diagnosis and permit appropriate gender assignment with a high degree of accuracy.

The size and location of the penis with respect to the scrotum should be carefully noted. Although the size of the phallus varies considerably, some guidelines are helpful.[70,88] The average length of the penis is $3.5 \pm 0.4$ cm at term, $3.0 \pm 0.4$ cm at 35 weeks' gestation, and $2.5 \pm 0.4$ cm at 30 weeks' gestation. At term, a diameter of 1 cm is average. A penis smaller than $1.5 \pm 0.7$ cm in full-term infants may raise the option of female gender assignment, except in cases of 17-ketosteroid reductase or 5α-reductase deficiencies, in which large body habitus or sex reversal at puberty, respectively, may favor or dictate male sex assignment. An early rectal examination

**TABLE 123-3**
**Rapid Diagnostic Algorithm**

| Y Chromosome Absent or Abnormal | | Y Chromosome Present | |
|---|---|---|---|
| *Symmetry* | *Asymmetry* | *Symmetry* | *Asymmetry* |
| 46,XX DSD [congenital adrenal hyperplasia] | Ovotesticular DSD | 46,XY DSD | 46,XX/46,XY MGD [Mixed gonadal dysgenesis] |

These two diagnostic criteria—presence or absence of Y chromosome and gonadal symmetry or asymmetry—allow the rapid, accurate assignment of a patient into one of the four diagnostic categories with approximately 90% accuracy.

**TABLE 123-4**
**Mutations in Genes Involved in Sex Determination and Development and Associated with Disorders of Sex Development**

| *Gene (Locus)* | *Protein and Proposed Function* | *Mutant Phenotype* |
|---|---|---|
| WT1 (11p13) | Transcription factor | Frasier syndrome; Denys-Drash syndrome with Wilms' tumor |
| SF-1 (9q33) | Transcription factor, nuclear receptor | Gonadal and adrenal dysgenesis |
| SOX 9 (17q24) | High mobility group (HMG) protein transcription factor | Camptomelic dysplasia and male gonadal dysgenesis or XY sex reversal |
| DAX-1 (Xp21.3) | Transcriptional regulator, nuclear receptor | Gonadal dysgenesis and congenital adrenal hypoplasia |
| SRY (Yp11) | HMG protein transcription factor | Gonadal dysgenesis, XX sex reversal |
| MIS (AMH) type II receptor (12q12-13) | Serine threonine kinase receptor | Persistent müllerian duct syndrome |
| MIS (AMH) (19p13) | Secreted protein, fetal müllerian duct regressor, Leydig cell inhibitor | Persistent müllerian duct syndrome |
| AR (Xq11-12) | Androgen receptor, ligand transcription factor | 46,XY DSD, CAS or PAIS |
| HSD17B3 (9q22) | 17-hydroxysteroid dehydrogenase–17-ketosteroid reductase 3 | 46,XY DSD |
| SRD5A2 (5p15) | 5α-steroid reductase type 2 | 46,XY DSD (may virilize at puberty) |
| CYP17 (10q24q25.) | 17-hydroxylase, 20,22-lyase | 46,XY DSD |
| CYP21 (6q21.3) | 21-hydroxylase | 46,XX DSD (Congenital adrenal hyperplasia) |
| HSD3B2 (1p13.1) | 3β-hydroxysteroid dehydrogenase type 2 | 46,XX DSD (Congenital adrenal hyperplasia) |
| CYP11B1 (8q24) | 11β-hydroxylase | 46,XX DSD (Congenital adrenal hyperplasia) |
| StAR (8p11.2) | Steroidogenic acute regulatory protein | Congenital lipoid adrenal hyperplasia |

From MacLaughlin DT, Donahoe PK: Sex determination and differentiation. N Engl J Med 2004;350:367-378.

may allow the detection of the uterus while it is still under the influence of placental human chorionic gonadotropin, after which the uterus softens. The presence and severity of hypospadias should be noted; the confluence point of the vagina with the urogenital sinus (UGS) (urethra) in relation to the bladder neck and perineum and the length of the vagina should also be noted. Palpation of the gonads can help differentiate the firm testis from the softer ovotestis, and the wrapping of the epididymis around the testis can help differentiate it from an ovary in the inguinal position.[45] Often the hypospadiac phallus is displaced posteriorly behind a prepenile scrotum.

## 46,XX DSD (OVERANDROGENIZATION OF GENETIC FEMALES, 46XX)

Female pseudohermaphroditism is a diagnostic problem if the patient is the proband for the family. If a sibling already has the disease, the level of awareness for this autosomal disorder will be high. Amniocentesis with cytogenetic analysis for the genetic defect allows early prenatal diagnosis. However, in unsuspected cases, when the child is born at term, the clitoris is hypertrophied, the gonads are symmetric and intra-abdominal, and the vagina fails to descend to the perineum and enters the UGS (urethra) distal to the bladder neck; however, a significant subset of patients may have a verumontanum, with the urethrovaginal confluence quite close to the bladder neck.[89] These patients can also have an enlarged, placentally stimulated, palpable prostate at the level of the verumontanum. The labioscrotal folds are rugated, enlarged, and, in some cases, completely scrotalized. In addition to normal ovaries, the uterus and Fallopian tubes are normal. The vagina, however, is foreshortened, as a result of having failed to migrate to the perineum. It is essential to measure the distance from the bladder neck to the UGS confluence at the time of panendoscopy to aid future plans for definitive reconstruction. The external genitalia are characterized by variable clitoral enlargement, ranging from trivial to severe. Some patients have a male-appearing phallus. The labia may be masculinized to form labioscrotal folds or, in severe cases, complete scrotal fusion may occur. Because the ovaries are normal, the gonads never descend into the labioscrotal folds or fused scrotum.[45,74] The karyotype is always 46,XX in females, MIS is undetectable, and a spot serum analysis reveals elevated 17-hydroxyprogesterone. Androgen levels are also elevated. Concomitant production of melanocyte-stimulating hormone can darken the genitalia and breast areolae. PCR with appropriate probes demonstrates point mutations in the *P450c21* gene.[69] Electrolytes are often normal at birth, but when maternal steroids wane after 5 to 7 days, potassium levels may become markedly elevated and serum sodium levels may fall. As a result, electrocardiography reveals inverted Twaves, which, if unattended, can lead to cardiac arrest. Hence this disorder must be considered a medical emergency in the new forum.

In rare cases with 3β-HSD deficiency, 17-hydroxypregnenolone, pregnenolone, and DHEA levels are elevated and serum 11-deoxycortisol or deoxycorticosterone levels are elevated in patients with P450c11 deficiency. Gender assignment in these patients is almost always female, except when the diagnosis is delayed and the patient has already been raised as a male.[90,91]

## 46,XY DSD (MALE PSEUDOHERMAPHRODITISM)

### Testosterone Deficiency

By definition, 46,XY DSD have deficient androgenization of the external genitalia with a 46,XY karyotype. If the disorder is caused by an enzymatic defect in the testosterone-androgen pathway, patients have low basal serum testosterone and stimulation by chorionic gonadotropin produces little or no increase in testosterone. Because the genes coding for the enzymes in the pathway have been cloned, PCR or direct sequencing can be performed to detect deficiencies in *StAR, 3β-HSD, CYP17,* or 17-ketosteroid reductase genes. The testes may be small and are often bilaterally and symmetrically undescended. The penis is small, and hypospadias is usually severe. Under the influence of normal MIS, there are no detectable müllerian structures. In some cases, the phenotype is completely female.[70,92] Gender assignment depends on the size of the phallus. It may be better to raise those with a small phallus as females, whereas it is invariably preferable to raise those with a reasonably sized phallus as males because they will respond to exogenous testosterone. Special consideration should be given to those rare children with 17-ketosteroid reductase deficiency, which may be better raised as males (P. K. Donahoe and R. Pieretti, oral communication).

### Androgen Receptor Deficiency

Cases in which the androgen receptor is severely dysfunctional, as occurs in CAIS (complete androgen insensitivity syndrome), previously known as *testicular feminization,* have been attributed to complete androgen receptor insufficiency.[93] The phenotype is completely female, so these children should be raised in concordance with that phenotype. No müllerian structures are present because high levels of biologically active MIS are produced. The testes are usually in the inguinal region, and their firmness and investing epididymis can be palpated to distinguish them from ovaries. The karyotype is 46,XY. Although the androgen receptor is deficient, levels of testosterone and MIS are high. PCR or sequencing of the androgen receptor gene can often pinpoint the molecular defect and provide the definitive diagnosis.

PAIS (partial androgen insensitivity syndrome) results in only partially masculinized 46,XY patients, with a wide variation from minimal to severe anomalies. As with testosterone-deficiency syndrome, the penis is small and hypospadiac. The testes may be small and are often undescended but symmetric, and müllerian structures are not present. The testosterone levels are normal, and MIS levels are elevated. Most abnormalities are caused by point mutations in the androgen receptor gene,[76,77] which can be detected by PCR and DNA sequencing. Only rarely have large deletions been found. Gender assignment, again, depends on the size of the phallus.

### 5α-Reductase Deficiency

46,XY DSD can also result from a deficiency of 5α-reductase, which is responsible for the conversion of testosterone to dihydrotestosterone. The normal action of 5α-reductase on the genital area results in elongation and ventral closing of the penile raphe, displacing the urethral orifice from the perineum to the center of the glans penis.[75] This process is abnormal in these patients, resulting in severe penoscrotal

hypospadias. Normal and symmetric testes can be either undescended or fully descended. The labioscrotal folds are also closed posteriorly to create partial or bifid scrotal sacs. The prostatic utricle is often quite enlarged. Again, the karyotype is 46,XY. Serum levels of testosterone are high, but levels of dihydrotestosterone are low. The MIS levels are normal. PCR and full DNA sequencing can be used to genotype and detect mutations in the 5α-reductase type 2 gene. Given the dramatic phenotypic conversion at puberty, it may be more appropriate to raise these children as males. It should be noted, however, that in this group, gender assignment involves the greatest dilemma in societies committed to two sexes, but not in societies that more readily accept assignment to a third sex.[50,94,95]

## CHROMOSOMAL ABNORMALITIES

### 46,XY Pure Gonadal Dysgenesis

Patients with pure gonadal dysgenesis are born as phenotypic females. Amniocentesis with a 46,XY karyotype that does not produce the expected phenotype on fetal ultrasonography now allows earlier diagnosis than was previously possible. Dorsal pedal edema and some Turner characteristics may be the only obvious somatic manifestations of the defect. Müllerian structures are present, but gonads are not palpable due to failure of gonadal differentiation. Testosterone and MIS are undetectable, indicating dysgenesis of the gonad. Candidate gene mutations include *SRY, SOX 9, WT1,* and *SF-1.*[2]

### Mixed Gonadal Dysgenesis

Patients with MGD are characterized by asymmetry, with a streak gonad on one side and a dysgenetic testis on the other. They also have retained müllerian structures.[80,81,96] The clitoris is usually hypertrophied. The most common karyotype is 45,X/46,XY, but 40% of patients have the 46,XY karyotype. Because the testes are dysgenetic, testosterone and MIS levels may be low. There is a propensity for neoplastic transformation to gonadoblastoma or seminoma (or both),[83,97,98] even as early as the neonatal period. These tumors can cause torsion and apparent loss of a gonad that, in rare cases, leads to a unilateral dysgenetic testis or streak ovary. Because gonadoblastomas may occur at any stage, gonadectomy and female reconstruction and rearing are the options usually chosen. The X-linked DAX-1, which may suppress testicular differentiation, may have a role in MGD, which is the least understood of the intersex abnormalities at the molecular level.[99] When we identify the genes responsible for the separation of paired chromosomes during meiosis, the defects responsible for this enigmatic abnormality may be discovered. We should mention a subgroup of 45,XO/46,XY who are diagnosed prenatally with normal external genitalia and raised as males—indicating a spectrum of the disorder.

### Ovotesticular DSD (True Hermaphroditism)

The molecular cause of this disorder remains enigmatic.[84,85] Patients with this disease also have asymmetry, with a testis on one side and an ovotestis on the other; however, various other gonadal combinations can occur. If an ovotestis is present, testis is always central and the ovarian tissue is polar.[86] Neoplastic transformation is not characteristic of these unique gonads. The müllerian structures are regressed on the side of the testicular tissue but retained on the side of the ovarian tissue and as a midline uterus as well, with the vagina entering the urethra as a urogenital sinus defect. The clitoris is hypertrophied. The karyotype is 46,XX in 90% of cases; the levels of testosterone and MIS are low or sometimes normal. Although early testicular differentiation occurs, spermatogenesis is not evident,[84] which may reflect the absence of other necessary Y-directed functions. Abnormalities in SRY have not been detected in these patients;[100] both the molecular cause and the reason for the asymmetry remain an enigma. The sex of rearing is dictated by the phenotype, which is directed by the predominant gonad.

# Medical Management

## 46,XX DSD (CAH)

Masculinized females with pseudohermaphroditism can be at profound risk for life-threatening complications including cardiac arrest in the prenatal period. Because maternal cortisone crosses the placenta and is released slowly from fat stores, the clinical manifestations of adrenogenital crisis may not become apparent until 5 to 7 days after birth. Heightened clinical awareness and prompt, appropriate metabolic treatment can prevent serious complications. Glucocorticoid replacement as oral hydrocortisone 8 to 10 mg/m$^2$ per day in two or three doses or cortisone acetate 25 mg/m$^2$ injected every 3 days[101] will prevent serious metabolic abnormalities associated with acute adrenal insufficiency.

Fludrocortisone (9α-fluorocortisol) 0.05 to 0.2 mg/day is started in severely virilized infants and in those less virilized with a family history of salt wasting as part of 46,XX DSD (CAH). Recent evidence that even patients with milder virilizing hermaphroditism have subclinical aldosterone deficiency has led to more liberal use of fluorocortisone, although some clinicians follow electrolyte levels and plasma renin activity before starting such treatment.

An infant in adrenal crisis should be rehydrated with isotonic saline. After the first hour, half-strength saline in 5% to 10% dextrose should be administered. This regimen corrects plasma sodium and chloride imbalances rapidly, but hyperkalemia and acidosis are corrected more slowly. Dramatic elevation of plasma 17-hydroxyprogesterone can be used to monitor the effectiveness of treatment. Infants (average 0.25 m$^2$) in adrenal crisis are treated with 25 mg hydrocortisone sodium succinate (2 mg/kg), whereas older children receive 50 to 100 mg. This preparation has both glucocorticoid and mineralocorticoid activity; the mineralocorticoid activity is equivalent to 0.1 mg of fludrocortisone. A similar regimen is used for infants exposed to the stress of surgery. Parents are taught to recognize situations that contribute to adrenal insufficiency such as high fever, exposure to hot environments, or surgery. Breast milk and prepared formulas are low in sodium, so table salt should be given as a supplement. Growth charts must be monitored carefully to avoid inadequate or inconsistent treatment or oversuppression and chronic adrenal insufficiency.

Prenatal diagnosis and treatment are now available.[102,103] Dexamethasone treatment, if used to suppress masculinization in utero, is initiated by the fifth or sixth week of gestation before the start of sexual differentiation. Dexamethasone crosses the placenta to suppress the fetal adrenal gland and

decrease fetal androgen production, thereby minimizing in utero virilization. The sex of the fetus is determined by chromosome analysis at amniocentesis or chorionic villus sampling, and PCR and DNA sequencing can be used to analyze the *CYP21* gene. Treatment is discontinued in males and unaffected females. Affected females can be treated to term. Currently, embryo selection or genetic manipulation can be done at the early blastocyst stage. Blastocysts with a normal *CYP21* gene can be preselected for subsequent implantation if a previous pregnancy produced a child with the CYP21 mutation.

### 46,XY DSD (MALE PSEUDOHERMAPHRODITISM)

46,XY DSD patients with poor penile development who have testosterone biosynthetic defects or androgen resistance may be considered for female gender assignment. However, for those with 5α-reductase or 17β-hydroxysteroid reductase deficiency, it may not be appropriate to assign a gender at birth. Patients assigned to the female gender should receive early surgical correction of the external genitalia and gonadectomy but do not receive hormone therapy until puberty, at which time they will require estrogen and progesterone treatment. Vaginal replacement should be planned for late puberty.

If it is elected to assign these infants to the male gender, 25 mg of testosterone enanthate or cypionate is given once every 3 or 4 weeks for about 3 doses to confirm that the penis responds to androgens or to improve the size of the penis before surgery. Repair should be done before 1 year of age if the size of the phallus permits. This approach takes advantage of an early period of presumed enhanced sensitivity to androgens. After one to three courses of monthly testosterone for 3 months, an interval of at least 1 month without testosterone must be allowed before undertaking hypospadias repair to reduce postoperative hyperactivity that can accompany testosterone therapy. If the child requires a staged procedure, testosterone therapy, if needed, can precede the second stage. Testosterone replacement is resumed at adolescence. Patients with 5 α-reductase deficiency should receive dihydrotestosterone replacement, if available. Otherwise, replacement can be achieved by giving higher doses of testosterone to overcome the enzyme block.

### CHROMOSOMAL ABNORMALITIES

In patients with MGD or ovotesticular disease assigned to the female gender, no steroidal replacement is required in childhood. However, if the child has been assigned to the male gender, presurgical testosterone stimulation of the penis may be required before hypospadias repair. Treatment does not recommence until adolescence. If the patient is assigned to the female gender, replacement of estrogen and progesterone is started at adolescence. Patients with 46,XY pure gonadal dysgenesis require neither surgical nor medical therapy as newborns, and estrogen and progesterone replacement begins at adolescence. Renal function must be followed carefully in patients with the various WT1 isoform defects. Adrenal replacement therapy may be complex in patients with SF-1 mutations characteristic of the adrenal hypoplasia congenita syndrome. Vaginal replacement should be planned for late puberty.

## Surgical Treatment of Urogenital Sinus Anomalies and Disorders of Sexual Differentiation

Patients with DSD and UGS abnormalities who have anatomic problems such as clitoral enlargement and labial fusion are a source of great concern and challenges for parents, patients, and the medical team involved in their treatment. Although we have witnessed significant advancements resulting from studies on clitoral innervation and new nerve-sparing clitoroplasty techniques,[15,104] we lack convincing long-term results regarding sexual function and acceptance of genital appearance in females with CAH because most of the published studies correspond to patients reconstructed, which have been revised.[107]

## Preoperative Evaluation

### IMAGING EVALUATION

A retrograde genitogram is performed by occluding the opening of the urogenital sinus with the balloon of an 8-Fr Foley catheter placed outside the meatus and secured in place with tape. Lateral and oblique images are then obtained. The study should be performed by the surgeon and an experienced radiologist. Next, the catheter should be advanced into the bladder for a vesicoureterogram (VCUG). The study allows a preliminary diagnosis of the level of confluence of the urogenital sinus in relation to the bladder neck, thus facilitating the planning of the surgical procedure (Figs. 123-4, *A* and *B*, and 123-5).

Ultrasonography gives valuable information about the urinary tract, and in most cases the uterus, vagina, and gonads can be visualized (Fig. 123-6, *A* and *B*). In those cases in which the anatomy is not well demonstrated, magnetic resonance imaging (MRI) of the pelvis could clearly outline the anatomy of the pelvic organs (Fig. 123-7).

## Laparoscopy

Laparoscopy provides excellent visualization of the pelvic structures and may play an important role in those cases that need a gonadal biopsy or gonadectomy. It can also be helpful for identification or removal of müllerian structures.[108,109] Also, laparoscopy can be used to perform other procedures such as a laparoscopic-assisted sigmoid vaginoplasty, or the excision of an enlarged müllerian duct remnant.

## Preoperative Preparation

It is important to prepare the bowel adequately before repair. This should be done at home because most children are preferentially admitted on the morning of surgery. For low repairs, magnesium citrate should be given on each of the 2 days before repair. For high repairs, Golytely, a polyethylene glycol isotonic solution, is administered by mouth beginning 3 days before surgery for 2 consecutive days, followed by magnesium citrate 1 day before surgery. In some cases, ondansetron may be indicated to prevent nausea, or Golytely can be

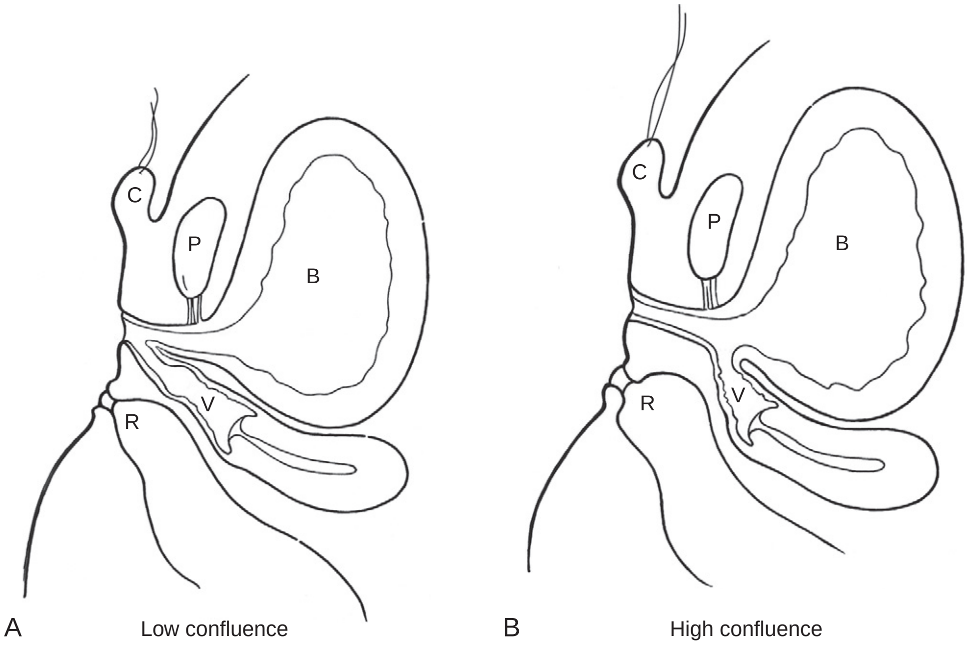


**FIGURE 123-4** **A,** Low-confluence urogenital sinus. **B,** High-confluence urogenital sinus. *B,* Bladder; *C,* Clitoris; *P,* pubis; *R,* rectum; *V,* vagina.

administered through a small nasogastric tube. It is important to discontinue Golytely at least 24 hours before surgery to avoid leakage during the procedure. Magnesium citrate, which shrinks the bowel, is given on the last day to prevent leakage. Oral administration of neomycin plus erythromycin can be used to reduce bacterial concentration.

As outlined earlier, stress doses of steroids, based on the weight of the child, are given at the time of anesthetic

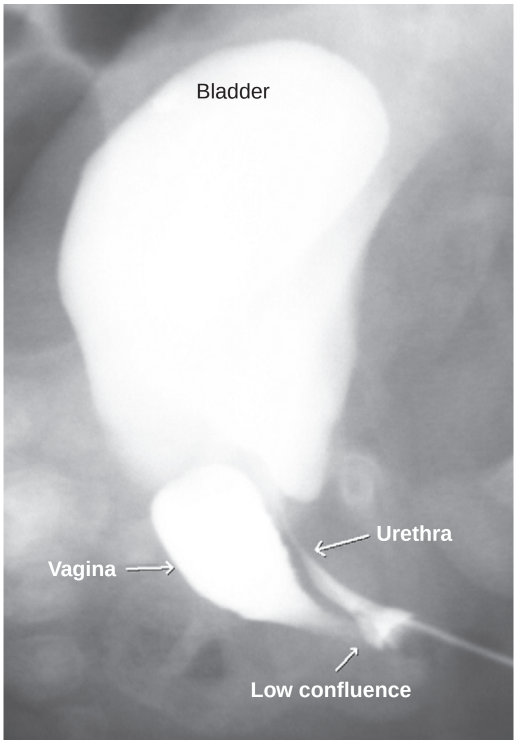


**FIGURE 123-5** Retrograde genitogram showing a low-confluence urogenital sinus in a patient with 46,XX DSD (CAH).

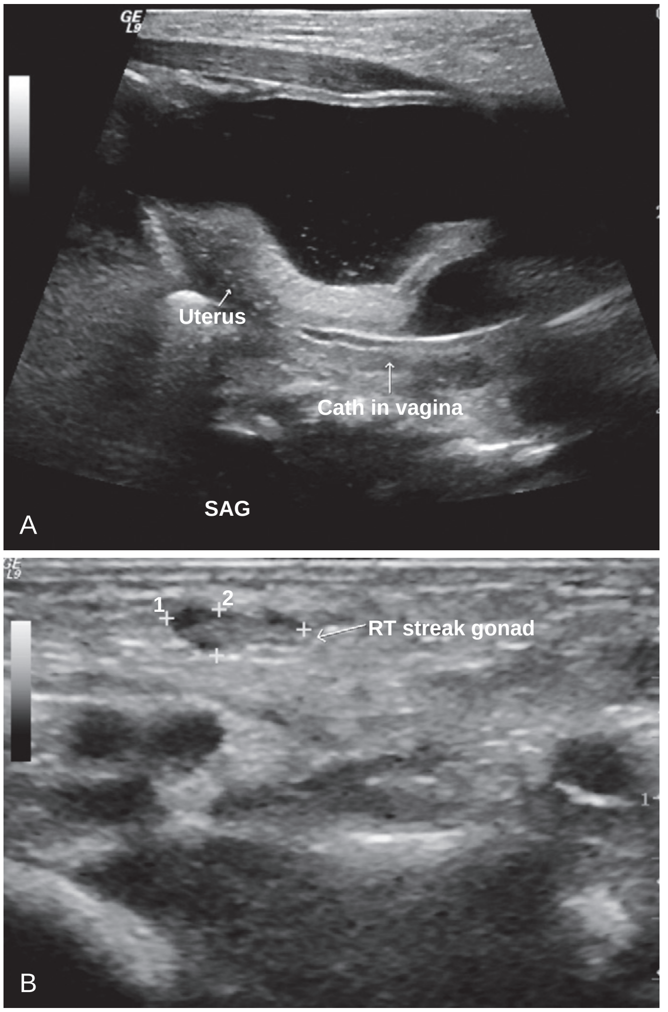


**FIGURE 123-6** **A,** Pelvic ultrasound in a patient with mixed gonadal dysgenesis demonstrating the bladder, a catheter inside the vagina, and the uterus. **B,** Ultrasound of the right inguinal region ultrasound showing a streak gonad.

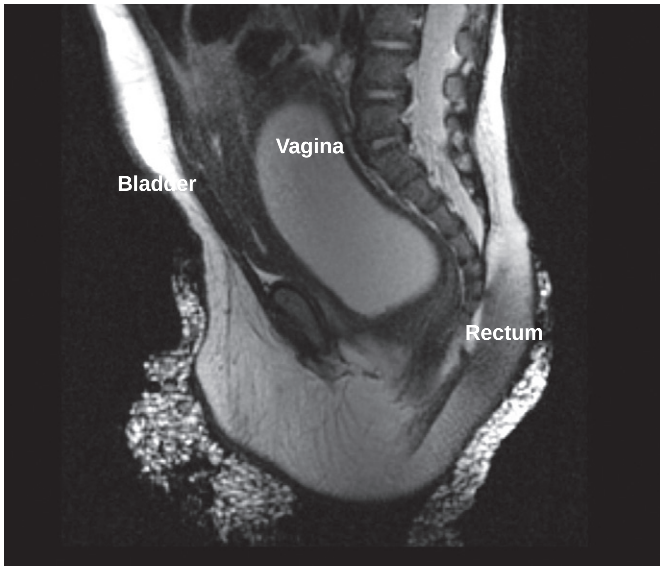


**FIGURE 123-7** Magnetic resonance imaging of the pelvis in a patient with a posterior cloaca (persistent urogenital sinus and rectovaginal fistula) showing an enlarged vagina, the bladder, and the rectum.

induction. Steroids are continued during surgery and for 2 to 3 days after surgery at double the usual oral dose, followed by a tapering of the dosage. Children on dexamethasone are asked to omit their medications, but children on prednisone take the usual morning dose on the day of surgery. Medications after surgery are planned with pediatric endocrinology consultation, and dosing is dependent on the length and extent of surgery and the expected length of hospitalization.

## Surgical Reconstruction

### PANENDOSCOPY

Each reconstructive procedure is preceded by a panendoscopy using a pediatric cystoscope with 0- and 30-degree optics. High-flow irrigation of the urogenital sinus assists finding a small vaginal orifice in the back wall of the UGS; in some cases, there may be only a pinpoint orifice, and in some patients probing with a 3-Fr ureteral catheter can be used to find a small vaginal orifice (Fig. 123-8). For surgical planning one must precisely define the location of the confluence point between the vagina and urethra in relation with the bladder neck. To do so, we use the verumontanum/external sphincter as a landmark. In addition, more accurate measurements can be obtained with a 3- or 4-Fr ureteral catheter with 1-cm markings passed alongside the cystoscope, with its tip placed at the bladder neck and using the catheter markings as a ruler. Those anomalies with the confluence point at or above the verumontanum/external sphincter are considered high, and those below are considered low (Fig. 123-4, *A* and *B*). Patients with 46,XX DSD, MGD, and ovotesticular DSD have a cervix at the most proximal part of the vagina. Patients with 46,XY DSD have either a small prostatic utricle or a deeper, more generous cavity that has no proximal cervix. This prostatic utricle is characteristically found in the center of a flattened verumontanum but has no surrounding prostatic tissue. In midlevel and high-confluence cases, a Fogarty catheter with a stopcock valve is passed into the vagina. The balloon is inflated, a small Foley catheter is placed in the bladder, and both are tied together.

## Reconstruction for Female Gender Assignment

All 46,XX DSD newborns should be assigned to the female gender, regardless of the extent of masculinization, and undergo surgical reconstruction consistent with the female gender assignment. Similar repairs can be used for selected patients who are not severely masculinized because of 46,XY DSD, MGD, or ovotesticular DSD. The mainstays of a feminizing genitoplasty are clitoroplasty, labioplasty, and vaginoplasty. Surgical procedures should preserve clitoral sensation and provide a female appropriate cosmesis, with a well-lubricated vagina that will allow pleasant and painless intercourse. It should be mentioned that recent trends have raised concerns regarding the benefits of clitoroplasty. Therefore it should be undertaken only after extensive discussions with the family because another option would be deferral until the patient is capable of deciding by herself.

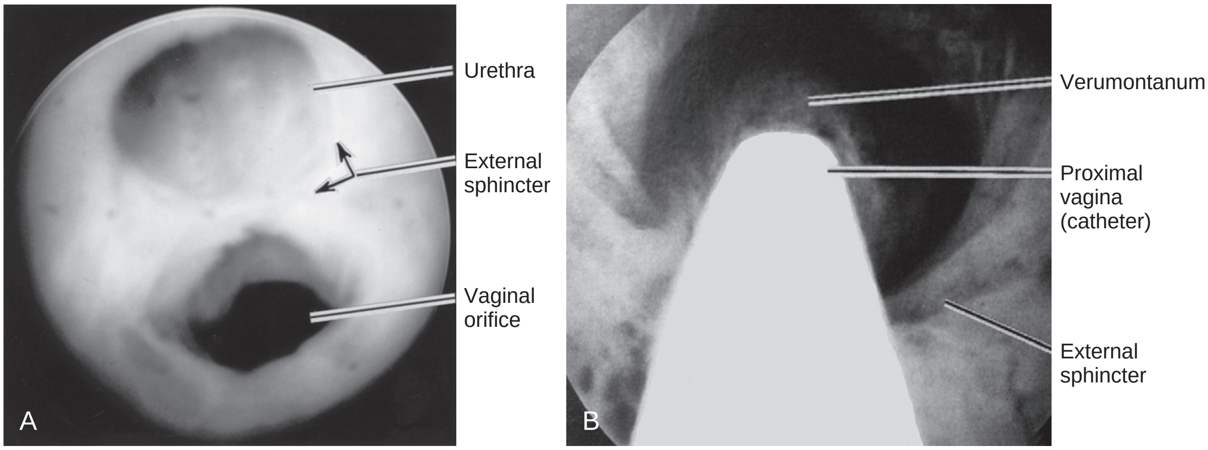


**FIGURE 123-8** Cystoscopic examination indicates whether the vagina joins the urethra in a high or low confluence. **A,** The vaginal orifice is clearly high. **B,** Catheter entering the vaginal opening at the verumontanum in a patient with severe masculinization from female pseudohermaphroditism.

## Planning and Timing the Surgical Reconstruction

The timing and magnitude of surgical reconstruction is the subject of significant controversy. Some groups advocate delaying sex assignment to an age in which each patient can make his or her own decisions[110]; however, as mentioned earlier, most of these studies analyze the outcomes of older surgical procedures.[111,112] We believe that newer techniques result in an improved cosmetic appearance, achieve a reduced complication rate, and are more likely to preserve sensation; however, long-term studies are required to evaluate the outcomes of these procedures, which include ventral clitoroplasty and the total and partial urogenital sinus mobilization (TUM and PUM).

We discuss with the parents all available treatment alternatives and recommend that the different steps of the surgical reconstruction should be incorporated into a single surgical procedure and be performed at an early age in order to take advantage of all available tissues, with the objective of achieving the best possible functional and cosmetic results. This approach is in keeping with the recommendations of an international group charged with drafting a consensus statement on the management of children with disorders of sexual differentiation.[1] Patients with a low-confluence urogenital sinus can be operated once their metabolic management is well controlled; in most cases we undertake an elective reconstruction at 3 to 6 months of age. Patients with a midlevel or high confluence can be electively repaired at 9 to 12 months of age.

## Clitoroplasty, Vaginoplasty, Labioplasty, Incorporated into a Single Procedure

Planning of the surgical reconstruction should incorporate the three components of a feminizing genitoplasty, in which the prepuce is used to create labia minora, the clitoris is reduced with preservation of sensation, and the labioscrotal swellings are used to fashion female-appearing labia majora and to enhance the vaginoplasty.

To optimize surgical exposure and elevate the perineum, we place our patients in a hyperextended lithotomy position with the buttocks lying over and slightly beyond several folded towels. As previously described, all procedures must begin with a panendoscopy.

## Clitoroplasty

Surgical procedures to correct the enlarged clitoris have undergone significant advances. Surgeons now recognize that preservation of clitoral sensation is essential for future orgasms. Clitoral resection and recession are only of historical interest and are no longer recommended. In cases with severe masculinization, the clitoris is too large, resembling a penis; in such cases, we discuss the anatomic characteristics with the parents and recommend a clitoroplasty. The goal of current techniques is to preserve sensation (neurovascular integrity) for future orgasms, provide an acceptable cosmesis, and avoid painful erections. Kogan described a subtunical excision of the erectile tissue, which has been used extensively and led to newer nerve-sparing techniques.[113] Baskin and colleagues (1999) found that distribution of the sensory nerves of the clitoris is similar to the sensory nerves of the penis. These nerves are found on the top or dorsal aspect of the clitoris and course under the pubis; circumferential branches from the dorsal neurovascular bundle encircle the clitoral shaft toward the ventrum, thus making a ventral approach to the corpora most likely to avoid nerve injury (Fig. 123-9).[104–106] In Baskin's technique corporal tissue proximal to the bifurcation is left intact. Hypothetically this preserved erectile tissue may play an important role in sexual function. In most cases we try to avoid reduction of the glans clitoris, aiming to preserve sensation, but in patients with a large clitoris a wedge of glans tissue may be cautiously excised from its ventral aspect (Fig. 123-10, *A* and *B*).

It is our practice to incorporate the three components into a unified surgical strategy. A 5-0 Prolene holding suture is placed in the glans. Two vertical incisions are outlined with a marking pen on each side of the urethral plate, and the meatus is circumscribed as one does for hypospadias surgery, taking care of leaving a redundant segment of dorsal inner foreskin to allow the fashioning of a hooded prepuce to preserve an important source of sensation (Fig. 123-11).[114] Prior injection of incisions with 1% lidocaine/1:200,000 epinephrine prevents excess blood loss. The vaginoplasty is incorporated into the surgical reconstruction, outlining a wide-base, inverted "U"-shaped perineal incision based on the anus; the apex of this is placed at the estimated final location of the vagina, using the ischial tuberosities as a landmark (see Fig. 123-14). The clitoris is degloved down to the peno-scrotal junction; the ventral strip of the urethral plate should be initially kept intact. Following degloving of the dorsal skin, the distal portion of the UGS (urethral plate) is divided horizontally below the glans clitoris. The urethral plate (UGS) is mobilized off the ventral aspect of

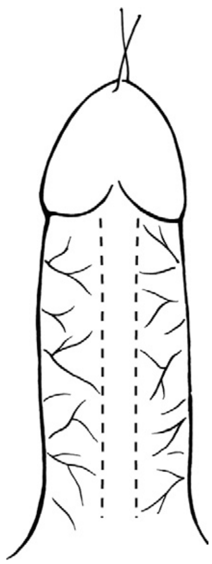

**FIGURE 123-9** Circumferential nerves branches coming from the dorsal neurovascular encircling the clitoral shaft toward the ventrum. Vertical incisions outlined on each side of the urethral plate for the excision of the erectile tissue.

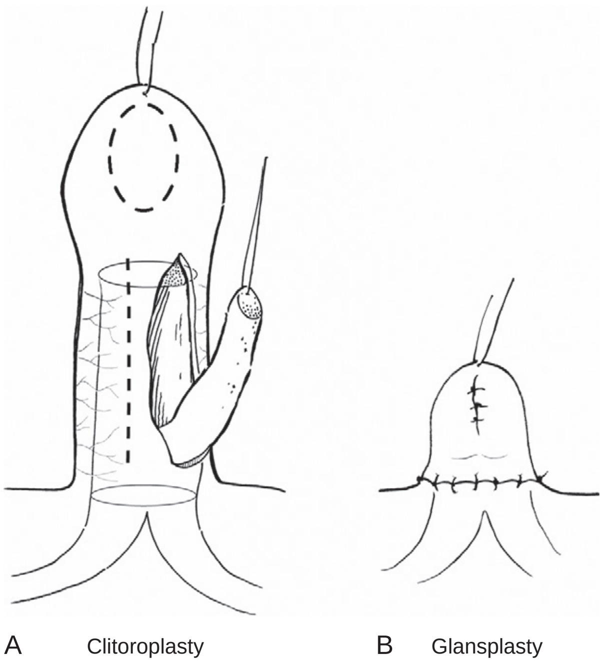


**FIGURE 123-10** **A,** Excision of erectile tissue. An elliptical incision is outlined on the ventral aspect of the glans for glansplasty. **B,** Completed clitoroplasty and glansplasty (body of the glans sutured to the corporal body stumps with absorbable sutures).

the clitoral shaft downward to below the bifurcation of the corporal bodies. Next, clitoral reduction is carried out; in our experience placement of a tourniquet is unnecessary because we have observed that bleeding from the erectile tissues is not significant, particularly in infants, although it can be considerable in the older child. Longitudinal ventral incisions are made; the erectile tissue is dissected within the bodies (see Fig. 123-10, *A* and *B*). The body of the glans is sutured to the corporal body stumps with absorbable sutures (Fig. 123-10, *B*). This step should, hypothetically, allow for painless engorgement of the proximally preserved corpora remnants with sexual activity. The redundant dorsal tunica albuginea and neurovascular bundle are placed in a subcutaneous pocket above the pubic bone, folded without impairing the neurovascular supply, and its lateral edges are sutured to the adjacent periosteum of the pubis. The reduced clitoral shaft is covered with surrounding fat tissue, thus fashioning a normal-looking mons pubis. In cases with a large glans clitoris, a wedge of glans tissue can be excised from the ventral aspect of the glans with careful reapproximation of the glans tissue with interrupted 6-0 polydioxanone sutures (PDS) (see Fig. 123-10, *A* and *B*). The dorsal mucosal collar should cover the glans partially, giving it a hooded appearance (see Fig. 123-11). The remainder of the dorsal prepuce is divided in the midline (Byars technique) and reattached to the mucosal collar as with hypospadias repair. The preputial skin wings are rotated inferiorly and incorporated lateral to the urethral plate to create labia minora (Fig. 123-12).

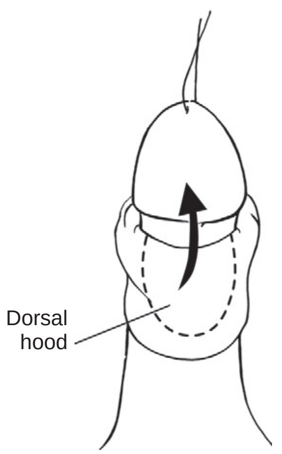


**FIGURE 123-11** Outlined incision to fashion a hooded clitoris from the dorsal foreskin.

## Labioplasty

Most girls with CAH have labioscrotal swellings that are more anterior than normal labia majora. Significant skin rugation may be present as well. To move this labioscrotal skin posteriorly, Y- shaped incisions are outlined with an extension posterior to the swellings. The scrotal flaps are cautiously defatted and moved posteriorly, beside the introitus, as bilateral Y-V advancements. The medial aspects of these skin flaps are then sutured to the lateral edges of the preputial skin flaps mobilized during clitoroplasty (now labia minora). The end result is an anatomically correct positioning of the labia minora and majora posteriorly, beside the introitus, rather than anterior-laterally (Fig. 123-13).

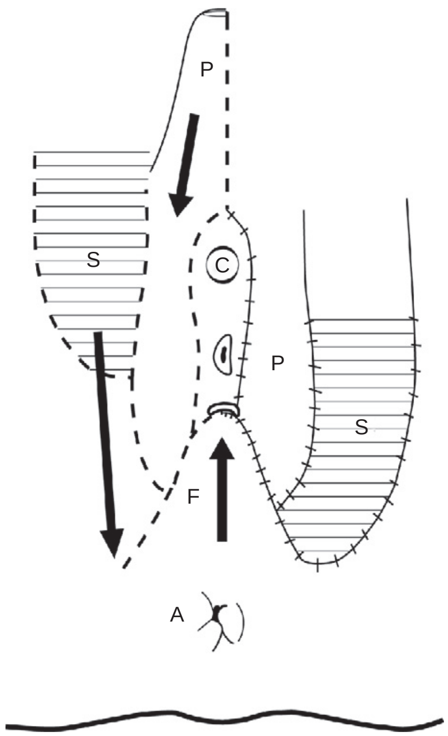


**FIGURE 123-12** Split prepuce used to create labia minora; labia majora Y-V-plasty; and flap vaginoplasty. *C,* Clitoris; *F,* flap; *P,* split prepuce; *S,* labioscrotal fold.

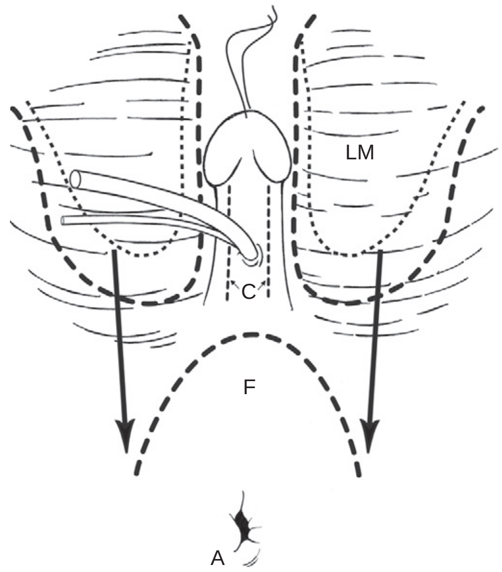


FIGURE 123-13 Bilateral Y-V advancement of the labia majora. The flaps are cautiously defatted and moved posteriorly, beside the introitus to enhance the vaginoplasty. The medial aspects of the skin flaps are sutured to the lateral edges of the preputial skin mobilized during clitoroplasty (now labia minora). *C,* Clitoris; *F,* flap; *LM,* labia majora.

# Vaginoplasty

The type of vaginoplasty required depends on the anatomic location of the merging point of the vagina into the urethra as a UGS. There are six types of vaginoplasty: cut-back, flap, pull-through, TUM and PUM, and vaginal replacement.

## LOW-CONFLUENCE FLAP VAGINOPLASTY

Flap vaginoplasty is only indicated for cases with a very-low-confluence UGS because otherwise it does not bring the merging point of the vagina with the urethra any closer to the perineum. The technique is based on the description by Fortunoff and colleagues of an inverted perineal skin U-flap that could be advanced into the opened vagina.[115] The posterior flap based on the anus is outlined with a marking pen, and anteriorly it should reach the edge of the sinus. A thick, long, flap is mobilized and then the posterior wall of the vagina is dissected with care not to enter the rectum. Next, the posterior wall of the sinus is opened longitudinally into a normal-caliber vagina to avoid a vaginal stricture. The apex of the flap is inserted into the apex of the vagina wall and secured in place beginning with three interrupted, full-thickness sutures of 4-0 Vicryl, which should be tied simultaneously to prevent tearing the fragile vaginal wall; the rest of the sutures are placed in a sequential manner. In low-confluence vaginoplasty, there is no need to insert a finger in the rectum, but a roll of petroleum jelly (Vaseline) gauze can be inserted in the rectum to avoid rectal injury (Fig. 123-14, *A* to *C*). In a low vaginoplasty there is no need to do a complete mobilization of the UGS. Once it is dissected off the corpora, the dorsal wall is opened longitudinally down to the vaginal opening to create a more normal-looking introitus. Later during labioplasty, the medial edge of the prepuce (labia minora) will be sutured to the outer edge of the opened, nonmobilized urethral plate/UGS.

## VAGINOPLASTY USING UROGENITAL MOBILIZATION

Total urogenital sinus mobilization (TUM) was described in 1997 by Alberto Peña as a technique to repair the UGS component of cloacal malformations.[116] Currently, this procedure, or a modification thereof, is being used by most surgeons for UGS repair.[117] Circumferential, partial mobilization of the UGS allows the midlevel vaginal confluence to be brought down to the perineum without tension, avoiding the need for separation of the vagina from the urethra as in the classical pull-through vaginoplasty. The Fogarty balloon, placed in the vagina during the panendoscopy, allows the identification of the confluence. Urogenital sinus mobilization has the advantage of better visualization of the merging point, and it

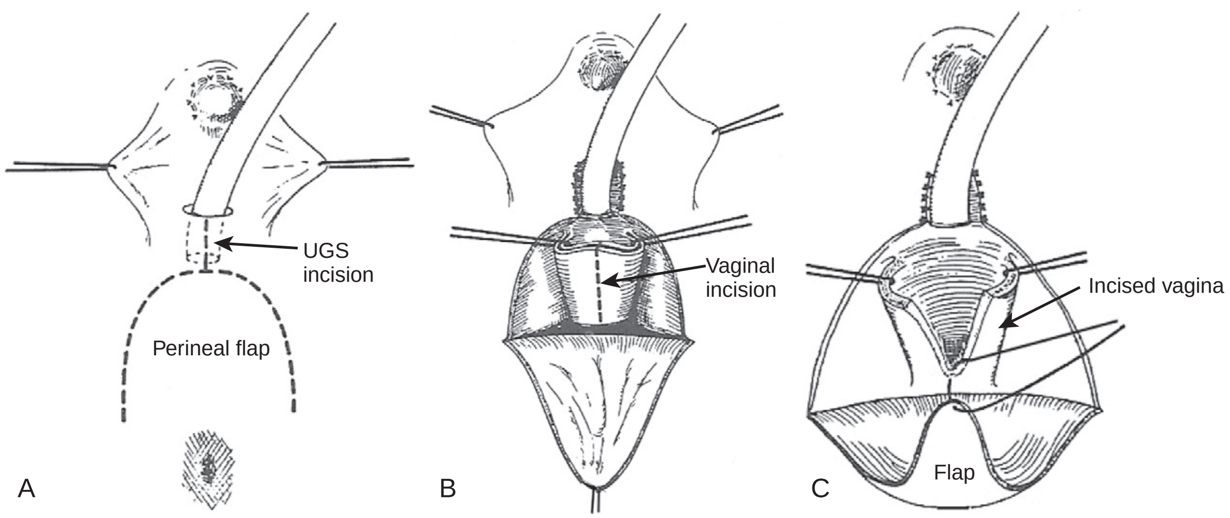


FIGURE 123-14 Flap vaginoplasty. **A,** Wide-based inverted perineal U-flap based on the anus. **B,** Dissected vagina with outlined back wall incision. **C,** Inverted U-flap sutured to back wall of the vagina.

obviates the need for vaginal separation, thus reducing the difficulty of the procedure. Also, in those cases where vaginal separation is required, it becomes less extensive. In this technique, because the confluence is brought closer to the perineum, the mobilization of skin flaps is minimized. The posterior dissection is similar to that done for a pull-through or flap procedure, with careful, midline mobilization of the UGS off the rectum. The anterior dissection in cases requiring a total urogenital sinus mobilization is done, staying close to the urogenital sinus under the pubis, and dividing the ligament from the pubis to the urogenital sinus, resulting in significant mobilization of the sinus, and in most cases the confluence can be brought more easily to the perineum (Fig. 123-15, *A*).

In response to concerns for possible complications of urinary incontinence, resulting from the circumferential dissection of the UGS beyond the pubourethral ligament, Rink and colleagues (2006) proposed the use of a PUM. In this technique the anterior dissection stops at the pubourethral ligament, aiming to avoid compromising the innervation to the bladder outlet (Fig. 123-15, *B*).[118] This procedure is adequate in most cases except for patients with a high confluence in whom additional mobilization beyond the pubourethral ligament may be necessary. Alternatively, if the perineum cannot be reached without tension the vagina must be sharply dissected from the back wall of the bladder before the anastomosis to the inverted perineal U-flap can be attempted. In these cases the use of a prone position can assist the dissection of the vagina off the bladder.

In both total and partial urogenital sinus mobilization, as previously described for low-confluence vaginoplasty, the distal segment of the vagina can be quite narrow; hence its posterior wall must be incised up to a normal-caliber vagina to avoid a vaginal stricture. The apex of the inverted perineal U-flap is inserted into the apex of the vagina wall and secured with interrupted full-thickness sutures of 4-0 Vicryl as previously described for a low vaginoplasty (see Fig. 123-14, *A* to *C*).

## SPLITTING THE UROGENITAL SINUS

As proposed by Rink, the urogenital sinus can be split to enhance the feminizing genitoplasty.[118] The common urogenital sinus can be used in the following manners: (1) In very-low-confluence cases we do not mobilize the urogenital sinus and incise it longitudinally on its ventral aspect up to the confluence point; the lateral aspects of the opened sinus are sutured to medial aspects of the prepuce wings, thus resulting in a more normal anatomic configuration; (2) ventrally to fashion a mucosa-lined vestibule, (3) dorsally to create a flap to enhance the anterior half of the vaginoplasty, and (4) laterally to create a flap that will be rotated to extend the vagina, thus completing the vaginoplasty (Fig. 123-16).

## PULL-THROUGH VAGINOPLASTY FOR MID- AND HIGH-LEVEL VAGINAL CONFLUENCE

Before the advent of the urogenital sinus mobilization procedures, the majority of girls were reconstructed using a pull-through vaginoplasty as described by Hendren and Crawford.[89] All patients undergo a total lower body preparation from nipples to toes, the legs are wrapped, and the lower body is

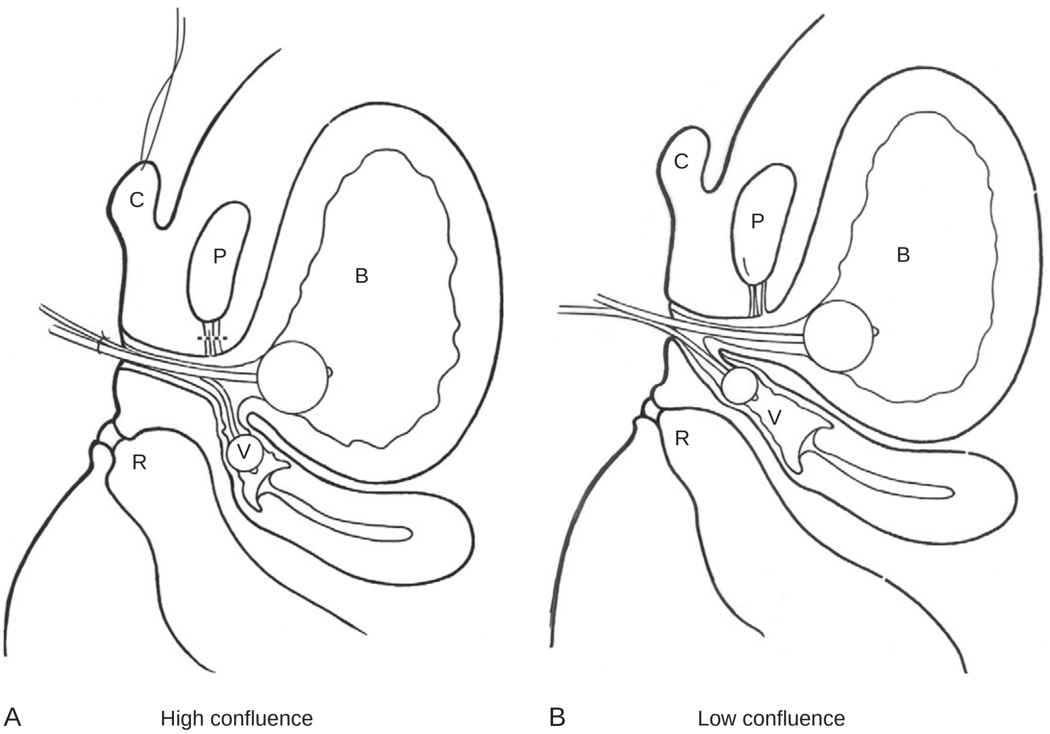


**FIGURE 123-15** **A,** Total urogenital sinus mobilization: mobilization of the urogenital sinus past the pubourethral ligament. *B,* Bladder; *C,* clitoris; *U,* uterus. **B,** Partial urogenital sinus mobilization: circumferential mobilization of the urogenital sinus stops at the pubourethral ligament. *B,* Bladder; *C,* clitoris, *U,* uterus.

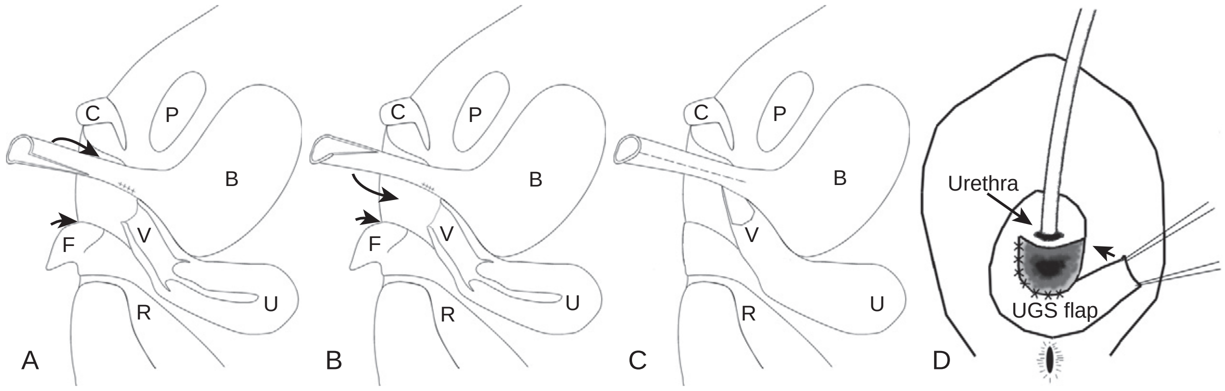


**FIGURE 123-16** Use of the redundant sinus. **A,** Split the sinus ventrally to fashion a mucosa-lined vestibule. **B,** Split the sinus dorsally to create a flap to enhance the anterior half of the vagina. **C** and **D,** Split the sinus laterally and rotate the flap to extend the vagina, thus completing the vaginoplasty.

passed through the aperture in drapes, which allows the patient to be rotated either supine or prone during the procedure. The initial aspects of the dissection are similar to the description previously mentioned for lower confluences. The operation begins with a panendoscopy, during which the confluence is localized, and a Fogarty catheter, connected to a stopcock valve, is maneuvered into the vagina, where the balloon is inflated and the valve closed. A Foley catheter is passed into the bladder; both catheters are secured together with a silk suture. An inverted perineal U-flap is made, the urogenital sinus is exposed, and the balloon of the Fogarty catheter is palpated. Intermittent insertion of a finger inside the rectum, to flatten out its anterior wall, reassures the surgeon that the rectum has not been injured. The vagina is mobilized circumferentially and meticulously separated off the bladder anteriorly.[119] The UGS is closed with interrupted stitches of 6-0 PDS. A labial flap or an anterior island flap, which for this procedure must be fashioned in the midline, can now easily reach the anterior vagina. In patients with a very high confluence we have found that rotating to the prone position improves visualization and exposure, allowing the vagina to be safely mobilized off the urogenital sinus and bladder.[120] The placement of a small malleable retractor into the vagina combined with slight upward traction assists the surgical dissection. The opening in the UGS is then closed with interrupted stitches of 6-0 PDS. The vagina is then mobilized circumferentially and brought to the perineum, where it is sutured to the perineal skin flap as described for vaginoplasty (Fig. 123-17).

## Postoperative Care of the Female Patient

At the end of each procedure a small Foley catheter is left indwelling for 3 to 4 days. The use of epidural anesthesia has improved pain management. Immobilization with a mermaid dressing in which the lower extremities are wrapped with stockinet prevents tension on the suture lines. A soft plastic foam or cotton is placed between the knees and ankles, and the anus is left exposed. The legs are loosely wrapped with an elastic bandage without covering the anus. The mermaid dressing is kept in place for 4 to 5 days. A broad-spectrum antibiotic is used during the first 2 postoperative days. Hormonal replacement appropriate to the patient's diagnosis is given.

## Reconstruction for Male Gender Assignment

The treatment strategy is similar for all patients assigned to the male gender. Most of these patients have a small penis with a penoscrotal, scrotal, or perineal hypospadias; a severe ventral curvature; and a partial or complete prepenile scrotum (Fig. 123-18). As expected, the dorsal foreskin is redundant and the glans is often split, lacking its normal conical configuration. Preoperative treatment with testosterone is helpful in those cases with a small penis.

Our preferred approach now is to perform a one-stage hypospadias repair in patients with an adequate urethral plate, using the extended applications of the tubularized incised plate urethroplasty described by Snodgrass.[121] In this technique the urethral plate is preserved; aggressive, meticulous degloving of the foreskin is undertaken beyond the hypospadiac meatus into the scrotum, thus achieving in many cases significant correction of the ventral curvature. Next, an artificial erection is induced and, if needed, additional ventral curvature correction is accomplished with a dorsal plication, placing one or two 5-0 Prolene stitches at the 12 o'clock position dorsally, at the point of maximum angulation. In some cases dissecting and elevating the urethral plate from the corpora cavernosa down to normal urethra can be done with excellent results. This maneuver can avoid the need to divide the urethral plate (Fig. 123-19). We perform the anastomosis in two layers, the first layer with interrupted subcuticular stitches of 7-0 PDS, followed by a second running layer of the same material. The suture line should be covered with a well-vascularized dartos flap harvested from the dorsal prepuce, or with a tunica vaginalis flap.

If the urethral plate cannot be preserved, a multistage repair is indicated. In some cases resection of the ventral tethering tissue and division of the urethral plate may not fully correct the ventral curvature; in these patients a dermal graft harvested from a non-hair-bearing donor is defatted and placed in normal saline solution. A transverse incision is made at the site of maximal concavity, and the inserted graft

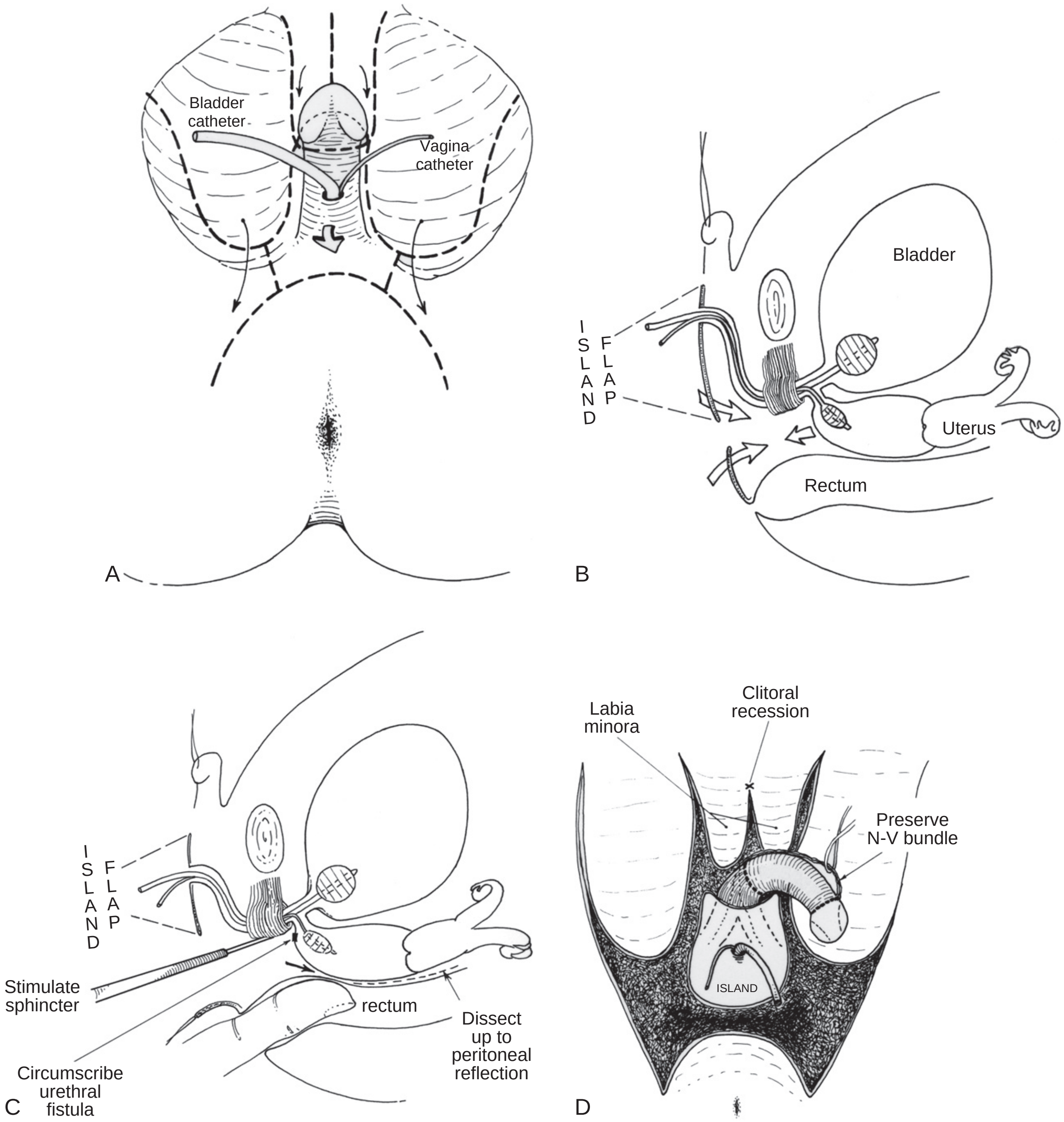


**FIGURE 123-17** Surgical reconstruction for female gender assignment. **A,** Locations of incisions viewed from the surgeon's perspective, from the perineum with the patient in the lithotomy position. **B,** Sagittal view showing the downward and inward direction of movement of the anterior island flap *(right-pointing arrows)* and the inward position of the posterior flap. The *smaller arrow* shows the distance that must be traversed by the vagina, which has been separated from the urethra. **C,** Dissection between the vagina and the rectum in a posterior direction and the beginning of the anterior separation of the vagina from the urethra. **D,** Completely dissected flaps.

*Continued*

is sutured to the edges of the defect while preserving the distal urethral plate. The second stage, composite repair, is performed 6 to 9 months later using an anterior, tubularized, incised plate urethroplasty combined with a posterior Thiersch-Duplay procedure. Also, the use of a buccal mucosa graft or an onlay island flap gives satisfactory results at this stage.

## Penoscrotal Transposition

Partial or complete penoscrotal transposition is often found in cases with penoscrotal and perineal hypospadias (see Fig. 123-18). The least severe forms are known as *bifid scrotum, pre-penile scrotum,* and *shawl scrotum.* The scrotoplasty should be delayed until after the hypospadias repair is

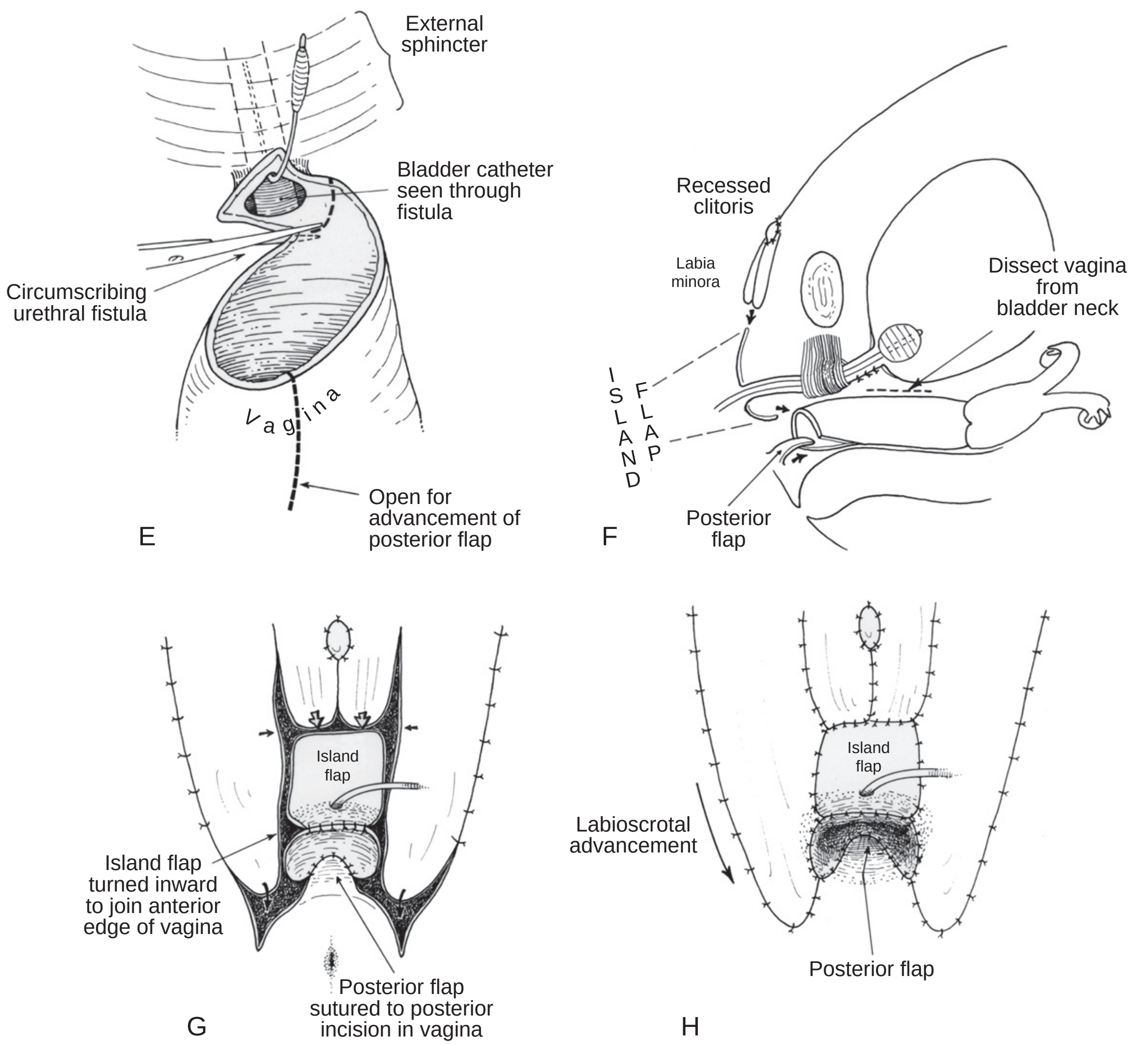


**FIGURE 123-17—CONT'D** **E,** Separation of the vagina from the urethra. **F,** Anterior plane of dissection behind the urethra and bladder. **G,** Advancement of the labioscrotal flaps to cover defects and inward rotation of the anterior island flap and the posterior U-flap to augment the introitus. **H,** Completed reconstruction.

**FIGURE 123-18** Patient with scrotal hypospadias, severe chordee, and scrotal transposition

completed because the base of the flaps needed for the hypospadias repair must be divided and displaced during correction of the prepenile scrotum. Six months or more should elapse between the urethroplasty and correction of the prepenile deformity. A square flap that circumscribes the base of the penis is displaced in a caudal direction, where it serves to lengthen the scrotum and further correct the bifid scrotal defect. The base of the penis is then advanced and held in place in a cephalad direction while the abdominal flaps are rotated in a posterior direction to the ventral base of the penis. During the forward, upward displacement of the penis, this is done to give it a more erect appearance. Rotation of the abdominal flaps, posterior and caudally, is extremely important. Otherwise, the base of the shaft skin will simply pull away from the apical position on the mons, creating an unacceptable tented appearance. The rotated abdominal flap must be of sufficient length to create half a diameter around the base of the penis to meet the flap from the other side without tension. Midline and lateral closure of the now-lengthened scrotum completes the repair and corrects the bifid scrotum. It is important that these patients stay on bed rest with urine diversion until the ventral base of the penis has effectively healed (Fig. 123-20, *A* to *F*).

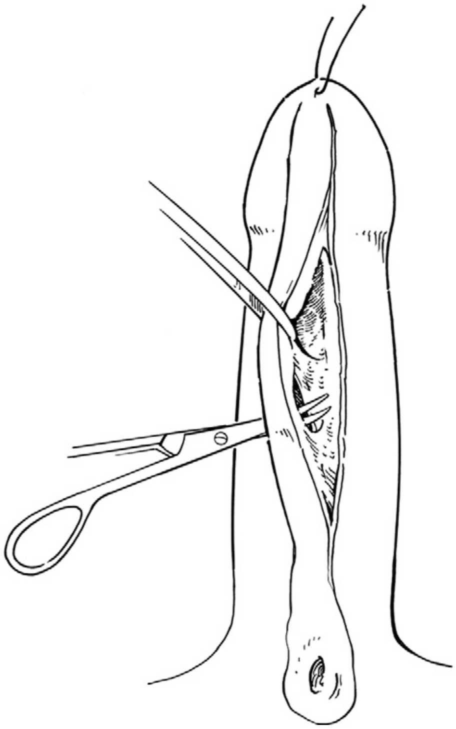

**FIGURE 123-19** Elevating the preserved urethral plate from the corpora cavernosa down to normal urethra for additional chordee correction.

## Müllerian Duct Remnants

In patients with severe hypospadias, ovotesticular disease, or MGD who have been assigned the male gender, the retained müllerian ducts can become quite enlarged, leading to recurrent urinary tract infections, epididymo-orchitis, urinary retention, secondary incontinence due to urine trapping, and infertility (Fig. 123-21). Also, malignant transformation has been reported. In such cases the müllerian duct remnant should be removed.

Surgical treatment of müllerian duct remnants is challenging because of their close proximity to the ejaculatory ducts, pelvic nerves, rectum, vas deferens, and ureters. A number of surgical approaches have been described including transperitoneal, posterior with rectal retraction, anterior and posterior saggital transrectal, transtrigonal, perineal, transurethral fulguration, laparoscopic, and robotic. We have successfully used the transtrigonal technique; however, the laparoscopic- or robotic-assisted procedures are less invasive and minimize possible damage to adjacent anatomic structures. The case shown in Figure 123-21 was successfully treated by a robotic-assisted laparoscopy.

One of the authors (Dr. Patricia Donahoe) has preserved the vas deferens as it courses within the outer wall of the dilated vagina.[122] Its position must be estimated until it exits at the site of the verumontanum. Lateral incisions are made on both sides of the predicted course of the vas deferens. The remainders of the müllerian structures are removed including the sometimes markedly dilated vagina. The strip of vaginal wall containing the vas deferens is tubularized with its mucosa internalized from the urogenital sinus to the point of entry of the vas deferens. Running absorbable suture can be used; one layer usually suffices (Fig. 123-22, *A* to *C*).

## Penile Agenesis

Penile agenesis is a rare condition occurring in 1 in 30 million births (Fig. 123-23).[123,124] It seems to be the result of a development failure of the genital tubercle during the fourth week of embryogenesis; the scrotum appears normal and contains normal testicles.[125] Patients can present with an imperforate anus and a recto-urethral fistula (Fig. 123-24), a recto-urethral fistula with a normal anus, or with the urethra located in the perineum inside a skin tag, resembling a foreskin.[123] Patients are otherwise normal 46,XY males.

Parents of affected children face a stressful decision, and for the surgeons penile agenesis is one of the most challenging conditions. In the past gender reassignment was the most frequent choice for these patients. Initial surgical treatment of female-assigned patients requires bilateral orchiectomy. Cases with an associated imperforate anus and recto-urethral fistula require an urgent colostomy and a vesicostomy. Those babies assigned to the female sex require the creation of a neovagina, which is most frequently performed with a sleeve of sigmoid colon. However, patients have been unhappy with the assigned female sex and prefer to be males.[126]

The diagnostic evaluation of patients with penile agenesis includes a renal ultrasound, pelvic MRI, retrograde urethrogram, and in cases associated with an imperforate anus a distal colonogram through the mucous fistula, using hydro-soluble contrast material combined with an antegrade VCUG via the cutaneous vesicostomy (see Fig. 123-24). Newborns with penile agenesis must be evaluated by a multidisciplinary team composed of surgeons, radiologists, geneticists, psychologists, endocrinologists, and pediatricians. Families must be given all available information regarding sex assignment, surgical procedures, and immediate and long-term results so that they can make a decision in the best interest of their child.

In adolescents and adults the most frequently used phalloplasty procedure is the microvascular transfer radial forearm flap, which is a complex and rare operation performed only in highly specialized centers. The recent description by De Castro of a phalloplasty technique and complete urethroplasty using a quadrangle lower abdominal flap can bridge the interval between childhood and adolescence until a more definitive procedure can be undertaken. In this procedure a quadrangle of lower abdominal flap is created, 4 × 5 cm for babies, and slightly larger in an older child to fashion the new penis (Fig. 123-25, *A* to *C*). De Castro recommends the use of oral or bladder mucosa for the urethroplasty,[127] although the single-stage buccal mucosa urethroplasty has had a high complication rate.

We favor staging the surgical reconstruction. As mentioned earlier, cases with an imperforate anus and a rectourethral fistula require an urgent colostomy with a mucous fistula and a vesicostomy, followed a few months later by a posterior saggital rectourethral pull-through, with subsequent closure of both the vesicostomy and colostomy. Patients born with a normal anus and a rectourethral fistula can be operated through a transperineal approach. We have used the quadrangle lower abdominal flap to fashion the neopenis in three patients, but we prefer a two-stage buccal mucosa urethroplasty to avoid or minimize complications.

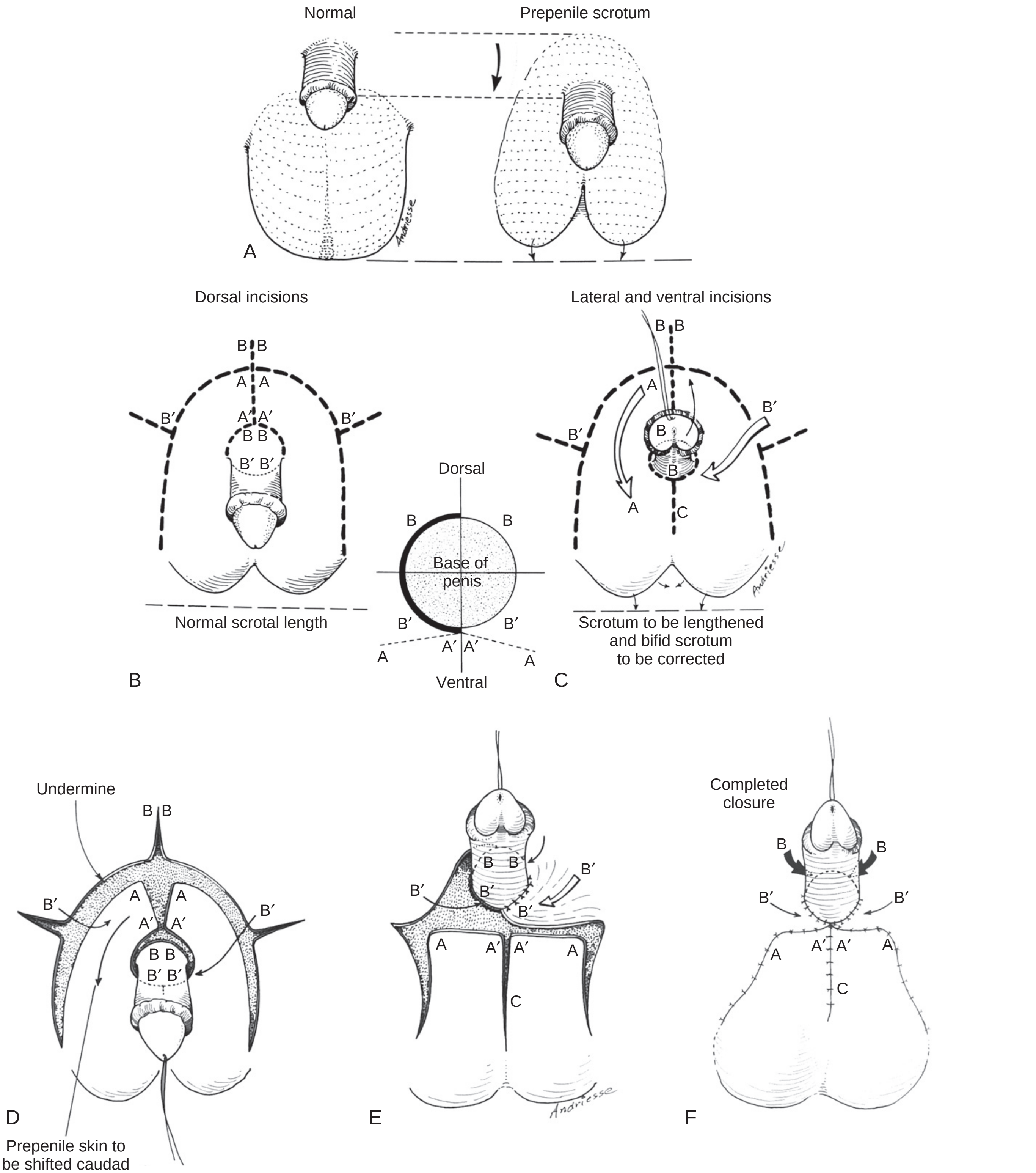


**FIGURE 123-20** Surgical correction of prepenile and bifid scrotum. **A,** Correction is reserved for phenotypic patients in whom abundant scrotal tissue lies in an anterior direction to the dorsal base of the penis in association with a bifid scrotum. **B** and **C,** Posterior transposition of the scrotum and anterior transposition of the penis are accomplished through a series of dorsal, lateral, and ventral incisions and the movement of anterior tissue. **D,** Generous abdominal skin flaps are raised with broad bases to retain blood supply. **E,** The anterior abdominal wall flaps are mobilized sufficiently to advance to the ventral base of the penis with no tension. This is necessary to prevent unsatisfactory tenting of the anterior or dorsal base of the penis. **F,** The remaining incisions are closed using fine absorbable suture. The transposed scrotalized skin, now in a caudal position, lengthens the scrotum and corrects the bifid appearance.

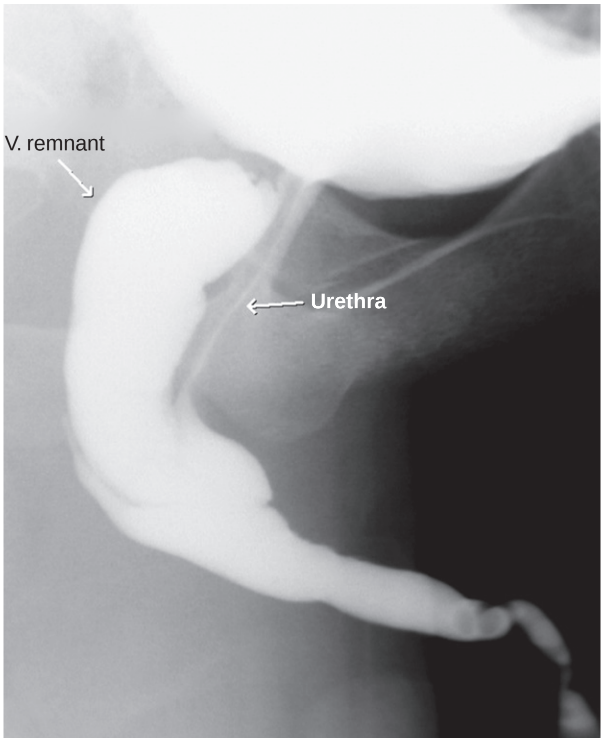


**FIGURE 123-21** Retrograde urethrogram showing an enlarged vaginal remnant in a patient with mixed gonadal dysgenesis reared as a male.

## Vaginal Agenesis

Vaginal agenesis, known as the *Mayer-Rokitansky-Kuster-Hauser syndrome,* is a rare abnormality affecting approximately 1 in 5000 to 10,000 females. In this condition there is absence of the proximal portion of the vagina, resulting from failure of the sinovaginal bulbs to develop and form the vaginal plate.

Two different types of Mayer-Rokitansky-Kuster-Hauser syndrome have been described; in the typical variety (type A) patients have symmetric uterine remnants and normal Fallopian tubes. Cases with the atypical form (type B) present with asymmetric uterine buds or abnormally developed fallopian tubes. The surgeon must be aware of the differences between the two types because the majority of associated findings in other organs or systems occur in type B patients.[128,129]

Skeletal anomalies are present in up to 12% of females affected with this condition, most commonly in type B cases including patients with congenital fusion of the cervical vertebra known as the *Klippel-Feil syndrome*.[130] Duncan proposed the term *MURCS association* to describe the combination of müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia.[131]

Renal anomalies present most frequently in patients with the type B variety[129]; these anomalies consist of either unilateral renal agenesis, horseshoe kidney, or ectopia of one or both kidneys, which occurs in 74% of affected patients.[132]

This condition can be discovered at birth when the examination does not reveal a vaginal opening, but most cases present with primary amenorrhea. A few patients complain of dyspareunia or failed intercourse. Physical examination reveals an absent vagina, but the hymen and a distal vaginal dimple or even an introitus are present because these structures are derived from the urogenital sinus. The diagnosis can be confirmed by pelvic ultrasound and MRI.

## Surgical Treatment of Vaginal Agenesis

Vaginal dilatation is a valid alternative in patients with a vaginal dimple or introitus. A program of daily, graduated dilatations over several months, using Hegar or similar sounds, can result in a good-sized vagina to allow intercourse. Once a satisfactory vaginal size is obtained, regular sexual intercourse maintains an adequate vaginal cavity.

Different techniques for vaginal construction in patients with vaginal agenesis have been used including the construction of a skin neovagina and the creation of an intestinal neovagina using sigmoid, cecum, and small intestine. Our preferred technique for vaginal replacement is the use of a 10-cm segment of distal sigmoid colon based on the left colic or superior hemorrhoidal vessels (Fig. 123-26, *A* and *B*). Mechanical and antibiotic bowel preparation must be done before the procedure. A lower transverse abdominal incision gives adequate exposure. A supine position with legs spread and the knees slightly bent, using Allen stirrups, is recommended.

The sleeve of sigmoid is selected between noncrushing clamps; a short distal sigmoid segment can be discarded to increase the length on the mesenteric vasculature for the neovagina. The sigmoid sleeve can be rotated 180 degrees to allow placement in the perineum. The proximal end is closed with two layers of absorbable suture material. Either a cruciate or H-shaped large perineal opening is made; the rectovesical space is dissected to create a large tunnel that will allow the easy introduction of two fingers in the perineum (Fig. 123-27). The sigmoid segment is pulled through the perineal channel and anastomosed directly to the perineum with absorbable sutures. Two-point fixation between the proximal end of the neovagina and the presacral fascia prevents prolapse of the bowel. We do not elevate the proximal vaginal dimple into the cul-de-sac to perform the anastomosis because in our experience, it results in a higher frequency of strictures. Alternatively, a laparoscopic-assisted procedure can be done with a satisfactory outcome.

The creation of a sigmoid neovagina has several advantages such as natural lubrication without excessive mucous production; long-term use of a stent is avoided, stenosis is infrequent, and most patients have normal sexual intercourse.

## Summary

The medical and surgical management of DSD should be undertaken by a multidisciplinary specialized team. The treatment plan must be thoroughly discussed with parents, with the goal of giving the child, thereafter, the most satisfactory quality of life possible. However, long-term studies are necessary to assess the functional and sensory outcomes of newer surgical techniques.

We recommend that surgeons taking care of these complex cases be familiar with all the available techniques so that satisfactory repairs can be performed either to support the male of female gender.

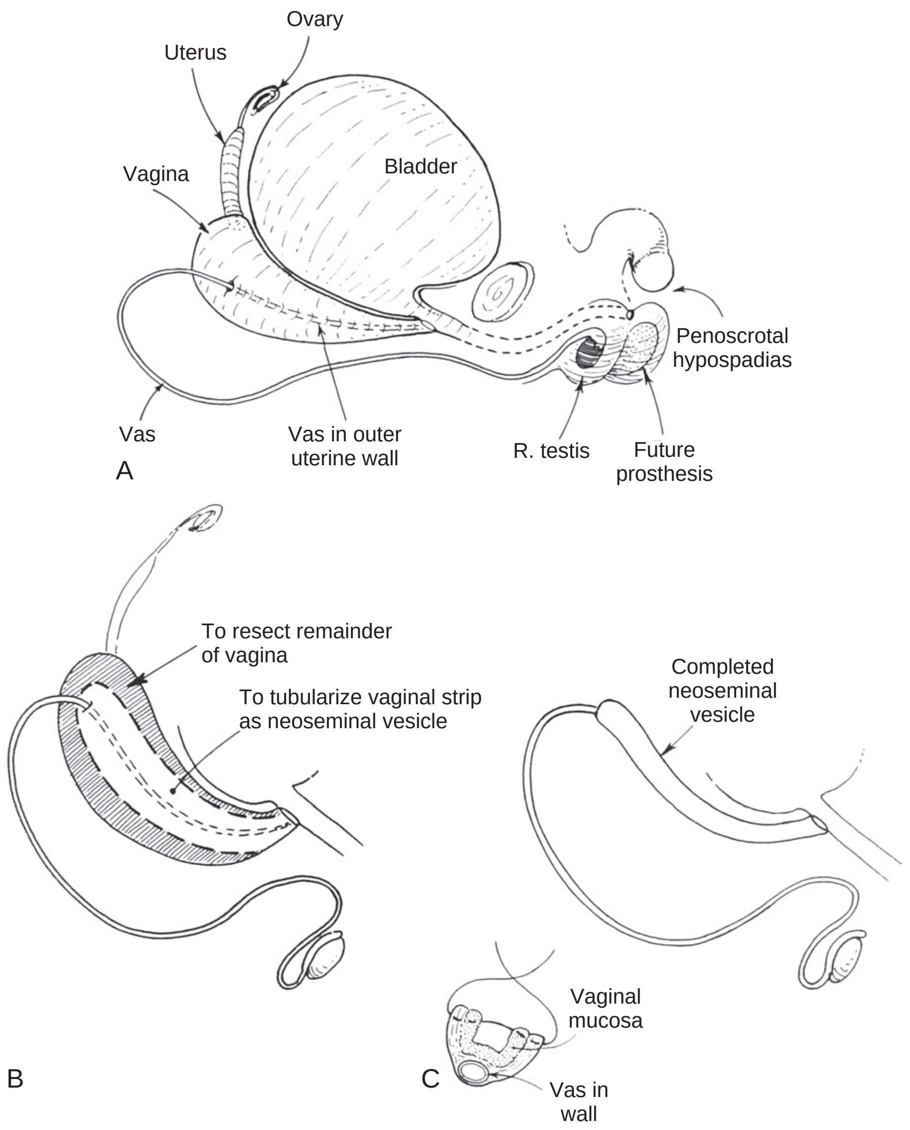


**FIGURE 123-22** Surgical management of retained müllerian ducts. **A,** In males with retained müllerian structures, every attempt is made to preserve the vas deferens, which often enters the side wall of the enlarged vagina and travels between the mucosa and muscularis or in the muscularis, as shown. **B,** A strip of vaginal wall containing the vas is preserved and tubularized, and the remaining vagina and uterus are removed. **C,** The remaining strip of vagina is closed from the entrance of the vas into the wall of the vagina to the narrowed neck, where the vas deferens joins the urethra.

**FIGURE 123-23** Patient with penile agenesis, imperforate anus, and a recto-urethral fistula.

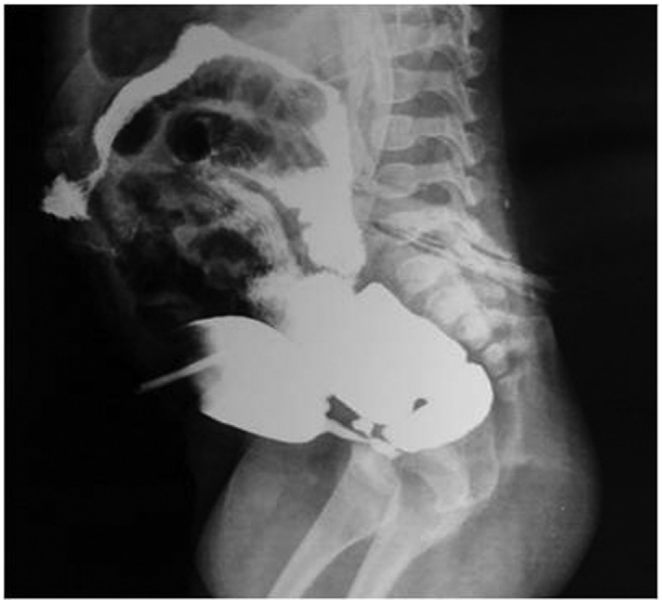

**FIGURE 123-24** Antegrade cystography and colonogram through the mucous fistula demonstrating a high imperforate anus with a rectourethral fistula in a patient with penile agenesis.

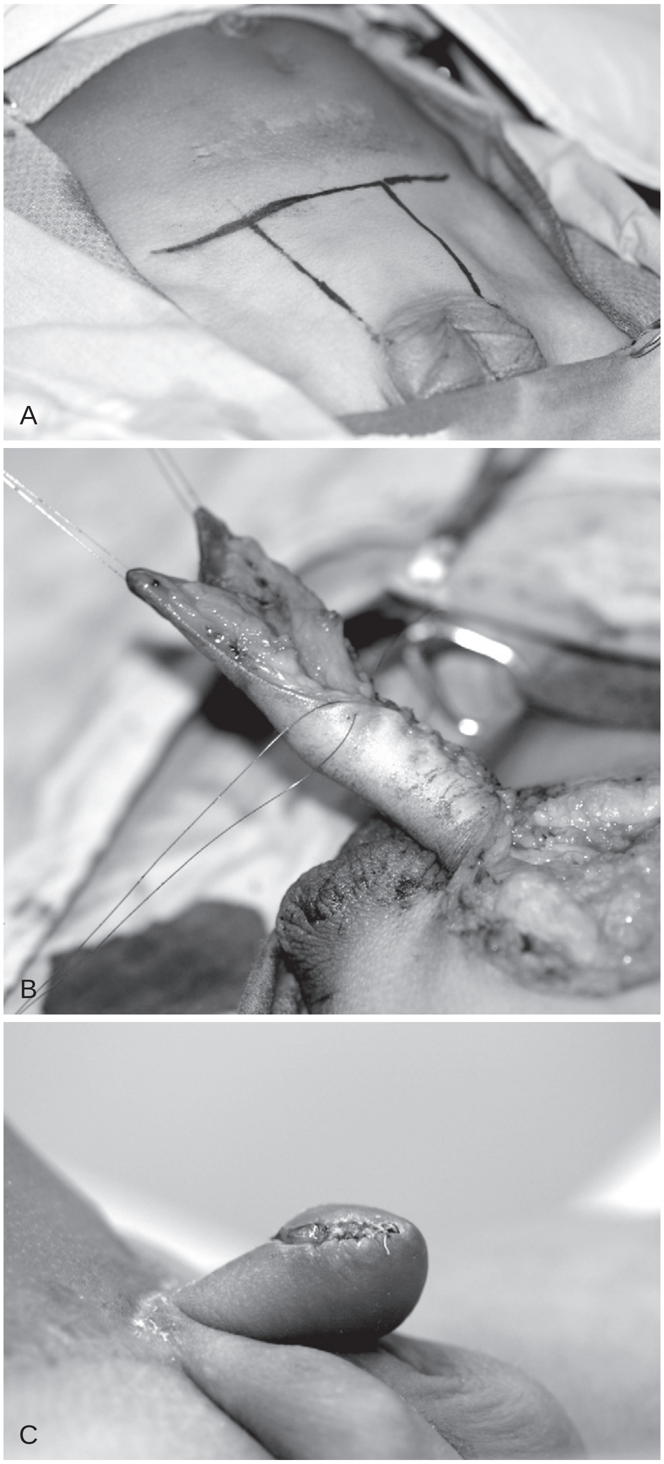


**FIGURE 123-25** **A,** Incisions for penile reconstruction using a lower abdomen rectangle flap. **B,** Penile construction in progress. **C,** 7 days postoperative picture of neopenis.

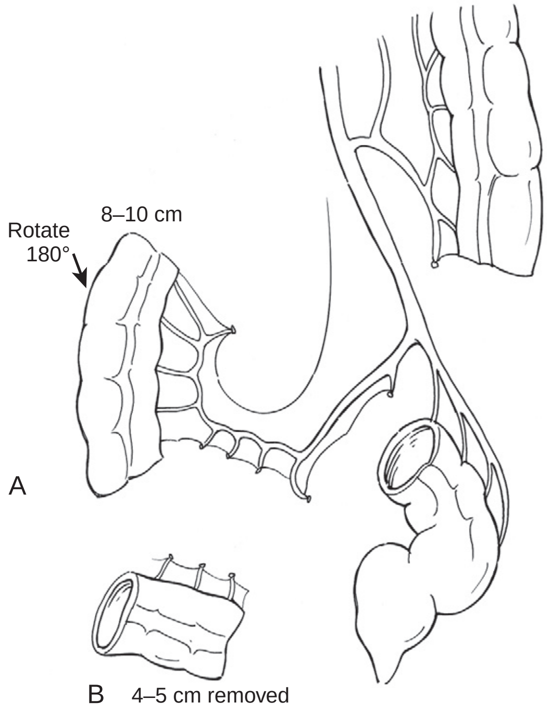


**FIGURE 123-26** **A,** Fashioning of an 8- to 10-cm sigmoid sleeve. **B,** A short distal sigmoid segment can be discarded to provide greater length on the mesenteric vascular pedicle so that the neovagina can reach the perineum under no tension.

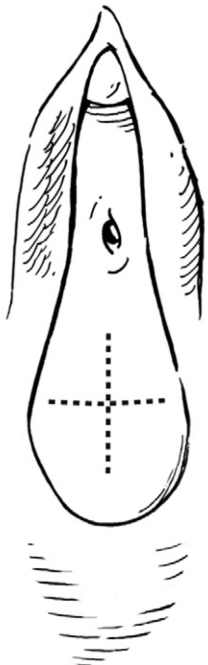

**FIGURE 123-27** Cruciate type of incision outlined on the perineum for the anastomosis with the sigmoid sleeve.

## Acknowlegments

The authors want to acknowledge the outstanding help of Dr. Anuradha Shenoy-Bhangle, Fellow in Pediatric Radiology at the Massachusetts General Hospital, with the preparation of the diagnostic images included in the chapter. Also, we want to acknowledge the outstanding help of Dr. Rafael Pieretti-Vanmarcke, Fellow in General Surgery, with the preparation of the figures included in the chapter.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 124

# Abnormalities of the Female Genital Tract

Marc R. Laufer

Abnormalities of the reproductive tract can present and be identified at birth through adulthood. Most genital anomalies in female infants present at birth and are congenital. In some instances, the abnormalities are discovered during evaluation of coexisting urologic problems or as the result of an association with a specific pattern of anomalies. Advances in perinatology, obstetrics, neonatology, and pediatric radiology have improved the recognition and subsequent care of female infants, children, and adolescents with genital tract anomalies. Many of these conditions are now being diagnosed during fetal life by prenatal maternal ultrasonography. A large number of these patients may also present at puberty with primary amenorrhea, pelvic/abdominal pain, and difficulty using a tampon or having sex.

In addition, females present with reproductive tract acquired conditions such as those related to infection, foreign bodies, trauma, and neoplasia. A thorough appreciation of normal anatomy and an understanding of the embryologic development of the female urogenital tract are necessary to understand the multiplicity of congenital anomalies and acquired conditions that may occur.

## Embryology

The female reproductive system is derived primarily from the müllerian or paramesonephric ducts. The ureteral bud arises from the mesonephric (wolffian) duct during the third week of gestation, interacting with the metanephric blastema to ultimately form the kidney and ureter. In the absence of a fetal testis, there is no production of androgen or müllerian-inhibiting substance (MIS), and consequently the wolffian duct distal to the ureteral bud is absorbed into the urogenital sinus. During the sixth week the paired paramesonephric (müllerian) ducts appear alongside the wolffian ducts with which they are intimately related. Between the sixth and eighth weeks of gestation, the paired müllerian ducts develop lateral to the wolffian ducts and then cross over the mesonephric ducts medially to fuse in the midline. Fusion occurs in a caudal to cranial direction, forming a single lumen. These fused müllerian ducts then join the urogenital sinus at the müllerian tubercle. By the 10th week of gestation, the ducts form a single midline tubular structure called the *uterovaginal canal.* The lateral aspect of the müllerian ducts, which remain separate (unfused), ultimately become the fallopian tubes. The caudal fused portion thickens and forms the uterus (fundus and body) and cervix.

The exact embryologic origin of the vagina is somewhat uncertain. Koff[1] suggested that the upper two thirds to four fifths of the vagina are probably formed from the fused müllerian duct, whereas the lower one third to one fifth is formed from the urogenital sinus. Although evidence supports the dual origin of the vagina, the exact contribution from each source is still unknown. By the ninth week of gestation, the fused müllerian ducts push the urogenital sinus caudad, creating the Müller tubercle. Vaginal development begins at the müllerian tubercle, where the uterovaginal canal joins the urogenital sinus. The tubercle thickens and elongates during the third to fifth months of gestation, forming bilateral endodermal invaginations called the *sinovaginal bulbs.* The bulbs grow, the müllerian tubercle regresses, and the distance between the uterovaginal lumen and the urogenital sinus increases. The sinovaginal bulb completes its growth by the 15th to 26th weeks of gestation, giving rise to a solid cord of tissue called the *primitive vaginal plate.* Canalization of this cord of cells begins at the urogenital sinus and progresses in a cephalad direction to form the distal third of the vagina. By the fifth month of gestation, continuity between the proximal and distal vaginal lumens is complete. Defects can occur during development, fusion, and canalization.

Failure of development may result in agenesis, failure of fusion leads to a variety of anomalies including duplication, and failure of the canalization phase results in formation of vaginal septa.[2] The close association and interaction between the müllerian and wolffian duct structures during embryogenesis may lead to associated anomalies between the genital and urinary systems.

Differentiation of the female external genitalia occurs between 12 and 16 weeks of gestation. In the absence of fetal androgen (particularly, dihydrotestosterone, and androgen receptor), the genital anlage develops passively into the external genitalia of the female. The genital tubercle elongates slightly and becomes the clitoris. The urethral folds form the labia minora and do not fuse; the unfused genital swellings form the labia majora. The urogenital groove remains open and forms the vestibule of the vagina.

# Vaginal Agenesis

Complete absence or agenesis of the vagina occurs with differing clinical situations. There can be pure müllerian agenesis with normal chromosomal and gonadal development with normal female hormonal production and variable uterine structures. There can also be androgen insensitivity with a defect in the androgen receptor in 46,XY individuals who develop female external genitalia, and because they make müllerian inhibiting substance, they have no uterus, cervix, or upper two thirds of the vagina.

Müllerian agenesis (also known as *Mayer-Rokitansky-Küster-Hauser [MRKH] syndrome*) probably results from a failure of the müllerian ducts to reach the urogenital sinus due to a disorder involving the ureterovaginal canal or the vaginal plate. The condition appears to be a sporadic polygenic multifactorial disorder occurring between the 4th and 12th weeks of gestation.[3] No specific genetic abnormality has been identified. Mayer[4] first reported vaginal agenesis in stillborn infants with multiple birth defects in 1829. Rokitansky[5] (in 1838) and Küster[6,7] (in 1910) further described this clinical entity and recognized the presence of a rudimentary uterus with normal ovaries and normal external genitalia (Fig. 124-1). Subsequently, in 1961 Hauser and colleagues[8] described the frequent association of renal and skeletal anomalies. Thus the combination of names as MRKH syndrome is used to describe this disorder. The incidence of vaginal agenesis varies from 1 in 4000 to 1 in 5000 live female births.[9–11] By definition, patients are 46,XX females with normal secondary sex characteristics that commonly present with amenorrhea.[11] Uterine development in these patients may vary from normal to the more characteristic rudimentary uteri with or without a lumen/endometrial cavity. Because of the lack of a vagina, they do not have menstrual bleeding but may present with cyclic cramping abdominal pain because of rudimentary functioning endometrium and retrograde menses. In addition, there can be a normal midline uterus with cervical and vaginal agenesis. The vagina is completely absent in 75% of cases, whereas 25% have a short vaginal pouch (often < 2.5 cm).

**FIGURE 124-1** External genitalia of vaginal agenesis. The normal appearance indicates how readily this diagnosis can be overlooked. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

Most patients have distal fallopian tubes[12] and ovaries. However, unilateral[13] and bilateral gonadal agenesis[14] have occasionally been observed in MRKH syndrome.

The association between congenital absence of the vagina and anomalies of the urinary tract is common, with approximately one third of these patients having renal abnormalities.[15,16] The most common abnormality is agenesis of one kidney or ectopia of one or both kidneys. Fusion anomalies such as horseshoe kidney and crossed renal ectopia are also commonly observed.[17]

Griffin and colleagues[16] reported skeletal anomalies in approximately 12% of MRKH patients. Two thirds of the patients with skeletal anomalies have spine, limb, or rib anomalies. Six percent of the skeletal malformations were of the Klippel-Feil type, which reflects an aberration in cervical thoracic somite development.[18] In 1979 Duncan and colleagues[19] reported on the frequency of these associated events and suggested that this combination of malformations be called the *MURCS association*. This is an acronym for müllerian duct aplasia, renal aplasia, and cervicothoracic somite association. MRKH syndrome may also occur in association with the TAR syndrome (thrombocytopenia-absent radius)[20,21] and rarely with anorectal malformations.[22] Radiographic abnormalities of the hand and hearing loss also have been observed.[23,24]

The McKusick-Kaufman syndrome (MKS) was described in 1964 in an Amish population and includes hydrometrocolpos due to vaginal atresia or aplasia, postaxial poly-dactyly, and congenital heart disease.[25–27] This is inherited in an autosomal recessive pattern, and a mutation in the *MKKS* gene has been identified in these cases.[28,29] Patients with MKS may have an overlap with the Bardet-Biedl syndrome (BBS).[27] Children with BBS have genital abnormalities and polydactyly in addition to retinitis pigmentosa, learning disabilities, central obesity, and cardiac abnormalities. Mutations in the *MKKS* gene occur in 10% to 15% of BBS patients. BBS can also be caused by the *BBS6* gene on chromosome 20p12, demonstrating heterogeneity.

Although some specific syndromes with known genetic inheritance have MRKH, the genetics/inheritance is not understood. Monochorionic monoamniotic twins have been reported to be discordant for MRKH.[30] In addition, assistant reproductive technologies have been successful in offering fertility options to MRKH patients with the assistance of a gestational carrier and the offspring have not been found to have MRKH.[31]

## DIAGNOSIS

Diagnosis of vaginal agenesis is most frequently made at the time of an evaluation of primary amenorrhea. Approximately 15% of girls presenting with primary amenorrhea will have MRKH syndrome. The diagnosis should be suspected when commonly associated defects (e.g., skeletal, renal, inguinal hernias) are identified in a young woman with amenorrhea.

A diagnosis of vaginal agenesis is emotional for the patient and the family. It is important to have educational information available.[32] Support for patients and their family can be provided from www.mrkh.org and www.youngwomenshealth.org. We have also found it greatly beneficial to have Social Work Service support for patients and families.

It is important to differentiate MRKH and androgen insensitivity syndrome (AIS), both of which present with primary

amenorrhea and absence of a functional vagina. With AIS there is absent or scant pubic hair, and in the postpubertal time period a normal "male range" serum testosterone is present. In the prepubertal time period, before elevation of testosterone, a chromosomal analysis is necessary to confirm the diagnosis. The presence of a Y chromosome increases the risk of dysgerminoma in the gonadal tissue, and thus removal of gonadal tissue is indicated. Women with AIS have a lack of müllerian structures (uterus, cervix, and upper vagina), due to the presence of müllerian inhibiting substance (MIS). Women with AIS tend to have the presence of the lower vagina, with 1 to 3 cm of a lower vagina. In contrast, women with MRKH have absence of müllerian structures with normal functioning ovaries and hormones. In addition, as noted earlier, these women have the ability to use their oocytes for assisted reproductive technologies (ART) and pregnancy with the use of a gestational carrier.

In recent years, instances of hydrocolpos have been noted on prenatal ultrasound studies. Prenatal magnetic resonance imaging (MRI) may also document such cases. Occasionally, the disorder can be diagnosed in the neonatal period in infants with an associated abdominal mass. In infants and older patients, a complete physical examination including vaginoscopy and cystoscopy, pelvic ultrasonography, computed tomography (CT), MRI,[33] and laparoscopy are the best means of making an accurate diagnosis and identifying associated urinary tract abnormalities. Ultrasound, MRI, and endoscopy avoid unnecessary exposure to radiation.

It is extremely important to adequately define the anatomy. From a gynecologic standpoint, this is best accomplished in the postpubertal period. For example, it is possible that a uterus, cervix, and upper vagina are present (agenesis of the lower vagina), and this is addressed differently than the presence of a midline uterus with cervical and vaginal agenesis. In the prepubertal time period, when the uterus, cervix, and upper vagina are not estrogenized and fully developed, the small structures may be unappreciated and thus an incorrect surgical procedure/management may be undertaken. Thus if there is no surgically pressing issue for a prepubertal intervention, then evaluation and treatment is best delayed until after puberty.

## TREATMENT

Treatment of vaginal agenesis depends on the anatomy of the individual patient. Functional, reproductive, and psychologic issues must be carefully evaluated and addressed, taking into account both the physical and intellectual maturity of the patient.[34–36] The goal of therapy is to provide adequate sexual function and deal with the psychologic impact that the patient has no uterus or vagina. Fertility is possible and is an option that should be offered to these patients because both ovaries are usually normal and successful in vitro fertilization with surrogate pregnancy has been achieved.[31,37] Psychologic studies have shown that infertility rather than expected difficulty with intercourse was the most problematic issue for MRKH syndrome patients to deal with.[38,39] Proper counseling of the patient and family members is essential. Patients and families need to be educated in all options for creation of a functional vagina, not just the technique preferred by or most familiar to the treating clinician.

The timing of creation of a functional vagina is important. In cases of MRKH and AIS it is best to wait for intervention until the patient is postpubertal and the young woman is interested in creating a functional vagina. It can be challenging to definitively identify the anatomy in an unestrogenized, prepubertal state. The surgeon may believe that the prepubescent patient has MRKH and create a vagina surgically only to find out later that there is a uterus, cervix, and upper vagina present and that the patient could have had a pull-through vaginoplasty with her native vagina and never needed a bowel vaginoplasty (see "Agenesis of the Lower Vagina" later). It is of utmost importance that the affected young woman decides which treatment plan to pursue and when to move ahead with it.

If uterine tissue is present, it is important to determine the size and location of the tissue and the presence or absence of a cervix. This can best be accomplished with MRI or three-dimensional ultrasound. If a cervix is absent, with the presence of a midline uterus, then we do not recommend attempts to connect the obstructed uterus to a created vagina due to the risk of ascending infection, sepsis, and death.[40] A patient with a midline uterus without a cervix should be maintained on hormonal therapy for menstrual suppression to decrease pelvic pain and endometriosis and maintain the options for the use of GIFT or ZIFT for conception, pregnancy, and a cesarean delivery.

In the majority of cases of müllerian agenesis, there is no uterus or cervix present and creation of a functional vagina should be undertaken when the young woman desires creation of a functional vagina.

The goal for creation of a functional vagina is pleasurable sexual intercourse with acceptable cosmesis of the external genitalia with minimal short- and long-term morbidity.

Over the years a variety of techniques have been used to develop a functional vagina. A native vagina is lined with stratified nonkeratinized squamous epithelium, is inclined posterosuperiorly, and has an average length of 9 cm on the posterior wall and 7.5 cm on the anterior wall. Ideally, the neovagina should be located appropriately (posterosuperiorly), be of adequate dimensions, be lined by elastile tissue (either mucosa or skin), be neither constantly moist nor malodorous, be hairless, and be sensate at least at the introitus.[41] The method of vaginoplasty used should be a simple, one-staged, easily reproducible procedure, with low morbidity and good outcomes (i.e., achieving painless sexual satisfaction). The ideal procedure has been elusive, and there are differences of opinion among various specialists concerning the most appropriate technique for neovaginal construction in patients with MRKH.[2,10,34,42–44]

### Nonoperative Management

A policy statement from the American College of Obstetrics and Gynecology in both 2002 and 2006 suggested that nonoperative management using vaginal dilators is the first line of treatment.[42,45] In 1938 Frank described the use of daily dilatation of the vaginal dimple for 20 minutes using Pyrex tubes in six patients with MRKH syndrome.[46] In 1983 Rock and colleagues reported that only 43% of patients were successfully managed by dilatation with identification of lack of patient compliance affecting the results.[47] Our team in Boston has shown 88% successful creation of a functional vagina. The length of time to success was found to depend on the number

of times per day that the dilator was used, with those using dilators at least once daily for 20 minutes being able to create a vagina in 4.3 ± 2.4 months.[48] We have found success with the use of hard dilators regardless of the depth of the native lower vagina. Because the native vaginal mucosa is stretched, there is normal lubrication and texture to the created vagina.

The dilation technique is best managed by a team of nurse and physician. Educational materials are the key to success. The young woman is instructed on the use of the hard dilator with constant pressure to the appropriate area twice daily. The angle of insertion of the dilator is a key to success (Fig. 124-2). Patients are asked to return monthly for examination to assure that the vagina is being created in the appropriate location and at the appropriate angle. The next size dilator is dispensed when appropriate. If the patient elects to cease or hold off on the process, she can resume when ready.

The vast advantages of this technique support the rationale for being the first-line therapy for vaginal agenesis in cases of MRKH and AIS. The advantages include the fact that this technique is under the control of the young woman, so if she elects to proceed at a faster or slower rate depending on circumstances in her life, she can easily adapt. In addition, it does not require anesthesia or a surgical procedure. Creation of a vagina with the use of dilators is also more cost effective than other treatment options.[49] Critics have concerns regarding adequate length of the vagina, poor lubrication, and dyspareunia during intercourse.

### Operative Management

A number of operative procedures have been advocated for creation of the neovagina including insertion of a skin-covered vaginal mold (Abbe-McIndoe procedure),[50,51] artificial skin grafts,[52] various fasciocutaneous[53] and myocutaneous flaps (gluteal-thigh flap, gracilis, rectus abdominis,[54] Malaga flap,[55] Singapore flap,[56,57] vulvovaginoplasty of Williams,[58] vulvovaginal flap (lotus petal labia majora flap),[59] horseshoe flap using labia minora,[60] labial flaps using tissue expanders,[61] full-thickness skin grafts with vacuum-assisted wound closure,[62] and the use of amnion[7,63] and peritoneum.[64] Varying laparoscopic techniques have been described.[65–67] The Vecchietti[68] procedure consists of intra-abdominal traction on the perineal membrane causing invagination of the shallow vaginal dimple. This requires a laparoscopic approach and long-term dilatation, and there have been reports of modifications and the development of revised instrumentation.[69] The Wharton procedure[70,71] simply places a condom-covered mold in a created space that is left in place for many months. Bowel vaginoplasty using cecum, small bowel, and sigmoid colon has been recommended as an alternative to these other procedures.[2,43,72,73] Some of the more popular procedures are presented here in more detail.

The most popular tissue for vaginal replacement during the past 3 decades has been the split-thickness skin graft as described by McIndoe.[51] The McIndoe procedure uses several split-thickness skin grafts, which are usually harvested from the buttocks (Fig. 124-3). The grafts are then refashioned over a vaginal mold that serves as a stent to form a neovagina. The neovagina is then transferred to its normal anatomic position in a space surgically created through an incision in the apex of the vaginal dimple with dissection superiorly between the urethra and bladder anteriorly and the rectum posteriorly. The dissection is carried up to the pelvic peritoneum to provide length and to avoid postoperative contracture. The labia are sutured over the mold to hold it in position. After 7 days of bedrest the patient is taken back to the operating room for cutting of the labial sutures, removal of the mold, and sewing of the edge of the perineal skin to the skin grafts. Postoperative hematoma and fistula due to pressure necrosis related to the mold are early complications. Use of an inflatable soft vaginal mold has been considered to reduce these risks. The reported complication rate is less than 10%. Follow-up reports have been encouraging,[74,75] but as with most surgical techniques, use of an inflatable mold is hampered by the need for regular and long-term home dilatation. Due to the use of dermis, lubricants are required, and a significant incidence of

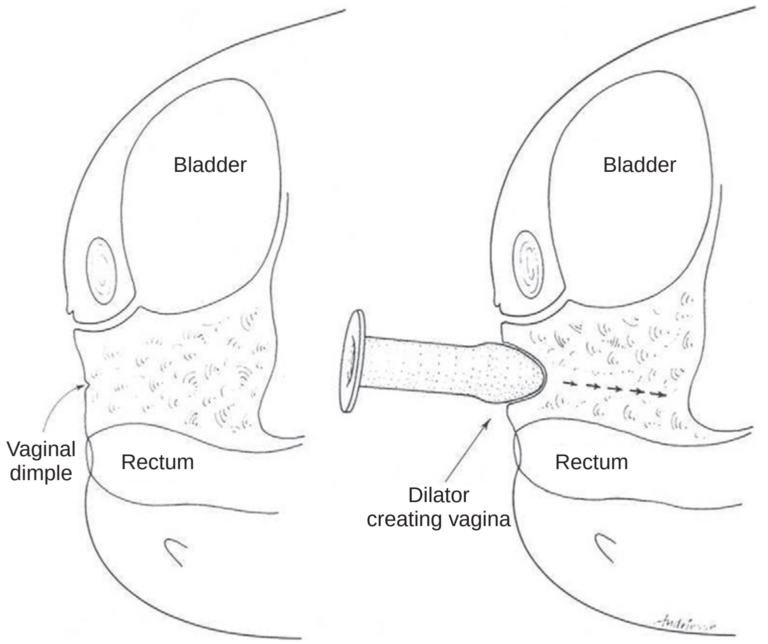


**FIGURE 124-2** Creation of a vaginal with the use of progressive perineal dilation. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

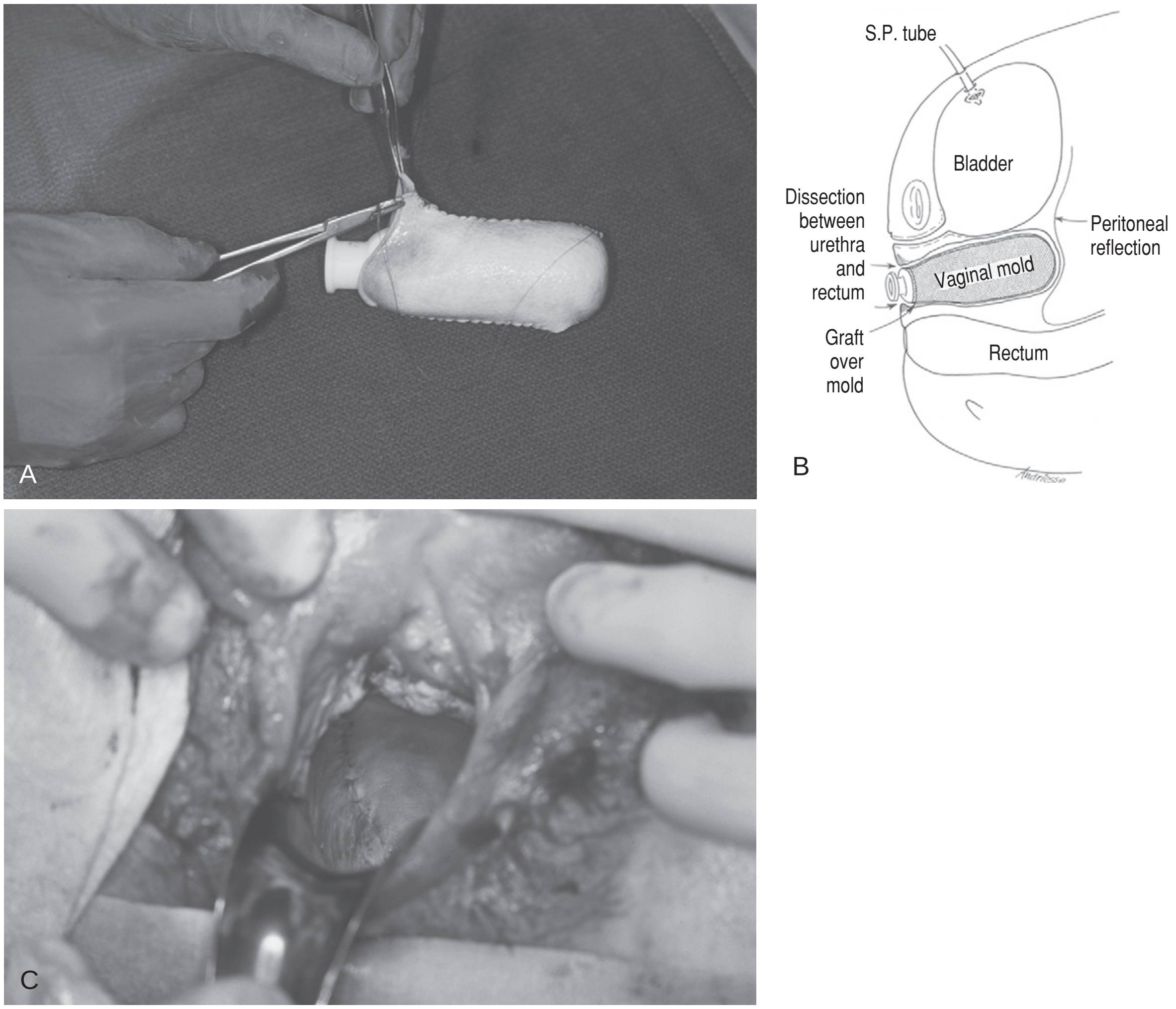


**FIGURE 124-3** The McIndoe procedure. **A,** Split-thickness skin graft sutured over a vaginal mold. **B,** The mold is placed in a surgically created space between the bladder and rectum. **C,** After the mold is removed, the skin graft can be seen in place. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

inadequate vaginal length, vaginal stenosis, and dyspareunia due to contraction of the split-thickness skin graft are drawbacks of this procedure.[76] Antibiotics and analgesics are necessary, and the mold requires changing under an anesthetic and replacement with a larger-sized stent.

In order to avoid the need for a skin graft donor site, the use of an acellular human dermal allograft has been reported.[52] Other substances have been recommended as variations on the technique. Amnion has been used to avoid the need for autologous graft sites; however, acquiring amnion requires scheduled cesarean section and tissue banking and donors must be carefully screened for HIV infection and Creutzfeldt-Jakob disease.[77] In order to avoid the issues of infection transmission, chemically processed and freeze-dried human amnion has been used.[78] The peritoneum has been used, as described in the Davydov procedure, to line the neovaginal space, but this requires laparotomy or laparoscopy.[64,67,79] A long-term follow-up study on the use of the Davydov procedure reports that sexuality approaches so-called "normal sexuality."[80]

As noted earlier, a variety of full-thickness skin flaps have been used to obviate the problem of contracture noted with split-thickness grafts. The disadvantage of using hair-bearing areas as the donor source of the flap for vaginal reconstruction is that hair growth results in neovaginal discharge and is associated with dyspareunia. These procedures also result in additional wounds at the donor sites.

Use of vulvar tissues to create a vagina grossly change the appearance of the external genitalia, and in the Williams vulvovaginoplasty (Fig. 124-4), an abnormal angle for intercourse is problematic, resulting in dyspareunia and making this operation undesirable.[58,77] Modifications to the Williams vaginoplasty have been proposed with the report of 200 patients with the Creatsas modification.[81,82]

Use of tissue expanders to create more tissue for a labia minora graft may prove useful, but late results are not yet available to ensure that labia minora flaps will result in adequate vaginal length and will endure.[60,61] Autologous buccal mucosa has been used successfully for vaginoplasty.[83,84] Lin and colleagues[85] described eight cases using buccal mucosal grafts. This technique requires a vaginal stent mold and dilatation. Complications included vaginal bleeding presumably from granulation tissue in one patient and a bladder injury in another. Baker and colleagues[84] reported on 21 patients

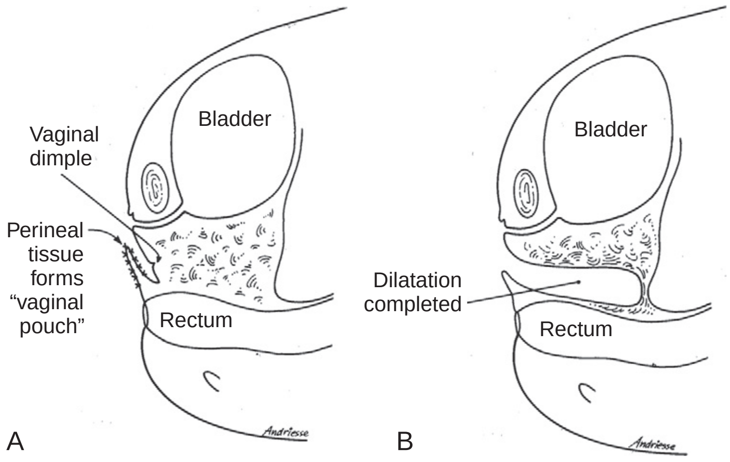


**FIGURE 124-4 A,** Schematic drawing at the completion of the Williams procedure. **B,** Schematic drawing months after completion of the Williams procedure with the creation of a vagina with the use of dilators and vaginal intercourse. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

with 5-year follow-up from buccal mucosa graft vaginoplasty. Artificial dermis and recombinant basic fibroblast growth factor (bFGF) have also been used to create a neovagina in hopes of accelerating epithelialization and reducing the incidence of bloody discharge from granulation tissue.[86] Because of the small numbers of patients involved in these studies, no conclusions can be made at this time regarding the efficacy of these techniques.

In the Vecchietti procedure,[68] at laparotomy (or laparoscopy[87]) and with modifications,[69] a suture is passed through the perineal membrane from above and then through a plastic olive and back up through the abdomen. The suture is then attached to a traction device strapped to the patient's abdomen for a week to 10 days, with pressure on the olive causing invagination of the vaginal dimple, creating a vaginal vault. Claims of early vaginal length of 10 to 12 cm and a 100% anatomic and functional success rate have been reported.[88] Complications include bladder and rectal fistula in a small percentage of cases. The traction method is associated with some degree of patient discomfort, is cumbersome, still requires long-term vaginal dilatation, and has not been widely adopted in the United States. Recent revisions to the technique and refinements to the surgical equipment have resulted in U.S. Food and Drug Administration approval and wider availability of the equipment for this technique.[69] It should be realized that this technique must be followed by the patient's use of manual dilation.

The Wharton procedure[71] involves placing a condom-covered mold in the neovagina to epithelialize vaginal granulation tissue. The process is lengthy because epithelialization may take 3 to 6 months to occur and is associated with prolonged bloody vaginal discharge owing to the presence of granulation tissue.

Schätz and colleagues[89] described initial dilatation of rudimentary müllerian ducts in three patients by gradually increasing the Hegar dilator size. The two cavities formed were joined into one by diathermy, and the resultant space is lined by smooth tissue. The dome of the space is composed of the peritoneum reflected from the bladder to the rectum. Sheares' modification of the Wharton technique[70] was applied, and an adjustable vaginal stent was placed in the space. Antibiotics and analgesics were administered for 8 days, and a Foley catheter was left in place for 1 week to avoid urinary retention. The vaginal mold was changed under anesthesia after 1 week, and a new mold was inserted. The mold remained in place 24 hours per day for 3 months and then at night thereafter until regular sexual intercourse was initiated. Periodic changing of the mold required general anesthesia. Subsequent neovaginal length was 7 to 10 cm, and the width was described as two fingerbreadths. Insufficient lubrication and dyspareunia were noted initially with sexual intercourse but resolved using lubricating gels. The two girls who experienced sexual relations expressed satisfaction with the procedure.[89] The extended period of time required to maintain the mold in place, the need for general anesthesia to repeatedly change the mold, inadequate lubrication, and lack of long-term follow-up data are drawbacks of this procedure.

### Bowel Vaginoplasty

The use of isolated bowel segments for vaginal replacement has historically been popular with pediatric surgeons and pediatric urologists. The use of rectum for the creation of a vagina was reported as early as 1892 but was not popular due to the need for a colostomy.[90] The use of isolated segments of small intestine for vaginal replacement was first described by Baldwin[91] in 1904 and performed in 1907.[92] Ruge was the first to use the sigmoid colon to replace the vagina in 1914.[93] Experience with this technique was reported by Fall[94] in 1940, but efforts were abandoned because of an unacceptably high mortality rate in the preantibiotic era. Attention was refocused on the use of small bowel and colon for vaginal replacement in 1972 by Pratt,[41] and there have been scattered reports in the literature ever since.[2,44,72,73,95–108]

Bowel vaginoplasty uses a section of bowel approximately 10 cm that is mobilized and retains its vascular pedicle to reach the perineum without compromise to the graft or the pedicle. A neovaginal space is dissected below the bladder and above the rectum from the perineum to the pouch of Douglas, and the bowel segment is sewn in place in an isoperistaltic or antiperistaltic orientation.[103–105] Most surgeons advocate anchoring the proximal bowel segment in order to decrease the risk of prolapse of the bowel vagina.[106–108]

Currently, an interposed segment of the sigmoid colon is preferred for vaginal replacement. When the use of this segment is unavailable because of previous surgery, the cecum is an acceptable alternative. Although small intestine has occasionally been used, results are not as gratifying because

of excessive mucus formation and friability of small bowel mucosa with intercourse.

Patients require mechanical bowel preparation for 24 hours before surgery. Perioperative systemic antibiotics are administered 30 to 45 minutes before the incision. The operation is accomplished with the patient in the lithotomy position with the legs positioned in stirrups so that the abdomen and perineum can be prepared in the same field. A Foley catheter is placed in the bladder, and the abdomen and pelvis can be approached through a Pfannenstiel or lower midline abdominal incision. Alternatively, the procedure has been carried out using a minimally invasive laparoscopic approach.[99,100,109] The peritoneal cavity is explored, and the genital organs are evaluated. If small rudimentary bicornuate uteri are noted, these are excised. Uncommonly, if a relatively normal uterus is observed, this is maintained (see options for uterus with cervical and vaginal agenesis later). The ovaries should be left in place to maintain the potential for in vitro fertilization with a gestational carrier should the patient desire to pursue this in the future.[37,35,36]

A 10- to 15-cm sleeve of sigmoid colon, based on the left colic or superior hemorrhoidal vessels, is sufficient to provide a functional neovagina. Keeping the segment short avoids excess mucus production, which can be associated with longer segments. The sigmoid segment is divided, and intestinal continuity is reestablished with either a stapled or hand-sewn end-to-end colocolostomy (Fig. 124-5). In patients with Mayer-Rokitansky syndrome or those with a hypoplastic vagina, an incision is made in the vertex of the vaginal dimple and a space is created between the bladder anteriorly and the rectum posteriorly up to the peritoneal reflection. Depending on the length of mesentery, the isolated segment is usually brought down to the perineum in an isoperistaltic fashion or rotated 180 degrees. The proximal end of the neovagina is then closed in two layers, with absorbable suture to form the vertex of the neovagina. An unrestricted one-layer anastomosis of the perineal opening to the distal end of the interposed colon segment using interrupted absorbable sutures (3-0 Vicryl or polydioxanone sutures) is then performed. A three-point fixation of the interposed segment to the

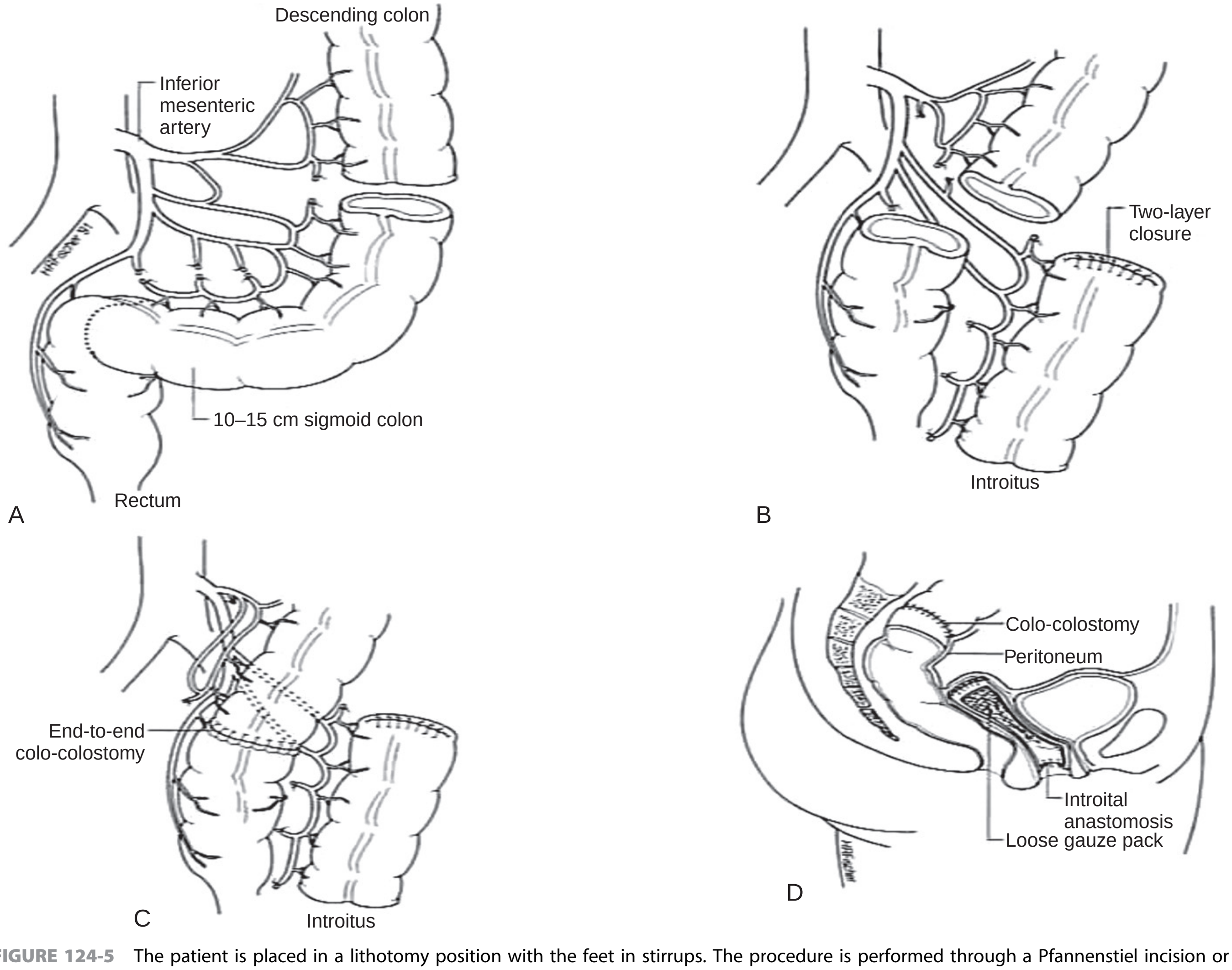


**FIGURE 124-5** The patient is placed in a lithotomy position with the feet in stirrups. The procedure is performed through a Pfannenstiel incision or laparoscopically. **A,** A 10- to 15-cm sigmoid colon segment is isolated. **B** and **C,** The proximal portion of the sigmoid neovagina is closed in two layers, and bowel continuity is restored by an end-to-end colon anastomosis. **D,** The isolated neovagina is then brought into the cul-de-sac, and the distal end of the sigmoid vagina is anastomosed to the vaginal remnant, if present, or to the small introital cuff with one layer of interrupted absorbable sutures. The interposed colon is sutured to the retroperitoneal tissues to prevent prolapse. A Vaseline gauze pack is placed in the new orifice.

retroperitoneum with nonabsorbable suture is essential to prevent prolapse.

Perioperative systemic antibiotics are discontinued after 24 hours. Analgesics are administered for 48 hours and discontinued after that time. Oral pain medication is available on request. The neovagina is stented for 5 days after the procedure with petrolatum gauze. A Foley catheter drains the bladder during the period of vaginal stenting. Patients are discharged when they are ambulating and tolerating a diet, usually on the fifth postoperative day. Patients are examined at 3 weeks and 3 months. If a stenosis is evident, dilatation under anesthesia is performed. Home dilatation is usually unnecessary. Bicycling should be avoided for a 6-week period. Other exercises are permitted as tolerated. Figure 124-6 shows the postoperative view after healing.

## RESULTS

Long-term follow-up and sexual satisfaction have been assessed in a few series of patients who have undergone bowel vaginoplasty. Communal and colleagues[106] used the standardized Female Sexual Function Index in 16 patients, and of the 11 who were sexually active and who responded, 8 (75%) reported satisfactory sexual function results after sigmoid vaginoplasty. Hensle and colleagues described their experience with intestinal-vaginal replacement in 44 patients ranging in age from 1 to 20 years.[44,72,110] Long-term results were assessed by a validated Female Sexual Dysfunction Questionnaire, and 78% of the 36 who responded reported sexual satisfaction.

Syed and colleagues[111] described the occurrence of diversion colitis in 3 of 18 children who had undergone sigmoid vaginoplasty between 18 months and 8 years of age. On the basis of the report by Syed and colleagues,[111] Edmonds[77] has suggested that the procedure not be performed in this young age group. Hiroi and colleagues[112] in Japan described the only case of malignancy occurring in a sigmoid vaginoplasty. A mucinous adenocarcinoma of the colovaginoplasty was observed 30 years after the procedure.

A 7-year follow-up study of 29 patients who underwent intestinal vaginoplasty has shown positive results, and the authors recommend the treatment, especially where there is a cultural moral taboo to the use of vaginal dilators in unmarried women.[104]

Pediatric surgeons have generally felt that the sigmoid colon is an ideal tissue for vaginal replacement. Unlike other methods of vaginoplasty, this procedure creates a vagina that is capable of providing natural lubrication during sexual activity. Many women do complain of the natural mucus production and state that they need to wear a pad daily. Limiting the length of the interposed segment to the usual vaginal length of 9 to 10 cm will reduce the risk of excessive mucus production. Recognized complications such as prolapse can be avoided by retroperitoneal fixation of the sigmoid segment. Use of the sigmoid colon rather than the small intestine will obviate some of the other complications including stenosis and excessive mucus production that were seen in the past. The fact that the procedure can be performed laparoscopically will reduce the risk of wound complications and intra-abdominal adhesions and make this procedure a more attractive alternative in the future.[99,109,113] It should be noted that the intestinal procedures do not eliminate the need for vaginal dilation because patients commonly complain of stenosis at the site of the anastomosis.

## REPRODUCTIVE ISSUES

Reproductive issues relating to MRKH can create emotional hardship for the affected young woman and her family.[35,36,38,114] In cases of MRKH, ovarian function is normal. Women may experience pain with ovulation or with ovarian cyst formation. The possibility for the use of Assisted


**FIGURE 124-6** **A,** Postoperative view of the perineum with the sigmoid vagina anastomosed to vaginal introitus. **B,** No. 26 Hegar dilator (6 inches long) reveals normal vaginal caliber and depth. Patients are advised to pass the dilator periodically to ensure continuation of adequate caliber. This procedure is not as important as it would be for a skin graft vagina, which will contract if not periodically dilated in this fashion or by coitus. (From Hendren WH, Atala A: Use of bowel for vaginal reconstruction. J Urol 1994;152:752.)

Reproductive Technologies (ART) has shown that there is normal response of the ovaries to controlled ovarian hyperstimulation for the retrieval of oocytes.[35,36,115,116]

If there is a midline uterus present with the absence of a cervix and vagina, the uterus can be maintained but it should not be attached to the neovagina due to the risk of ascending infection, sepsis, and death.[40] Instead, the vagina can be created by the selected modality and the uterus can be maintained for ART. In order to maintain the uterus and avoid pain with retrograde menstruation and the risk of the development of endometriosis, the patient should be treated with continuous monophasic combination hormonal therapy. The patient is asked to take the monophasic progesterone dominant oral contraceptive pill daily without breaks or placebos for the suppression of retrograde menses. This treatment plan maintains the uterus without risk of ascending infection and preserves the option for fertility. In this clinical scenario, pregnancies have been reported.[117]

The etiology of MRKH is unknown, but reports have shown that a specific genetic abnormality has not been identified. We recently reported a case of monozygotic (monoamniotic/monochorionic) twins in which only one twin exhibited MRKH.[30] In addition, in 58 women with MRKH undergoing ART with gestational carriers, none of the 17 female offspring had MRKH.[31] Thus women with MRKH who desire fertility can use their oocytes, fertilized with a partner's or donor's sperm, and the conceptus is implanted and carried in a gestational carrier.

# Congenital Vaginal Obstruction

Congenital vaginal obstruction is probably caused by incomplete canalization of the vagina and can occur at differing levels. The obstruction can result from an imperforate hymen, agenesis of the lower vagina, or a transverse vaginal septum. It is important to differentiate these anomalies because the appropriate surgical management varies greatly.

## IMPERFORATE HYMEN

Perforation of the hymen usually occurs during the fifth month of gestation. The hymen occurs at the junction of the sinovaginal bulbs with the urogenital sinus and is usually perforated during fetal life. Failure of perforation to occur results in an imperforate hymen.[11,77] Different types of hymens are shown in Figure 124-7. An imperforate hymen can result in gross distention of the vagina, which can be filled with fluid (hydrocolpos), mucus (mucocolpos), pus (pyocolpos), or blood (hematocolpos), or in distention of both the vagina and uterus, which is termed hydrometrocolpos, mucometrocolpos, pyometrocolpos, or hematometrocolpos.

Congenital vaginal obstruction is most commonly caused by simple obstructive anomalies and can include agenesis of the lower vagina, segmental agenesis, or transverse vaginal septum.

## DIAGNOSIS

Imperforate hymen usually presents in the newborn period when there is increased mucus production from maternal estradiol production or at the time of menarche.[100] The mucus distention will usually resolve with time because there is cessation of the estradiol stimulation. The imperforate hymen that is asymptomatic (not causing compromise of urination or other issue) can be observed and addressed as an adolescent or surgically addressed in the newborn period of time.

An imperforate hymen can be suspected on prenatal ultrasound.[118] In the fetus, the imperforate hymen appears as a thin membrane associated with a distended vagina (sonolucent mass) and spread labia majora. Imperforate hymen and hydrocolpos can be diagnosed as early as the second trimester. Neonates with vaginal obstruction can present with a lower midline abdominal mass. Frequently, these infants have associated urinary tract obstruction. The abdominal mass is the distended vagina, which results from continued collection of cervical gland secretions in response to maternal estrogens. Abdominal ultrasonography reveals a large midline

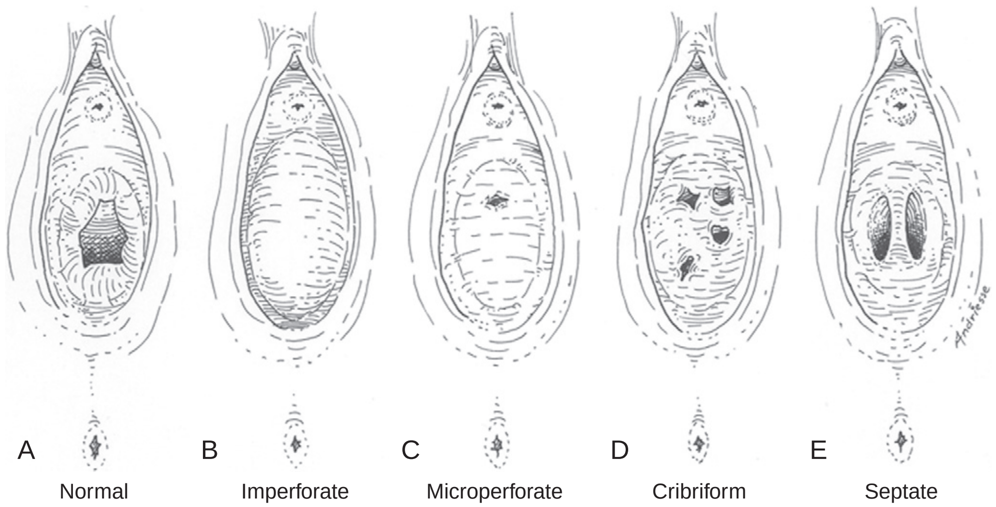


FIGURE 124-7 Types of hymens: **A,** normal, **B,** imperforate, **C,** microperforate, **D,** cribriform or complex, and **E,** septate. (From Emans SJ. Office evaluation of the child and adolescent. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

sonolucent mass. This mass causes forward displacement of the bladder and posterior displacement of the rectum. Percutaneous needle aspiration and injection of contrast medium may aid in the diagnosis and can be done through the perineum or the anterior abdominal wall (Fig. 124-8). If no abdominal mass is present at birth, the condition is often not detected until early adolescence. At the time of puberty, symptoms may include amenorrhea, cyclic abdominal pain, and an abdominal mass secondary to hematocolpos or hydrometrocolpos (Fig. 124-9). Introital examination may show a bulging membrane with bluish discoloration behind it due to hematocolpos.

### TREATMENT

An imperforate hymen in neonates that bulges at the introitus can be easily incised, but there is a risk that when the hymenal tissue is no longer bulging, the edges of incised tissue will adhere, resulting in a persistent structural issue. That is the rationale for not performing a cruciate incision type procedure in either the infant or adolescent (Fig. 124-10). This technique will result in achieving adequate drainage, but there is high risk of reobstruction. We thus recommend the use of an elliptical incision and removal of the excess hymenal tissue. It is necessary to clearly identify the anatomy at the time of the drainage/corrective procedure to ensure that a common urogenital sinus or other urinary tract anomaly is not associated with the obstructive anomaly.

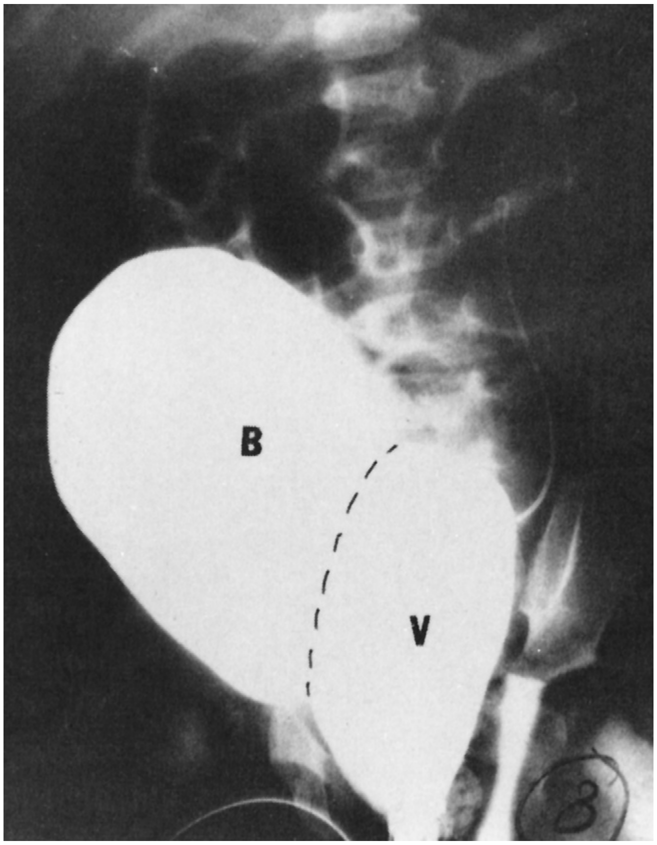


**FIGURE 124-8** Percutaneous injection of an obstructed vagina *(V)* in a newborn, with simultaneous cystogram of bladder *(B)* and retrograde catheterization of a solitary left ureter and kidney.

## Agenesis of the Lower Vagina

Agenesis of the lower vagina (ALV) (Fig. 124-11) occurs with a normal upper vagina in patients with a uterus and cervix. The presentation is similar to an imperforate hymen, and the diagnosis is determined by physical examination and imaging studies.

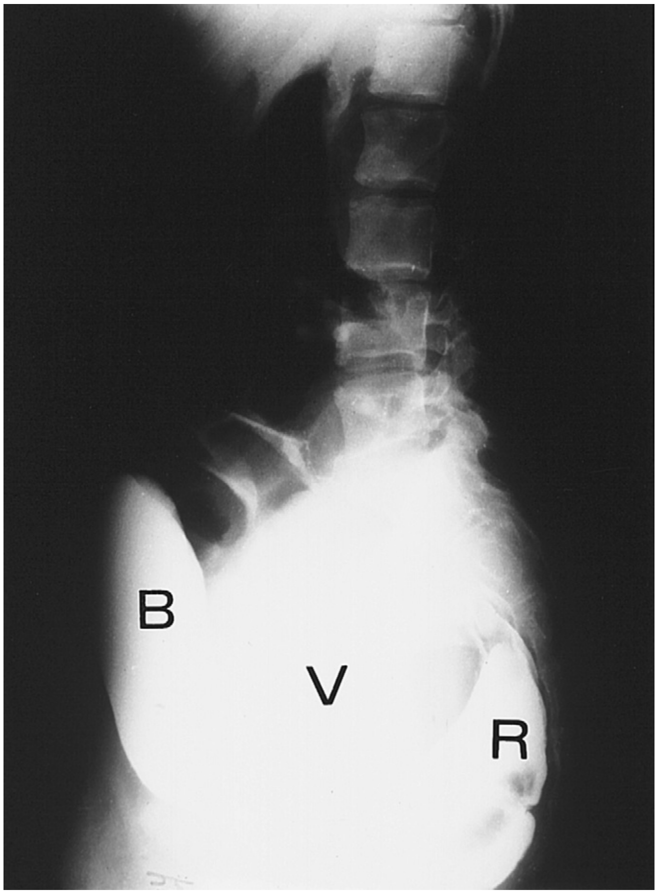


**FIGURE 124-9** Lateral view of a contrast study in a patient with a midline mass pushing the bladder *(B)* forward and the rectum *(R)* in a posterior direction. *V* indicates the obstructed vagina.

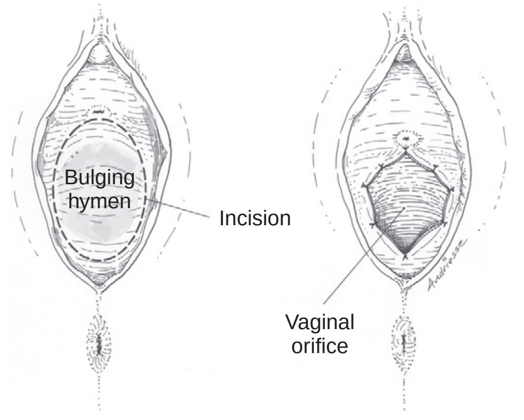


**FIGURE 124-10** Surgical correction of imperforate hymen. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

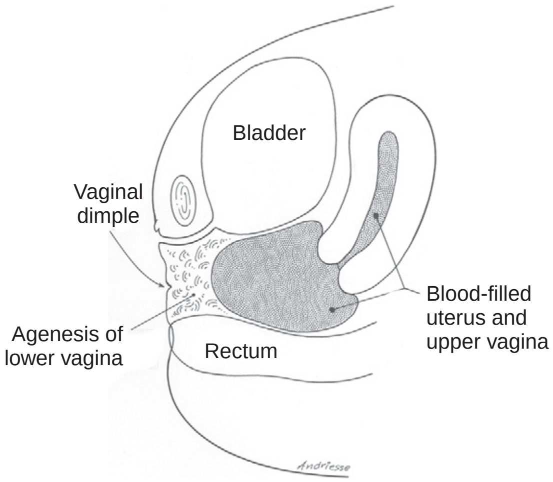


**FIGURE 124-11** Agenesis of the lower vagina with a blood-filled upper vagina. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

### DIAGNOSIS

The external appearance of ALV can easily be confused with an imperforate hymen. The key means to a correct diagnosis include the observation that there are normal fronds of hymen and there is not just a membrane of tissue. In addition, the examiner may be able to insert a finger in the rectum (with the patient in the dorsal supine position) and appreciate a space between the obstructed vagina and the location for the introitus (see Fig. 124-11). The surgeon may not appreciate the difference until an operation is in progress. If there is some amount of areolar tissue until the obstructed vagina is reached, then this is ALV and not an imperforate hymen. Note the distance that has been dissected before reaching the vaginal mucosa in Figure 124-12, *A*. This is an important differential because if the upper vagina is distended and pointing toward the introitus, the blood acts as a natural tissue expander and increases the amount of native vaginal tissue. Once the obstruction is relieved and the old blood is evacuated, the native upper vagina will tend to retract back up toward the uterus. This is the reason the native vaginal tissue must be sewn to the newly created introitus (Fig. 124-12, *B* and *C*). A flexible vaginal dilator should be used 24 hours a day 7 days a week for some number of months so that stenosis of the vaginal orifice will not occur and a fistulous tract will not form if the upper vagina retracts after the pull-through vaginoplasty.

## Transverse Vaginal Septum

Transverse vaginal septum (TVS) can occur at varying levels of the vagina (Fig. 124-13) and is referred to as low, middle, and high transverse vaginal septum. Although highly variable, it

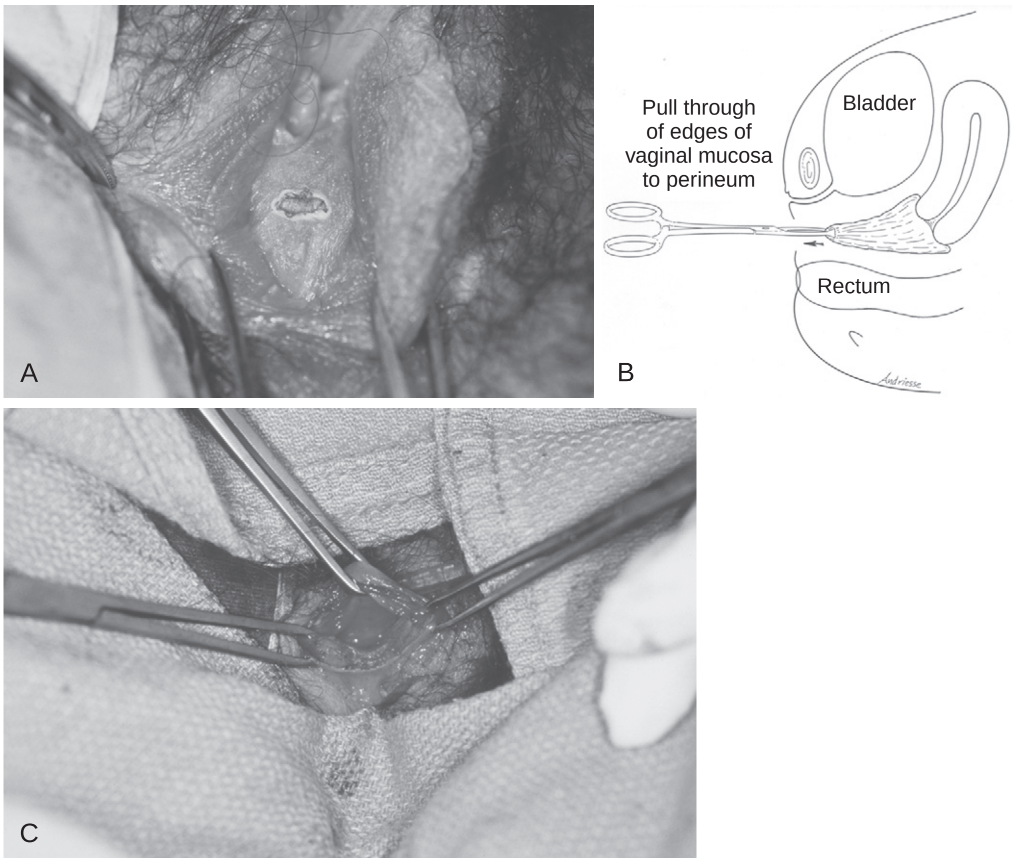


**FIGURE 124-12** **A,** Transverse incision is made to create the vaginal orifice. The dissection is carried through the areolar type tissue to reach the obstructed vagina. **B,** After drainage, the previously obstructed upper vaginal tissue is pulled through to the perineum to create a patent tract. **C,** The normal upper vagina has been pulled down and will now be sewn in place. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

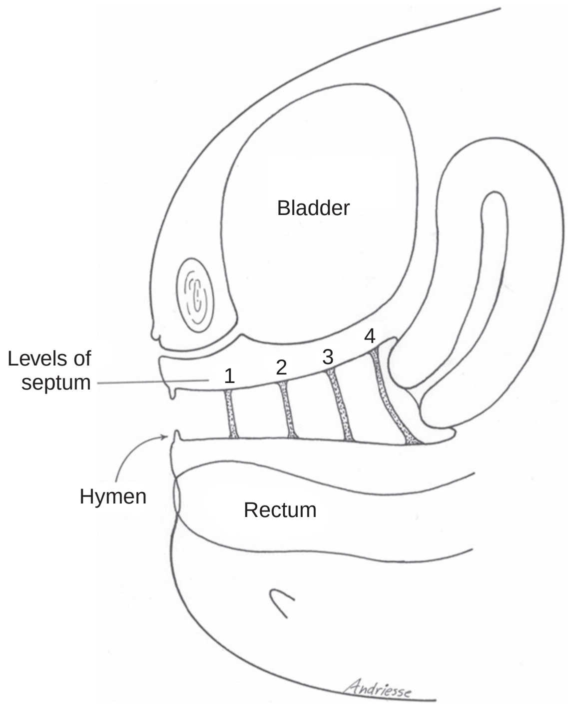


**FIGURE 124-13** Locations of transverse vaginal septum. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

has been reported that approximately 46% of vaginal septa occur in the upper vagina, 40% in the middle vagina, and 14% in the lower vagina.[119] The septum can be obstructing or have a small perforation either in the midline or laterally. The presentation will vary depending on whether there is a perforation.

Pelvic ultrasonography is usually diagnostic of hematocolpos. The high transverse vaginal septum is best treated by draining the vagina by cutting into the septum, resecting the septum, and performing a simultaneous transperineal vaginal pull-through procedure attaching the upper and lower vagina using absorbable sutures. This condition is best addressed after menarche, and the patient is asked to wear a flexible vaginal dilator to avoid circumferential stricture.

The results with lower septum defect repair are much better than outcomes achieved with high vaginal septum defects due to difficulty with the use of dilators reaching the area of the high septum.

# Anomalies of Fusion

## VAGINAL DUPLICATION

Disorders of embryogenesis that produce duplication anomalies of the vagina and uterus occur at approximately 9 weeks of gestation and involve a complete or partial failure of union of the two lateral müllerian ducts. These anomalies[120] are common and can include two uteri and two cervices with two separate vaginas (uterus didelphys) or a single vagina (uterus duplex bicollis). They may also consist of two uteri fused with a single cervix and a single vagina (uterus duplex unicollis or bicornuate uterus) (Fig. 124-14).

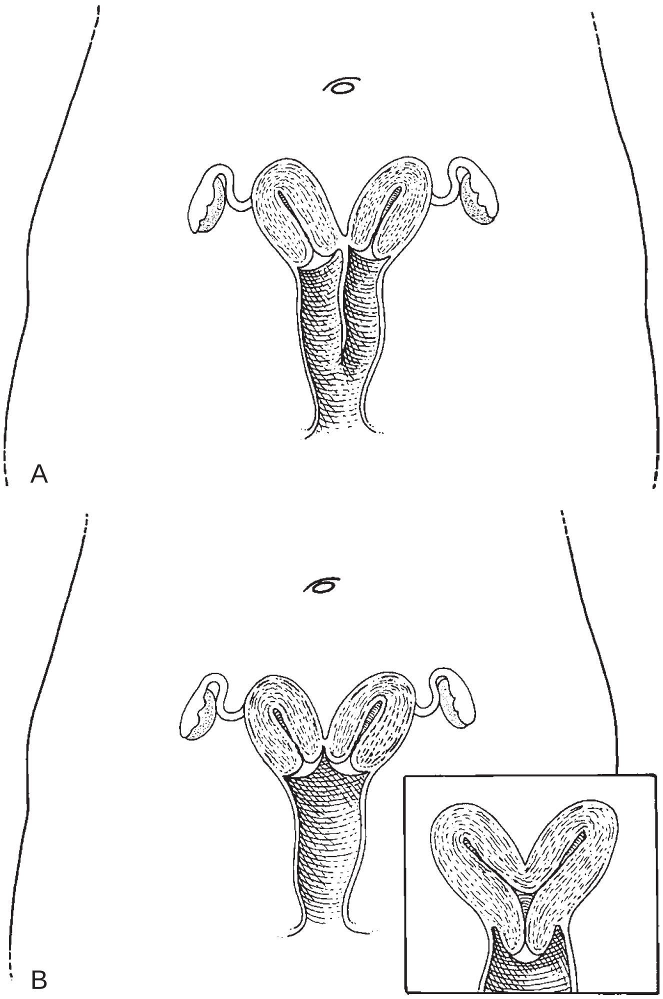


**FIGURE 124-14** Fusion anomalies of the uterus **(A)** and vagina **(B).**

## OHVIRA

In cases of complete vaginal duplication, one vagina can be obstructed and the other can be patent, which is referred to as *obstructed hemivagina with ipsilateral renal anomaly* (OHVIRA)[121] or Herlyn-Werner-Wunderlich syndrome (Fig. 124-15).[122,123] Urinary tract anomalies may confound the situation with an ectopic ureter inserting into a duplicated imperforate hemivagina, resulting in a mass.[13,44,124] The external genitalia will usually appear normal. The diagnosis of uterus didelphys and a unilateral obstructed vagina should be entertained as part of the differential diagnosis in a newborn with a sonolucent abdominal mass. The mass usually pushes the bladder forward and the normal vagina in a posterior direction. Pelvic examination without possible vaginoscopy is helpful in this situation and may reveal a bulging mass high in the vaginal side wall. A simple incision of the obstructing septum with resection of a "window of tissue" often provides adequate drainage; however, further resection of the septum is necessary to prevent possible collection of bacteria on the abnormal side and abscess formation and is usually performed after menarche.[11,121] We advocate a single procedure for OHVIRA during adolescence.[121] Rarely a staged procedure is necessary but is useful when the procedure must be performed on children (due to urinary symptoms, pain, or infection) and when there is a pyocolpos with associated inflammation in the adolescent.

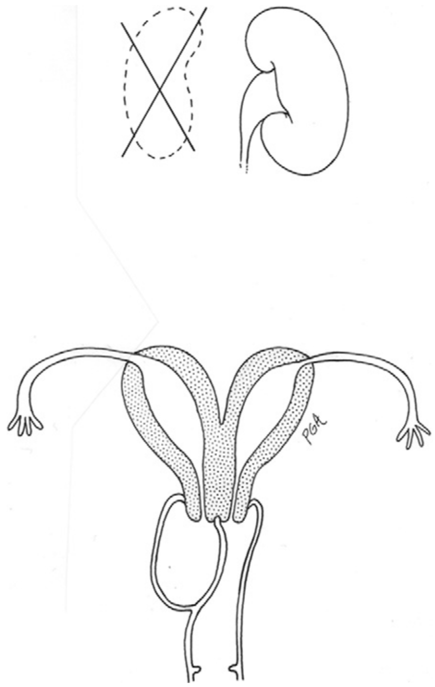


**FIGURE 124-15** Obstructed hemivagina with ipsilateral renal anomaly [OHVIRA]. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

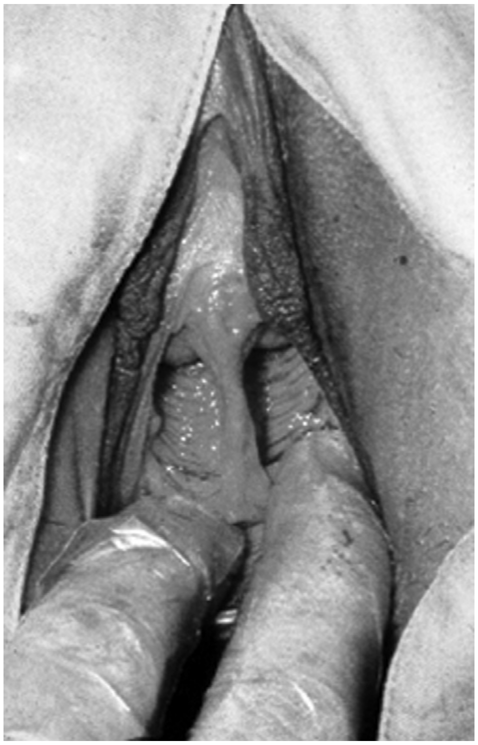

**FIGURE 124-16** Longitudinal vaginal septum. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

# Longitudinal Vaginal Septum

For nonobstructed longitudinal vaginal septum (Fig. 124-16), a surgical excision of the septum is required only if the young woman desires such a procedure. Some patients complain that they need to use a pad in addition to a tampon (because the tampon is absorbing menstrual blood from only one of the two vaginas). Some maintain the longitudinal vaginal septum and have no issues with sexual activity or vaginal delivery. Most have two cervices, so a Papanicolaou smear must be obtained from both.

The septum should be excised by "wedging" out the fibrous septal tissue. Great care is necessary to avoid the bladder above, the rectum below, and the septal tissue between the two cervixes at the apex. Once the septal tissue is excised, the normal vaginal mucosa from one vagina is sewn to the other vagina to create a smooth vaginal mucosa and close the resulting defect. Excision of the septal tissue removes the fibrous tissue to avoid dyspareunia.

If there are two systems that are not obstructed, each can function independently, as two unicornuate systems, from a fertility standpoint.[125]

## RUDIMENTARY UTERINE HORNS

A young woman may present with pain and regular menses. The possibility of a patent unicornuate system (Fig. 124-17) and an obstructed hemi uterus (Fig. 124-18) should be considered. The obstructed hemi uterus may be appreciated on ultrasonography or MRI. In cases of MRKH, if rudimentary uteri are present, they may be difficult to appreciate even on MRI.[126]

The obstructed hemi uterus should be removed so that the patient will no longer have retrograde menses and pain. The procedure can be performed laparoscopically. The cervix should be canalized, and blue dye should be injected at the time of the laparoscopy so that it can be confirmed which

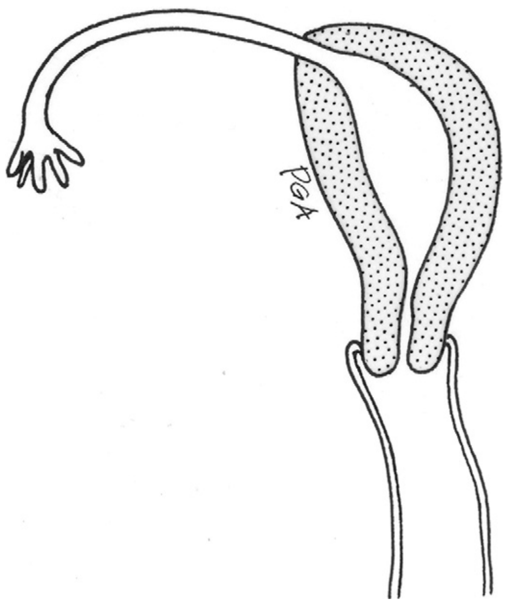


**FIGURE 124-17** Unicornuate system. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

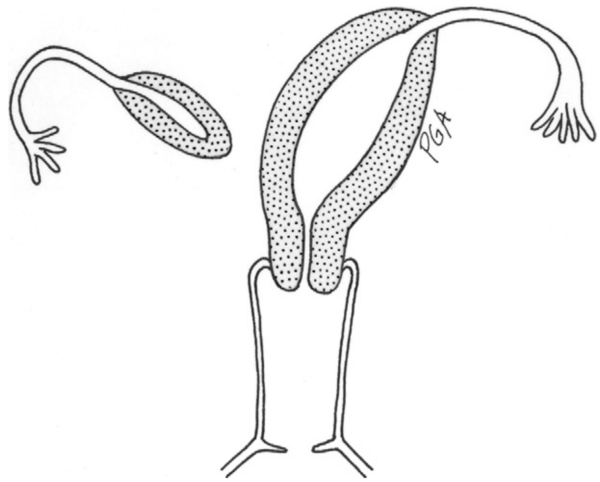

**FIGURE 124-18** Unicornuate system with an obstructed hemiuterus. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

uterus communicates with the cervix (Fig. 124-19). The remaining unicornuate system will most likely function normally but has an increased risk of breech presentation and premature labor.[35,125]

## Urogenital Sinus Anomalies

The urogenital sinus is defined as a common channel into which both the urinary and genital tracts open. The common urogenital sinus is a normal stage of embryonic development in both sexes. In normal females, an arrest in development of the müllerian ducts at 9 weeks' gestation, after fusion with the urogenital sinus, manifests as a urovaginal confluence or common urogenital sinus. An arrest of vaginal differentiation at a slightly later date can lead to varying degrees of persistence of the urogenital sinus seen clinically (Fig. 124-20). A long urogenital sinus with a short vagina and high urethral opening will result if the defect occurs at an early stage. Conversely, a short urogenital sinus with an almost normal vaginal vestibule and low urethral orifice will occur if the arrest occurs late in development.[127] Early defects with a high insertion of the vagina and urethra into the urogenital sinus are frequently associated with an anteriorly displaced anus. This indicates poor formation of the urorectal septum.

### DIAGNOSIS

Adequate definition of the patient's anatomy is essential for proper evaluation of any urogenital sinus anomaly. A retrograde genitogram (Fig. 124-21) can assist in the definition of the urogenital sinus by delineating the length of the common channel and identifying the anatomic relationship of the vagina and urethra.[128] This procedure is best done with a blunt adaptor placed against the perineal opening to instill the contrast agent. Cystoscopy and vaginoscopy should be performed in each case.

### TREATMENT

Once the anatomy of the defect has been clearly identified, various treatment options can be considered. A simple U-flap vaginoplasty[129] can be done if the urogenital sinus is low and the common channel is short. In the cases of a urogenital sinus with a high confluence of the bladder and vagina, Donahoe and Gustafson[130] advocate an inverted perineal U-flap in combination with bilateral buttock flaps to augment the vagina. However, the urogenital sinus is frequently associated with an anteriorly placed anus, which requires posterior relocation of the anus before the perineal skin flap vaginoplasty is done.[131] If the vagina enters the urogenital sinus too far proximally, a division of the vaginal moiety from the urogenital sinus in conjunction with a pull-through vaginoplasty will be necessary. A confluence of both the vagina and the bladder high in the urogenital sinus requires a pull-through vaginoplasty and often requires the creation of a neourethra from the anterior vaginal wall.[132]

## Cloacal Malformations

Cloacal malformations result from the combination of a urogenital sinus with an anorectal anomaly.[133] In the early embryo there is a cloacal stage during which there is a single common tract. At 4 to 6 weeks' gestation, the urorectal septum divides the allantois from the hindgut. If this separation does not take place, a common cloaca will result. Infants

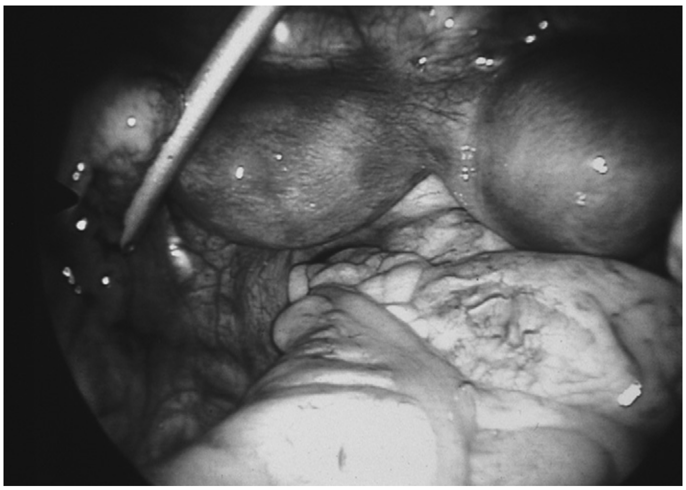

**FIGURE 124-19** Unicornuate system with a right obstructed hemiuterus. Note blue dye coming from left fallopian tube after injection of dye into the single cervix. (From Laufer MR. Structural abnormalities of the female reproductive tract. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

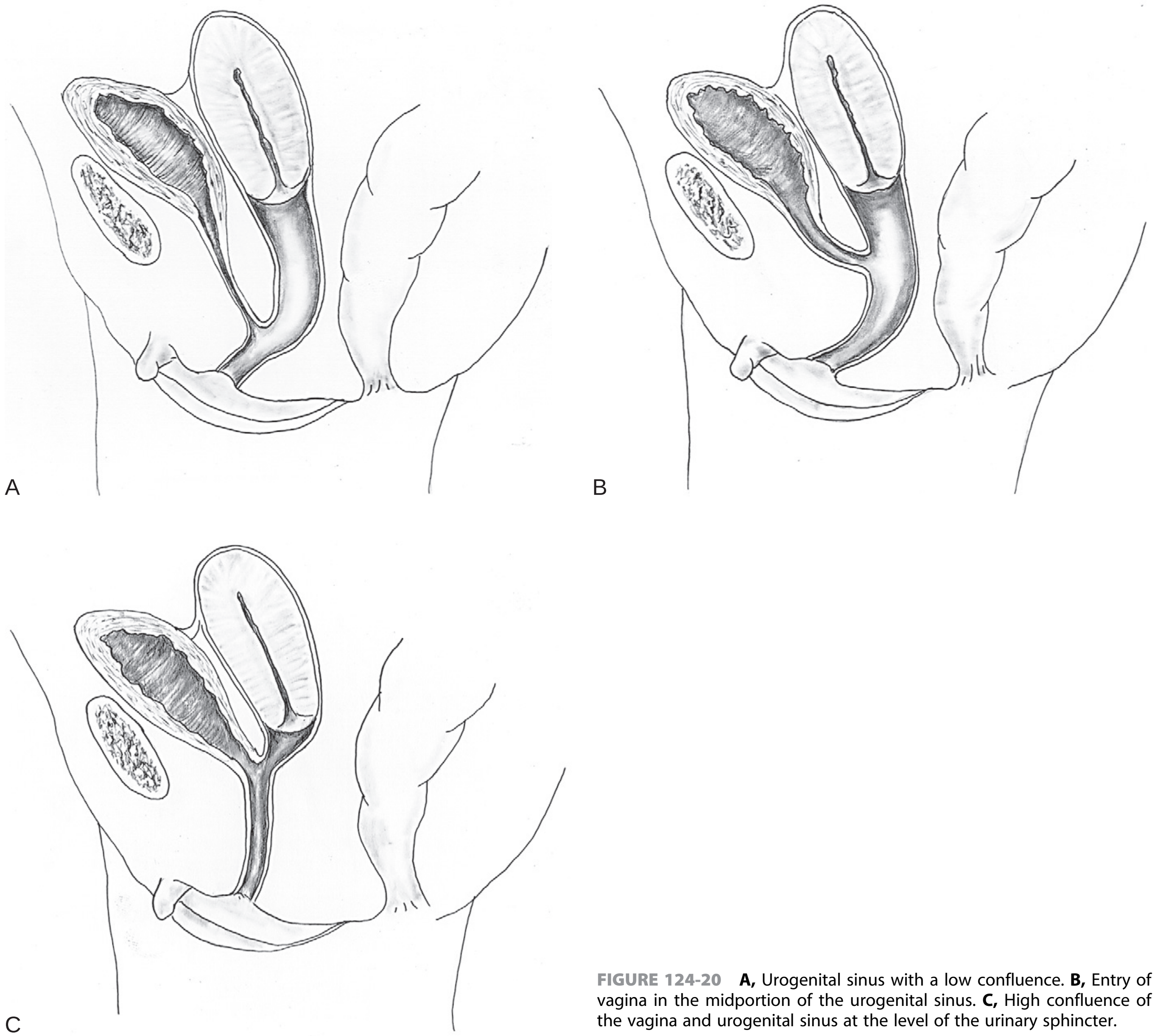


**FIGURE 124-20** **A,** Urogenital sinus with a low confluence. **B,** Entry of vagina in the midportion of the urogenital sinus. **C,** High confluence of the vagina and urogenital sinus at the level of the urinary sphincter.

with this defect present at birth with abdominal distention and an abnormal perineum. They usually have no anus or vagina but possess a single perineal opening. The phallus-like structure frequently has a hooded appearance, which gives a masculinized gender appearance (Fig. 124-22). The bladder may enter the cloaca immediately inside the perineal opening and may be associated with a relatively normal length urethra. Conversely, the bladder may enter the cloaca very high and be located in proximity to the bladder neck. The entrance of the rectum into the cloaca can similarly be either high or low (Fig. 124-23).[134] Vaginal anomalies are common in patients with a cloaca, and vaginal duplication is seen most often. There may also be significant perineal obstruction in these neonates, resulting in both hydrocolpos and an obstructive uropathy (Fig. 124-24).

## DIAGNOSIS

Diagnosis of a cloacal anomaly is confirmed by a retrograde contrast study through the single perineal opening. Frequently, these studies demonstrate a confluence of both the genitourinary and gastrointestinal systems. Blask and colleagues[135] reported on the usefulness of ultrasonography in nine neonates who had either an obstructed urogenital sinus or a cloacal anomaly. On abdominopelvic ultrasonography, the bladder was often compressed by the distended vagina and difficult to visualize. Typically, the vagina was markedly distended with urine and a vaginal fluid-debris level distinguished the vagina from a distended bladder. However, all components of the cloacal anomaly are often not identified on ultrasonography or retrograde studies. Therefore it is only

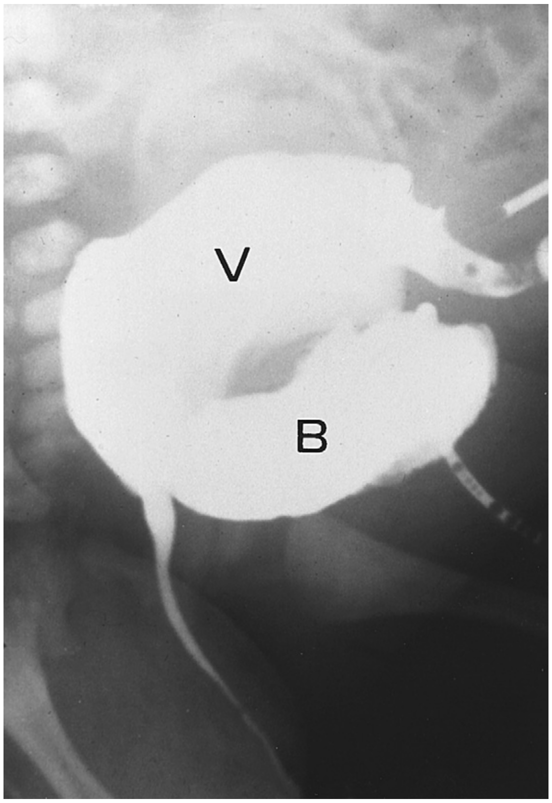


**FIGURE 124-21** Retrograde genitogram of a urogenital sinus showing a high confluence of the bladder *(B)* and vagina *(V)* into a long urogenital sinus.

**FIGURE 124-22** Perineum of a patient with a cloacal anomaly.

at the time of panendoscopy or an open surgical procedure that the exact anatomy can be defined. Complete definition of the patient's anatomy is the first principle of treatment.[136] Information concerning cloacal exstrophy can be found in Chapter 119.

# Other Gynecologic Issues

## LABIAL ADHESIONS

Labial fusion is a common finding in infants and young children. Labial fusion may present as a primary skin bridge and may be associated with or identified at the time of an evaluation of a urinary tract infection. The etiology of labial adhesions is unknown. In most cases the adhesions are asymptomatic and do not require an intervention. They will usually resolve completely with exogenous estrogen production with puberty. The adhesions may be symptomatic, causing irritation, pulling sensation, or complaints of wetness due to trapping of urine in the vagina such that the child wipes after urination and then stands, only to have resulting wetness in her underwear from spontaneous evacuation of the trapped vaginal urine. In symptomatic cases the labial adhesions will easily respond to the twice-daily application of topical estrogen cream or a mild corticosteroid such as betamethasone 0.05%. A surgical intervention is rarely necessary and is reserved for cases of complete obstruction and the inability to urinate. If a surgical intervention is required, great care should be taken to make sure that the lysis of adhesions is performed without cutting into the normal labial tissue. If the normal labial tissue is incised, bleeding may occur and resulting scar tissue may not be estrogen responsive in the future. Thus daily topical application of conjugated estrogen cream should be the first line of therapy in almost all cases of labial adhesions.

## MASSES OF THE INTROITUS

A mass presenting at the introitus between the labia is often a diagnostic dilemma. The differential diagnosis includes prolapse of the urethra, prolapsed ectopic ureterocele, prolapsed yolk-sac tumor, and rhabdomyosarcoma (sarcoma botryoides). It is important to recognize each of these clinical entities and to understand the diagnostic and treatment criteria for each.

## URETHRAL PROLAPSE

Prolapse of the urethra (Fig. 124-25) occurs most commonly in the prepubescent years. Affected children frequently present with blood spotting on the underwear and a mass at the introitus. The tissue appears inflamed and friable and represents a prolapsed portion of the anterior or posterior urethra. The cause remains unclear. An accurate diagnosis depends on recognition of the entity. No special diagnostic studies are necessary. Medical treatment with sitz baths and topical estrogen cream is usually successful. Once treated medically with topical estrogen, an examination is necessary to be certain that a urethral polyp is not present. Operative treatment is rarely required, even in cases of distal necrosis. If a surgical procedure is used, it usually involves simple excision of the prolapsed segment, with suturing of the normal urethra to the meatus.[137] With a surgical procedure, complications are uncommon except for mild degrees of meatal stenosis after excision of the prolapsed segment. Valerie and colleagues[138] noted recurrence of prolapse in 1 of 20 patients treated by excision.

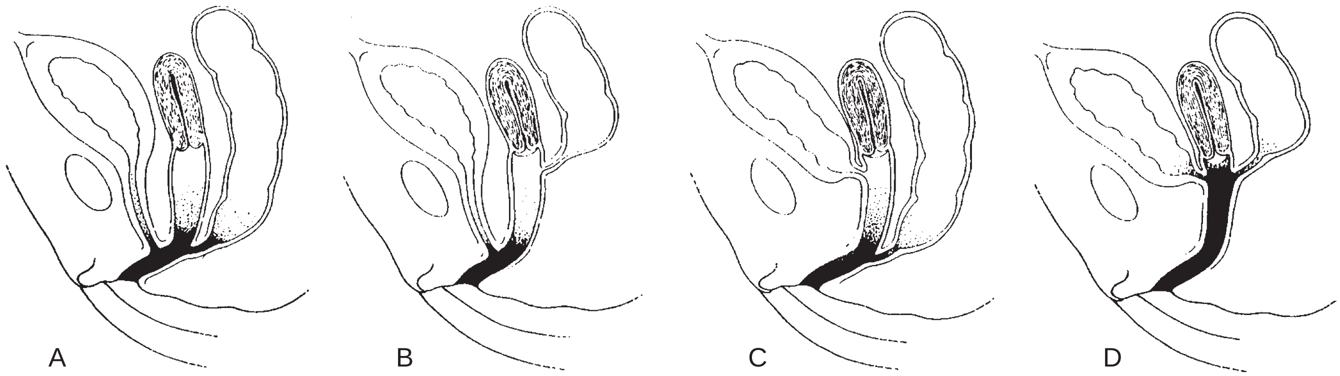


**FIGURE 124-23** **A** to **D,** Various forms of the cloacal anomaly demonstrating proximal and distal forms.

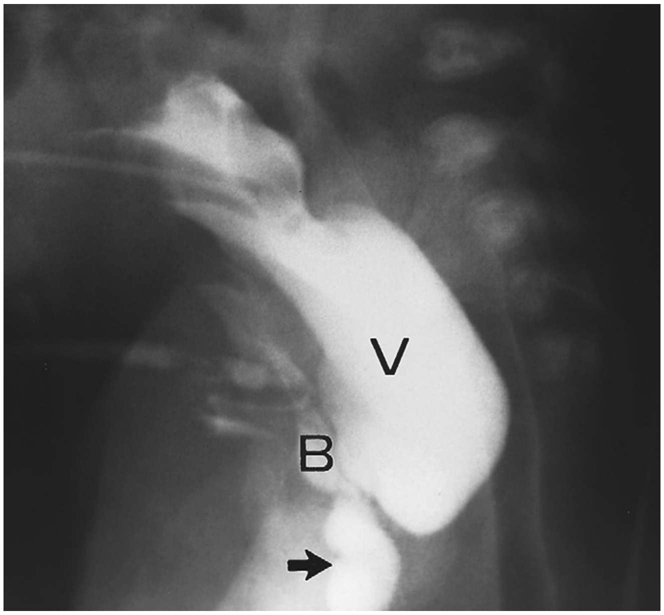


**FIGURE 124-24** Antegrade study of the bladder *(B)* and vagina *(V)* in a patient with a cloacal anomaly. A dilated urogenital sinus *(arrow)* and relative obstruction at the perineal outlet are shown.

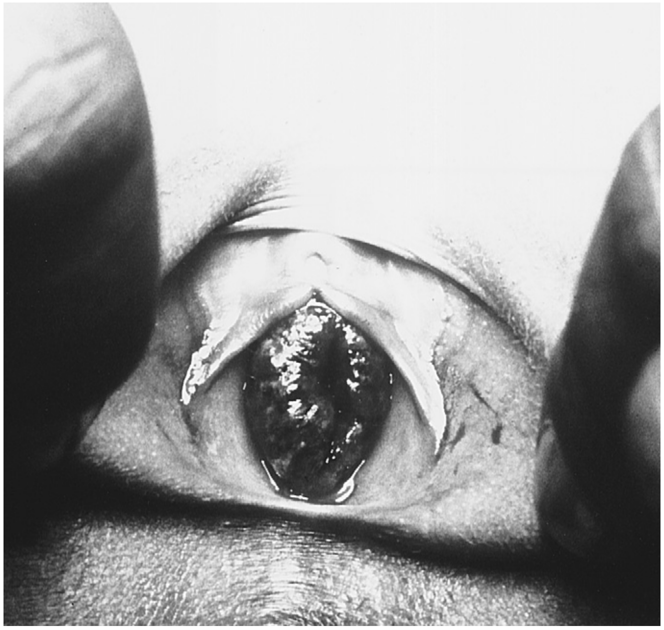

**FIGURE 124-25** Prolapsed urethra in a 9-year-old girl. Note the congested, necrotic appearance of the prolapsed tissue.

## PROLAPSED ECTOPIC URETEROCELE

Prolapsed ectopic ureteroceles can present as an intralabial introital mass (Fig. 124-26).[139] They are usually smooth and white or slightly edematous lesions that extrude from the urethral meatus. The urethral meatus can often be seen above the lesion. The diagnosis can usually be made on intravenous urography, which demonstrates a lower pole collecting system that is pushed laterally and inferiorly (i.e., drooping lily sign). The ureter is displaced away from the midline on the affected side, and the bladder has a filling defect (see Fig. 124-26).[140] Current management of these lesions is presented in Chapter 114.

## SARCOMA BOTRYOIDES

Sarcoma botryoides, or rhabdomyosarcoma of the bladder or vagina, is the most common malignant condition of the lower genitourinary system presenting in infancy.[141] The tumor may be observed protruding from the introitus. It often presents as blood spotting on the undergarments with the diagnosis then achieved by vaginoscopy and biopsy.[142] The lesion, as the name denotes, appears as a lobulated, grapelike mass (Fig. 124-27). The extent of the lesion is best determined by pelvic ultrasonography and CT. Rhabdomyosarcoma occurring at this primary site (vulvovaginal) is associated with an excellent outcome, with more than 90% of patients surviving with limited fertility-preserving surgery (including vaginoscopic resection) and multimodal chemotherapy.[142–146] Further details concerning management can be found in Chapter 34.

## YOLK SAC TUMOR

The vagina is a usual primary site for yolk sac tumors. These neoplasms can present protruding from the introitus or with vaginal spotting or bleeding.[147] These lesions are classified as endodermal sinus tumors (germ cell tumors), and affected patients frequently have an elevated serum alpha fetoprotein

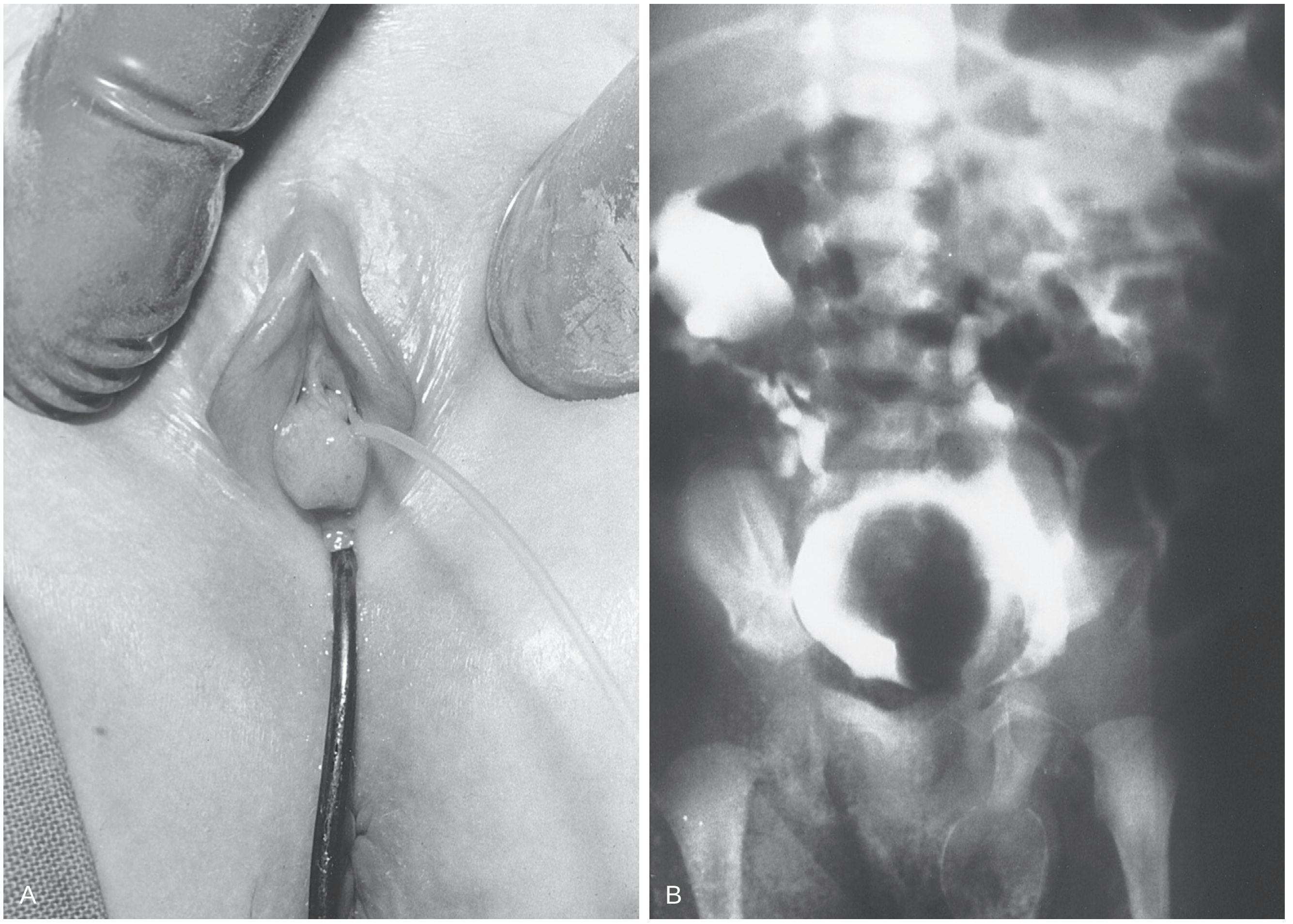

FIGURE 124-26 **A,** Prolapsed ureterocele in a 3-year-old girl. Note the white, healthy appearance of the cystlike structure. **B,** Intravenous urogram in a patient with an ectopic ureterocele demonstrating a right lower pole collecting system being pushed in a lateral and inferior direction (drooping lily sign) along with a filling defect in the bladder.

FIGURE 124-27 Sarcoma botryoides. (From Emans SJ. Vulvovaginal problems in the prepubertal child. In Emans SJ, Laufer MR [eds]: Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2011.)

level. Germ cell tumors are treated with platinum-based chemotherapy programs and often have an excellent outcome (85% survival). Fertility-sparing vaginal surgery and adjuvant chemotherapy have been successful in these cases.[148,149] In fact, some cases have demonstrated resolution of the tumor with chemotherapy alone.[150] This topic is presented in depth in Chapter 39.

## MISCELLANEOUS INTROITAL LESIONS

Paraurethral cysts also present as interlabial masses in female infants.[151] They tend to displace the urethral meatus and vaginal introitus to one side. A normal urethra and vaginal introitus can usually be identified (see Fig. 124-20). These cysts are probably embryologic remnants of Skene glands or the Gartner duct. Most of these cysts regress spontaneously and rarely need to be incised and drained. The Gartner duct cysts are remnants of the wolffian duct and may be associated with unilateral renal dysplasia[152] and duplicated collecting system with ectopic ureter emptying into the vagina or rarely the cyst wall.[153,154] Goldstein and colleagues[153] were the first to describe the relationship of the Gartner duct cyst and ipsilateral renal agenesis in 1973. Both patients in that report had a bicornuate uterus. Patients often present with urinary tract infection and incontinence due to the ectopic ureter emptying into the vagina or the Gartner cyst wall.[155,156] Once the urinary tract abnormalities have been addressed, the Gartner cyst can either be excised or marsupialized.

# Other Vaginal Tumors

## HEMANGIOMA

Hemangiomas can occur in the vagina, as they can in many other tissues. Vaginal hemangiomas are occasionally extensive and coexist with hemangiomas affecting the skin and subcutaneous tissues of the perineum and perianal areas and rectal wall.[157] Conservative management is usually recommended because the natural history of these lesions suggests that spontaneous resolution will occur over a period of months to years. Ulceration and bleeding are complications that may require treatment with corticosteroids and interferon-α.[157] Failure of conservative treatment may require excision. Further information regarding hemangiomas is available in Chapter 124.

## ADENOCARCINOMA OF THE CERVIX AND VAGINA

Adenocarcinoma of the cervix and vagina is rare in children. Less than 3% of sexually active adolescents may show evidence of cervical intraepithelial neoplasia, and annual Papanicolaou smears have been recommended. In 1971 Herbst and colleagues[158] described the occurrence of clear cell adenocarcinoma of the vagina in young adolescent girls who were progeny of mothers who had received diethylstilbestrol during pregnancy. Offspring of women with this history are recommended to have a gynecologic examination by age 14 or after menarche and then annually thereafter. Vaginal clear cell adenocarcinoma has been observed in an infant who presented with hematuria.[159] In 2004 McNall and colleagues[160] reviewed 37 patients 18 years of age or younger with vaginal or cervical mesonephric adenocarcinoma and clear cell adenocarcinoma. The patients' ages ranged from 7 months to 18 years. The most common presenting symptoms were vaginal bleeding (89%) and/or discharge (16%). Sixty-two percent were exposed to diethylstilbestrol. Eight of 27 girls (21%) with vaginal tumors had metastases at diagnosis. Delay in diagnosis was common because of the lack of an appropriate pelvic examination in patients younger than 13 years old. Nine patients (36%) had not reached menarche. Seventy-six percent had International Federation of Gynecology and Obstetrics (FIGO) stage I or II disease, whereas 24% had stage III or IV (advanced-stage) disease. Twenty-two girls (58%) underwent a radical operative procedure (radical hysterectomy or pelvic exenteration): 19 had stage I or II disease, and in 3 the stage was undocumented. Seven of these patients received radiation therapy. Seven girls (18%) had tumor excision alone combined with radiation therapy in three and chemotherapy and radiation in one. Seven patients with advanced disease had no surgery. Three received radiation therapy, three had chemotherapy, and one had both. Overall, the 3-year disease-free survival was 71% (27/38). Ten patients died of progressive or recurrent disease. Relapse was an ominous finding. Sites of recurrence were the lungs in six patients, the lymph nodes or soft tissues in two, and the brain in one. The 3-year survival estimate for those undergoing surgical removal of tumor was 85%. Girls with tumor excision (conservative surgery) did better than those with radical surgery (100% 3-year survival vs. 78%), although there were only seven patients with tumor excision and four received adjuvant therapy. The study did not evaluate tumor size. Two of the seven patients with tumor excision had stage III disease, whereas all of those undergoing radical surgery had stage I or II disease. The only statistically significant predictors of survival were surgical resection and the presence of metastases at diagnosis. The data suggest that conservative surgical treatment with adjuvant therapy may obviate the need for radical surgery. A prospective randomized study in a larger number of patients is necessary to confirm these observations. Because of the rarity of the tumor, this may be difficult to achieve. Long-term follow-up is important in these patients because late recurrences have been observed.[161,162]

*The complete reference list is available online at www.expertconsult.com.*

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# Part IX

# SPECIAL AREAS

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CHAPTER 125

# Vascular Anomalies

Ann M. Kulungowski and Steven J. Fishman

A reliable classification system for vascular anomalies was developed 30 years ago.[1] Vascular anomalies are divided into two categories, tumors and malformations, on the basis of clinical behavior and cellular kinetics.[2] Vascular tumors are characterized by endothelial hyperplasia; vascular malformations arise due to vascular dysmorphogenesis and exhibit normal endothelial turnover.[2] The classification scheme provides the framework for understanding the pathophysiology, diagnosis, and prognosis of these lesions.

Pediatric surgeons are often called on to assist with diagnosis and treatment of vascular anomalies. The majority of lesions are noted at birth or during infancy because they commonly involve the skin. A thorough history and physical examination leads to the correct diagnosis in more than 90% of patients. Familiarity with the field of vascular anomalies, its classification scheme, and use of correct nomenclature will ultimately improve outcomes for patients affected by these lesions.

## Historical Perspective

Historically, vascular birthmarks were thought to be imprinted on the unborn child due to a mother's emotions.[1,3] The use of adjectives such as "strawberry" and "port wine" are reflected in this doctrine of maternal impressions.[4] Physicians preferred the Latin term *naevus maternus*. In the nineteenth century, Virchow is likely the first to have categorized vascular anomalies on the basis of histologic features.[4]

For centuries, the field has been plagued by overlapping vernacular, clinical, and histopathologic terms resulting in misdiagnosis, inappropriate treatment, and misdirected research. A common example is the continued application of the word "hemangioma" to describe vascular lesions of any kind irrespective of behavior and biology. The biologic classification system in use today was formally accepted in 1996 by the International Society for the Study of Vascular Anomalies (Table 125-1).[5] In addition to classifying tumors and malformations based on cellular and clinical behavior, they also exhibit their own unique radiographic findings and immunohistochemical properties.[2]

## Vascular Tumors

### INFANTILE HEMANGIOMA

Infantile hemangiomas (IHs), benign tumors of the endothelium, are the most common tumor of infancy (Fig. 125-1). It occurs in approximately 4% of white-skinned infants. A frequently quoted study probably overestimated the incidence of 10% by including other vascular lesions.[6] The incidence is lower in dark-skinned babies. There is a female-to-male preponderance of 3:1 to 5:1.[2] Extremely-low-birth-weight infants (<1000 g) have the highest incidence of IHs, approaching 23%.[7] Additional risk factors include advanced maternal age, multiple gestations, and placental abnormalities.[8]

IHs most often occur as a single cutaneous lesion (80%) with a predilection for the head and neck (60%), trunk (25%), and extremities (20%) (see Fig. 125-1).[9] Multiple tumors are present in up to 20% of patients and, when present, may signal involvement of extracutaneous organs such as the liver or gastrointestinal (GI) tract.[2] Median age of onset is 1 to 2 weeks. A premonitory cutaneous mark such as a pale spot or faint macular stain is present at birth in 30% to 50% of cases.[2] The majority (90%) of IHs are small, localized lesions that do not involve aesthetically or functionally vital structures.[2,10]

A hallmark of IH is its predictable life cycle (Fig. 125-2). During the proliferating phase, there is rapid growth of the tumor, which typically lasts until 10 to 12 months of age. Superficial hemangiomas are red; deeper lesions may be noted later as a blue mass visualized through the skin. Around 12 months of age, growth of the IH plateaus, marking the beginning of the involuting phase. Over the next 6 to 7 years, the crimson color fades, the center becomes pale, and the lesion appears to deflate.[2] By 5 years of age, 50% of tumors have completed involution, which increases to 70% at 7 years of age. There is often continued gradual regression of the color and bulk of the tumor until 10 to 12 years of age.[11] When the IH has ceased involuting, it enters the involuted phase. At the end of involution, 50% of patients have nearly normal skin in the area of the prior lesion. Large tumors can leave lax, redundant skin and/or a fibrofatty residuum. Previously ulcerated lesions can leave permanently damaged skin, scars, and discoloration.[2]

Endangering or life-threatening IHs are rare.[12] Recognition of the anatomic distribution of the lesions helps predict possible complications. Cervicofacial and subglottic IHs can be life-threatening due to airway obstruction.[2] Subglottic IHs are characterized initially by hoarseness and later biphasic

**TABLE 125-1**
**Classification of Vascular Anomalies**

| *Tumors* | *Malformations* |
|---|---|
| **Hemangioma** | **Slow-flow** |
| **Infantile Hemangioma** | Capillary |
| **Congenital Hemangioma** | Lymphatic |
| - Rapidly involuting congenital hemangioma (RICH) | - Microcystic |
| - Noninvoluting congenital hemangioma (NICH) | - Macrocystic |
| | - Mixed |
| | - Lymphedema |
| | - Gorham-Stout disease |
| | - Lymphangiectasia (pleural, pulmonary, intestinal) |
| | Venous |
| **Kaposiform Hemangioendothelioma** | **Fast-flow** |
| **Kaposiform Lymphatic Anomaly** | Arteriovenous fistula |
| **Tufted Angioma** | Arteriovenous malformation |
| **Cutaneovisceral Angiomatosis with Thrombocytopenia** | |
| **Angiosarcoma** | |
| **Kaposi Sarcoma** | |
| **Pyogenic Granuloma** | **Complex-Combined** |
| | Capillary-lymphatico-venous (Klippel-Trenaunay) |
| | Capillary-arteriovenous (Parkes Weber) |
| | Lymphatico-venous |
| | Rare syndromes (see text) |

stridor around 6 to 12 weeks of age. Ulceration of the eyelid, nasal tip, lip, and ear can be disfiguring. Periorbital IHs can block the visual axis and cause deprivation amblyopia; upper eyelid and supraorbital lesions can distort the cornea, producing astigmatic amblyopia. Infants with periorbital hemangioma should be examined by a pediatric ophthalmologist. GI IHs can cause GI bleeding. Complications of hepatic hemangioma include high-output cardiac failure, hypothyroidism, and abdominal compartment syndrome.

The occurrence of multiple IHs is called hemangiomatosis (see Fig. 125-1, *left, middle*). In this setting, the cutaneous lesions are usually tiny (<5 mm) and domelike, but some may have the more typical appearance of a single tumor. Occult visceral lesions may be present when multiple cutaneous IHs (usually five or more) are found. Screening ultrasonography may be indicated. The liver is the most frequently involved location.

***Etiology and Pathogenesis*** The exact etiology and pathogenesis of IH remains to be elucidated. There is emerging evidence for an endothelial stem/progenitor cell as the cellular origin of hemangioma.[13–15] The source of these endothelial progenitors remains elusive. Some studies suggest a population of resident angioblasts, arrested in an early stage of vascular development, as a source. Hemangioma endothelial cells may be of placental origin because they coexpress several markers: glucose transporter-1 (GLUT-1), type III iodothyronine deiodinase, Fc$\gamma$-RIIb, merosin, and Lewis Y antigen.[16–20] Disruption of the maternal-fetal barrier may allow an embolic nidus of placental endothelial cells to reach fetal tissues through the permissive right to left shunt of fetal circulation.[21] This could explain the increased incidence of IH observed with chorionic villus sampling and prematurity, sometimes a result of placental disorders.[22]

The characteristic growth and involution of IH seen on physical examination parallel the cellular activity of the tumor. During the proliferating phase, angiogenesis occurs as endothelial cells rapidly divide, forming a mass of sinusoidal vascular channels with feeding arteries and draining veins.[23–25] A proangiogenic environment is created by the presence of factors such as basic fibroblast growth factor, vascular endothelial growth factor, and matrix metalloproteinases. In contrast, angiogenesis is decreased during the involuting phase as endothelial cells undergo apoptosis.[26] This coincides with increased expression of angiogenesis inhibitors such as interferon-$\beta$ and tissue inhibitor of metalloproteinase.[23,24]

***Associated Structural Abnormalities*** Congenital abnormalities are rarely associated with IH, but larger hemangiomas and those encountered in the midline merit attention. A subgroup of patients with IH exhibits associated structural anomalies of the brain (e.g., posterior fossa abnormalities), cerebral vasculature (e.g., hypoplasia or absent carotid and vertebral vessels, aneurysms), eye (e.g., cataracts and optic nerve hypoplasia), aorta (e.g., coarctation), and chest wall defects (e.g., sternal clefts) in the neurocutaneous disorder called PHACES syndrome (*P*osterior fossa malformations, *H*emangioma, *A*rterial anomalies, *C*ardiac defects, *E*ye anomalies, and *S*ternal defects).[27–30] Tumors of the lumbosacral region may occur along with spinal dysraphism abnormalities such as a tethered cord or lipomeningocele. Ultrasonography is used to screen infants younger than 4 months of age for the presence of

**FIGURE 125-1** Morphologic variation of infantile hemangioma (IH). Proliferating phase IH on the trunk *(left)*. Multiple cutaneous dome-shaped IHs, which are often seen in association with hepatic hemangioma *(left, middle)*. Proliferating IH in the perineum *(right, middle)*. Reticular IH over the midline *(right)*.

FIGURE 125-2 Progression and involution of infantile hemangioma (IH) in the beard distribution. Proliferating IH at 2 weeks of age *(top, left)*. Corticosteroid treatment initiated. After 2 weeks of therapy *(top, middle)*. Notice ulcerated area in lower lip. Ulceration has healed after 6 weeks of corticosteroid (2 months) *(top, right)*. Continued proliferation of IH despite therapy (3 months) *(bottom, left)*. Corticosteroid was weaned with rebound growth (age 11 months) *(bottom, middle)*. Propranolol therapy was initiated. After 6 months of propranolol therapy *(bottom, right)*. IH has decreased in size (18 months).

occult spinal dysraphism; magnetic resonance imaging (MRI) may be necessary in older children. Anorectal and genitourinary anomalies can occur with IH of the pelvis or perineum, sometimes as part of PELVIS syndrome (*P*elvic hemangioma, *E*xternal genital malformations, *L*ipomeningocele, *V*esicorenal, *I*mperforate anus, *S*kin tags).[31] A macular, network-like hemangioma of the lower extremity has been seen with structural anomalies of the ventral-caudal region, visceral hemangiomas, and cardiac overload.[32]

***Radiologic Features*** Radiographic studies assist with classifying indistinguishable vascular tumors. Ultrasonographic features of proliferating IHs include a focal fast-flow soft tissue mass with increased vessel density.[33,34] MRI is the second-line study and reserved for further clarification in the face of diagnostic uncertainty to confirm the extent and tissue characteristics of the lesion. MRI characteristics of a proliferative-phase IH reveal a solid mass with dilated feeding and draining vessels (Fig. 125-3). IHs are of variable intensity on T1 and are hyperintense on T2.[35] Flow voids are seen around and within the mass.[35] As the IHs involute, vessels decrease in size and number. Involuted IHs are seen as avascular fatty masses on MRI.[36]

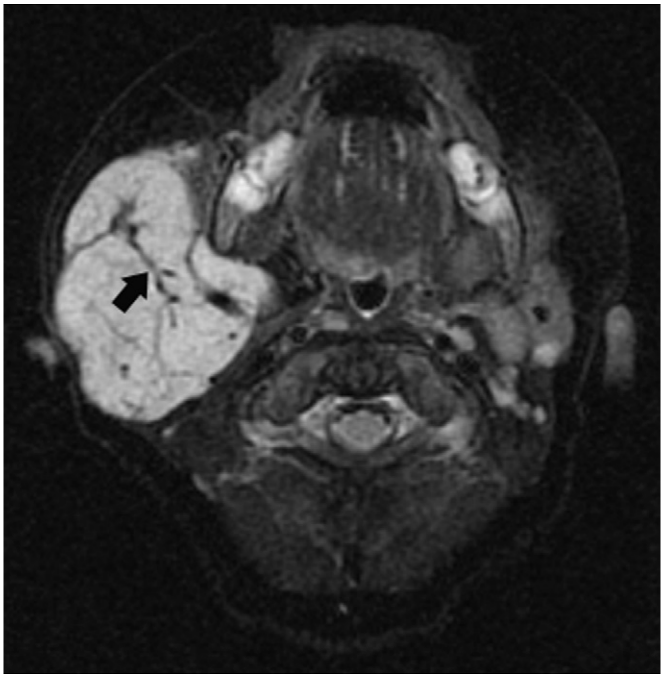

FIGURE 125-3 Magnetic resonance imaging (MRI) of infantile hemangioma (IH). Axial T2 weighted fat-saturation MRI sequence of a parotid IH, which shows a well-circumscribed, uniformly hyperintense mass with dilated feeding and draining vessels *(arrow)*.

***Treatment***

**Observation and Local Treatment** The majority of IHs require no specific treatment other than observation. Even if the proper decision is not to intervene, this does not mean that

nothing should be done.[2] The consultant plays a crucial role in providing guidance and support.[37] Regularly scheduled follow-up is imperative. Serial photographs are useful to document progression, response to treatment, and subsequent regression. Disfiguring hemangiomas, particularly when located on the face, frequently evoke strong parental emotions of loss and grief. Deformity and severe complications occur in 10% cases.[12]

The most frequent complications of proliferating cutaneous IHs include epithelial breakdown, ulceration, bleeding, and pain. The lips, perineum, and parotid area are especially vulnerable to ulceration.[38] Treatment of ulceration includes daily cleansing; application of petrolatum and viscous lidocaine may be used for pain control. Superficial ulceration usually heals within days to weeks, whereas a deep ulceration may take several weeks.[2] Eschars should be debrided and treated with wet-to-dry dressings to stimulate granulation tissue. Total excision of an ulcerated IH is usually reserved for lesions of the chest, scalp, extremity, and rarely for facial lesions when primary closure is possible.

**Pharmacotherapy** Systemic pharmacologic intervention may be necessary for endangering, ulcerating, problematic, or life-threatening IHs. Corticosteroids inhibit the vasculogenic potential of hemangioma-derived stem cells, as well as the expression of vascular endothelial growth factor.[39] Prednisone or prednisolone is administered in the morning at 2 to 3 mg/kg/day for 2 weeks. Initial improvement in color and tension is usually evident in the first 1 to 2 weeks. If the IH stabilizes, the dosage is tapered every 2 to 4 weeks with a goal of discontinuation by 10 to 11 months of age. The overall response rate is 80% to 90%. In some cases the tumor may exhibit rebound growth as the corticosteroid is tapered. A return to the initial dose and slower taper will usually suffice. Possible side effects of corticosteroid include Cushingoid facies, irritability, GI reflux, a slowing in the rate of height and weight gain, steroid-induced cardiomyopathy, and hypertension.[40–42] Nearly all children (88%) return to their pretreatment curves for height and weight within 24 months.[41] Live vaccines (e.g., polio, measles, mumps, rubella, varicella) should not be administered during corticosteroid treatment.

Intralesional injection of corticosteroid for well-localized tumors of the nasal tip, cheek, lip, or eyelid is used to minimize deformity. There are reports of retinal artery occlusion and eyelid necrosis, presumably from embolization of colloidal particles.[43,44] Compression at the periphery of the lesion will help minimize this risk. Triamcinolone (25 mg/mL) is injected slowly at a low pressure with a 3-mL syringe and 25-gauge needle. The dosage is 3 to 5 mg/kg per injection.[45] Additional injections can be done at 6- to 8-week intervals; usually, three to five are necessary.[45] Response rates are similar to that of oral corticosteroid.

Propranolol, a nonselective beta blocker, is being used with increasing frequency for the treatment of IHs.[46] Early reports suggest that propranolol may be as efficacious as corticosteroids for the treatment of problematic IHs.[46–48] The mechanism of action for propranolol is unknown; theories include vasoconstriction of the tumor vasculature or downregulation of angiogenic proteins.[46,48] An ongoing, prospective, randomized controlled trial will help elucidate propranolol's safety, efficacy, and tolerability for the treatment of IHs.

Recombinant interferon-alfa has fallen out of favor as second-line therapy due to the risk of spastic diplegia, which occurs in 5% to 20% of treated infants, particularly those younger than 6 months of age.[49,50] More suitable second-line agents are chemotherapeutic drugs with antiangiogenic properties such as vincristine. The drugs are administered in a low-dose, high-frequency metronomic regimen.

**Embolic Therapy** Rarely, embolization is indicated for IHs that result in congestive heart failure and do not respond to drug therapy. Hepatic hemangiomas are the most common lesions to require embolization. Its effectiveness is determined by the ability to occlude a large percentage of the shunts. Infants are maintained on pharmacotherapy even after an apparently successful embolization.[2]

**Laser Therapy** Flashlamp pulsed-dye laser is not beneficial for nascent or proliferating hemangiomas. It penetrates only the most superficial portion of the dermis and leaves the majority of the lesion untreated. Moreover, a superficial IH is often the tumor that requires no treatment and involutes without a trace. Laser treatment carries the risks of scarring, ulceration, and hypopigmentation. In the involuting/involuted phase, remnant telangiectasias can be effectively treated with pulsed-dye laser. The use of endoscopic continuous-wave carbon dioxide laser can control proliferating, unilateral subglottic IHs.[51]

**Surgical Therapy** Indications for surgical resection vary according to patient age and hemangioma stage. During infancy (proliferating phase), excision may be necessary for IHs causing ulceration, obstruction, and bleeding. Occasionally, a well-localized or pedunculated lesion may be removed when the scar formed would be similar to that if the excision were to occur at a later stage. Sites most amenable to resection during this phase include the scalp, trunk, and extremity due to skin laxity. IHs of the forehead, eyelid, cheek, lips, nose, nasal tip, ear, and neck require surgical expertise.

IHs of the stomach, small intestine, or colon can present with mild or life-threatening GI bleeding during infancy. Endoscopy or laparoscopy, or both, are sometimes necessary to localize lesions of the small bowel.[52] Most infants with GI hemangiomas are medically managed with pharmacotherapy and intermittent blood transfusions. Focal lesions that are not responsive to drug therapy can be treated with endoscopic band ligation or segmental bowel or wedge resections. More commonly, though, GI hemangiomas present with diffuse, patchy involvement, making endoscopic and surgical intervention problematic.[53] Extensive resections should not be performed. These infants should be supported medically. Involution and cessation of bleeding will eventually occur.

Removal of IHs during the involuting phase may be considered for large, protuberant lesions, which are likely later to be associated with excess skin or a large fibrofatty residuum. Indications for resection include inevitable excision, need for staged excision, ability to hide the scar, and desire to avoid an altered self-image.[2] Waiting until the involuted phase to determine the need for resection is reasonable barring any endangering or life-threatening complications. Many IHs involute, leaving normal or minimally blemished skin. Ulceration increases the likelihood of scar. Excision may be considered during late childhood (involuted phase) for damaged skin and contour deformity.

Surgeons would agree that the scar for resection of IH should be minimized irrespective of indication and timing.[54] Lenticular excision with linear closure is the usual method for removal of an ovoid mass. The incisional length often

extends beyond the lesional border into uninvolved skin in an effort to avoid terminal dog-ears. Lenticular excision may be used when a transverse incision is necessary. Convex areas such as the cheek and forehead are susceptible to central flattening when lenticular excision and linear closure are used. Instead, circular excision and intradermal purse-string closure are particularly applicable. Radial folds may be evident initially and usually smooth out rapidly within weeks.[54] Staged excisions are possible with this method.

## CONGENITAL HEMANGIOMA

Unlike IHs, congenital hemangiomas are present at birth and do not exhibit postnatal growth. Two different lesions are recognized: rapidly involuting congenital hemangioma (RICH) and noninvoluting congenital hemangioma (NICH). Most lesions are solitary. There is no gender bias. These lesions are further distinguished from IH by staining negatively for GLUT-1.

RICHs undergo involution early, often beginning before birth. Involution is complete between 6 and 14 months of age.[55] RICHs commonly affect the head/neck and extremities.[55,56] On physical examination, the lesions are raised, firm, pink to violaceous with central depression or ulceration and a surrounding pale rim (Fig. 125-4). Coarse telangiectasias are often present.[55] After involution, the residual area often appears deflated and is not accompanied by the usual fatty residuum of IH.[56] Prenatal detection is possible because RICHs arise in utero.[55,57,58]

NICHs present as bossed, round-to-ovoid shape lesions in shades of pink to purple. The average diameter is 5 cm. There may be overlying coarse telangiectasia.[59] NICHs most commonly affect the head/neck (43%) followed by the limbs (38%) and trunk (19%). As the name implies, NICHs do not undergo involution and persist essentially unchanged.[59] Although they are tumors histologically, the static behavior of NICHs resembles that of a malformation.

RICHs and NICHs are fast-flow by Doppler evaluation. RICHs exhibit large flow voids near the surface and have areas that enhance inhomogenously on MRI. Arterial aneurysms and direct arteriovenous shunts can be seen on angiography.[56] NICHs and IHs are indistinguishable radiographically. The differential diagnosis of congenital hemangioma includes infantile fibrosarcoma.[60] Biopsy must be performed when the diagnosis is in question. The periphery of the lesion should be included in the biopsy specimen because lobular architecture is preserved here in congenital hemangioma.[56]

## HEPATIC HEMANGIOMA

Infantile hepatic hemangiomas (HHs) must be differentiated from so-called “hepatic hemangiomas” that are seen in adulthood. Adult “hepatic hemangiomas,” also referred to as “cavernous hemangiomas,” are actually venous malformations. Conversely, hepatic hemangiomas of infancy are true vascular tumors. HHs present in one of three recognizable patterns: focal, multifocal, and diffuse.[61] The majority of HHs are not life-threatening and involute without long-term sequelae.

Focal HHs are likely the hepatic equivalent of the cutaneous RICHs. Focal HHs are GLUT-1 negative. These tumors are fully grown at birth and involute faster than multifocal or diffuse lesions, which are typical infantile hemangiomas. There is no gender predilection. Cutaneous IHs are rarely present. They can be detected on antenatal ultrasound because they develop antenatally.[62] Transient thrombocytopenia and anemia are observed in some infants due to intralesional thrombosis. Contrary to previous beliefs, true Kasabach-Merritt phenomenon is not observed with focal HH. Most lesions are discovered as an abdominal mass in an otherwise healthy infant. A subset of these focal lesions, however, results in high-output cardiac failure due to the presence of macrovascular high-flow shunts (arteriovenous or portovenous). These shunts can cause steal accounting for blood-flow demands above and beyond the hypervascular tumor parenchyma. As the tumor involutes, the shunts usually close. The benefit of pharmacotherapy is unknown because these lesions are biologically distinct from cutaneous and hepatic infantile hemangiomas and involute rapidly. Nevertheless, medical therapy is attempted when treatment is indicated because it is less invasive and more widely available than embolization. Skilled pediatric interventional radiologists can frequently successfully embolize symptomatic shunts to improve heart failure while protecting major hepatic vessels. Resection is almost never indicated.

Multifocal HH is a true infantile hemangioma. This lesion was formerly known as *infantile hemangioendothelioma* because of histologic similarities with kaposiform hemangioendothelioma, a cutaneous tumor with a more aggressive behavior (see later). Females are more affected than males. These lesions are GLUT-1 positive. Most infants are asymptomatic and require no treatment. Multifocal HHs often come to

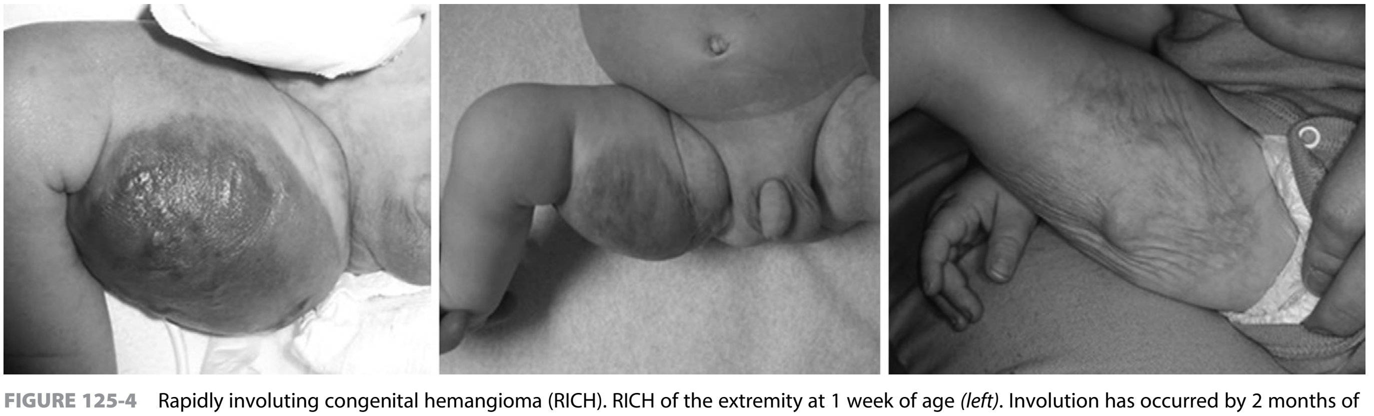

**FIGURE 125-4** Rapidly involuting congenital hemangioma (RICH). RICH of the extremity at 1 week of age *(left)*. Involution has occurred by 2 months of age *(middle)*. By 1 year of life the RICH has completely involuted *(right)*.

clinical attention while screening for visceral hemangioma on the basis of the presence of multiple cutaneous infantile hemangiomas. Occasionally, an infant can present in high-output cardiac failure due to macrovascular shunting. Corticosteroid is used to treat symptomatic infants in an effort to close shunts. Propranolol use is increasing.[63] Asymptomatic infants without shunts do not require therapy. Embolization is sometimes necessary to improve heart failure when the lesions are refractory to pharmacotherapy or if time is insufficient to allow for clinical improvement. Infants with multifocal HHs should be followed closely with serial abdominal ultrasonography until involution of their hemangiomas.

Diffuse HHs are the most feared. These lesions are also true IHs. There is a female gender bias. The normal liver parenchyma is almost completely replaced by innumerable compact, nodular tumors. The massive hepatomegaly can compress the inferior vena cava and thoracic cavity leading to abdominal compartment syndrome, respiratory distress, and multiorgan failure. All IHs express type 3 iodothyronine deiodinase, which converts thyroid hormone to its inactive forms, resulting in an acquired hypothyroidism.[20] This is most prevalent in diffuse HHs but is sometimes seen with multifocal HHs. Levels of type 3 iodothyronine deiodinase are proportional to tumor burden, placing infants with diffuse HHs (and occasionally larger multifocal HHs) at risk for hypothyroidism. Exogenous thyroid hormone replacement, often in large quantities, is necessary to prevent mental retardation and cardiac failure.[20] Serum TSH should be checked in all patients with larger multifocal and diffuse HHs. Hypothyroidism improves with tumor involution. Corticosteroid and increasingly propranolol are given for diffuse HHs to accelerate tumor involution. Hepatic transplantation may occasionally be indicated in some infants in extremis without time to wait for a response to pharmacologic therapy.[61] Other extraordinary maneuvers in the presence of respiratory distress and abdominal compartment syndrome include temporary abdominal enlargement with Silastic sheets or silos and low-dose vincristine treatment.[64,65]

HHs exhibit unique radiographic patterns, which aid in diagnosis. On computed tomography (CT), focal HHs are heterogeneous. Enhancement is usually centripetal with central sparing due to thrombosis or necrosis. Calcifications can also be evident and increase as the tumor involutes.[66] MRI of focal HHs shows a well-defined, solitary, spherical tumor (Fig. 125-5). It is hypointense relative to liver on T1 and hyperintense on T2. Centripetal enhancement is seen on gadolinium sequences. The solid, nonthrombosed portions at the periphery demonstrate intense homogeneous enhancement (see Fig. 125-5). Centrally there is heterogeneous enhancement due to necrosis, thrombosis, or intralesional hemorrhage.[61]

Multifocal and diffuse HHs on CT appear as multiple well-defined, spherical lesions. Multifocal HHs will have intervening normal hepatic parenchyma, whereas diffuse lesions nearly totally replace the liver. Without contrast the lesions are hypodense relative to the liver. They enhance centripetally with contrast. In comparison with focal lesions, there is no thrombosis, necrosis, or central sparing. The supraceliac aorta is usually dilated and tapers distally. Enlarged hepatic arteries and veins may indicate shunting.[66] Flow-voids can be seen in and around the lesions. On MRI, the lesions enhance homogenously and are hypointense relative to liver on T1 and hyperintense on T2 (see Fig. 125-5).[66]

Close follow-up is mandatory, especially in the first few months of life, because clinical deterioration is possible. The differential diagnosis of HH is broad and includes arteriovenous malformation, arterioportal fistula, mesenchymal hamartoma, hepatoblastoma, angiosarcoma, and metastatic neuroblastoma. Percutaneous needle or open biopsy should not be delayed in the face of diagnostic uncertainty.

## PYOGENIC GRANULOMA

Pyogenic granuloma is a benign, acquired vascular lesion of the skin and mucous membranes seen in children and pregnant women.[67] Pyogenic granulomas rarely occur before 6 months of age. The etiology is unknown. Most lesions are not associated with trauma or dermatologic conditions.[67] They develop as small erythematous papules that enlarge to 5 mm to 10 mm, mostly seen in the head and neck area (Fig. 125-6). The lesions bleed easily and are often pedunculated.[68] Treatment options include curettage, full-thickness excision with linear closure, shave excision and cautery, cautery alone, and laser phototherapy.[69] Silver nitrate can be used for small pyogenic granulomas. Larger lesions may require liquid nitrogen. Recurrence is high (45%) when pyogenic granuloma is not completely excised or ablated.[67]

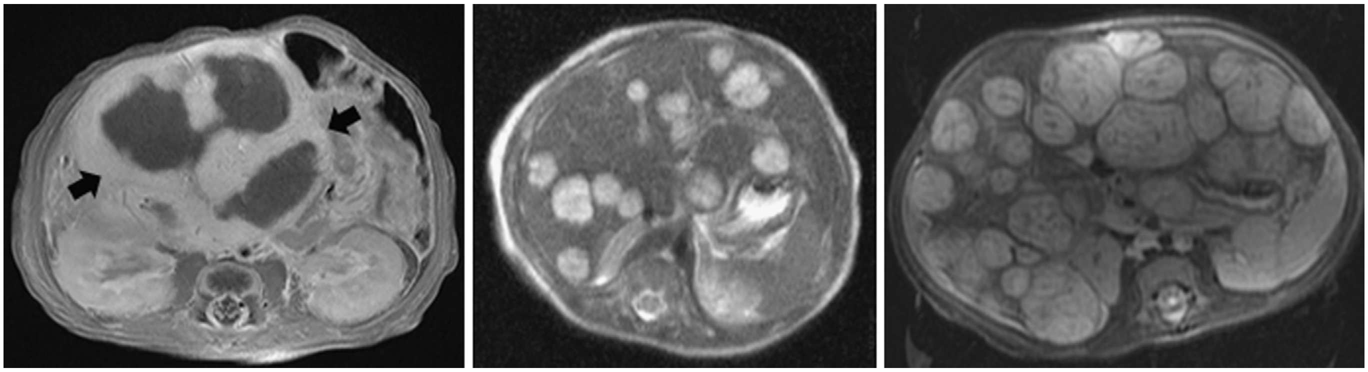

**FIGURE 125-5** Axial magnetic resonance images of hepatic hemangioma. T1 postcontrast appearance of a focal hepatic hemangioma *(left)*, which demonstrates peripheral enhancement *(arrows)* with sparing centrally due to thrombosis or scar. T2 images of multifocal hepatic hemangioma *(middle)*. Lesions are hyperintense relative to liver. T2 sequences of diffuse hepatic hemangioma show near-total hepatic parenchymal replacement *(right)*.

**FIGURE 125-6** Pyogenic granuloma.

## KAPOSIFORM HEMANGIOENDOTHELIOMA AND KASABACH-MERRITT PHENOMENON

Sixty years after the initial report by Kasabach and Merritt, we have learned that the findings of an enlarging vascular lesion and thrombocytopenia are never associated with infantile or congenital hemangioma.[70] Additional features of Kasabach-Merritt phenomenon include microangiopathic hemolytic anemia and a mild consumptive coagulopathy.[71] Kasabach-Merritt phenomenon occurs with more aggressive and invasive vascular tumors such as kaposiform hemangioendothelioma (KHE), kaposiform lymphatic anomaly (KLA), and tufted angioma (TA).[72–74] These tumors are biologically distinct from infantile hemangioma.[75] The term "Kasabach-Merritt phenomenon" is often used mistakenly to describe transient moderate neonatal thrombocytopenia seen with focal hepatic hemangioma (RICH), as well as a localized intravascular coagulopathy seen with some extensive venous and lymphatic malformations.

KHE and TA are typically present at birth, although they may also appear postnatally. There is an equal gender distribution. The tumors are unifocal and mostly located on the trunk and extremities. KHE can occur in the retroperitoneum. TA appears as erythematous macules; Kasabach-Merritt phenomenon may also be evident. KHE is more extensive than tufted angioma and can rapidly expand. KHE continues to proliferate into early childhood followed by incomplete regression in midchildhood. The superficial component of KHE appears in the skin and causes a red-purple discoloration with surrounding ecchymosis (Fig. 125-7). Generalized petechiae may be apparent due to profound thrombocytopenia (<10,000 platelets/μL). Infants with Kasabach-Merritt phenomenon are at risk for intracranial, pleural, pulmonary, peritoneal, and GI hemorrhage. Thrombocytopenia is unresponsive to platelet transfusion due to intralesional trapping. The prothrombin time and activated partial thromboplastin time are usually normal to mildly elevated. D-dimer is increased while fibrinogen is low. KHEs less than 8 cm in size are less likely to have Kasabach-Merritt phenomenon.[76]

Histopathology of KHE reveals aggressive infiltration of normal tissues by sheets or lobules of oval or spindled endothelial cells, dilated lymphatic channels, and slitlike vascular spaces filled with hemosiderin and compacted erythrocytes suggesting stasis.[74] When lymphatic channels predominate, the condition is called KLA. The microscopic appearance of TA shows tufts of capillaries in the middle to deep dermis.[77]

On MRI, KHE demonstrates enhanced signal on T2. Tumor margins are not well defined. The tumor does not respect tissue planes as it passes through skin down to muscle. There is stranding in the subcutaneous fat due to lymphatic obstruction or invasion. Feeding and draining vessels are small relative to tumor size. Osteolysis may be evident when KHE is adjacent to bone.[74] Imaging patterns are similar for TAs.

The treatment for KHE and TA with Kasabach-Merritt phenomenon is primarily medical. Due to its size and permeation of multiple tissue planes, KHE can rarely be resected safely. Drug options include corticosteroid, vincristine, or interferon. No treatment is uniformly effective. Vincristine has been associated with improved platelet counts.[71] Platelet transfusions should not be given unless there is active bleeding. Heparin should be avoided because it can stimulate tumor growth, exacerbating platelet trapping and thrombocytopenia. For KHE not associated with Kasabach-Merritt phenomenon, the decision to treat should be based on size, location, treatment side effects, and long-term complications (such as joint

**FIGURE 125-7** Kaposiform hemangioendothelioma (KHE) with Kasabach-Merritt phenomenon (KMP). KHE of the chest at 2 years of age *(left)*. Appearance at 6 years of age after treatment with vincristine and resolution of KMP *(middle)*. Tumor regression has resulted in joint contracture. Further involution at 8 years of age *(right)*.

contracture or myofascial pain syndromes).[76,78] All infants should be followed closely because mortality is high (20% to 30%). Previously quiescent tumors can be associated with recurrent Kasabach-Merritt phenomenon.

### OTHER RARE AND MALIGNANT VASCULAR TUMORS

Infants with cutaneovisceral angiomatosis with thrombocytopenia present with multiple red to brown cutaneous lesions in one or multiple sites. The skin lesions are present at birth and may be mistaken for infantile hemangioma. Infants may present with GI bleeding or hemoptysis. GI endoscopy demonstrates multiple, flat, red lesions. The lung parenchyma may also be involved. The lesions proliferate throughout early infancy. Histology shows variable endothelial hyperplasia. Due to the rarity of cutaneovisceral angiomatosis, optimal treatment has not been delineated. It is postulated that angiogenic inhibitors may be of benefit.[79]

Angiosarcoma is a rarely encountered aggressive malignancy in children. It is characterized by rapidly proliferating, infiltrating anaplastic cells derived from blood vessels. Angiosarcomas occur in soft tissue, bones, and viscera (liver, spleen, and heart). More common locations in the pediatric age group include the head, neck, and mediastinum.[80] Environmental exposure to arsenic and vinyl chloride can increase the risk of angiosarcoma. The most efficacious treatment is resection. Curative resections are rare given that many angiosarcomas are not limited to one anatomic area. They have a high rate of local recurrence and metastasis.

Kaposi sarcoma is a low-grade vascular neoplasm mediated by the human herpesvirus-8. The endemic/African clinical subtype is seen in the pediatric population. Unlike adults, children rarely present with cutaneous findings. Generalized lymphadenopathy may be their only presenting symptom. Definitive diagnosis requires histologic examination.[81]

## Vascular Malformations

Vascular malformations are localized or diffuse errors of development that may affect any segment of the vascular tree including arterial, venous, capillary, and lymphatic vessels. They are named on the basis of the predominant channel type and flow characteristics (Table 125-1). Slow-flow anomalies include capillary, lymphatic, and venous malformations; fast-flow lesions include arteriovenous malformations and arteriovenous fistulae. Vascular malformations, unlike vascular tumors, which expand postnatally, exhibit growth commensurate with that of the child. The prevalence of congenital vascular malformations is 1.2% to 1.5%.[21] Most vascular malformations are sporadic. Some inherited forms have been observed, usually in autosomal-dominant pattern. Multiple lesions are frequently observed in the familial forms.[82,83] Unfortunately, vascular malformations tend to enlarge during puberty and recur after treatment.

### EMBRYOLOGY AND DEVELOPMENT OF THE VASCULAR AND LYMPHATIC SYSTEMS

The development of the embryonic vascular system involves two separate but intimately connected processes: vasculogenesis and angiogenesis. Vasculogenesis is the formation of new vascular channels. Angiogenesis is the formation of new blood vessels from preexisting vessels by budding or branching. Around the third week of development, embryonic blood vessels begin developing when mesodermally derived hemangioblasts aggregate to form blood islands. The inner cells of the blood islands become hematopoietic stem cells. The outer layer differentiates into angioblasts, endothelial cell precursors. Proliferating angioblasts form a capillary-like network, which constitutes the primary vascular plexus. Angiogenesis occurs as this plexus is reorganized into a functional vascular system and new capillaries begin sprouting.[21,84]

The predisposition of endothelial precursors to differentiate into distinct channel types is imprinted early in embryogenesis by the detection of unique cell-surface markers.[85] Arterial endothelial cells express ephrin-B2, and venous endothelial cells express Eph-B4.[86] The recruitment of periendothelial cells stabilizes the vessel wall and allows for deposition of the extracellular matrix and basement membrane. Vascular endothelial growth factor, platelet-derived growth factor-$\beta$, angiopoietins and their receptors, and transforming growth factor-$\beta_1$ all play roles in vessel assembly and maturation.[87]

The lymphatic system begins its formation near the end of the sixth week, only after the establishment of functional blood vessels.[88,89] Lymphatics most likely arise from veins.[88–91] The earliest indication of the future lymphatic system is the appearance of lymphatic vessel endothelial hyaluronan receptor (LYVE-1) in a number of the endothelial cells lining the anterior cardinal vein.[88,92] A subpopulation of these LYVE-1 venous endothelial cells begin to express the transcription factor prospero-related homeobox 1 (PROX-1) on one side of the anterior cardinal vein.[91] As development continues, the number of PROX-1 cells increases and they ultimately migrate from the veins to establish primitive lymph sacs.[91] PROX-1 acts as a master regulator of lymphatic endothelial differentiation.[93] Lymph sacs are formed close to major veins throughout the embryo. Lymphatic endothelial cells sprout from the sacs to form the peripheral lymphatic network.[88,89] Lymphatic endothelial cells express vascular endothelial growth factor receptor-3, which via interaction with its ligand, vascular endothelial growth factor-C, promotes and guides the budding of lymphatic endothelial cells.[91,94]

### CAPILLARY MALFORMATIONS

Capillary malformation (CM) is the proper name for "port-wine stain." *Nevus flammeus neonatorum,* also known as "angel kiss" (on the forehead) and "stork bite" (on the nuchal area), are faint macular stains seen in 50% of Caucasian neonates. They are due to transient dilation of dermal vessels. These lesions predictably fade, whereas a CM does not. CMs affect 0.3% of infants with an equal sex distribution.[95] Most CMs are sporadic, but some are inherited in an autosomal dominant pattern.[96] They are present at birth and appear as flat, pink-red, cutaneous patches. They can be localized or extensive and can be found anywhere on the body (Fig. 125-8). CMs are composed of dilated, ectatic capillary-to-venule-sized vessels in the superficial dermis. Histopathology demonstrates a paucity of nerves surrounding these vessels.[97] With age, the vessels gradually dilate due to lack of innervation, explaining the observed darkening and nodular expansion.[98] Associated hypertrophy of the subcutaneous tissue, muscle, and

**FIGURE 125-8** Diffuse capillary malformation with overgrowth. Posterior view shows the capillary malformation involving the right arm, trunk, and left leg. Soft tissue overgrowth of the left leg is apparent.

bone underlying a CM is common, and when located on an extremity a limb length discrepancy may be apparent.

Occasionally, the presence of a CM signals an underlying structural abnormality. A CM overlying the cervical or lumbar spine may be associated with an occult spinal dysraphism or tethered cord. Encephalocele or ectopic meninges may be found beneath an occipital CM. Children with CMs in the distribution of the ophthalmic and maxillary branches of the trigeminal dermatomes should be evaluated for Sturge-Weber syndrome. This syndrome consists of a facial CM with ipsilateral ocular and leptomeningeal vascular anomalies. Extensive leptomeningeal involvement can manifest as seizures, contralateral hemiplegia, and variable motor and cognitive delays. CMs are also seen in complex-combined vascular malformations.

Treatment for CM is indicated primarily for cosmetic purposes. Vascular-selective pulsed dye lasers cause photothermolysis of the CM and will improve the appearance by lightening the color of the lesion in 70% of patients.[99] Early, thin CMs such as in the neonate respond well especially when located on the lateral aspect of the face. Complete eradication of the CM is difficult, and despite multiple laser sessions some lesions continue to darken.[100] The timing of therapy remains controversial. Initiating treatment before 6 months of age is an option and short-term follow-up appears promising.[101] Surgical intervention may be required for associated soft tissue hypertrophy and limb length discrepancy.

### Cutis Marmorata Telangiectatica Congenita

Cutis marmorata telangiectatica congenita (CMTC) is a rare vascular anomaly.[102] The involved skin is bluish to deep purple in color with a characteristic reticular vascular pattern. Cutaneous marbling is apparent at room temperature and becomes more pronounced with lower temperatures and crying. The affected skin is depressed and can ulcerate and bleed. CMTC occurs in a localized, segmental, or generalized distribution. It is more frequent on the trunk and lower extremities.[103,104] Histopathology reveals dilated capillaries in the papillary dermis and proliferation of blood vessels in the reticular dermis with occasional dilated veins and venous lakes.[105] It is sporadic and has no gender bias. The etiology of CMTC is unknown.

The clinical course of CMTC is benign with partial regression of the capillary stains in the first year of life, which continues into adolescence. Atrophy, pigmentation, and prominent veins often persist into adulthood. CMTC has been “associated” with abnormalities of many kinds including neurologic, skeletal, and cardiovascular.[106] Stenosis of the common iliac and femoral arteries with resultant claudication has been observed in children with CMTC of the lower extremity.[106,107]

### Telangiectasia

Tiny acquired capillary vascular marks, commonly referred to as *spider nevi* or *spider telangiectasias,* can appear on children in the preschool and school-aged years. There is no gender bias, and epidemiologic studies suggest that they may be present in nearly half of all children.[21] Spontaneous resolution is possible, but pulsed-dye laser can eradicate the lesion.

Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) is an autosomal dominant disorder that commonly results from mutations in endoglin, activin receptor-like kinase 1, or rarely Smad4. These genes encode proteins that modulate transforming growth factor-β signaling in vascular endothelial cells.[108] Mutations lead to the development of fragile telangiectatic vessels and arteriovenous malformations (AVMs). There is marked intrafamilial phenotypic variation. A definite diagnosis of hereditary hemorrhagic telangiectasia is made in the presence of at least three separate manifestations: spontaneous recurrent nosebleeds; mucocutaneous telangiectasia (frequently located on the fingertip pulps, lips, oral mucosa, or tongue); visceral involvement (GI tract, pulmonary, hepatic, cerebral, or spinal AVMs); and family history.[109] Presentation with spontaneous recurrent nosebleeds before school age is most common. Approximately one third of patients have chronic anemia due to lower GI bleeding, which usually becomes apparent in adulthood.[108] In infancy and early childhood, hepatic AVMs of hereditary hemorrhagic telangiectasia can be mistaken for hepatic hemangiomas.

## LYMPHATIC MALFORMATION

Lymphatic malformations (LMs) are frequently called “lymphangiomas,” erroneously suggesting a proliferative tendency. LMs are not tumors. Their pathogenesis is unknown. LMs of the neck and axilla may be due to failure of lymphatic sacs to communicate with the central venous system. Sequestration of lymphatic buds may account for peripheral lesions. Typical LMs seem to be sporadic. Heritable forms of lymphedema, also a type of LM, have been identified.[82]

LMs are classified as microcystic, macrocystic, or combined macrocystic and microcystic lesions (Table 125-1). The difference is clinically and therapeutically useful. Size is

distinguished by whether or not the cystic cavity can be successfully aspirated, resulting in visible decompression. LMs may be focal, discrete masses or infiltrate multiple anatomic locations.

LMs are usually apparent at birth and tend to occur in areas of major lymphatic channels, especially the cervical and axillary locations (Fig. 125-9). They can be found in all tissues or organ systems with the exception of the central nervous system. LMs most commonly appear as ballottable masses with normal overlying skin, although a blue hue may result if large underlying cysts are present. Dermal involvement can appear as puckering or deep cutaneous dimpling. LMs in the subcutis or submucosa appear as tiny clear to white vesicles. Intravesicular bleeding is evidenced by dark red, dome-shaped nodules. Histologically, LMs appear as thin-walled vascular channels lined by lymphatic endothelial cells, which are immunopositive for podoplanin (D2-40) and LYVE-1.[110] The lumens may be empty or filled with a proteinaceous fluid containing macrophages and lymphocytes.[111]

Increasingly, mass lesions and vascular anomalies are detected on antenatal ultrasound.[57,112] The term *cystic hygroma* is used in perinatology to describe a lymphatic anomaly distinct from LMs seen in postnatal pediatrics. A fetal cystic hygroma consists of collections of lymphatic fluid due to a maldevelopment of the cervical lymphatic sacs. Nuchal thickness greater than or equal to 2.5 mm, measured between 10 and 14 weeks gestation, is considered abnormal. Some authors reserve the term cystic hygroma for only those with visible septations and refer to the rest as *simple increased nuchal translucency.*[112] A fetal cystic hygroma ranges from 6.5 to 7.9 mm.[112,113] The finding of a first-trimester septated cystic hygroma has definitively been shown to be associated with a higher risk of aneuploidy, cardiac malformation, and perinatal death over simple increased nuchal translucency.[112] Chromosomal abnormalities such as Down syndrome or Turner syndrome are observed in 50% of fetuses with cystic hygroma; however, 17% to 25% of these pregnancies will result in the birth of a healthy newborn.[112,113] Resolution of a fetal cystic hygroma improves the chance of a normal outcome to as high as 95%.[112]

Fetal cystic hygroma and simple increased nuchal translucencies are always situated in the posterior neck and can extend down the entire dorsum of the fetus.[112] This posterior location is distinct from cervical LMs located in the submandibular, supraclavicular, and anterior/lateral neck regions (see Fig. 125-9). LMs are usually not detected until the second or third trimesters, unlike the more concerning fetal cystic hygroma, which is seen by 14 weeks.[57] Unfortunately, because of continued use of the imprecise term cystic hygroma, some families receive misinformation regarding their true diagnosis and conclude incorrectly that their fetus cannot survive or will have chromosomal abnormalities. Antenatal consultation with pediatric specialists knowledgeable about vascular malformations can benefit families. Reassurance can be given that a lateral or anterior LM is not associated with chromosomal or developmental disorders. It also provides an educational opportunity to discuss the concerns facing a child with a cervicofacial LM.

Large cervicofacial LMs detected in utero should raise concern about potential airway obstruction leading to asphyxia in postnatal life. Results from prenatal ultrasound and fetal MRI allow for assessment of potential airway difficulties at birth. When the risk of airway obstruction is high, consideration should be given to delivery of the fetus via an ex-utero intrapartum treatment (EXIT) procedure.[114] Although the EXIT procedure had early popular appeal, experience has shown that most LMs are compressible, allowing for intubation after delivery in the face of airway compromise. Differentiating LM from teratoma, which is usually firm and noncompressible, is an important distinction in delivery planning.

Fetal pleural, pulmonary, and peritoneal lymphangiectasia may also present in utero as pleural effusions or ascites. These may be isolated or may be a manifestation of Turner, Noonan, or other syndromes. Secondary hydrops fetalis may develop secondary to large pleural effusions. Diagnosis is confirmed when a tap shows more than 80% lymphocytes on the

**FIGURE 125-9** Cervical lymphatic malformation (LM). Prenatal magnetic resonance image shows a fetus with a right cervical macrocystic LM *(left, arrowhead).* Postnatal appearance of the same infant at 1 week of age *(right).*

differential cell count. After chromosomal studies, fetal intervention, when indicated, consists of repeated taps or shunting into the amniotic fluid.[115–117]

The morbidity of LMs is anticipated by anatomic location and extent. Proptosis can result from periorbital and orbital lesions. Facial LMs can be associated with skeletal overgrowth, macroglossia, and macrocheilia.[10] Tongue and oral floor lesions can cause chronic airway problems, recurrent infection, and functional issues related to speech, oral hygiene, and malocclusion.[118] Cervical or axillary LMs can signal an associated mediastinal LM. Chylous pericardial and pleural effusions can be associated with diffuse thoracic lymphatic anomalies or rare abnormalities of the thoracic duct or cisterna chyli. GI LMs can cause chronic protein-losing enteropathy resulting in profound hypoalbuminemia. Pelvic lesions can cause recurrent infections, constipation, and bladder outlet obstruction. LMs in the extremity may result in overgrowth and limb length discrepancy. Gorham-Stout syndrome is a rare, potentially fatal form of skeletal and soft tissue LM. It is characterized by the gradual and often complete resorption of one or multiple skeletal elements (hence the synonym “vanishing bone disease”), which may result in pathologic fractures.[111]

Lymphedema, also a type of LM, is characterized by localized accumulation of protein-rich fluid in the superficial, interstitial space causing enlargement of the subcutaneous tissue; over time, deposition of adipose and fibrous tissue further increases limb volume.[119] It may be primary (idiopathic) or secondary (acquired). The vast majority of patients with primary lymphedema have no family history, but a genetic basis has been found in some families.[120] Milroy disease, a congenital form of lymphedema, is an autosomal dominant condition linked to chromosome 5q35.3, which codes for a mutation in the vascular endothelial growth factor receptor 3 gene.[121,122] Sporadic forms also occur. Greater than 90% of patients with Milroy disease present with lymphedema below the knees.[83] Intrauterine pleural effusion and hydrops fetalis have been observed.[123,124] Skin biopsy from the swollen feet of patients with Milroy disease shows abundant skin lymphatics suggesting malfunction.[125] Meige disease typically presents in puberty. It is an autosomal dominant disorder with variable penetrance and phenotype. Families with lymphedema distichiasis (double row of eyelashes) have been found to have a mutation in transcription factor FOXC2, which plays a role in somite development.[126–128] Systemic involvement such as intestinal lymphangiectasia, ascites, pleural or pericardial effusions, and pulmonary lymphangiectasia have been observed in patients with primary extremity lymphedema.[125]

Ultrasonography is useful to characterize superficial and well-localized LMs. MRI allows for determination of extent and type (microcystic versus macrocystic) (Fig. 125-10). LMs are hyperintense on T2-weighted and turbo-STIR images.[129] Fluid-fluid levels are often seen in macrocystic LMs as a result of layering of blood, protein, or both. Cyst walls and septae enhance with contrast.[36] Microcystic LMs show an intermediate signal on T1 and intermediate to high signal on T2 spin echo sequences.[129] Conventional contrast lymphangiography can be useful for characterization of lymphatic anomalies of the thoracic duct and chylous effusions, allowing for localization of abnormal channels or sites of leakage.[130] It has largely been abandoned in small children due to technical difficulties and morbidity.[131] Lymphoscintigraphy is minimally invasive and safe in infants and children.[132]

The indications for treatment of LMs vary with extent and location. The most common complications requiring treatment include bleeding and infection. Intralesional bleeding, either spontaneous or due to local trauma, can cause expansion. Previously imperceptible lesions may suddenly appear. On physical examination, the LM may be firm and ecchymotic. Treatment is focused on pain control. Intralesional bleeding may transform macrocystic lesions into microcysts.

LMs, unlike other vascular anomalies, may swell in response to systemic viral or bacterial infection. Usually, there are no consequences of this passive engorgement. If accompanied by the rapid onset of localized swelling, tenseness, erythema, and systemic signs of infection, antibiotics (oral or intravenous depending on severity) should be initiated. Frank septic shock may be the presenting symptom in patients with occult retroperitoneal and mesenteric LMs. Bacterial cellulitis is a serious complication of cervicofacial LM due to the risk of airway obstruction, possibly requiring emergent intubation.

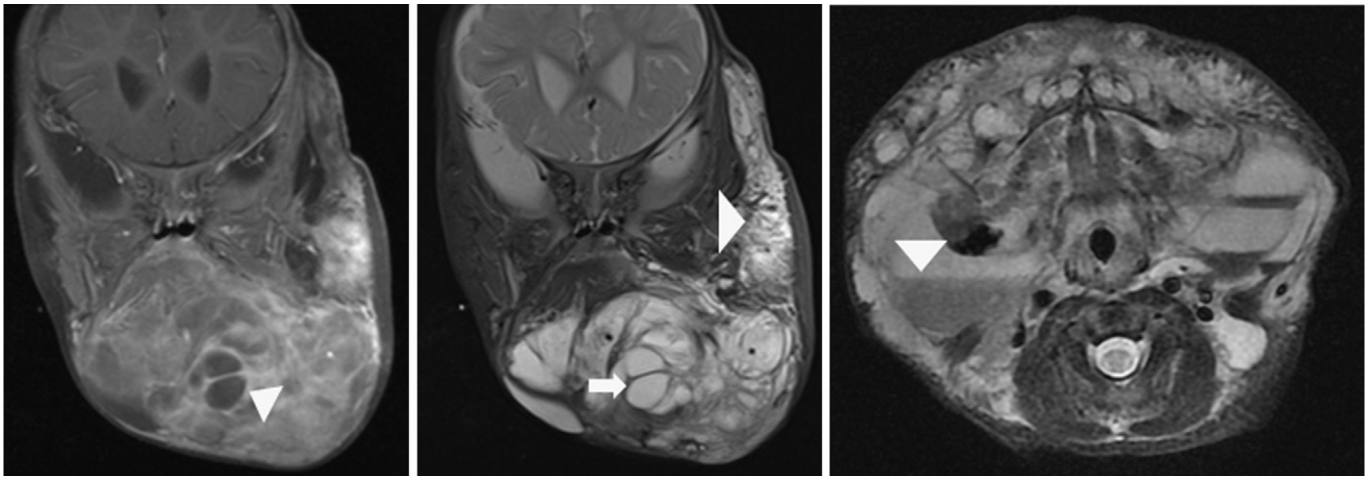

**FIGURE 125-10** Magnetic resonance image of cervicofacial lymphatic malformation (LM). Coronal T1 image of an extensive cervicofacial LM *(left)*, which shows contrast enhancement of septations and rims of cysts *(arrowhead)*. Coronal T2 image *(middle)*, which demonstrates macrocysts *(arrow)* and microcysts *(arrowhead)*. Macrocystic component with a fluid-fluid level *(right, arrowheads)*.

LMs may be treated with sclerotherapy, surgical resection, or both. Sclerotherapy works well for macrocystic LMs and in many cases may render lesions undetectable. Common sclerosants include pure ethanol, sodium tetradecyl sulfate, and doxycycline. Technically, sclerotherapy is usually straightforward. The cystic cavity is entered by direct puncture, and the fluid is aspirated. The needle is maintained in situ, and the sclerosant is injected. Multiple punctures, aspirations, and injections are often performed. Ultrasound guidance is useful. Staged sessions may be necessary for larger lesions. Sclerotherapy preceding resection can shrink LMs, allowing for less morbid surgical procedures. LMs may reexpand after treatment, requiring additional procedures. Microcystic LM is less responsive to sclerotherapy. Superficial lymphatic vesicles can be treated with local intravesicular injection to improve leakage. Complications of sclerotherapy to be avoided include injury to adjacent nerves, necrosis of overlying skin, and cardiotoxicity related to overdose.

The only potential for a definitive cure of LM is surgical resection. Operations near vital structures can be long and tedious. Serial, staged excisions are often necessary, while ensuring complete resection in a given anatomic area as much as possible, because repeat excision of the same area is technically difficult and increases morbidity.[2] Dissection in previously sclerosed areas can be challenging because of fibrosis and scarring, although some authors have found excision after sclerotherapy to be easier.[133] General principles regarding surgical procedures include (1) limiting resection to a defined anatomic region; (2) minimizing blood loss and planning for replacement; (3) performing closed suction drainage of the resection cavity. The "recurrence" rate after macroscopically complete resection ranges from 17% to 40%.[134] The perceived recurrence is thought to be due to growth and expansion of affected lymphatics in the remaining, seemingly normal, yet involved tissue. Sometimes cutaneous "warty" lymphatic vesicles develop in the scar. These can be treated easily with intravesicular sclerotherapy, cauterization, laser coagulation, or excision.

## VENOUS MALFORMATION

Venous malformations (VMs), often incorrectly referred to as *cavernous hemangiomas,* are slow-flow lesions. They may be seen at birth or become apparent later depending on location. VMs are most common in the skin and soft tissues but can be located anywhere in the body (Fig. 125-11). They present in a heterogeneous fashion including simple varicosities and ectasias, discrete spongy masses, or a diffuse network of complex channels that permeate an organ or tissue. VMs grow proportionately with the child and tend to expand slowly with time. Some VMs will dilate when placed in a dependent position or during a Valsalva maneuver. Phlebothrombosis is common and may be painful. Phleboliths can also be easily palpated in many VMs. Histologically, a VM is composed of thin-walled, dilated abnormal channels with clumping of vascular smooth muscle cells. There is often evidence of clot formation and fibrovascular ingrowth.

Most VMs are sporadic (90%). Somatic mutations in the tyrosine kinase receptor TIE2 have been discovered in approximately 50% of sporadic VMs.[135] An autosomal dominant inheritance pattern occurs in cutaneomucosal venous malformation, which accounts for only 1% to 2% of lesions. Mutations in the *TEK* gene, which encodes TIE2, have been identified.[136,137] Cutaneomucosal VMs are dome shaped and range in size from tiny to several centimeters. Glomuvenous malformations account for 5% of lesions and are also inherited in an autosomal dominant fashion.[83] The lesions are mostly superficial and occur as multiple blue to deep-purple nodules or confluent, cobblestone-appearing plaques frequently on the trunk or extremities.[45] They are caused by loss-of-function mutations in glomulin, which derails vascular smooth muscle cell differentiation.[138]

Complications of VMs are related to their location. Cervicofacial VMs are often unilateral. They may distort facial features and cause exophthalmia, dental malalignment, and obstructive sleep apnea. Limb length discrepancy can be seen in an affected limb. VMs involving the synovial lining of the

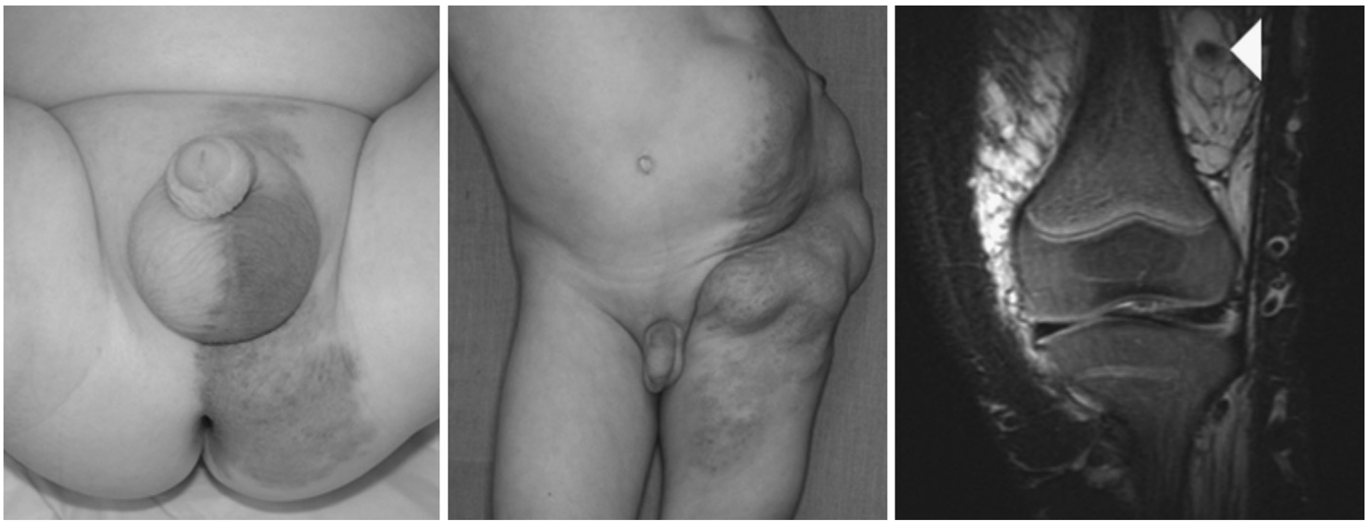

**FIGURE 125-11** Venous malformation (VM). VM of the perineum *(left)*. Truncal VM *(middle)*. Coronal fast spin-echo inversion recovery magnetic resonance image of a VM of the knee *(right)*. There is diffuse involvement of the quadriceps muscle. A phlebolith is present *(arrowhead)*.

knee can cause episodic pain due to repeated bloody effusions. Hemarthrosis may lead to degenerative arthritis.[2]

VMs of the GI tract can be solitary or multifocal. They can involve any or all layers of the bowel wall and can be small or massive. The majority of GI VMs occur as transmural lesions of the left colon and rectum with variable local extension into pelvic structures.[2,53,139] GI bleeding may be the initial symptom. Discoloration in the perineum may indicate an underlying rectal VM. Mesenteric and portal venous anomalies may be associated with GI VMs. A rectal VM associated with ectasia of mesenteric veins is a risk factor for portomesenteric venous thrombosis.[140]

Blue-rubber bleb nevus syndrome (BRBNS) represents a rare disorder consisting of multifocal VMs that affect the skin and GI tract primarily. This should not be confused with benign or malignant blue nevi. The cutaneous lesions of BRBNS are VMs, not true nevi; they are often quite numerous (Fig. 125-12). They range in color from blue to purple and are commonly found on the palms and soles of the feet.[141] There is often a large dominant VM. Diagnosis of GI VMs is generally based on endoscopic findings. As with other GI VMs, chronic bleeding and anemia can result. Intussusception may also occur.[142]

VMs with phleboliths and those that are large ($\geq$10 cm$^2$) and/or deep are more likely to cause a localized intravascular coagulopathy.[143] Constant activation of coagulation caused by stasis and stagnation of blood within the malformation leads to the consumption of coagulation factors. Thrombin is produced and converts fibrinogen into fibrin. Fibrinolysis elevates fibrin degradation products and can be measured by obtaining D-dimer levels.[144] Occasionally, fibrinogen levels are also low.[143,145] Coagulation studies (prothrombin time, activated partial thromboplastin time, and D-dimer and fibrinogen levels) should be reviewed before invasive procedures in patients with extensive VMs. Low-molecular-weight heparin can be given during the perioperative period to improve the hematologic status for patients with elevated D-dimer levels. Platelet counts can be slightly decreased in the 100,000 to 150,000/mm$^3$ range (unlike the marked thrombocytopenia seen with Kasabach-Merritt phenomenon).[144]

Imaging modalities useful for the diagnosis of VM include ultrasonography, MRI, and venography. MRI is the most informative. Lesions are hyperintense with T2 sequences (see Fig. 125-11). Identifiable spaces separated by septations can be seen. The vascular spaces of VM enhance with contrast, whereas LM does not; the exception to this rule is an LM with intralesional bleeding. Phleboliths are often seen as signal voids on all sequences. High-flow vessels are not seen within or around the lesions. Magnetic resonance venography helps delineate deep venous anatomy, especially of the extremity.[36] Doppler ultrasonography reveals soft, compressible masses with monophasic low velocity.[45]

The indications for treatment of VMs include pain, functional loss, bleeding, and appearance. No known systemic pharmacologic agents induce involution of vascular malformations, and therefore they are not used for VMs. Compression therapy aims to reduce swelling and pain in diffuse VMs of the extremities. Sclerotherapy can be effective for symptomatic VMs. Sclerosing agents cause direct endothelial damage, thrombosis, and scarring. Large VMs are accessed by direct puncture under fluoroscopy. Compression and tourniquets can be used to limit venous drainage and minimize systemic delivery of the sclerosant. Staged sessions and occasional embolization of large draining channels are sometimes necessary. Possible local complications are blistering, full-thickness cutaneous necrosis, and nerve injury.[146] Systemic complications include hemolysis, sudden pulmonary hypertension, and cardiac and renal toxicities. Unfortunately, many VMs recanalize and expand after treatment, thus requiring additional procedures.[147] Focal VMs can often be successfully excised. Sclerotherapy before resection may allow removal of larger lesions.[146] Staged subtotal resections may be necessary. Transfusion dependent anemia due to GI VMs should be evaluated for surgical resection. Multifocal VMs of BRBNS can be removed via wedge excision and polypectomy by intussusception of successive lengths of intestine. Intraoperative enteroscopy aids to identify location of all lesions. This technique provides the only chance for cure.[141] Diffuse colorectal VMs causing significant bleeding may be treated with colectomy, anorectal mucosectomy, and coloanal pull-through.[148]

## ARTERIOVENOUS MALFORMATION

Arteriovenous malformations (AVMs) are fast-flow malformations characterized by abnormal collections of arteries and veins that directly communicate (shunts), thus bypassing

**FIGURE 125-12** Blue rubber bleb nevus syndrome. Characteristic dome-shaped plantar lesions *(left)*. Serosal view of venous malformations (VMs) in the small intestine *(middle)*. Endoluminal appearance of a VM in the colon *(right)*.

the high-resistance capillary bed. The shunts comprise the epicenter of the AVM, called the *nidus*. Intracranial AVMs are more common than extracranial AVMs. Areas affected by extracranial AVMs in decreasing frequency are the head and neck, limbs, trunk, and viscera. AVMs may be apparent at birth but are often misdiagnosed initially as a capillary malformation or infantile hemangioma due to pink staining in the overlying skin (Fig. 125-13). The diagnosis becomes more obvious later, particularly during adolescence, when they are more likely to expand.[149] On palpation, the area may be warm with an underlying palpable thrill. Manual compression of feeding arteries and draining veins results in a slowing of the heart rate known as *Nicoladoni sign*.[150] The natural history of AVMs can be documented by a clinical staging system (Table 125-2).[151] As an AVM grows, it can become more mass-like, causing ulceration of the overlying soft tissue, bleeding, pain, or heart failure. Lower-extremity AVMs often develop curious, dry, brown-violaceous-colored plaques.[2]

The majority of AVMs are sporadic. Some forms are heritable (e.g., the autosomal dominant disorder capillary malformation-arteriovenous malformation [CM-AVM], which is caused by mutations in *RASA*).[152] The hallmark of CM-AVM is the randomly distributed, pink to red, multifocal CMs accompanied by a fast-flow vascular lesion such as an intracranial or extracranial AVM, Parkes Weber syndrome (PWS), or a vein of Galen aneurysmal malformation in one third of patients.[153]

Ultrasonography and Doppler imaging can quickly detect the fast flow of an AVM. Dilated feeding arteries and draining veins can be seen as areas of contrast enhancement on CT, signal flow voids (black tubular structures) on spin echo MR images, and signal enhancement (white tubular structures) on gradient sequences including MR angiography. Ability to discern the nidus is variable. Unlike infantile hemangioma, there is no obvious parenchymal mass.[36] Muscle enlargement, bony changes, and increased fat may be seen.

**TABLE 125-2**
**Clinical Staging System for Arteriovenous Malformation**

| *Stage* | *Clinical Findings* |
|---|---|
| I (Quiescence) | Pink-blue warm stain, shunting on Doppler examination |
| II (Expansion) | Enlargement, pulsation, thrill, bruit, tense veins |
| III (Destruction) | Dystrophic skin changes, ulceration, bleeding, pain, or tissue necrosis |
| IV (Decompensation) | Cardiac failure |

Superselective angiography has its role at the time when treatment is planned and often more clearly delineates the nidus (see Fig. 125-13).[2]

Many AVMs require treatment as a result of continued lifelong expansion. Angiographic embolization alone or in combination with surgical excision is the mainstay of treatment. Controversy exists about when to intervene. In the early stages, the full extent of the lesion may not be appreciated at the time of resection, which could result in local recurrence and complicate future procedures. Meanwhile, a well-localized stage I AVM is often more amenable to resection and complete removal. During infancy, treatment is rarely indicated except in rare cases of postnatal heart failure. After a complete diagnostic evaluation, infants and children should be followed annually. Extremity AVMs can result in limb length discrepancy. Stage I and II AVMs are generally observed. Treatment is usually delayed until symptoms indicative of stage III develop: tissue destruction, pain, bleeding, or ulceration. For treatment initiated at any age or stage, proximal feeding arteries must never be ligated or embolized. The nidus of the AVM tends to recruit nearby arteries leading to ongoing growth and continued progression when feeders are ligated.[25] Furthermore, despite temporary improvement

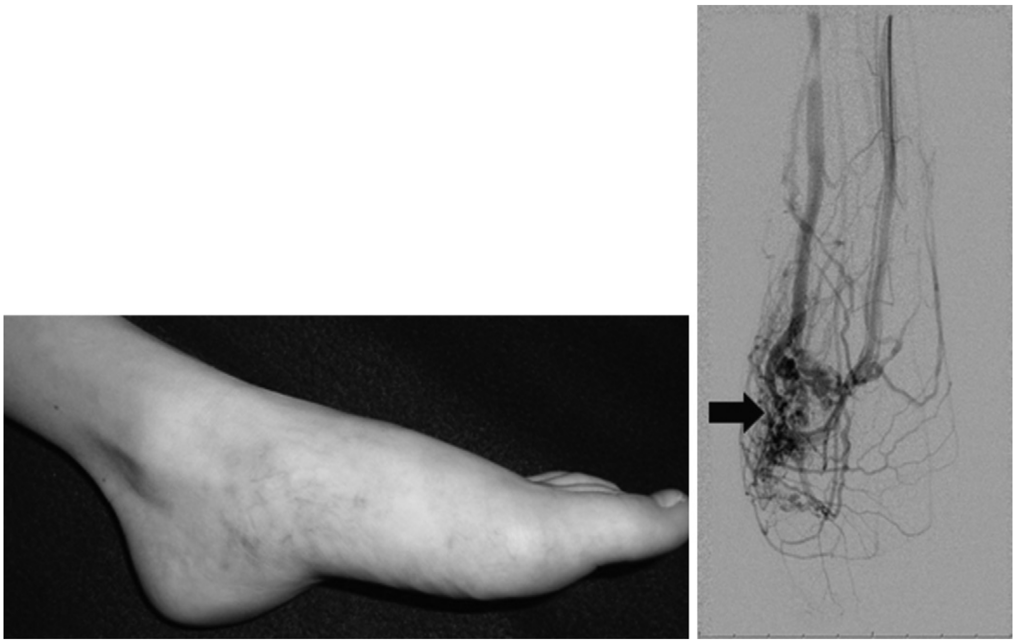

**FIGURE 125-13** Arteriovenous malformation of the foot. AVM of the foot shows faint pink staining of the overlying skin *(left)*. Angiographic appearance of the AVM *(right),* which delineates the nidus *(arrow).*

in bleeding and heart failure, occlusion of feeding arteries precludes future embolization.

All efforts to treat an AVM should be directed toward the nidus. Superselective arterial or retrograde venous embolization can decrease pain and bleeding. Embolic agents include destructive liquids such as ethanol, glue, onyx, particles, or coils. Repeated and staged embolizations are usually necessary. Symptomatic improvement is only temporary because it is nearly impossible to occlude all microscopic arteriovenous shunts. The preferred strategy consists of arterial embolization of the nidus followed by surgical resection 2 to 3 days later. Preoperative embolization decreases intraoperative blood loss but does not decrease the extent of resection. Complete removal of the nidus and overlying soft tissue and skin is the goal; this will decrease recurrence. Resection extent is determined by reviewing the earliest radiologic imaging, preferably before any treatment. Primary closure is sometimes possible. More frequently, though, skin grafting or tissue transfer is necessary. The best results are seen with well-localized AVMs. These patients must be followed closely with physical examination and MRI or ultrasonography because the recurrence rate is high. In some cases, AVMs are unresectable. Amputation is a last resort for debilitating AVMs of the extremities.[2,25,45] Drugs that inhibit angiogenesis and extracellular matrix remodeling are being explored given poor outcomes with other modalities.[154]

**FIGURE 125-14** Capillary-lymphatico-venous malformation of the lower extremity. Note the soft tissue hypertrophy and lateral position of the capillary malformation. Acral anomalies are also present.

# Complex-Combined Vascular Malformations

Like single-channel-type vascular malformations, combined lesions are also categorized as slow-flow and fast-flow (See Table 125-1). These disorders are usually associated with hypertrophy and skeletal overgrowth.

## CAPILLARY-LYMPHATICOVENOUS MALFORMATION

Klippel-Trenaunay syndrome is a well-known eponym for capillary-lymphatico-venous malformation (CLVM).[2] It is often incorrectly called "Klippel-Trenaunay-Weber syndrome," suggesting a relation to PWS, a fast-flow malformation consisting of a capillary-arteriovenous malformation in association with limb hypertrophy. CLVM is usually diagnosed at birth by the presence of an enlarged lower extremity with lateral capillary malformations (CMs), lymphatic vesicles, and visible varicosities. CLVM can be suspected on antenatal imaging but often cannot be confirmed until delivery because congenital lymphedema, PWS, and CLOVES syndrome (*C*ongenital, *L*ipomatous, *O*vergrowth, *V*ascular malformations, *E*pidermal nevi and *S*pinal/skeletal anomalies/scoliosis) are included in the differential diagnosis.

CLVM most frequently involves the lower extremity (88%) but can involve the upper extremity (29%) and trunk (23%).[155] The deformity can range from barely perceptible capillary staining with mild soft tissue overgrowth to a grotesquely deformed limb (Fig. 125-14). Soft tissue and skeletal hypertrophy of the involved limb predominate. CLVM of the torso and upper extremities may involve the mediastinum or retropleural space. The affected extremity may be short or hypotrophic in 10% of patients. Lymphatic anomalies include lymphedema or lymphatic cysts (macrocysts or microcysts). Lymphatic vesicles often erupt through the CM. LMs are common in the buttock, perineum, and pelvis. Persistent embryonic veins are found in patients with lower extremity CLVM; the most common is the marginal vein of Servelle. Branches of the marginal vein become prominent due to incompetent valves. The deep venous system may be absent.

Pelvic, perineal, and genital involvement is common in CLVM. The vascular malformations may cause bladder outlet obstruction. In some infants and children, extension of an LM through the inguinal canal is mistaken for an inguinal hernia. LMs in the perineum can serve as an infectious source. The rectum is variably involved. Portomesenteric venous thrombosis and portal hypertension have been observed in some patients.[156] Venous abnormalities of the lower limbs often extend into the pelvis, connecting anomalously with the femoral and iliac veins and inferior vena cava. This aberrant connection can result in pulmonary embolism in 4% to 25% of cases.

MRI and MR venography (MRV) provide the foundation for describing the type, location, and extent of the vascular malformation components of CLVM. Hypertrophic fatty tissue in areas of overgrowth can be evaluated (Fig. 125-15). MRV delineates the normal state of the veins and reliably demonstrates the anomalous venous channels present in CLVM of the extremity. The lateral marginal vein of Servelle can be seen coursing along the lateral calf and thigh (see Fig. 125-15). Microcystic LMs can be seen in the abdominal wall, buttock, and extremity, whereas macrocysts are seen in the pelvis and perineum. Plain radiographs are used to evaluate and follow limb-length discrepancies. Venography may be used to map

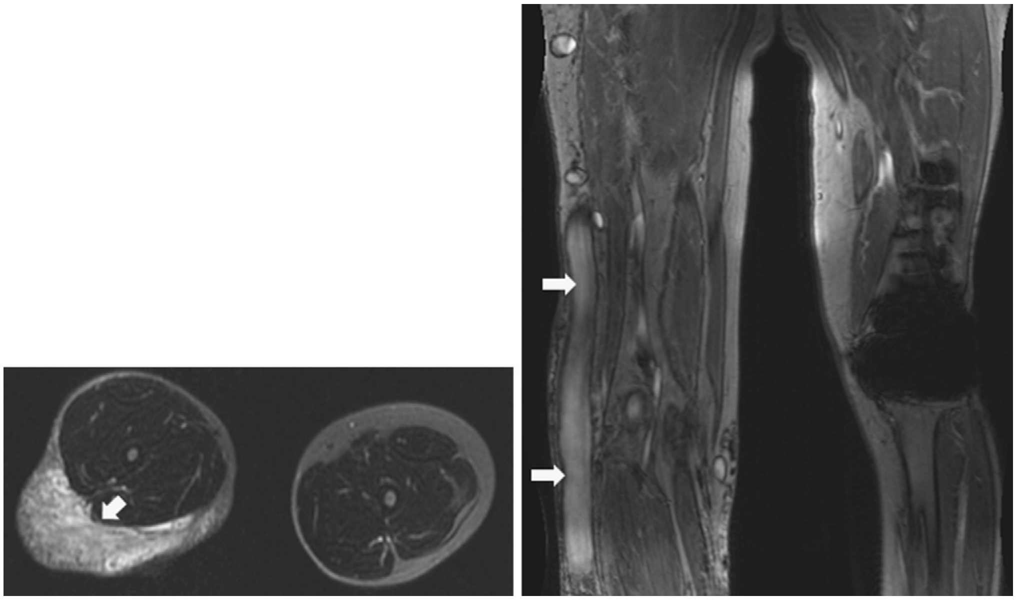

**FIGURE 125-15** Imaging of lower extremity capillary-lymphatico-venous malformation (CLVM). Axial T2 view of CLVM of the right leg *(left)* shows predominantly extrafascial soft tissue overgrowth and microcystic lymphatic malformation *(arrow)*. Magnetic resonance venogram *(right)* depicts the lateral marginal vein of Servelle *(arrows)*.

the venous drainage of the extremity when resection or sclerotherapy is being considered.

In general, treatment for CLVM is conservative and focused on symptoms. Compression therapy is the mainstay of conservative treatment. It can be delayed until the child is walking. Lymphatic oozing may improve with compression therapy. Sclerotherapy can be used to treat macrocystic LMs and venous components. Intradermal lymphatic vesicles can also be sclerosed. Persistent embryonic and other anomalous veins may be amenable to endovenous laser ablation or resection. Veins with direct connections to the femoral or iliac veins or inferior vena cava should be considered for pre-emptive ablation or resection to prevent pulmonary embolism.

Surgical debulking procedures can be of tremendous physical and psychological benefit (Fig. 125-16). The location of the soft tissue overgrowth, either extrafascial or intrafascial, is critical in determining which patients will benefit from staged contour resection. In general, intrafascial overgrowth should not be debulked due to risk of injury to major neurovascular structures and immobility. Truncal and thoracic wall CLVM are also amenable to staged resections. Excision of mediastinal and intrathoracic components is performed only when symptomatic. Postoperative healing can be problematic regardless of location since flaps are made of abnormal tissue with poor lymphatic drainage and altered circulation. Prolonged closed-suction drainage is used. Perioperative

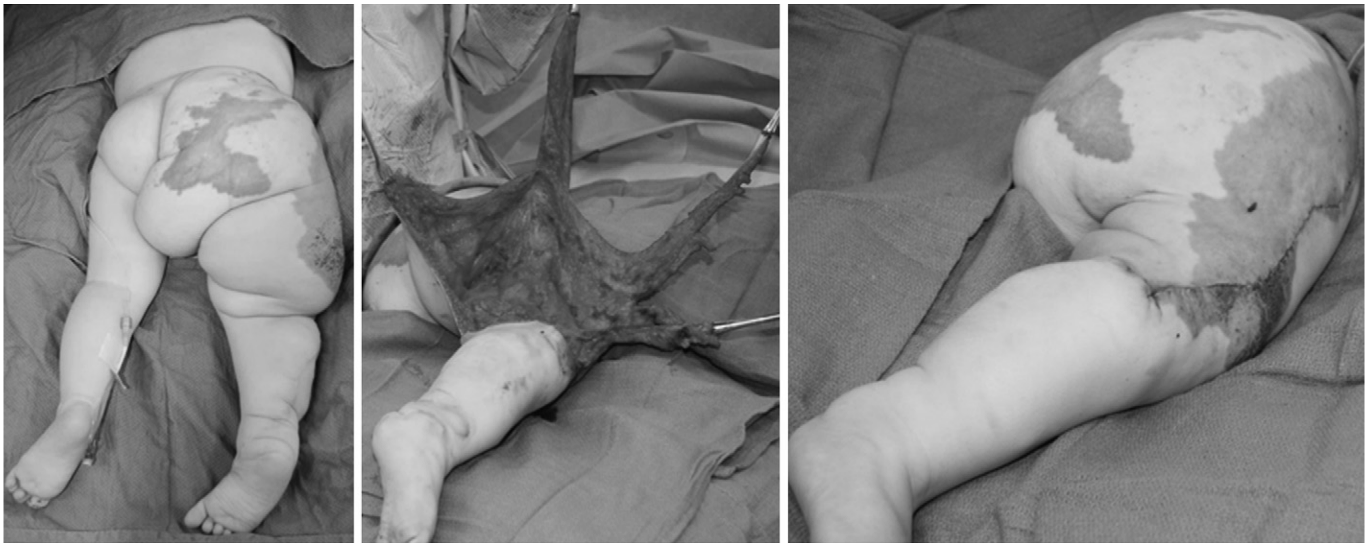

**FIGURE 125-16** Debulking of capillary-lymphatico-venous malformation. Overgrowth of right buttock and extremity *(left)*. Intraoperative appearance of buttock flaps and excision of soft tissue overgrowth *(middle)*. Postoperative appearance of leg *(right)*.

anticoagulation and placement of a temporary inferior vena cava filter to decrease deep venous thrombosis and prevent pulmonary embolism should be considered for extensive surgical procedures.[25]

Gross foot enlargement that impairs ambulation and the ability to wear shoes requires orthopedic corrective procedures and partial amputations to permit the use of custom footwear.[25] Limb length discrepancy should be monitored annually by an orthopedic surgeon. Differences less than 0.5 cm require no therapy. Those between 0.5 and 2 cm are managed non-operatively with internal or external heel lifts. Discrepancies in the legs greater than 2 cm are often treated with epiphysiodesis at the distal femoral growth plate around 12 years of age. Correction of upper extremity discrepancies is not necessary.

## PARKES WEBER SYNDROME

Capillary-arteriovenous malformation (CAVM) and capillary-arteriovenous fistulas (CAVFs) correspond to the eponym Parkes Weber syndrome. Lymphatic anomalies are often present (capillary-arteriovenous-lymphatico-venous malformation). The syndrome is characterized by the presence of a confluent or patchy capillary malformation with multiple underlying micro-AVFs (Fig. 125-17). There is soft tissue and skeletal hypertrophy of the affected limb, usually a lower extremity.[153] The bony overgrowth can result in a limb length discrepancy. The stained areas are usually warm; a thrill may be palpable. Hand-held Doppler examination often reveals increased flow and low-resistance run-off when placed over the stained areas.

De novo or inherited mutations in RASA1 have been identified in those patients with multifocal CMs.[153] The genetic mutation in those without multifocal CMs is yet to be elucidated (see Fig. 125-17). The distinction between the two presentations is clinically relevant. Some patients with RASA1 mutations have been found to have vein of Galen aneurysmal malformations and tumors similar to those observed in neurofibromatosis.[153]

On imaging, the involved extremity usually has fusiform subcutaneous, muscular, and bony overgrowth with diffuse microfistulas. Angiography and venography can reveal generalized arterial and venous dilation and a soft tissue blush involving muscles and subcutaneous fat.

Some patients with PWS are incorrectly diagnosed as having CLVM or diffuse capillary malformation with overgrowth. An accurate diagnosis is critical. Up to 30% of patients with PWS exhibit signs of cardiac volume overload, which is generally well tolerated.[153] In rare instances, cardiac failure can develop secondary to shunting through the arteriovenous fistulas. Infants and children are seen yearly and monitored for axial overgrowth, signs of cardiac failure, and cutaneous problems related to ischemia. Treatment is reserved for symptomatic patients. Flow reduction may be accomplished with repetitive superselective embolization to improve heart failure.[2] Limb amputation may be required for recalcitrant disease.

## CLOVES SYNDROME

Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies are recognized as features in a new syndrome.[157,158] CLOVES syndrome's main features are truncal lipomatous masses, vascular malformations, and acral/musculoskeletal anomalies (Fig. 125-18). The key feature is the presence of a truncal lipomatous mass,

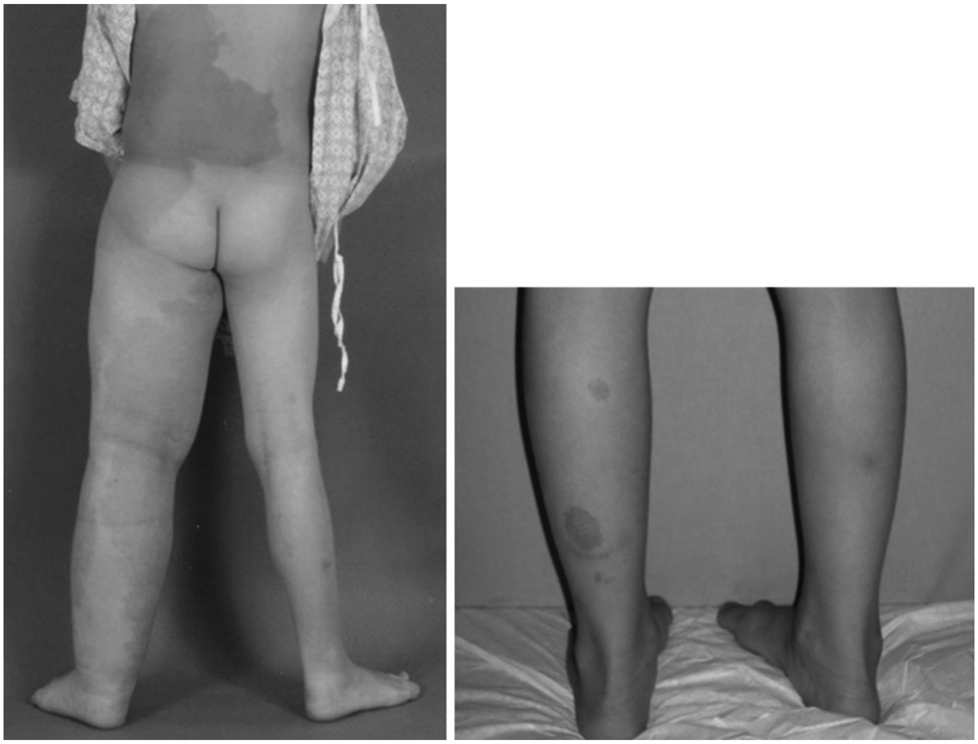

**FIGURE 125-17** Parkes Weber syndrome and capillary malformation-arteriovenous malformation (CM-AVM). Parkes Weber syndrome of the left lower extremity *(left)*. Notice geographic CM with fusiform, symmetric hypertrophy of the entire leg and foot. Characteristic appearance of CMs seen in CM-AVM *(right)*.

FIGURE 125-18 CLOVES syndrome. Truncal lipomatous mass in an infant *(left)*. A common acral skeletal anomaly is depicted showing widened triangular feet and polydactyly *(middle)*. Coronal fast spin-echo inversion recovery magnetic resonance image of a truncal lipomatous mass *(right, arrowheads)*. Scoliosis is also apparent.

which is usually evident at birth. The lesions may be mistaken for an LM; however, the truncal masses are hypervascular and exhibit rapid postresection recurrence. On imaging, the lesions are also infiltrative and can extend into adjacent areas such as the retroperitoneum, mediastinum, and pleural cavity. The lipomatous growths may involve the spinal column and epidural space. Compression of the cord, thecal sac, and nerve roots can occur.

Vascular malformations are also present with slow-flow lesions having been identified in all documented cases.[157,158] CMs can be seen on the trunk. LMs are often located adjacent to or within the truncal lipomatous masses. VMs, in the form of phlebectasia, can course over or around the truncal lesions and can be a source of pulmonary embolus. Paraspinal AVMs can result in paresis and spasticity. MRI with venous and arterial sequences to determine the presence, location, and extent of these lesions should be obtained early in life. Acral deformities include large, wide feet and hands; macrodactyly; and a wide sandal gap. Scoliosis has been documented in 50% of patients.[157]

### PTEN HAMARTOMA-TUMOR SYNDROME

Mutations in the PTEN (phosphatase tensin homolog on chromosome 10) gene cause two autosomal dominant disorders that have predisposition for cancer, Bannayan-Riley-Ruvalcaba and Cowden syndromes. These two entities comprise the PTEN hamartoma-tumor syndrome. Bannayan-Riley-Ruvalcaba syndrome is characterized by macrosomia at birth, macrocephaly, lipomas, hamartomatous intestinal polyposis, and variable degrees of developmental delay. Genital lentiginosis, seen best in males as freckling on the glans penis, can be present at birth or develop in early childhood or puberty. Cowden syndrome is characterized by multiple hamartomas and neoplasias of ectodermal, mesodermal, and endodermal origin. Vascular anomalies are present in about 50% of patients with PTEN mutations and are typically multifocal intramuscular combinations of fast-flow channels and ectopic fat.[159] The presence of a fast-flow lesion in a macrocephalic patient should raise suspicion of PTEN hamartoma-tumor syndrome.

## Conclusions

The past 30 years have witnessed remarkable gains in understanding the pathogenesis of vascular anomalies. Confusing nomenclature has been supplanted by precise terminology based on a genetic-anatomic-histologic classification system. Multidisciplinary vascular anomaly centers combine medical, surgical, radiologic, and pathologic expertise, assisting proper diagnosis and treatment of what were previously hopeless situations.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 126

# Pediatric Arterial Diseases

James C. Stanley and Jonathan L. Eliason

Arterial occlusive and aneurysmal diseases in infancy, childhood, and adolescence are uncommon. An understanding of their etiology, manifestations, and treatment is often based on anecdotal case reports. Nevertheless, the more frequent use of contemporary imaging and advances in vascular surgery have defined the management of most arterial diseases affecting pediatric patients. This chapter addresses common arterial problems affecting the aortic, renal, splanchnic, extremity, and cerebrovascular circulations.

## Aortic Disease

### ABDOMINAL AORTIC COARCTATION AND HYPOPLASIA

Coarctation and hypoplasia of the abdominal aorta are uncommon and are often associated with coexisting splanchnic and renal artery occlusive disease.[1–6] The anatomic location of the aortic narrowing is important, with 69% being suprarenal, 23% intrarenal, and 8% infrarenal (Figs. 126-1, 126-2 and 126-3).[5] The contemporary classification of aortic coarctation is based on the most superior level of the narrowing. It is the most cephalad extent of the disease that defines the complexity of the aortic reconstruction, with considerable differences if the celiac artery (CA) and superior mesenteric artery (SMA) are involved, compared with the renal arteries alone. Most aortic coarctations are diminutive vessels, having an hourglass appearance.

The cause of most abdominal aortic coarctations appears related to events occurring around day 25 day of fetal development when the two embryonic dorsal aortas fuse and lose their intervening wall to form a single vessel. Overfusion of the two embryonic dorsal aortas or their failure to fuse with subsequent obliteration of one of these vessels would predictably result in an aortic narrowing.

Developmental overfusion of the two primitive dorsal aortas receives support in patients with decreased aortic diameters who have single origins of the lumbar arteries. In addition, the presence of multiple renal arteries to one or both kidneys in these patients is nearly twice that observed in the general population, lending further support to a developmental etiology.[5,7,8] Normal aortic development occurs at approximately the same embryonic time that the multiple metanephric arteries involute, leaving a single renal artery. It is likely that if aortic narrowings exist, flow disturbances will occur in the vicinity of what would usually be the principal renal artery and diminish its hemodynamic advantage, allowing persistence of adjacent metanephric channels.

Certain well-known genetic diseases appear to be associated with these arterial anomalies. The most common is neurofibromatosis-1 (NF-1), in which patients exhibit an unusually high frequency of developmental abdominal aortic coarctations and renal artery stenoses.[5] Because of the protean nature of NF-1 and infrequent genetic analyses of patients with abdominal aortic coarctation, the exact frequency of this disease is likely to exceed the 29% reported in a recent University of Michigan series. The primary vascular pathology in neurofibromatosis appears to be related to an inhibition of vessel growth, not entrapment or invasion of the arterial wall by neural elements. Williams' syndrome is a second genetic disease associated with atypical abdominal aortic narrowings.

Viral-mediated events may impede transition of fetal mesenchymal tissue to vascular smooth muscle or alter its organization and growth in utero. They may also result in developmental aortic narrowings. Certain viruses including rubella are cytocidal and inhibitory to cell replication, with intimal fibroplasia and aortic hypoplasia occurring as a consequence. In this regard, fibroproliferative intimal disorders have been documented in the aorta and large elastic arteries of 16.5% of patients exhibiting the congenital rubella syndrome.[9]

Panaortitis with adventitial or periadventitial fibrosis and associated inflammatory cell infiltrates, suggesting an active or chronic aortitis, is another well-recognized cause of abdominal aortic coarctations. The proposition that most abdominal aortic coarctations are a variant of an inflammatory aortitis like Takayasu disease is quite controversial yet such may be the most common cause of these aortic narrowings in the subcontinent populations of Asia and South America.

Associated narrowings of the abdominal aortic branches are common in these patients. Nearly 90% of those with abdominal aortic coarctation have renal artery stenoses.[5] Splanchnic arterial occlusive disease occurs in 62% of these patients, with both CA and SMA stenoses and occlusions involved in 82% of the affected patients.[5]

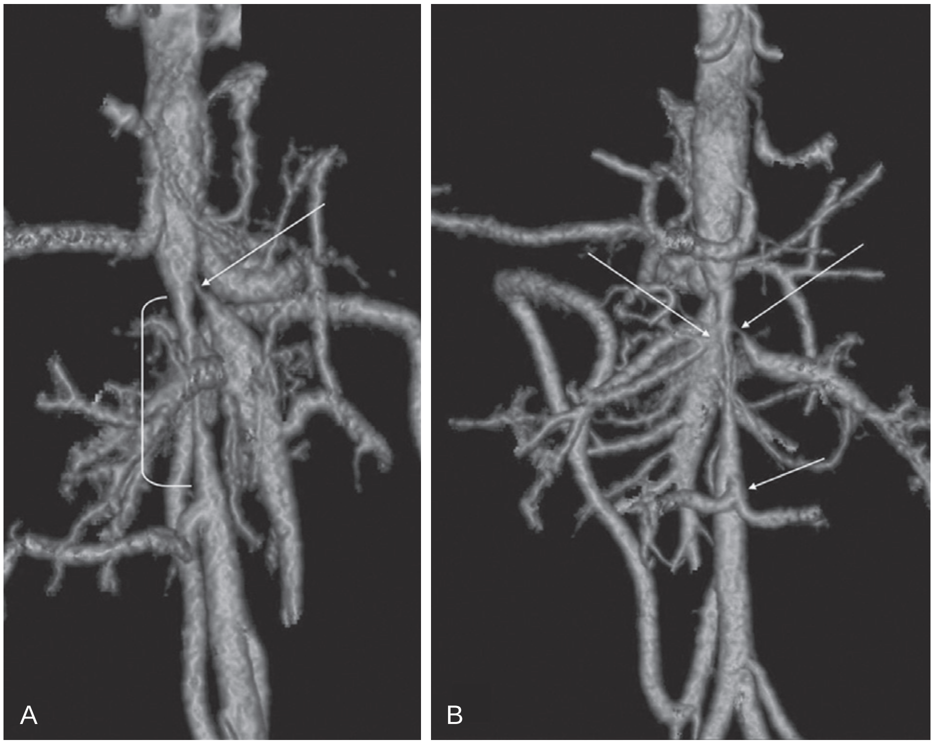


**FIGURE 126-1** **A,** Suprarenal abdominal aortic coarctation (*bracket*) with superior mesenteric artery stenosis (*arrow*) and **B,** bilateral renal artery stenoses (*arrows*). Note common trunk of lower lumbar artery (*arrow*) on posterior projection. (From Stanley JC, Criado E, Eliason JL, et al: Abdominal aortic coarctation: Surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aortoaortic graft. J Vasc Surg 2008;48:1073-1082.)

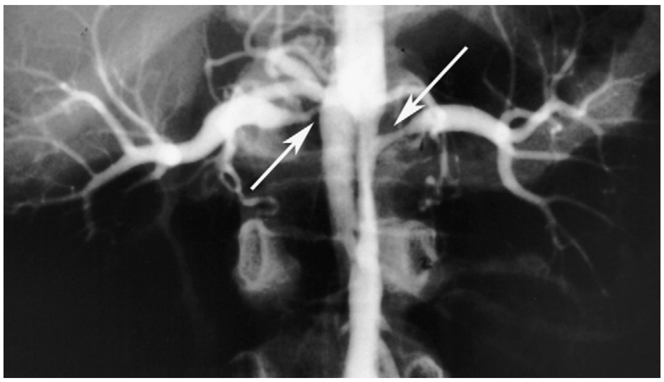

**FIGURE 126-2** Intrarenal abdominal aortic coarctation with bilateral artery stenosis (*arrows*). (From Stanley JC, Criado E, Eliason JL, et al: Abdominal aortic coarctation: Surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aortoaortic graft. J Vasc Surg 2008;48:1073-1082).

Clinical manifestations of this disease usually reflect uncontrolled hypertension due to suprarenal or intrarenal aortic narrowings. Two thirds of developmental coarctations and a quarter of those having inflammatory-related aortic narrowings have associated renal artery stenoses. The secondary hypertension in these instances is usually resistant to simple pharmacologic control. Occasionally, a patient reports exercise-related lower extremity fatigue, but true claudication is rare.[5] Symptomatic intestinal ischemia is uncommon, affecting only 6% of those having known CA and SMA disease accompanying their aortic narrowings.[10]

**FIGURE 126-3** Infrarenal abdominal aortic coarctation manifest by tubular stenosis extending from dilated inferior mesenteric artery to the aortic bifurcation.

Abdominal aortic coarctations usually cause signs or symptoms during the first or second decade of life in contemporary times. An earlier review noted that patients had reached a mean age of 22 years before the diagnosis was actually confirmed.[3] Untreated, this entity has been associated with

stroke, progressive left ventricular hypertrophy, congestive heart failure, flash pulmonary edema, and less often with renal insufficiency.[11,12] In one review, 55% of untreated patients died at a mean age of 34 years.[3]

Treatment of abdominal aortic narrowings in children has most often entailed open surgery.[5] Historically, thoracoabdominal bypass was the conventional means of treating these patients (Figs. 126-4 and 126-5). In more recent years patch aortoplasty has become preferred when it can be performed safely (Figs. 126-6 and 126-7). Both procedures can be technically challenging, especially in the face of coexisting splanchnic or renal disease requiring simultaneous treatment.

Thoracoabdominal bypass grafts originate from the distal thoracic aorta above the diaphragm or from the supraceliac aorta at the diaphragmatic hiatus and are passed behind the left kidney to the distal aorta. Expanded Teflon grafts are favored because of their greater stability regarding postimplantation dilatation. Graft diameter should be chosen to be as big as possible, short of being so large that excessive luminal thrombus would accumulate. The intent is to oversize grafts compared with the aorta, with anticipated growth otherwise resulting in a graft too small to maintain normal distal pressures and flow. In the ideal circumstance, one should use a graft whose size would not represent an energy-consuming constriction as the child grows into maturity. This means having a conduit at least 60% or 70% the size of the adult aorta. In early childhood the use of large conduits may not be possible. Graft length is a nonissue in older children and

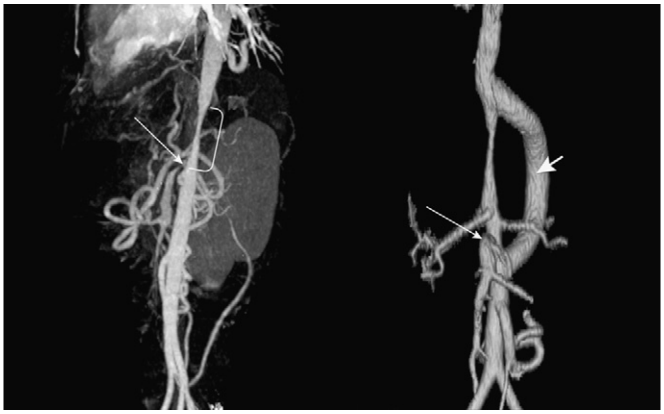

**FIGURE 126-4** *Left,* Suprarenal coarctation (*bracket*) with superior mesenteric artery stenosis (*arrow*). *Right,* Subsequent thoracoabdominal bypass (*broad arrow*) with aortic implantation of superior mesenteric artery (*arrow*). (From Stanley JC, Criado E, Eliason JL, et al: Abdominal aortic coarctation: Surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aortoaortic graft. J Vasc Surg 2008;48:1073-1082.)

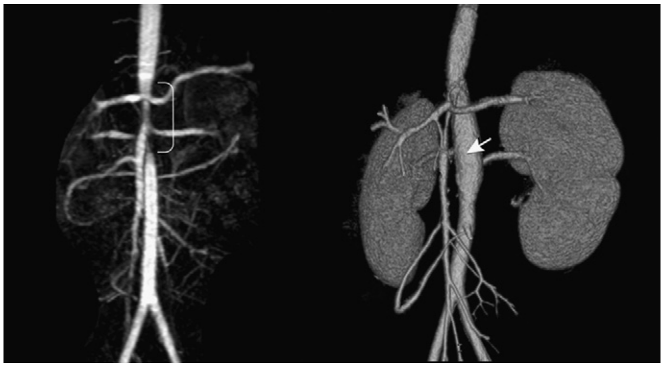

**FIGURE 126-6** *Left,* Suprarenal coarctation (*bracket*) with bilateral renal artery ostial stenoses. Preoperative magnetic resonance angiography. *Right,* Subsequent patch aortoplasty (*broad arrow*) with aortic diameter exceeding that of uninvolved proximal and distal aorta. Reimplantation of the renal arteries accompanied the aortic reconstruction. (From Stanley JC, Criado E, Eliason JL, et al: Abdominal aortic coarctation: Surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aortoaortic graft. J Vasc Surg 2008;48:1073-1082.)

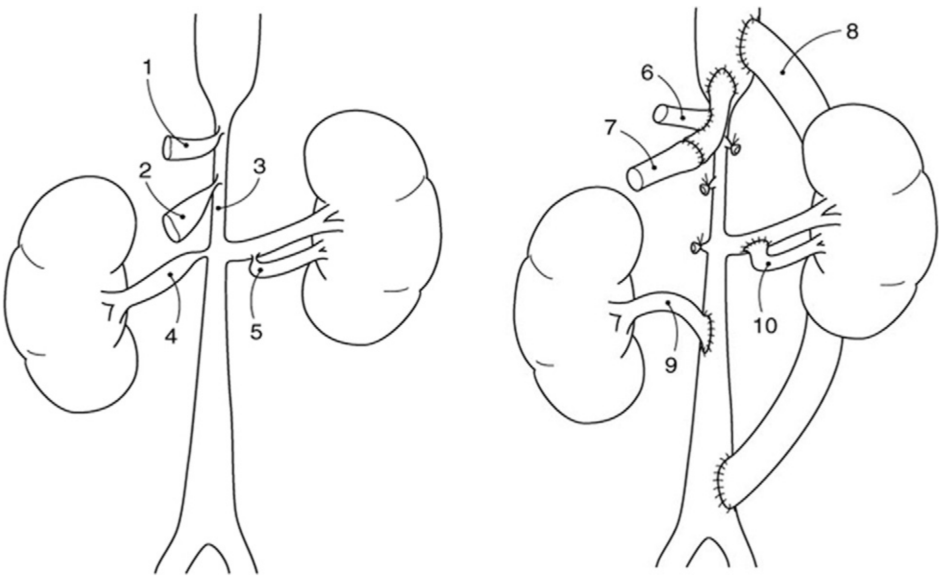


**FIGURE 126-5** Complex aortic, splanchnic, and renal arterial reconstruction: *1,* Celiac artery (CA) stenosis; *2,* Superior mesenteric artery (SMA) stenosis; *3,* suprarenal midabdominal aortic coarctation; *4,* right renal artery ostial stenosis; *5,* left segmental renal artery stenosis; *6,* CA implanted onto aorto-SMA bypass (with autogenous internal iliac artery graft); *7,* reconstructed SMA; *8,* thoracoabdominal aortic bypass; *9,* right renal artery reimplantation onto aorta; *10,* left segmental renal artery implantation onto adjacent segmental renal artery. (From Upchurch GR Jr, Henke PK, Eagleton MJ, et al: Pediatric splanchnic arterial occlusive disease: Clinical relevance and operative treatment. J Vasc Surg 2002;35:860-867.)

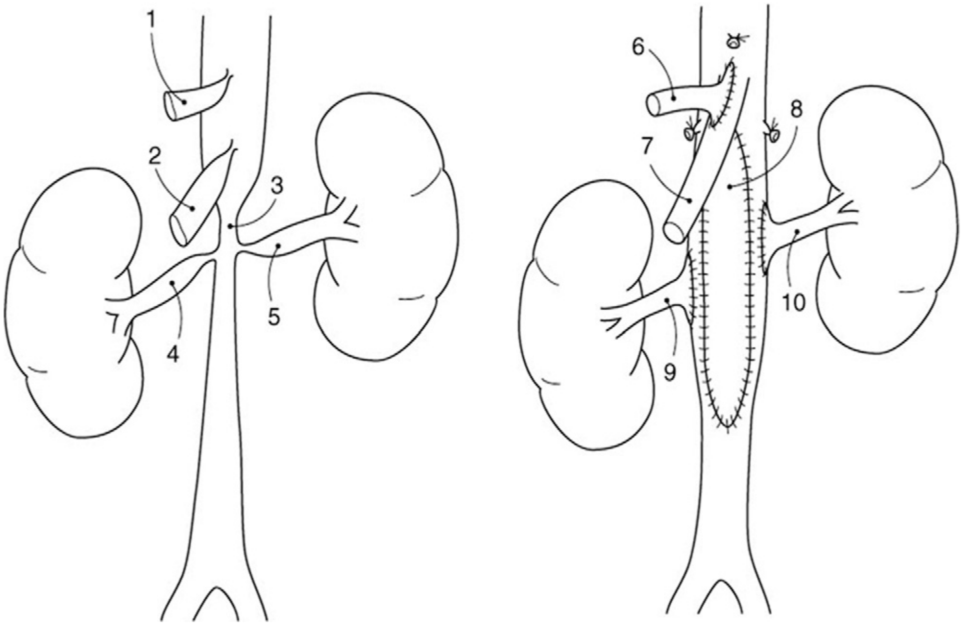


**FIGURE 126-7** Complex aortic, splanchnic, and renal arterial reconstruction: *1,* Celiac artery (CA) stenosis; *2,* superior mesenteric artery (SMA) stenosis, *3,* interrenal midabdominal aortic coarctation; *4* and *5,* right and left renal artery stenosis; *6,* CA implanted onto stenotic SMA origin; *7,* widely patent SMA; *8,* polytetrafluoroethylene patch aortoplasty; *9* and *10,* bilateral implantation of renal arteries onto aorta. (From Upchurch GR Jr, Henke PK, Eagleton MJ, et al: Pediatric splanchnic arterial occlusive disease: Clinical relevance and operative treatment. J Vasc Surg 2002;35:860-867.)

adolescents, with axial growth from the diaphragm to pelvis being minimal after reaching an age of 9 or 10 years.

Patch aortoplasty is usually undertaken when the coarctation segment has a large enough diameter to allow completion of an anastomosis without an overlap of sutures from the opposing sides of the patch. Whenever possible, patches in children should be large enough, similar to thoracoabdominal graft sizing, so as to not be constrictive with growth into adulthood, yet not so generous as to risk development of an extensive lining of unstable thrombus. Teflon graft material is again favored over Dacron graft because of the latter's propensity for dilatation years after implantation.

Reoperations are infrequent but may be required for anastomotic narrowings or if a patient outgrows the adequacy of the primary aortic reconstructive procedure. The fact that nearly 10% of the cases in a recent report from the University of Michigan required late secondary operations supports the importance of long-term follow-up of these patients.[5]

Simultaneous visceral artery reconstructions depend on the clinical relevance of the nonaortic disease, as well as the proximity of the aortic reconstruction to the affected aortic branches. Renal artery stenoses causing secondary renovascular hypertension justify their reconstruction. A mandate to reconstruct the CA or SMA applies only to symptomatic cases. Nevertheless, a relative indication to prophylactically reconstruct these vessels exists when performance of an aortoplasty or renal revascularization would make a subsequent CA or SMA revascularization exceedingly difficult. When the aortic reconstruction is distant from the CA or SMA, such as with thoracoabdominal bypass, a concomitant splanchnic revascularization is less likely to be warranted.

Treatment of select focal abdominal aortic coarctations distant from the renal and splanchnic branches may involve endoluminal interventions. When such is undertaken, stent placement is necessary to overcome the significant recoil of these hypoplastic and highly fibrotic aortic narrowings.[13–15] However, one should remain cautious about accepting the long-term benefits of endoluminal treatment of abdominal aortic coarctation in children. Given the high frequency with which the visceral arteries are involved in abdominal aortic narrowings, the number of lesions amenable to endovascular repair is likely to be limited.

More than 90% of patients with abdominal aortic coarctation benefit when treated with a patch aortoplasty or a thoracoabdominal bypass.[5] Accompanying postoperative morbidity is low, and mortality should approach zero. Nevertheless, long-term follow-up of these young patients with annual noninvasive assessments of lower extremity blood flow is recommended. Imaging with magnetic resonance angiogram (MRA) studies or computed tomography angiogram (CTA) should be obtained if any evidence of diminished blood flow exists.

## ABDOMINAL AORTIC ANEURYSMS

Abdominal aortic aneurysms (AAAs) are rare in children. All are considered life threatening. The etiology is often difficult to ascertain, but in general these AAAs have been categorized as (1) infectious, (2) related to known vascular disease entities, or (3) due to unknown congenital developmental misadventures. The clinical manifestations vary widely among these different categories. The diagnosis typically follows imaging with ultrasonography, MRA, or CTA.

Infectious AAAs associated with umbilical artery catheterizations (UACs) account for approximately one third of aortic aneurysms reported in children. These aneurysms may present anytime during the first 2 years of life, but most are encountered in the newborn period. Repeated UAC insertion and prolonged UAC use have been implicated as risk factors for this type of AAA. Whether these aneurysms are the result

of a bacteremic invasion of a catheter-injured aorta or due to an infected thrombus is problematic, but the outcome is destruction of the involved vessel and aneurysm formation. More than 75% of these aneurysms are associated with a *Staphylococcus aureus* or *Staphylococcus albus* infection.[16] The resulting AAAs are usually saccular, and more than 50% involve the abdominal aorta (Fig. 126-8). Aortic infection related to UAC represents a life-threatening illness,[16,17] with AAA rupture being the most serious complication. These infected AAAs, with rare exception, require early operation. Interventions range from simple aortic ligation to aneurysmectomy with an autologous or synthetic graft aortic reconstruction. Long-term antibiotic administration must accompany these procedures.

**FIGURE 126-8** Aortic and iliac artery aneurysms due to infection secondary to umbilical artery catheterization.

Aortic aneurysms in childhood may also be related to known vascular diseases, the more common of which deserve mention. Tuberous sclerosis (TS) is an autosomal dominant disease with hamartomas in multiple organ systems, with central nervous system involvement manifest by learning difficulties and seizures, as well as vascular lesions.[18,19] Most TS-related aortic aneurysms are abdominal in location, with less frequent thoracic aortic involvement. Fatal rupture of these AAAs is well recognized.[19,20] Treatment strategies are often complex and tailored to anatomic involvement, with a frequent need to reconstruct the splanchnic and renal vessels (Fig. 126-9).

Ehlers Danlos syndrome (EDS) includes a spectrum of disorders with vascular involvement. This is especially the case in type IV EDS, an autosomal dominant disease resulting in defective type III collagen production. It is often manifest by spontaneous rupture of a hollow viscus or large arteries. Among 132 vascular complications in 24 patients with EDS, 17 had thoracic or abdominal aortic involvement including dissections, aneurysms, and ruptures.[21] Unfortunately, the true prevalence of this disease is unknown, in that catastrophic complications of EDS resulting in death may occur before a definitive diagnosis is established. Vascular surgery in these patients is often required, but because of vessel fragility and bleeding, operative treatment must be approached with extreme care.[22]

Marfan syndrome is an autosomal dominant disorder, affecting collagen cross-linking due to mutations in the fibrillin-1 gene. Infantile arterial involvement in Marfan syndrome is rare. The vast majority of these children have cardiac problems including dilation of the aortic root, mitral valve prolapse, and valvular regurgitation.[23] Nevertheless, 20% of these children develop aortic aneurysmal changes as they grow older.[24]

Takayasu aortoarteritis is also a recognized cause of pediatric aortic aneurysm formation, pseudoaneurysm formation, aortic stenoses, and aortic dissections.[25,26] The clinical presentation may be marked by systemic symptoms of inflammation or may be related to aortic involvement. Aortic

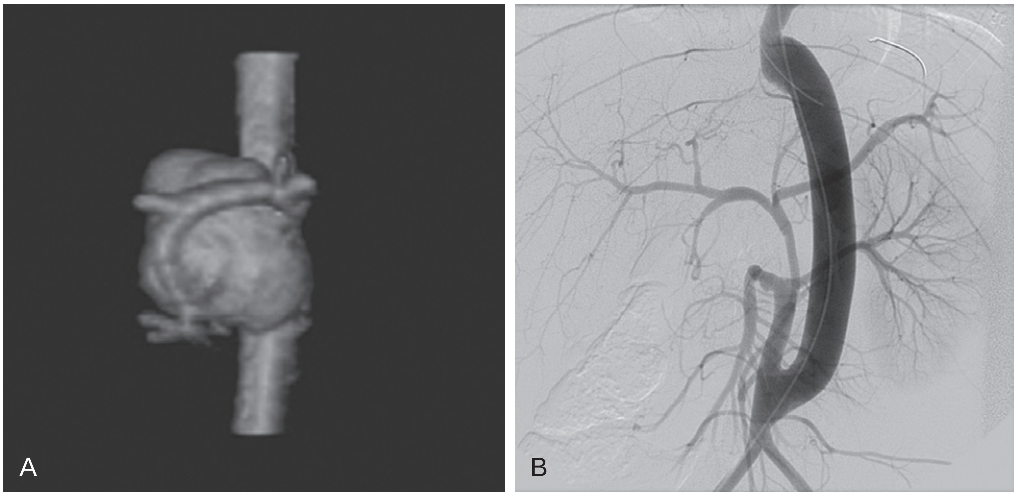


**FIGURE 126-9** **A,** Preoperative tuberous sclerosis-related abdominal aortic aneurysm with renal and splanchnic arterial involvement. **B,** Postoperative appearance following aneurysmectomy, aortic reconstruction, and revascularization of the celiac and superior mesenteric arteries.

reconstructions are less urgent in this group of children and are best undertaken when the aortoarteritis is quiescent.

Certain pediatric AAAs are not infectious or related to an underlying connective tissue disease. Their etiology is related to developmental events evolving during fetal growth (Fig. 126-10). Aneurysms in this group are commonly associated with stenotic lesions and multiple aneurysms in other locations. Concomitant renal, upper extremity, or iliac artery aneurysms occur most often in these children, with cerebrovascular, mesenteric, and lower extremity arterial involvement being less common.[27]

Seven children, ranging in age from 2 weeks to 8 years, have undergone surgical repair of their AAAs at University of Michigan from 2002 to 2010, with six survivors. The AAAs involved 10 renal arteries in five patients, all of whom were hypertensive. No two aneurysms were of the same clear etiology, and aortic reconstructions varied in each case including concomitant renal or splanchnic arterial reconstructions in four children.

### ABDOMINAL AORTIC THROMBOSIS

Acute thrombotic occlusions of the aorta and its branches have multiple causes including prothrombotic coagulation disorders, sepsis, and certain cardiopulmonary diseases. However, iatrogenic injury is the most common inciting event, usually a complication of a neonatal UAC.[17,28,29] Some degree of aortic thrombosis accompanies 20% to 30% of UACs,[30] and 89% of neonates experiencing aortic thrombosis had indwelling arterial catheters.[31]

Clinical presentations vary widely from silent thromboses to profound tissue ischemia manifest by lower extremity discoloration and multiple systemic organ failure. Overall mortality with neonatal aortic occlusion approaches 15% to 20%.[31,32] Diagnoses are most often made with Doppler evidence of absent extremity blood flow in the face of no palpable peripheral pulses and CTA or MRA imaging confirming the aortic involvement. Intravenous digital subtraction arteriography has a role in select patients. Conventional catheter-based diagnostic arteriography in the neonate is ill-advised but may provide a means for delivering lytic agents in select cases. In that setting, access may be best through an umbilical artery catheter.[29]

Treatment of acute aortic thromboses in neonates is initiated with heparin anticoagulation. Fibrinolytic therapy, a challenge because of low plasminogen levels in the newborn, is an important therapy.[33–35] Heparin administration should accompany tissue plasminogen activator (tPA) infusions in these cases. Hemorrhagic complications may accompany tPA therapy and such risks must be weighed when considering the benefits of lytic treatment. Mechanical thrombectomy using small balloon catheters or polyethylene tubing advanced through an aortotomy allows disobliteration of the aorta and extraction of branch thrombus.[17]

Aortic thromboses in older children and adolescents are frequently associated with intimal flaps and dissections caused by blunt trauma.[36,37] Abdominal and chest injuries occurring in motor vehicle accidents and falls from great heights are common contributors to this trauma. Other life-threatening injuries often accompany the aortic thrombosis in these cases. Obvious pulse deficits and tissue ischemia are manifestations of aortic occlusion in these older children with the diagnosis being confirmed by CTA, MRA, or conventional arteriography.[38] Aortic interposition or bypass grafts are usually undertaken in these instances with nonanatomic axillofemoral or thoracoabdominal bypasses required if intestinal perforation has contaminated the immediate area of aortic injury. Endovascular repairs offer certain benefits in the adolescents having severe coexisting injuries in addition to the aortic injury.[39,40]

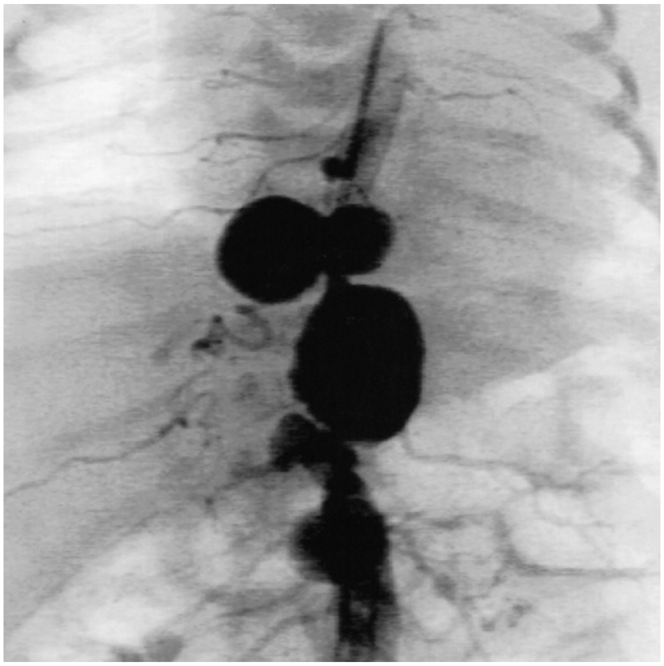

FIGURE 126-10 Idiopathic multiple aortic aneurysms in a newborn.

# Renal Artery Disease

### RENAL ARTERY STENOSIS

Occlusive disease affecting the renal arteries is the third most common cause of hypertension in children following coarctation of the thoracic aorta and parenchymal renal disease. The precise incidence of this type of secondary hypertension in children is unknown but is likely to account for 5% to 10% of those exhibiting marked blood pressure elevations. Pediatric renovascular hypertension, when unrecognized and untreated, has been associated with hemorrhagic stroke, hypertensive encephalopathy with impaired mental development, and failure to thrive. Poorly controlled hypertension may result in left ventricular hypertrophy and severe diastolic dysfunction. When the entire renal mass is involved, flash pulmonary edema associated with renal insufficiency may occur.

Pediatric renal artery stenoses represent a spectrum of diseases. Most developmental renal artery stenoses encountered in North American Caucasian children[11,12] are different from the inflammatory aortoarteritis related stenoses that dominate reports from the Asian subcontinent.[41–43] The cause of most developmental renal occlusive lesions are the same as those causing abdominal aortic coarctations.[5,11] Many of these patients have NF-1.[7,11,44,45] The vast majority of renal artery

narrowings are ostial in location, representing true hypoplastic stenoses (Fig. 126-11).

Recognition of renal artery stenotic disease in children requires detailed vascular imaging.[11,46] Conventional catheter-based digital-subtraction arteriography has been a standard, but at many institutions it is being replaced with newer CTA technology.[5] Nevertheless, digital-subtraction arteriography should be pursued when a strong suspicion of renovascular disease exists.[5] Screening modalities including MRA, nuclear renal scans with ACE inhibitors, and deep abdominal ultrasonography all have value but are currently too inconsistent to be used as confirmatory diagnostic or prognostic tests.

Optimal surgical therapy depends on the specific character of the renal artery disease being treated. The most common surgical procedure has been renal artery implantation into the aorta, as well as into the main or adjacent segmental renal arteries (Figs. 126-12 and 126-13).[11] Aortorenal bypasses with vein grafts were frequently used in the past but are not favored because in follow-up more than half of these conduits undergo aneurysmal deterioration.[47] The internal iliac artery has become the preferred conduit for aortorenal bypasses (Fig. 126-14). Splenorenal reconstructions with a direct anastomosis of the splenic and renal vessels are not favored because of coexistent or later development of a celiac artery stenosis that would perpetuate the hypertensive state. Resections of the stenotic renal artery with primary reanastomosis, focal arterioplasty, or open operative dilation are less common reconstructive procedures. Nephrectomy may be appropriate for irreparable renal disease including multiple intrarenal stenoses not amenable to open in situ or ex vivo repairs, as well as diminutive kidneys 2 to 3 cm in size. In these cases it is assumed that the contralateral kidney will suffice in keeping the child from going into renal failure. There is a certain logic in undertaking single-stage vascular reconstructive procedures given that a later operation in the same anatomic area entails significant hazards of reoperations.

**FIGURE 126-11** Ostial main renal artery stenoses.

**FIGURE 126-12** Bilateral renal artery-aortic implantations. Note the residual origins of the native renal arteries. (From Stanley JC, Zelenock GB, Messina LM, Wakefield TW: Pediatric renovascular hypertension: A thirty-year experience of operative treatment. J Vasc Surg 1995; 21:212-227.)

Undertaking surgical therapy in small infants is controversial. Technical challenges exist in reconstructing renal arteries less than 2 mm in diameter and renal revascularization in these circumstances should be pursued only when uncontrolled severe hypertension or renal failure threaten the patient. Renal revascularizations are most likely to be successful after age 3 years, and deferring reconstructive procedures in younger children when possible is reasonable. Drug treatment of hypertension in the young child may be difficult and requires frequent and fastidious monitoring.

Large clinical experiences with pediatric-aged renovascular hypertension are uncommon.[11,48–51] The University of Michigan series included 39 girls and 58 boys, aged from 3 months to 17 years, who underwent operation from 1963 to 2006.[11] All but one patient had refractory hypertension not responsive to contemporary medical therapy. Developmental renal artery stenoses accounted for 80% of the renal artery disease. Splanchnic arterial occlusive lesions affected 24%, and abdominal coarctations affected 33%. Primary renal artery operations were undertaken 132 times. Procedures included resection beyond the stenosis and implantation into the aorta in 49, renal artery in 7, or SMA in 3; aortorenal and iliorenal bypasses with vein or iliac artery grafts in 40; focal arterioplasty in 10; resection with reanastomosis in 4; operative dilation in 4; splenorenal bypass in 2; and primary nephrectomy in 13 when arterial reconstructions proved impossible. Bilateral renal artery operations were done in 32 children. The fact that 17 underwent CA or SMA reconstruction, 19 underwent patch aortoplasty, and 11 underwent thoracoabdominal bypass underscored the complexity of disease being treated. Thirty secondary renal artery procedures were done in 19 patients including nine nephrectomies. Hypertension was cured in 68 children (70%), improved in 26 (27%), and unchanged in 3 (3%). Follow-up averaged 4.2 years. No patients required dialysis, and there were no operative deaths.

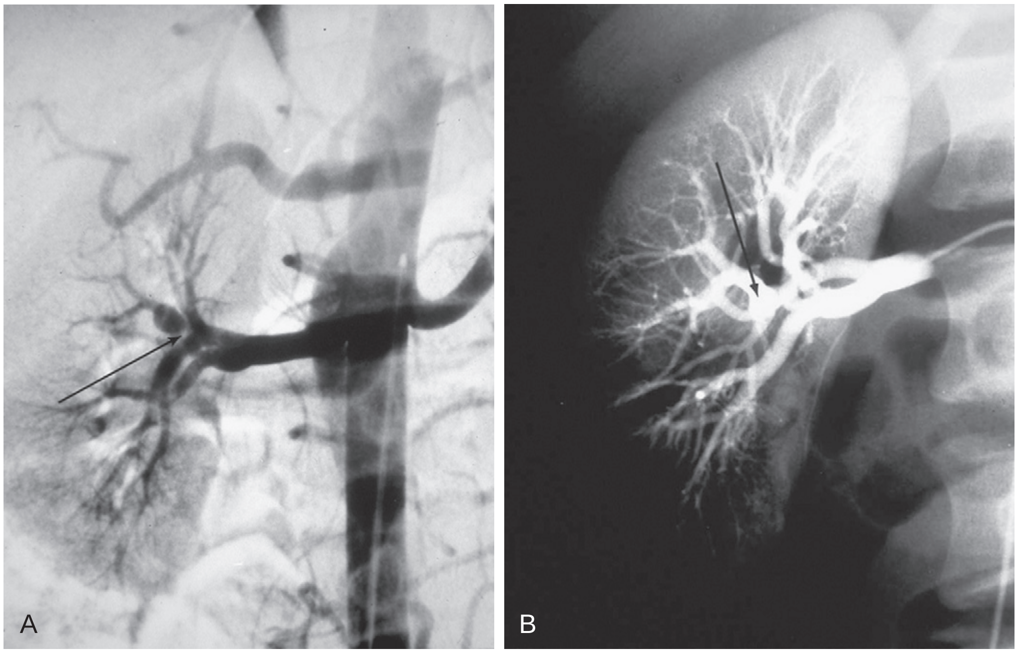


FIGURE 126-13 **A,** Focal stenosis of intraparenchymal segmental renal artery with poststenotic dilation (*arrow*). **B,** Segmental renal artery implantation into the distal main renal artery (*arrow*). (From Stanley JC, Zelenock GB, Messina LM, Wakefield TW: Pediatric renovascular hypertension: A thirty-year experience of operative treatment. J Vasc Surg 1995;21:212-227.)

A second large series was reported from the Hospital Beaujon in France.[48] That series encompassed 78 children, 35 boys and 43 girls, ranging in age from 1.4 to 18 years. There were 91 primary revascularization procedures and 15 nephrectomies. These numbers were quite similar to the University of Michigan series. A third series emanated from the Cleveland Clinic involving 56 children including 23 boys and 33 girls ranging in age from 0.7 to 21 years.[49] They reported 46 primary operations and 10 primary nephrectomies. A fourth series was from Vanderbilt University and the Children's Hospital of Philadelphia.[50] This experience included 50 children, 24 boys and 26 girls, ranging in age from 0.4 to 16 years. These children were subjected to 28 primary reconstructive procedures and an additional 12 primary nephrectomies. The latter two series, unlike the University of Michigan experience, did not contain many patients treated for aortic or splanchnic arterial disease.

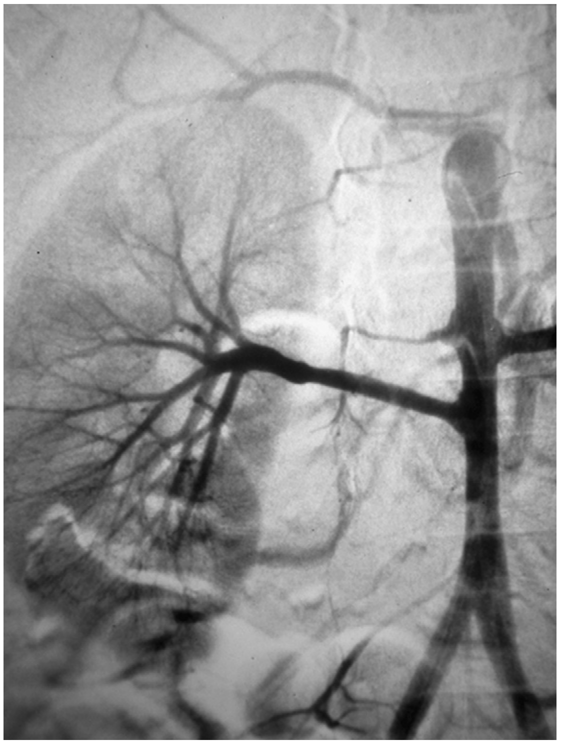

FIGURE 126-14 Aortorenal bypass with an internal iliac artery graft. (From Stanley JC, Zelenock GB, Messina LM, Wakefield TW: Pediatric renovascular hypertension: A thirty-year experience of operative treatment. J Vasc Surg 1995;21:212-227.)

Outcomes regarding blood pressure control were remarkably similar at the University of Michigan, Vanderbilt-University-Children's Hospital of Philadelphia, and Cleveland Clinic, with respective *cure* rates of 70%, 70%, and 66%; reported *improvement* rates of 27%, 26%, and 23%; and *failure* rates of 3%, 4%, and 11%. Surgical therapy in all three of the former experiences consisted of conventional open operative interventions.

The role of percutaneous transluminal angioplasty (PTA) in treating pediatric renovascular hypertension remains controversial.[52,53] Failure following PTA for developmental disease might be anticipated, given the excessive elastic tissue in many stenoses that would predictably contribute to early postdilation recoil, as well as the minute caliber of developmentally narrowed vessels that might lead to their disruption. Nevertheless, a small number of recent reports suggest success with catheter-based interventions.[54,55] It is of note that if the disease being treated is a quiescent inflammatory aortoarteritis, then more salutary outcomes would follow PTA than might be the case if treating developmentally hypoplastic renal arteries. However, even in the former setting recurrent stenoses are frequent.[42,43]

### ACUTE RENAL ARTERY DISSECTIONS AND THROMBOSES

Acute renal artery dissections and thromboses are most often a result of UAC in the neonate or iatrogenic events accompanying diagnostic or therapeutic catheterizations in older children. Among adolescents, blunt or deceleration injury with stretching and dissections of the renal artery is a common cause of an acute occlusion. Flank pain, hematuria, and hypertension are frequent manifestations of acute renal artery occlusions with evolving renal infarction in these children.

Acute thrombosis of an otherwise nondiseased renal artery resulting in interruption of blood flow for more than 90 minutes invariably results in an irreversible loss of renal function. Nevertheless, an attempted operative repair is justified, especially when treating a vascular injury to a solitary kidney or bilateral injuries.[56] Endovascular interventions offer a less invasive means of treating select patients in this setting.[10]

Surgical therapy in the chronic setting and in cases of subtotal occlusions may require an aortorenal bypass. Revascularization attempts in these children are justified if sufficient parenchyma exists and nuclide studies suggest the affected kidney to be functioning at 10% to 20% of the contralateral unaffected kidney. Nephrectomy is undertaken when recovery of renal function is impossible.

### RENAL ARTERY ANEURYSMS

The clinical relevance of renal artery aneurysms in children is poorly understood including an undefined risk of rupture.[11,57] Aneurysms affecting the renal artery are generally of two categories.

The most common aneurysms are those associated with an underlying congenital vasculopathy or a connective tissue disorder. More often than not the congenital nature of this remains unknown, although in some patients genetic diseases like Ehlers-Danlos are obvious. These aneurysms usually occur at branch points as saccular lesions (Fig. 126-15). Their discovery usually occurs as an incidental finding during imaging for other suspected vascular or renal diseases. An occasional aneurysm may have been the source of embolic material responsible for distal arterial occlusion, renal ischemia, and secondary renovascular hypertension.

Treatment is recommended for extraparenchymal aneurysms in hypertensive children or when they exceed 1 cm in diameter regardless of blood pressure levels. Larger aneurysms may be excised with a primary angioplastic closure, and smaller ones plicated with fine cardiovascular suture in the form of a closed aneurysmorrhaphy. Aneurysms arising within the cortical substance may be treated with catheter-delivered occlusive material or carefully delivered absolute alcohol. In that setting there is a predictable loss of kidney substance beyond the aneurysm.

The second group of renal aneurysms are due to poststenotic turbulent blood flow. Renal artery aneurysms in this category were encountered in 8 children among 97 treated for renovascular hypertension at the University of Michigan.[11] These aneurysms tend to be more globular than saccular. Treatment in these cases necessitates eliminating the stenosis with a renal artery reconstruction similar to that in managing renovascular hypertension. Accompanying such a revascularization is aneurysm excision and angioplastic closure of the residual opening at the base of the aneurysm or a closed aneurysmorrhaphy in the case of small aneurysms.

**FIGURE 126-15** Renal artery aneurysm involving second order segmental renal artery. Note the relative hypoperfusion of the upper pole.

# Splanchnic Artery Disease

### SPLANCHNIC ARTERY STENOSES AND ANEURYSMS

Occlusive disease of the splanchnic arteries is rare in pediatric-aged patients and is an even rarer cause of clinically relevant intestinal ischemia.[58] These stenotic narrowings usually affect the origins of the celiac and superior mesenteric arteries (Fig. 126-16). They are recognized most frequently during arteriographic studies for suspected aortic or renal artery pathology.

Developmental lesions appear related to embryonic events similar to those causing aortic and renal artery narrowings. These events likely affect the reorganization of the ventral segmental vessels associated with the cephalic roots of the vitelline arteries that form the CA and SMA. This results in an ostial stenosis or occlusion. Minimal CA and SMA narrowings demonstrated at a young age may not become intrinsically narrower as the child grows, but the vessel origin may simply remain the same size as everything else becomes larger. Thus the artery's origin becomes proportionately narrower until it becomes a critical stenosis.[58] This entire process suggests a major growth arrest of the aortic origins of these arteries.

Symptomatic splanchnic artery disease presents as postprandial intestinal angina with periumbilical discomfort that lasts for the duration of small bowel transit of the ingested

**FIGURE 126-16** Severe celiac artery and superior mesenteric artery ostial stenoses evident on a lateral aortogram.

food. These children develop a food aversion and exhibit a failure to gain weight. In extreme cases they may experience weight loss.

Operative treatment of pediatric splanchnic arterial occlusive disease is complex.[58,59] A mandate to reconstruct these vessels applies only to symptomatic cases. A relative indication to reconstruct the CA or SMA exists when performance of a primary procedure such as patch aortoplasty or renal revascularization would potentially place these splanchnic arteries at risk of occlusion. In these circumstances the proximity of the origins of the CA and SMA to the other reconstruction may justify a prophylactic splanchnic revascularization.

In certain children internal iliac artery grafts are used to treat lengthy CA or SMA stenoses. Anastomoses are fashioned with interrupted sutures when reconstructing small arteries 2 to 3 mm in diameter. In older adolescents, a continuous suture may be used to complete anastomoses of larger splanchnic arteries (see Fig. 126-5). In other children, aortic implantation of the CA or SMA after spatulation of the transected vessel beyond its stenotic origin is favored over an aortosplanchnic bypass (see Figs. 126-7 and 126-17).[58] Children treated by both methods have invariably gained weight and are free of abdominal discomfort.[58] Percutaneous transluminal balloon angioplasty with or without stenting for these developmental ostial lesions is not appropriate and ill-advised.

Splanchnic arterial occlusive disease when encountered in childhood has an uncertain natural history. Long-term follow-up of these children with periodic imaging studies in those operated on seems appropriate, and regular clinical assessment of those not subjected to surgical therapy is recommended. In regard to the latter, it is important to remember that most CA and SMA stenoses are asymptomatic because of the IMA serving effectively as a source of collateral circulation. Unoperated patients should be aware of their splanchnic arterial anatomy and be able to pass this information on to anyone undertaking a later abdominal operation. In these individuals, inadvertently interrupting the collateral circulation might cause catastrophic intestinal ischemia.

The median arcuate ligament syndrome is a poorly defined disorder that has been sporadically described in children.[60,61]

**FIGURE 126-17** *Left,* celiac artery occlusion and severe ostial stenosis of the superior mesenteric artery (SMA). *Right,* Postoperative documentation of widely patent SMA implanted onto anterior aorta. (From Upchurch GR Jr, Henke PK, Eagleton MJ, et al: Pediatric splanchnic arterial occlusive disease: Clinical relevance and operative treatment. J Vasc Surg 2002;35:860-867.)

Compression or entrapment of the celiac artery by unyielding fibers of the diaphragmatic crura the aortic hiatus is a recognized anatomic finding. Intermittent upper abdominal pain has been reported to be the most common clinical manifestation alleged to occur in symptomatic cases. Weight loss in children has not been a constant accompanying finding in these individuals. Treatment usually includes transaction of the compressing tissue and skeletonization of the celiac artery. Celiac artery narrowing may persist if secondary mural fibrosis has occurred, but such is less likely to occur in children compared with adults. Early relief of symptoms is expected, but long-term outcomes remain to be defined.

Splanchnic artery aneurysms in children are uncommon.[57] The etiology that underlies these lesions becomes an important determinant of therapy. Blunt or deceleration injury to the liver and spleen may result in small pseudoaneurysms recognized on a computed tomography (CT) study, but such may often be safely followed without a specific intervention. Most small pseudoaneurysms thrombose without sequelae. Endovascular embolic obliteration of large or unstable aneurysms in these solid organs is usually possible in older children and adolescents.

Splanchnic artery aneurysms associated with childhood Ehlers-Danlos syndrome or Kawasaki disease, as well as some of the necrotizing arteritides such as polyarteritis nodosa, are unlike those traumatic lesions affecting the liver and spleen. The former aneurysms carry a potential risk of rupture or thrombosis. Most are diagnosed by CTA or MRA studies. Treatment includes endoluminal catheter-directed thrombosis, simple ligation, or aneurysmectomy with an arterial repair if necessary. Explicit clinical guidelines have yet to be established in the management of these rare aneurysms.

# Extremity Arterial Disease

## ACUTE LOWER EXTREMITY ARTERIAL OCCLUSION

Catastrophic lower extremity arterial occlusion in pediatric patients is uncommon.[62] It is often a consequence of UAC thromboembolic events in the neonate and femoral artery thromboses following arterial catheterizations or cannulations in the management of congenital heart disease.[63–66] In older children and adolescents, both penetrating and nonpenetrating arterial injuries can cause profound lower extremity ischemia.[67,68] On rare occasions less common etiologies of acute arterial occlusion exist including thrombosed aneurysms, paradoxical emboli, and thromboembolism associated with bacterial endocarditis.[69]

In the very young an isolated femoral artery occlusion without initial evidence of severe ischemia may be managed conservatively with heparin anticoagulation. Some have reported acceptable results of nonoperative therapy even in patients with critical ischemia.[70] The relative effectiveness of the collateral circulation in these circumstances usually preserves limb viability. If impending tissue loss or ischemic nerve dysfunction exists, then an open revascularization is appropriate and preoperative imaging is important by CTA or conventional arteriography by way of umbilical artery catheterization. In instances where further catheterizations should be avoided, an intravenous digital subtraction arteriography often suffices (Fig. 126-18). In cases of arterial injury due to blunt trauma or orthopedic trauma with long-bone fractures or posterior knee dislocations, the exact level of the injury may be difficult to discern and imaging in this setting will be essential to the diagnosis and proper treatment.

In situations of limited lower extremity arterial injury, a local resection and primary repair may be possible. Interrupted sutures in young children with spatulation of the involved vessels, so as to create an ovoid anastomosis, will lessen the risk of later stenosis of the repair. In older patients a patch angioplasty or bypass in the lower extremity with reversed saphenous vein is appropriate (Fig. 126-19).[63,71] Late aneurysmal deterioration of these grafts is unlikely, in contrast to their use in renal artery reconstruction.

## CHRONIC LOWER EXTREMITY ARTERIAL OCCLUSIONS

Chronic lower extremity ischemia in children has the potential to lead to growth retardation and later limb length discrepancies.[63,72] Arterial catheterization-related thromboses are the most common cause of delayed lower extremity ischemia.[63] In this regard, limb length discrepancy rates of 8% have been reported after femoral catheterizations.[73]

Chronic limb ischemia in children is often initially unrecognized because of the child's ability to develop extensive collaterals, with palpable pulses in the affected extremity similar to those in the uninvolved opposite extremity. Thus

**FIGURE 126-18** Intravenous digital subtraction arteriogram documenting occluded right external iliac and common femoral arteries. Iodinated contrast was injected centrally through a catheter advanced through the right brachial vein under fluoroscopic guidance to the junction of the vena cava and right atrium. (From Cardenau JD, Henke PK, Upchurch GR Jr, et al: Efficacy and durability of autogenous saphenous vein conduits for lower extremity arterial reconstructions in preadolescent children. J Vasc Surg 2001;34:34-40.)

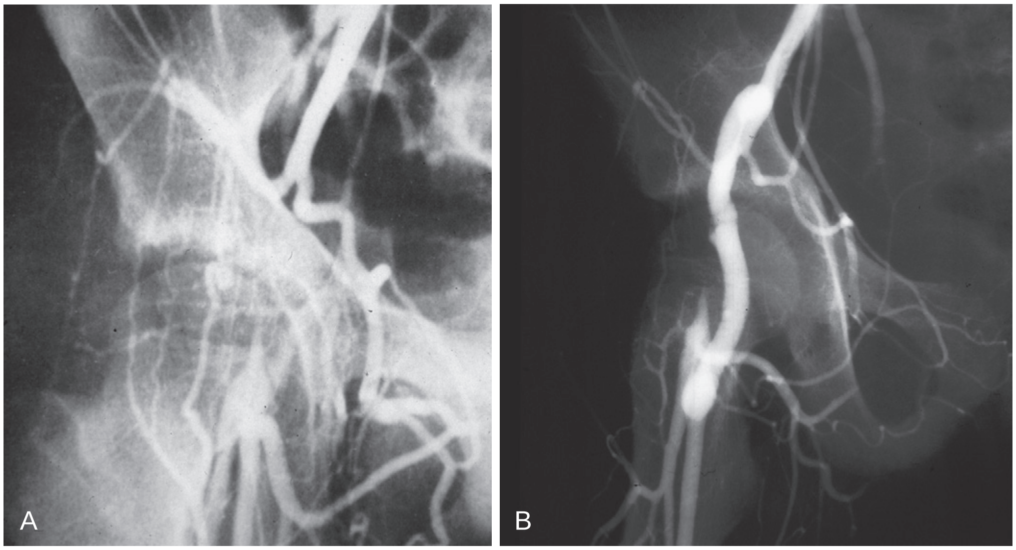


**FIGURE 126-19** **A,** Occlusion of common femoral and external iliac arteries due to thrombosis after cardiopulmonary bypass cannulation of the vessel in a child with a limb length discrepancy. The deep femoral and superficial femoral arteries are reconstituted through abundant collaterals. **B,** Subsequent iliofemoral bypass graft with saphenous vein.

it is often not until a discrepancy in limb length develops with gait abnormalities or the child complains of exercise-related symptoms that the diagnosis is even considered.

Simple Doppler ankle-brachial indices (ABIs) may suggest limb ischemia. However, detection may be evident only if a substantial decline in ABI occurs following treadmill exercise. Conventional arteriographic studies will best define the suspected occlusion in these children. Intravenous digital subtraction arteriography with newer computer-enhanced imaging has proven useful in defining these lesions while avoiding further vascular complications. Both MRA and CTA are evolving as commonly performed imaging techniques, but MRA may not provide small vessel detail and caution is appropriate regarding excessive radiation exposure if serial CTA studies are necessary.

Interestingly, 93% of patients in one study whose acute ischemia was managed without operation had their ABI return to normal after being treated with heparin anticoagulation alone.[74] Thus a normal resting ABI in the presence of an occluded iliac or femoral artery does not necessarily eliminate the risk for later growth problems. It is advised that arterial reconstruction using vein or synthetic grafts is appropriate for occluded iliofemoral or femoral arteries before a child enters rapid growth phases. Revascularization before adolescence when long bone growth is the most active is important to lessen limb length discrepancies. In the past, it had been generally accepted that late operation would not reverse an existing limb length discrepancy, but this has not always proven to be the case.

## UPPER EXTREMITY ARTERY OCCLUSIONS

Upper extremity ischemia is most commonly associated with blunt or penetrating trauma, shoulder or elbow dislocations, or supracondylar humerus fractures. Concomitant nerve injuries accompany many of these vascular injuries. Diagnosis is usually suspected from the clinical findings of pallor, reduced or absent pulses, and weakness with repetitive motions.

Formal imaging is not necessary if the site of injury is obvious by physical examination. In such a setting a standard vascular repair should be pursued if the ischemia is severe with impending tissue loss or pain with minimal activity. Lesser degrees of acute ischemia may abate with development of collateral vessels. In those children, especially the very young, conservative nonoperative therapy may be appropriate. If exercise-related claudication occurs later, a formal revascularization may be undertaken. In many early cases with a focal injury, the involved arterial segment may be excised, the vessel mobilized so as to have no tension on it, and a primary reanastomosis undertaken. In other cases a bypass with autologous saphenous or basilic vein may be required.

Subclavian-axillary artery occlusion is an unusual complication of the birthing process (Fig. 126-20). Mechanisms causing this complication are believed to be similar to those cited for brachial plexus birth injuries. Arterial occlusions may result from intimal fracture secondary to stretching of the vessel or from direct compression due to thoracic outlet closure or shoulder dislocation. Acute ischemia placing the limb at jeopardy in these neonates is rare. Development of more severe symptoms is related to damage of collateral arterial flow around the obstructed vessel. Subclavian artery sacrifice for Blalock-Taussig procedures rarely causes acute ischemia because the collaterals are carefully preserved.[75] Exercise fatigue may accompany later growth abnormalities. Diminutions in longitudinal bone growth and muscle mass are common with subclavian artery occlusion. Growth disturbance alone is not an indication for surgical intervention, inasmuch as upper extremity limb length discrepancies are well tolerated and do not carry the same clinical significance as they do in the lower extremities. Carotid-subclavian or carotid-axillobrachial bypasses in late childhood are often required to relieve symptomatic forearm and hand ischemia.

## EXTREMITY ARTERIAL ANEURYSMS

Upper and lower extremity arterial aneurysms are rare, being associated with penetrating and blunt trauma, iatrogenic pseudoaneurysms following arterial punctures and catheterizations,

FIGURE 126-20 High-grade stenosis of proximal subclavian artery with poststenotic dilation and an axillary artery occlusion associated with birth trauma.

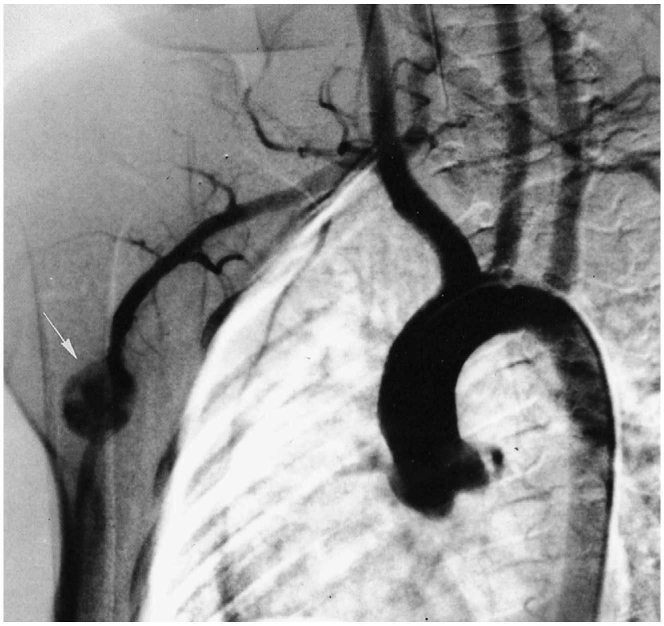

FIGURE 126-21 Brachial artery aneurysm associated with Kawasaki disease.

and nontraumatic aneurysms in cases of Kawasaki disease, Ehlers-Danlos syndrome, and other infrequently encountered vasculopathies. Aneurysms, regardless of etiology, affecting the larger arteries of both upper and lower extremities carry a greater risk of thromboembolism than rupture. Depending on the presence of collateral vessels, most of these aneurysms should be treated operatively with either ligation or vascular reconstruction.[76]

Peripheral aneurysms in Kawasaki disease are of particular note (Fig. 126-21). The syndrome affects children younger than 4 years of age in 80% of cases,[77] and the most lethal aspect of this disease relates to its cardiac complications. Nearly 15% of these children develop coronary aneurysms, which are prone to thrombose, causing myocardial infarction and sudden death. Operative interventions for peripheral aneurysms in children with Ehlers-Danlos syndrome often involve simple ligation with large suture or umbilical tape, with formal arterial reconstructions undertaken when the ligation may cause critical limb ischemia. Ultrasound-guided percutaneous thrombin injection as a means of occluding traumatic and iatrogenic pseudoaneurysms has merit, but such must not result in propagation of thrombus and subsequent severe limb ischemia.[78]

# Cerebrovascular Disease

Ischemic strokes in childhood and adolescence are rare and often multifactorial.[79] Contributing to these strokes are numerous prothrombotic states including protein C and S deficiencies, antithrombin III deficiency, hyperhomocysteinemia, and sickle cell disease; structural cardiac defects accompanying congenital heart disease; a remote history of varicella zoster infection; a recent history of head or neck trauma; and various arteritides such as Takayasu disease (Fig. 126-22). A comprehensive investigation of pediatric patients experiencing a stroke should include characterization of the extracranial and intracranial vessels by

FIGURE 126-22 Magnetic resonance angiography of Takayasu disease evident by stenoses of left carotid and subclavian (*arrowhead*) arterial origins. Irregular narrowing of distal aortic arch (*arrow*).

MRA, CTA, or a conventional digital subtraction arteriogram. Such imaging will lessen the chance of overlooking a lesion amenable to surgical correction.

## CAROTID ARTERY OCCLUSION

Carotid artery stenoses or occlusions were present in approximately 50% of ischemic stroke patients studied at a major children's hospital.[80] Moyamoya disease accounted for nearly a third of these cases. Moyamoya disease is characterized by occlusions of the terminal branches of the internal carotid artery and proximal middle cerebral artery, with a "plume-of-smoke" appearance of the resulting collaterals that typify this entity. Moyamoya disease is a noninflammatory vasculitis of unknown etiology. It is seen most often in children from Southwest Asia, although all racial groups have been reported affected. The use of anticoagulants and calcium channel blockers in the acute setting have a place, although the exact benefits are ill defined. Most relevant to surgeons is recognition of the importance of maintaining normotension, euvolemia, and normocapnia during anesthesia to lessen the risk of further cerebral ischemic injury.[81–83] The operative revascularization procedures including superficial temporal-middle cerebral artery bypass or indirect revascularization procedures are complex and generally lessen the risk of future stroke.[84] The role of thrombolysis in children experiencing a stroke is still undetermined.[85]

Dissections affect the upper cervical region of the internal carotid artery and are known to follow excessive hyperextension or forceful rotation of the head and neck.[86–88] Spontaneous dissections of this type are uncommon in children. Carotid artery dissections are usually accompanied by severe facial and neck pain (hemicrania) and are often associated with syncope, near syncope, a seizure, or stroke. The majority of patients will exhibit Horner syndrome. Treatment is usually conservative, with the use of anticoagulation. The mural hematomas associated with the dissection frequently resolve, leaving a near normal artery. When such does not occur and the child is experiencing cerebral ischemic symptoms, operative therapy is recommended. Resection of the affected carotid artery and reconstruction with an interposition graft is appropriate in that setting.

## CAROTID ARTERY COILING

Developmental coiling and tortuosity of the extracranial internal carotid artery have been reported to affect a quarter to nearly half of young children undergoing arteriographic studies (Fig. 126-23).[65,89] The true incidence of this abnormality is likely less because those being studied may represent a selected group, but nevertheless these findings are not rare in the very young.

Coiling and tortuosity of the internal carotid artery are normal findings in the fetus. As the heart and great vessels migrate caudally, the vessel usually straightens. Occasionally the embryonic tortuosity persists. Frequent demonstration of bilateral abnormalities lends credence to arrested development as the basis of these lesions. The patterns of internal carotid artery coiling and tortuosity range from gentle S-shaped tortuosities to complete coiling.[89] These changes characteristically begin a few centimeters beyond the common carotid artery bifurcation.

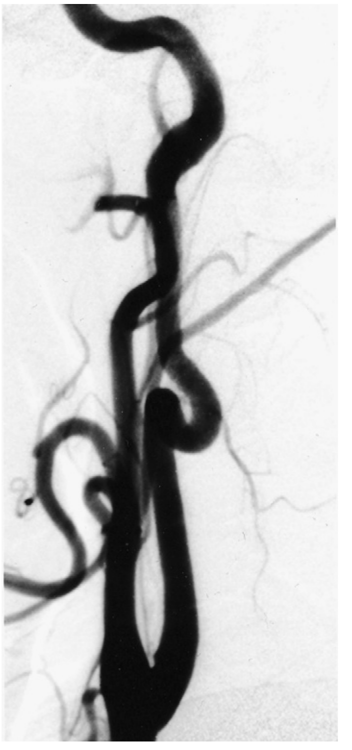

**FIGURE 126-23** Internal carotid artery coiling.

Most children with internal carotid artery coiling are asymptomatic. However, neurologic symptoms including transient ischemic attacks, hemiparesis, and seizures have been alleged to be associated with coiling in certain individuals.[90] Although the subject of considerable controversy, there may be a small number of children having lateralizing neurologic symptoms who may benefit from surgical intervention.[91] Reimplantation of the internal carotid artery more proximally onto the common carotid artery or excision of the redundant artery with reanastomosis is the most frequent reconstruction undertaken in symptomatic children.

## CAROTID ARTERY ANEURYSMS

Aneurysms of the proximal extracranial carotid artery are rare in children.[92] True aneurysms are usually manifestations of a generalized vascular disease like Ehlers-Danlos syndrome. Traumatic pseudoaneurysms are uncommon and are usually the consequence of blunt trauma (Fig. 126-24). Other traumatic aneurysms represent a complication of tonsillectomy or, occasionally, errant placement of central venous catheters. Most carotid artery aneurysms deserve early operative treatment to lessen the risk of cerebral embolization. Simple arterial suture of the entrance into a pseudoaneurysm or an interposition graft, usually with an internal iliac artery segment, in the case of extensive aneurysmal involvement is appropriate. There may be a role for endoluminal therapy, with placement of covered stents in certain children.[93]

Small mural aneurysms affecting the internal carotid artery adjacent to the upper cervical vertebrae are often due to violent head trauma with stretching and fracture of the vessel wall. These may be the source of emboli or thromboses acutely


**FIGURE 126-24** Internal carotid artery aneurysm following blunt trauma.

causing a massive stroke. Anticoagulant and antiplatelet therapy lessen these events. Lining the involved artery with a covered stent or replacement with an interposition graft may be advised if recurrent cerebral ischemic symptoms occur despite medical therapy.

## VERTEBRAL ARTERY DISSECTIONS AND OCCLUSION

Injury of the vertebral artery due to forceful stretching or blunt trauma may result in a dissection causing an acute stroke.[88,94] However, many dissections are initially asymptomatic. CTA imaging in children with severe head and cervical spine trauma may allow earlier recognition and treatment of these lesions. Simple administration of heparin and antiplatelet agents has been successful in many patients.[95] Operative revascularization is usually deferred to symptomatic patients due to chronic occlusions in whom rotational nystagmus and other posterior circulatory phenomena can be demonstrated.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 127

# Congenital Heart Disease and Anomalies of the Great Vessels

Richard G. Ohye and Jennifer C. Hirsch

Congenital cardiac malformations are the most common congenital defects, with an incidence of 0.5% to 1% of live births (excluding trivial lesions and bicuspid aortic valves). Although the technical details of the repair of complex malformations are beyond the scope of this textbook, pediatric surgeons should have a basic understanding of the anomalies and their repair because they are often involved in the management of these patients. All patients undergoing open cardiac surgical procedures receive standard gram-positive antibiotic prophylaxis at the time of surgery. Prophylaxis for future noncardiac surgical procedures is based on the current American Heart Association guidelines recommending prophylaxis for any patients with significant residual defects or significant valvar dysfunction. Prophylaxis is not required for patients who have patch material in place for greater than 6 months. The pediatric surgeons' "encounters" with the pediatric cardiac population may occur in many different contexts: (1) A cardiac malformation may be present or suspected in a fetus for whom the pediatric surgeon is consulted for a general surgical malformation, the prognosis of which may be affected by the cardiac defect (i.e., giant omphalocele); (2) intestinal ischemia is often suspected in premature infants with a patent ductus arteriosus or term babies with cardiac malformations leading to decreased splanchnic blood flow; (3) cardiac defects are common in patients with esophageal atresia, with aortic arch anomalies presenting specific challenges to pediatric surgeons; (4) vascular anomalies such as a persistent left superior vena cava may be associated with cardiac malformations and pose problems during attempts at central venous access; (5) polysplenia/asplenia and intestinal malrotation are frequent in patients with situs inversus; and (6) finally, pediatric surgeons may be involved in postcardiac surgery ECMO or may be called urgently for insertion of a peritoneal drainage catheter after an infant has undergone a cardiac surgical procedure. For all these reasons, pediatric surgeons should understand the anatomy and pathophysiology of common malformations of the heart and great vessels.

## Patent Ductus Arteriosus

The ductus arteriosus is a normal fetal structure that communicates between the pulmonary trunk or proximal left pulmonary artery (PA) and the proximal descending thoracic aorta (Fig. 127-1). During fetal development, this vessel provides a pathway for blood leaving the right ventricle to bypass the high-resistance pulmonary vascular bed and traverse the systemic circulation instead. Histologically, the media of the aorta and PA contain circumferentially arranged elastic fibers, whereas the media of the ductus is composed mostly of smooth muscle cells. Normally after birth, the rise in oxygen tension that accompanies ventilation of the lungs signals closure of the ductus. In a full-term infant, closure of the ductus is usually complete by 12 to 24 hours. Closure of the ductus creates a fibrous cord called the *ligamentum arteriosum.* Failure of closure of the ductus leads to the condition known as *patent ductus arteriosus* (PDA). The incidence of isolated PDA is approximately 1 in 1200 live births and accounts for about 7% of all congenital heart defects.[1] The incidence is higher in preterm infants (>20%).[2] This defect may occur in isolation or in association with a number of other anomalies. In some heart defects in which there is inadequate pulmonary blood flow (such as pulmonary atresia) or inadequate systemic blood flow (e.g., severe coarctation of the aorta), persistent patency of the ductus is desirable. The discovery of prostaglandins to maintain ductal patency has played a significant role in improving the survival of such patients.[3]

### NATURAL HISTORY AND DIAGNOSIS

The pathophysiology of PDA involves shunting of blood across the ductus. The shunt volume is determined by the size of the ductus, as well as the ratio of pulmonary to systemic vascular resistance. Pulmonary vascular resistance drops dramatically at birth and continues to decrease over the first weeks of life. This leads to left-to-right flow across the ductus. Excessive pulmonary blood flow typically leads to congestive heart failure, and in extreme cases, hypotension and systemic malperfusion may also occur. For patients with a large PDA who survive infancy, there is a risk of developing pulmonary

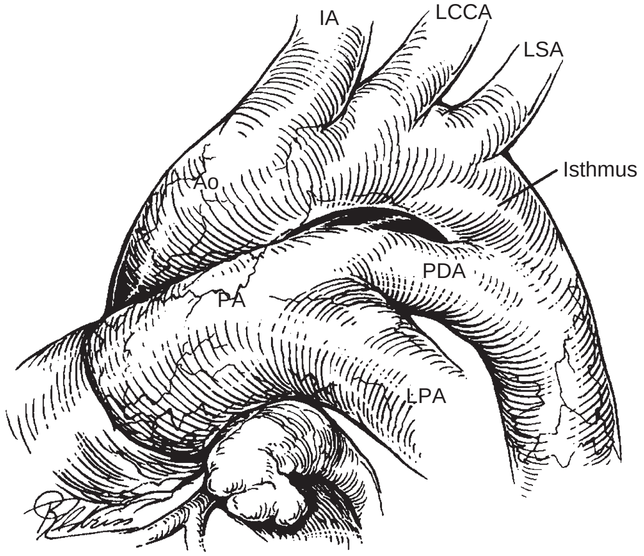



FIGURE 127-1 Anatomy of patent ductus arteriosus (PDA) as seen from a left thoracotomy. The ductus extends from the main pulmonary artery (PA) and enters the proximal descending thoracic aorta distal to the left subclavian artery (LSA). Ao, aorta; IA, innominate artery; LCCA, left common carotid artery. (From Hillman ND, Mavroudis C, Backer CL: Patent ductus arteriosus. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

vascular obstructive disease. In these cases, Eisenmenger's physiology may develop when pulmonary vascular resistance exceeds systemic vascular resistance, leading to a reversal of shunting across the ductus (from left to right to right to left), causing cyanosis and, eventually, right ventricular failure. Some patients with a small PDA may remain asymptomatic until adulthood. Endocarditis and endarteritis have been reported as long-term complications of PDA.[4]

The clinical manifestations of PDA are determined by the shunt volume and the presence of associated cardiac defects. Left-to-right shunt flow leads to volume overload of the left heart. Signs of congestive heart failure in infants commonly include tachypnea, tachycardia, and poor feeding. Older children may present with recurrent respiratory infections, fatigue, and failure to thrive. Physical findings include a widened pulse pressure and an active precordium. Auscultation reveals a continuous "machinery" murmur heard best along the left upper sternal border. Radiographic findings include increased pulmonary vascular markings and left heart enlargement generally in proportion to the degree of shunting. Electrocardiography may demonstrate left ventricular hypertrophy and left atrial enlargement. Echocardiography is currently the diagnostic method of choice and can additionally rule out the presence of associated defects. Cardiac catheterization is reserved for two principal indications. First, in older patients with suspected pulmonary hypertension, it can be used to evaluate for pulmonary vascular obstructive disease. Second, transcatheter techniques have been developed to occlude the ductus in selected cases.[5–7]

## MANAGEMENT

Three management schemes for the closure of a PDA exist: pharmacologic therapy, surgical closure, and endovascular device closure. Indomethacin and ibuprofen, cyclooxygenase inhibitors, are useful for stimulating PDA closure in premature infants.[8] Indomethacin and ibuprofen are known to have a number of possible side effects including hypotension, decreased gastrointestinal blood flow (which may lead to necrotizing enterocolitis or spontaneous intestinal perforation), decreased renal blood flow, and interference with platelet function. Due to an improved side effect profile regarding gastrointestinal bleeding and renal dysfunction, ibuprofen is the current drug of choice.[9] It is rarely effective in full-term babies. The dosing regimen is 10 mg/kg intravenously, followed by 5 mg/kg intravenously at 24-hour intervals for a total of three doses. This approach is successful in nearly 80% of premature infants.[9,10] Contraindications to ibuprofen therapy include sepsis, renal insufficiency, and bleeding disorders. Failure of ibuprofen after two complete courses results in referral for surgical closure.

The surgical approach to the PDA is usually via a left posterolateral thoracotomy through the third or fourth intercostal space (Fig. 127-2). The pleura is divided longitudinally over the proximal descending thoracic aorta. The vagus nerve is thereby lifted medially. Dissection is carried out to demonstrate unequivocally the distal transverse aortic arch and ductus. In some cases the ductus may be the largest vascular structure present, so it is critical that it not be confused with the aorta. Once the anatomy is confirmed, the ductus is gently dissected. Ductal tissue is extremely friable, especially in premature infants, so direct manipulation is not recommended.

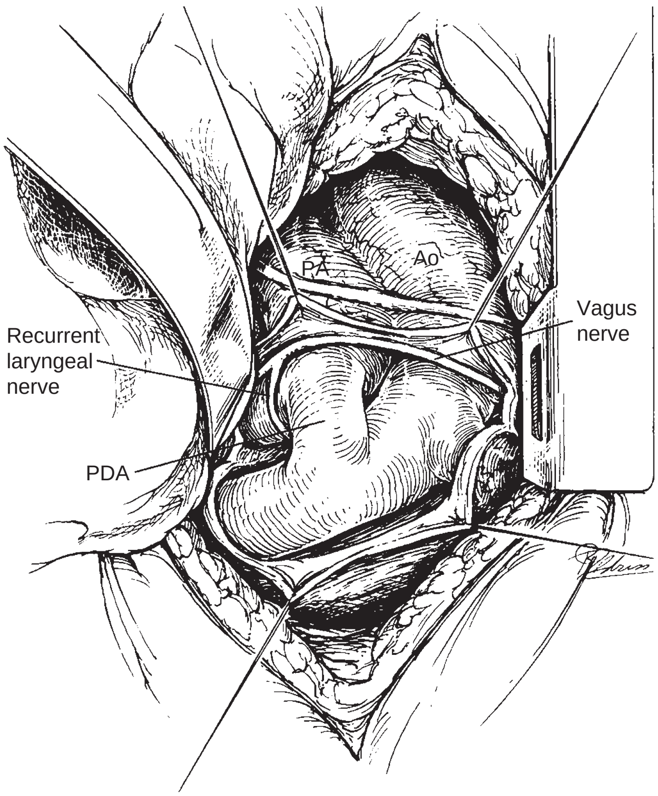



FIGURE 127-2 Exposure of patent ductus arteriosus (PDA) by left thoracotomy. The mediastinal pleura has been divided and reflected with preservation of the vagus and recurrent laryngeal nerves. Ao, aorta; PA, pulmonary artery. (From Hillman ND, Mavroudis C, Backer CL: Patent ductus arteriosus. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

The recurrent laryngeal nerve curves behind the ductus and must be preserved during the dissection. The ductus may be occluded with a surgical clip or silk ligature, or it may be divided between ligatures (Fig. 127-3). The latter is preferred in most cases; however, in premature infants, the safest approach is clip occlusion. The surgical procedure is commonly performed in the neonatal intensive care unit, which avoids problems associated with patient transfer.[11,12]

Recently, PDA ligation has been performed using video-assisted thoracoscopy.[13] This approach has the potential benefits of decreased pain and shorter hospital stay. Disadvantages include a substantial learning curve and increased operating time.

Several endovascular devices have been developed for the purpose of transcatheter occlusion of the PDA.[5–7] These devices have proved to be so successful that at most centers, transcatheter occlusion has become the treatment of choice for older infants and children with small- to moderate-sized PDAs. Surgical therapy is reserved for patients with larger-sized ducts.

## RESULTS

Closure of the PDA by surgical or transcatheter approach can be performed with a mortality close to zero.[11] Potential morbidity from surgical therapy may include pneumothorax, recurrent laryngeal nerve injury, phrenic nerve injury, and chylothorax. Most patients should experience a normal life expectancy following PDA ligation. Long-term survival in premature infants depends primarily on the extent of prematurity and the presence of associated anomalies.

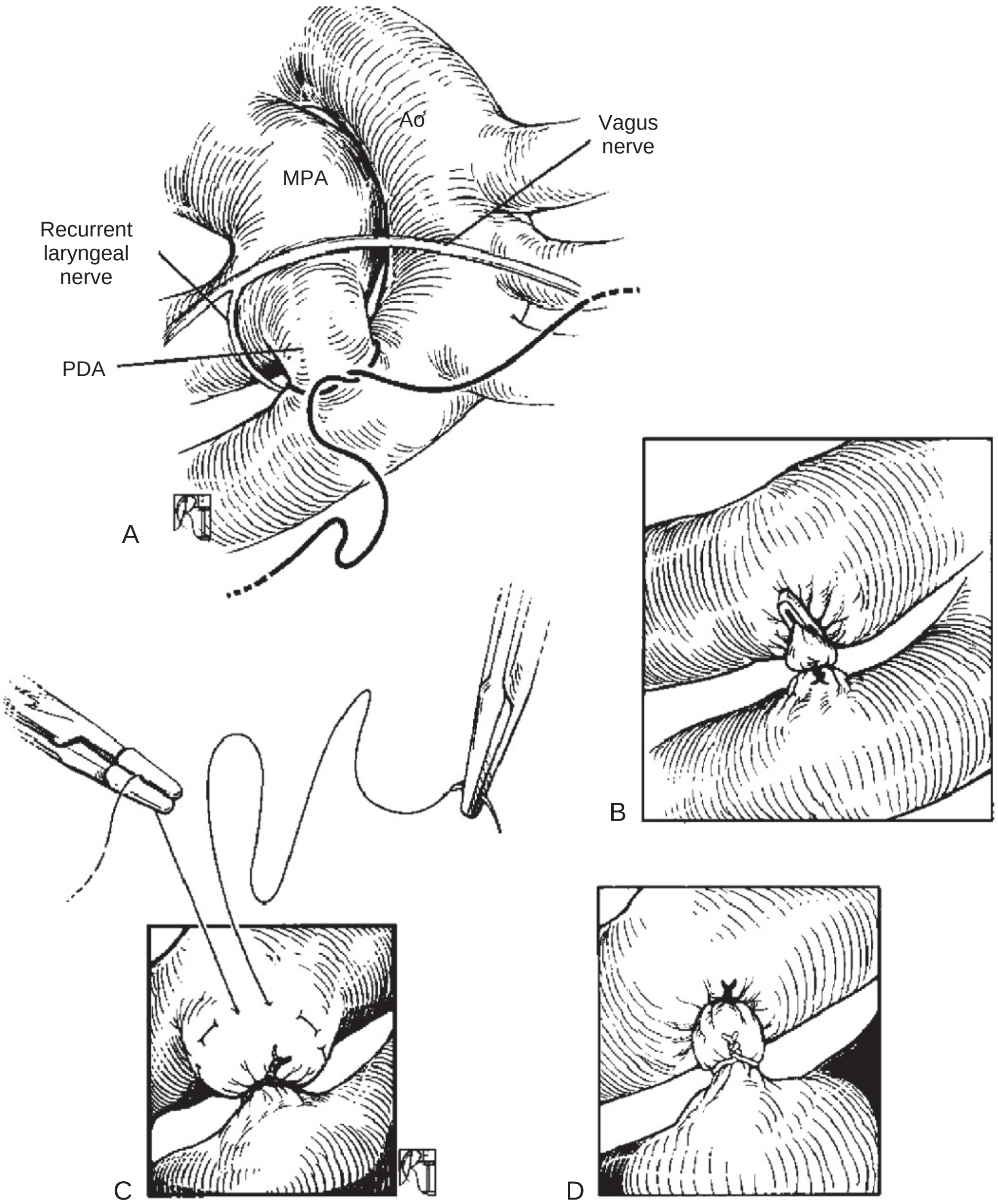



**FIGURE 127-3** Various techniques for control of the patent ductus arteriosus (PDA). **A**, Simple ligation. **B**, Ligation and hemoclip application. **C** and **D,** Ligation and adventitial pursestring. Ao, aorta; MPA, main pulmonary artery. (From Hillman ND, Mavroudis C, Backer CL: Patent ductus arteriosus. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

# Coarctation of the Aorta

Coarctation of the aorta is a congenital narrowing of the proximal descending thoracic aorta near the insertion of the ductus arteriosus (or ligamentum arteriosum). This creates obstruction to blood flow and results in a pressure load on the left ventricle. The incidence of coarctation is about 0.5 per 1000 live births, and its prevalence is 5% of congenital heart defects.[1] Coarctation is commonly associated with other heart defects including bicuspid aortic valve (in > 50% of cases), patent ductus arteriosus, and ventricular septal defect. Other left-sided obstructive lesions may be present including aortic arch hypoplasia, aortic stenosis, mitral stenosis, and left ventricular hypoplasia.

## NATURAL HISTORY AND DIAGNOSIS

Two patterns of presentation are based on anatomy, age, and symptoms (Fig. 127-4). In infantile coarctation, patients develop symptoms in the first week of life. These infants have such severe aortic obstruction that perfusion of the lower body depends on flow from the ductus arteriosus. Spontaneous ductal closure (which also tends to worsen the aortic obstruction) then precipitates ischemia to tissues beyond the coarctation. The resultant pressure load on the left ventricle may lead to congestive heart failure. Patients may exhibit shock with severe acidosis, oliguria, and diminished distal pulses. Survival for these patients is unlikely without intervention.

The second pattern of presentation is sometimes called *adult coarctation*. Patients with adult coarctation are usually asymptomatic during infancy and present later in life with hypertension. These patients generally develop extensive collaterals, which serve to bypass the obstruction. Life expectancy for these patients is limited due to the development of heart failure later in life and the cumulative risk of endocarditis (frequently involving a bicuspid aortic valve) or endarteritis (in the poststenotic aorta at the site of the turbulent jet), aortic rupture, or intracranial hemorrhage (from Berry aneurysms, which are more common in patients with coarctation).[14]

Coarctation can usually be diagnosed clinically. The newborn infant with significant coarctation may appear normal at birth but following ductal closure develops signs of heart failure such as irritability, tachypnea, and poor feeding. Lower-extremity pulses are absent, and upper-extremity pulses may be weak. Chest radiography may show cardiomegaly and pulmonary venous congestion. There is a left ventricular strain pattern on the electrocardiogram. Echocardiography is usually diagnostic, demonstrating anatomic narrowing at the coarctation site with a loss of pulsatility in the descending aorta; additional cardiac defects are also demonstrable.

In older children and adults, there is usually a pressure gradient between the arms and legs, which can be identified by measuring cuff pressures in all four extremities. Radiography may demonstrate rib notching, which is secondary to the development of large intercostal collaterals that erode into the inferior aspects of the ribs. Echocardiography is usually sufficient to confirm the diagnosis in older patients; however, computed tomography (CT) and magnetic resonance imaging (MRI) provide excellent anatomic detail, which may aid in therapeutic planning. Cardiac catheterization is usually not necessary.

## MANAGEMENT

The diagnosis of coarctation usually mandates surgical correction; however, the acute medical management of the sick neonate demands careful attention. Prostaglandin $E_1$ is usually effective for reopening the ductus when administered within 7 to 10 days after birth; its effectiveness wanes when initiated after 2 weeks of life. Intravenous fluids, inotropic agents, and correction of anemia may also be important for the resuscitation of the patient with coarctation.

Surgical exposure of coarctation is performed by left posterolateral thoracotomy through the third or fourth intercostal space. The mediastinal pleura overlying the left subclavian artery and proximal descending thoracic aorta is incised, and the descending aorta, transverse arch, brachiocephalic vessels, and ductus (or ligamentum) are mobilized. Care is taken to avoid injury to the vagus nerve and its

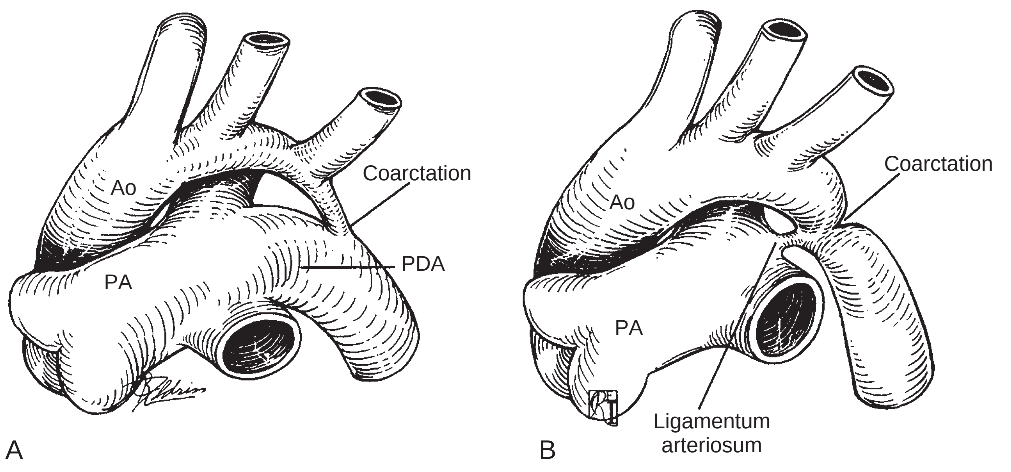



FIGURE 127-4 **A**, Infantile coarctation of the aorta (Ao). The isthmus (segment of the aorta between the left subclavian artery and ductal insertion) is hypoplastic, and the descending aorta receives most of its flow from the ductus. **B**, Adult coarctation with juxtaductal narrowing of the aorta and a prominent posterior shelf. The ductus has contracted to form the ligamentum arteriosum. PA, pulmonary artery; PDA, patent ductus arteriosus. (From Backer CL, Mavroudis C: Coarctation of the aorta. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

recurrent branch. The coarctation is usually evident externally by narrowing or posterior indentation; however, the degree of internal narrowing is usually much more severe. A dose of heparin (100 units/kg) may be given intravenously for patients younger than 2 years. Proximal and distal control of the aorta is achieved using clamps. Usually the proximal clamp is positioned on the transverse arch between the innominate and left carotid vessels with concomitant occlusion of the left carotid and left subclavian. In infants and children, the preferred surgical approach to coarctation is resection with extended end-to-end repair (Fig. 127-5).[15] A generous resection of the coarctation segment is performed. The proximal aorta is then spatulated along the lesser curvature and the distal aorta along the greater curvature. An extended end-to-end anastomosis is then performed.

In older children and adults, it may not be possible to perform a resection with primary repair without creating excessive tension on the anastomosis, which might lead to hemorrhage or scarring with recurrent coarctation. In these cases, an alternative strategy is indicated. In children, in whom further growth is expected, the coarctation may be repaired by patch aortoplasty.[16,17] Less initial dissection is required. After achieving proximal and distal control, a longitudinal aortotomy is made across the area of narrowing. A patch of polytetrafluoroethylene or the left subclavian artery can be used to patch augment the coarctation. By avoiding circumferential prosthetic material, growth potential of the native aortic tissue is preserved. In adults, growth is no longer an issue and resection of the coarctation may be performed with subsequent placement of an interposition graft (either polytetrafluoroethylene or Dacron).

During the operative repair of coarctation, injury to the spinal cord is a major concern. In patients who do not have well-formed collaterals, ischemia of the spinal cord may be precipitated by aortic cross-clamping and paraplegia may result. Standard protective measures include induction of mild hypothermia (35° C), maintenance of a high proximal aortic pressure, and minimization of cross-clamp time. In older children and adults

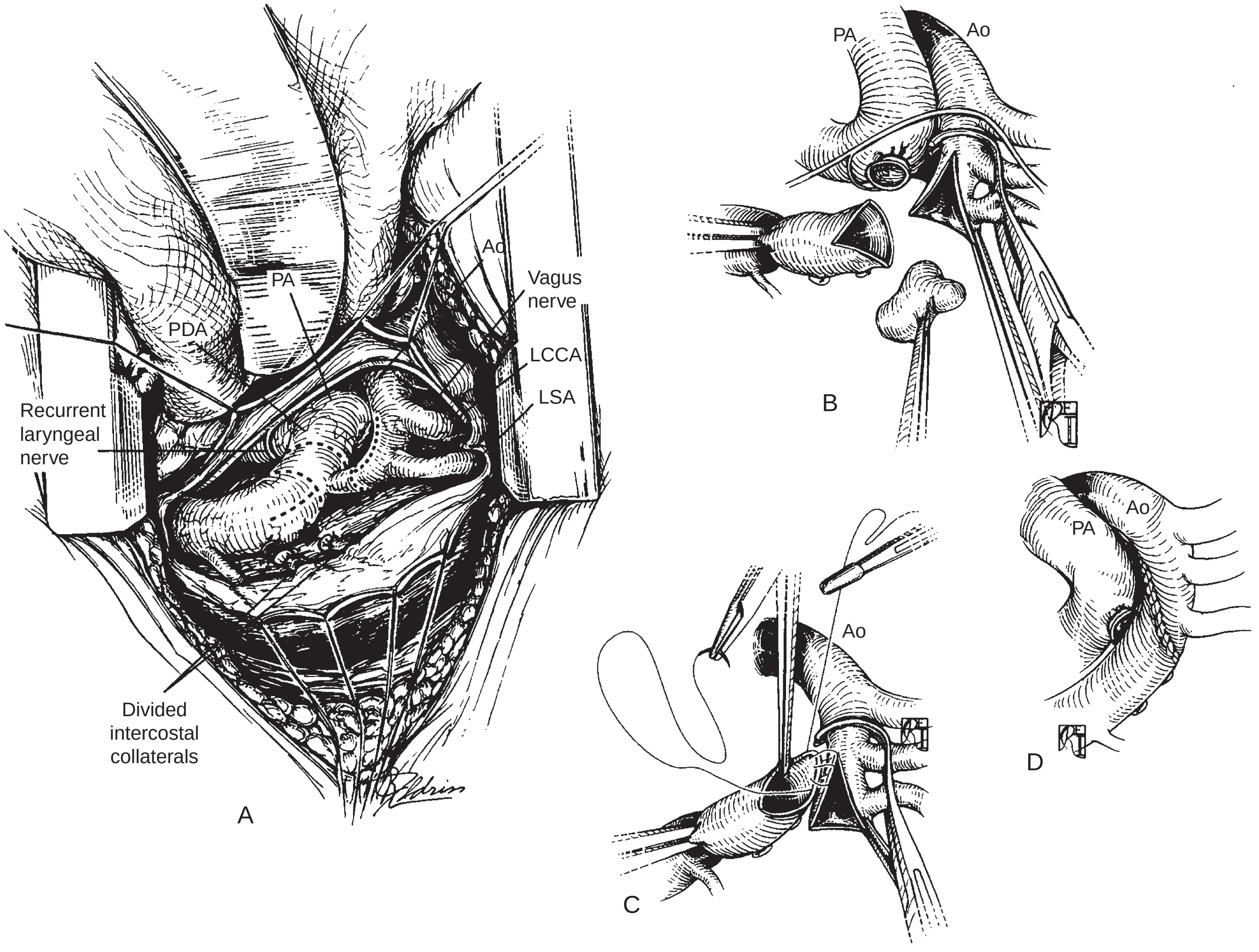



**FIGURE 127-5** Resection with extended end-to-end anastomosis. **A**, Exposure by left posterolateral thoracotomy. Vessels are mobilized and intercostals divided when necessary. **B**, The ductus is ligated and divided. Proximal and distal control is achieved, and the coarctation segment is resected. The proximal and distal aortic segments are spatulated along the lesser and greater curvatures, respectively. **C**, The anastomosis is performed using a running technique. **D**, The completed repair. Ao, aorta; LCCA, left common carotid artery; LSA, left subclavian artery; PA, pulmonary artery; PDA, patent ductus arteriosus. (From Backer CL, Mavroudis C: Coarctation of the aorta. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

with inadequate collateral flow, distal aortic perfusion may be maintained by the technique of left heart bypass (in which the left atrium is cannulated for drainage of oxygenated blood, which is then delivered to the femoral artery or distal aorta using a centrifugal pump).[18] Overall, the incidence of paraplegia following coarctation repair is less than 1%.[19]

Following repair, patients may develop severe hypertension. This can be managed using intravenous beta blockers (such as esmolol). Uncontrolled hypertension may lead to the complication of mesenteric arteritis. Hypertension usually resolves within days to weeks after repair, although older children and adults may require permanent antihypertensive therapy. Repair of coarctation during infancy is thought to minimize the risk of late hypertension.[20]

Transcatheter therapy has been attempted as primary therapy for coarctation, but this approach is controversial.[21–24] Limitations of this approach include the incidence of recurrent coarctation, the potential need for multiple interventions, injury to the femoral vasculature (for access), and incidence of aneurysm formation. Technical success rates range from 80% to 98% with a reintervention rate of 10% to 20%.[25,26] Balloon angioplasty is generally recommended for the treatment of recurrent coarctation following surgery, in which its efficacy is on the order of 90%.[27–29]

### RESULTS

The early mortality following repair of coarctation in neonates is 2% to 10%, while the risk in older children and adults is about 1%.[15,30] The incidence of recurrent coarctation following resection and end-to-end repair is about 4% to 8%.[15,31] The long-term survival following coarctation repair is determined by the presence of associated defects and the persistence of hypertension.

## Atrial Septal Defects

Atrial septal defects (ASDs) are the third most common congenital heart defect, occurring in 1 out of 1000 live births and representing 10% of congenital heart defects.[1] In order to understand the terminology of ASDs, a review of normal atrial septation is useful. During embryologic development, the septum primum initially divides the common atrium. The ostium primum, which exists at the inferior edge of the septum primum, is obliterated as the septum primum fuses with the endocardial cushions. The ostium secundum forms in the midportion of the septum primum and is then covered by the septum secundum, which descends from the roof of the atrium along the right side of the septum primum. This arrangement creates a flap valve whereby blood from the inferior vena cava may preferentially stream beneath the edge of the septum secundum and through the ostium secundum into the left atrium. Following birth, the septum secundum fuses with the septum primum, thereby sealing the interatrial communication (Fig. 127-6).

Atrial septal defects may be classified on the basis of this embryology. The most common defect is the secundum atrial septal defect (80%), which occurs when the ostium secundum is too large for complete coverage by the septum secundum

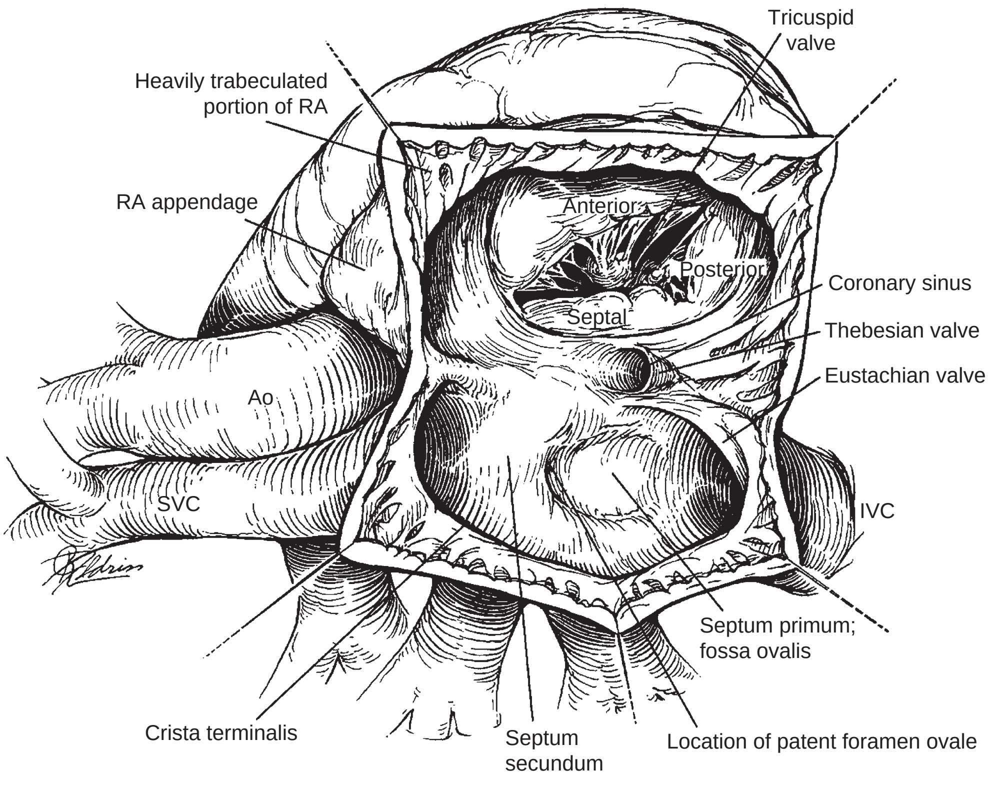



**FIGURE 127-6** Normal intraatrial anatomy as viewed by the surgeon through a right atriotomy. Ao, aorta; IVC, inferior vena cava; SVC, superior vena cava; RA, right atrium. (From Backer CL, Mavroudis C: Atrial septal defect, partial anomalous pulmonary venous connection, and scimitar syndrome. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

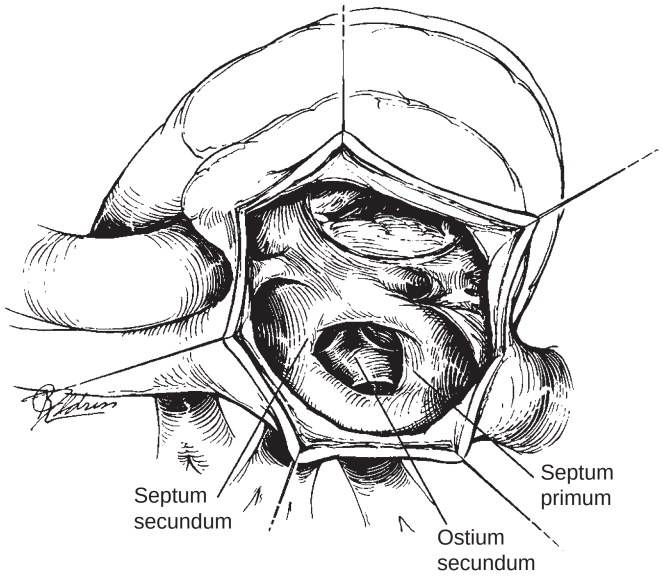



**FIGURE 127-7** Ostium secundum atrial septal defect. Note the deficiency of the septum primum in the region of the normal fossa ovalis. (From Backer CL, Mavroudis C: Atrial septal defect, partial anomalous pulmonary venous connection, and scimitar syndrome. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

(Fig. 127-7). Failure of postnatal fusion of the septum secundum to the septum primum results in a persistent slitlike communication known as a patent foramen ovale (PFO). A primum atrial septal defect (10%) represents persistence of the ostium primum, which occurs as a result of failure of fusion of the septum primum with the endocardial cushions. This defect is discussed in the section on atrioventricular septal defects. Sinus venosus ASDs (10%) are caused by abnormal fusion of the venous pathways with the atrium; these defects can be located high in the atrial septum near the orifice of the superior vena cava, or, less commonly, they may be low in the atrial septum near the orifice of the inferior vena cava (Fig. 127-8). Sinus venosus ASDs occur commonly with partial anomalous pulmonary venous return, usually with the right upper pulmonary vein draining into the superior vena cava near the cavoatrial junction. An uncommon type of ASD is the unroofed coronary sinus septal defect. This occurs when there is loss of the common wall between the coronary sinus and left atrium adjacent to the atrial septum. This unroofing of the coronary sinus results in a communication between the right and left atria at the site of the coronary sinus.

## NATURAL HISTORY AND DIAGNOSIS

Shunting at the atrial level occurs primarily during diastole and is determined in part by the size of the atrial defect and more importantly by the relative ventricular compliance. In other words, blood preferentially fills the more compliant chamber. At birth, both chambers are equally compliant, but as pulmonary vascular resistance falls, the right ventricle remodels and becomes more compliant. As a result, shunting across an ASD in postnatal life is from left to right. This results in a volume load on the right heart. A volume load is a burden created by additional venous return to a chamber during diastole.

The volume overload created by an ASD is usually well tolerated. As a result, patients are frequently asymptomatic. Congestive heart failure is rare in infants. Children may develop symptoms of exertional dyspnea, exercise intolerance, or recurrent respiratory infections. Older patients with untreated ASDs tend to develop atrial dysrhythmias, and adults may develop congestive heart failure and right ventricular dysfunction. Pulmonary vascular obstructive disease may develop as a late complication of untreated ASD; severe pulmonary hypertension has been shown to develop in 14% of adults

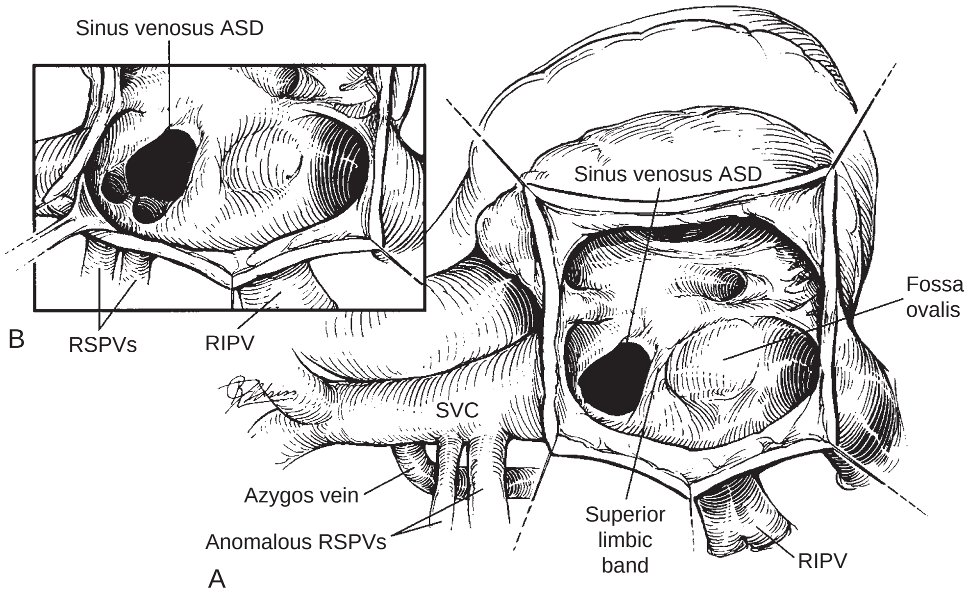



**FIGURE 127-8** Sinus venosus atrial septal defect. **A**, Defect near the superior cavoatrial junction cephalad to the superior limbic band. Note the anomalous drainage of right superior pulmonary veins (RSPVs) to the superior vena cava (SVC) and normal drainage of the right inferior pulmonary veins (RIPVs). **B**, Another type of sinus venosus ASD with anomalous RSPVs draining adjacent to the defect. (From Backer CL, Mavroudis C: Atrial septal defect, partial anomalous pulmonary venous connection, and scimitar syndrome. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

with untreated large ASDs between the ages of 20 and 40 years.[32] Paradoxical embolization (deep venous thrombus passing to the systemic circulation via the ASD) is also an important potential complication of ASD.

On physical examination, a patient with an ASD has fixed splitting of the second heart sound and a systolic ejection murmur at the left upper sternal border due to relative pulmonary stenosis (increased flow across a normal pulmonary valve). A chest radiograph shows cardiomegaly, and electrocardiography frequently demonstrates incomplete right bundle branch block. Echocardiography confirms the clinical diagnosis of ASD and clarifies the anatomy. Cardiac catheterization is rarely necessary for diagnostic purposes but may be necessary to evaluate pulmonary vascular resistance in older patients. Cardiac catheterization is most widely used with therapeutic intent (device closure).

### MANAGEMENT

Due to the long-term complications associated with ASD, repair is recommended for all patients with symptomatic defects and in asymptomatic patients in whom the ratio of pulmonary to systemic blood flow (Qp/Qs) is greater than 1.5. Repair is usually performed in children before school age. Closure of ASDs may be accomplished surgically or using a device deployed in the cardiac catheterization laboratory.

Surgical repair of ASDs is relatively straightforward (Fig. 127-9). Surgical closure is recommended for large secundum defects and most other types of ASDs. The heart is exposed by median sternotomy. Cardiopulmonary bypass is necessary using bicaval cannulation and mild hypothermia. Following aortic clamping and arrest of the heart with cardioplegia, the atrial septum is exposed through a right atriotomy. The defect is then closed using a patch (polytetrafluoroethylene or autologous pericardium) with a running polypropylene suture. If there is anomalous pulmonary venous return, a baffle may be created to redirect the flow across the atrial septal defect into the left atrium. Small defects and PFOs can be closed primarily without a patch. In all cases, care is taken to de-air the left atrium to avoid the complication of air embolization.

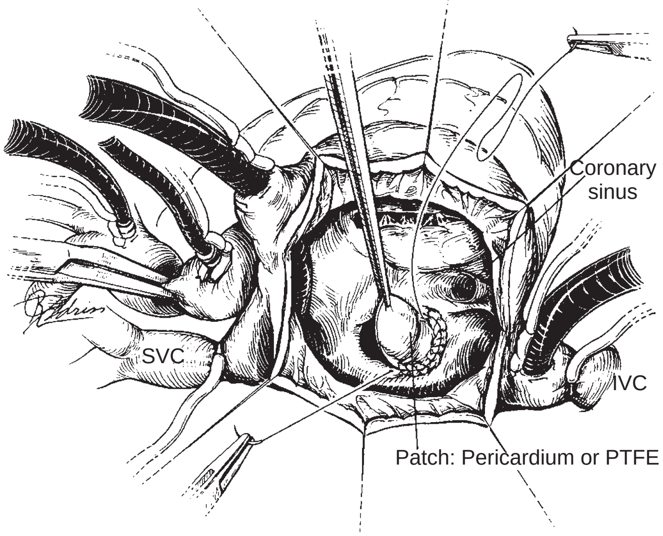



FIGURE 127-9 Patch closure of an ostium secundum atrial septal defect. Bicaval cannulation is used, and cardioplegia is infused through the aortic root to arrest the heart following application of the aortic crossclamp. IVC, inferior vena cava; SVC, superior vena cava. (From Backer CL, Mavroudis C: Atrial septal defect, partial anomalous pulmonary venous connection, and scimitar syndrome. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

Small-to-moderate secundum ASDs and PFOs can now be closed using transcatheter techniques. Device closure of these defects has now become the standard of care at most centers with a device deployment rate of 96% with complete closure at 24 hours of 99% or greater.[33,34]

### RESULTS

ASD closure by either approach is successful.[35] Mortality is less than 1%. Morbidity is infrequent. The long-term survival for patients undergoing ASD repair in childhood is normal.[36,37]

## Ventricular Septal Defects

Ventricular septal defects (VSDs) are the most common congenital heart anomalies (with the exception of bicuspid aortic valve), occurring in 4 of 1000 live births and representing about 40% of congenital heart defects.[1] There is heterogeneity with respect to the location, size, and number of defects present. Associated cardiac defects are common. VSDs occur as a result of failure of ventricular septation. They are most commonly classified on the basis of their location: perimembranous (80%), inlet (5%), outlet (10%), or trabecular (5%) (Fig. 127-10). The most common, perimembranous VSDs, are located in the area of the membranous septum, near the point of contact of the tricuspid, mitral, and aortic valve annuli. Inlet defects are located beneath the septal leaflet of the tricuspid valve. Outlet defects are also known as *supracristal* or *doubly committed subarterial*. These defects are bordered superiorly by both semilunar valves. Outlet defects are more common in the Asian population. Trabecular (or muscular) VSDs are completely bordered by muscle. They are frequently multiple and may be associated with perimembranous or outlet defects. The size of VSDs varies. A VSD is defined as nonrestrictive when its size (or the cumulative size of multiple defects) approximates that of the aortic annulus.

### NATURAL HISTORY AND DIAGNOSIS

The physiology of a VSD involves left-to-right shunting primarily during systole. This creates a volume load on the left heart (the left atrium and ventricle receive the increased venous return during diastole). The right ventricle is not volume loaded (blood is ejected from the left ventricle through the VSD and directly into the pulmonary circulation); however, it does experience a pressure load. Shunt volume across a VSD is determined by the size of the defect and by the ratio of pulmonary-to-systemic vascular resistance. As pulmonary vascular resistance decreases during the first few weeks of life, the shunting across a VSD tends to increase. Therefore a VSD that was asymptomatic at birth may eventually cause severe congestive heart failure.

The natural history of patients with VSD is variable. Most VSDs are restrictive and tend to close spontaneously during

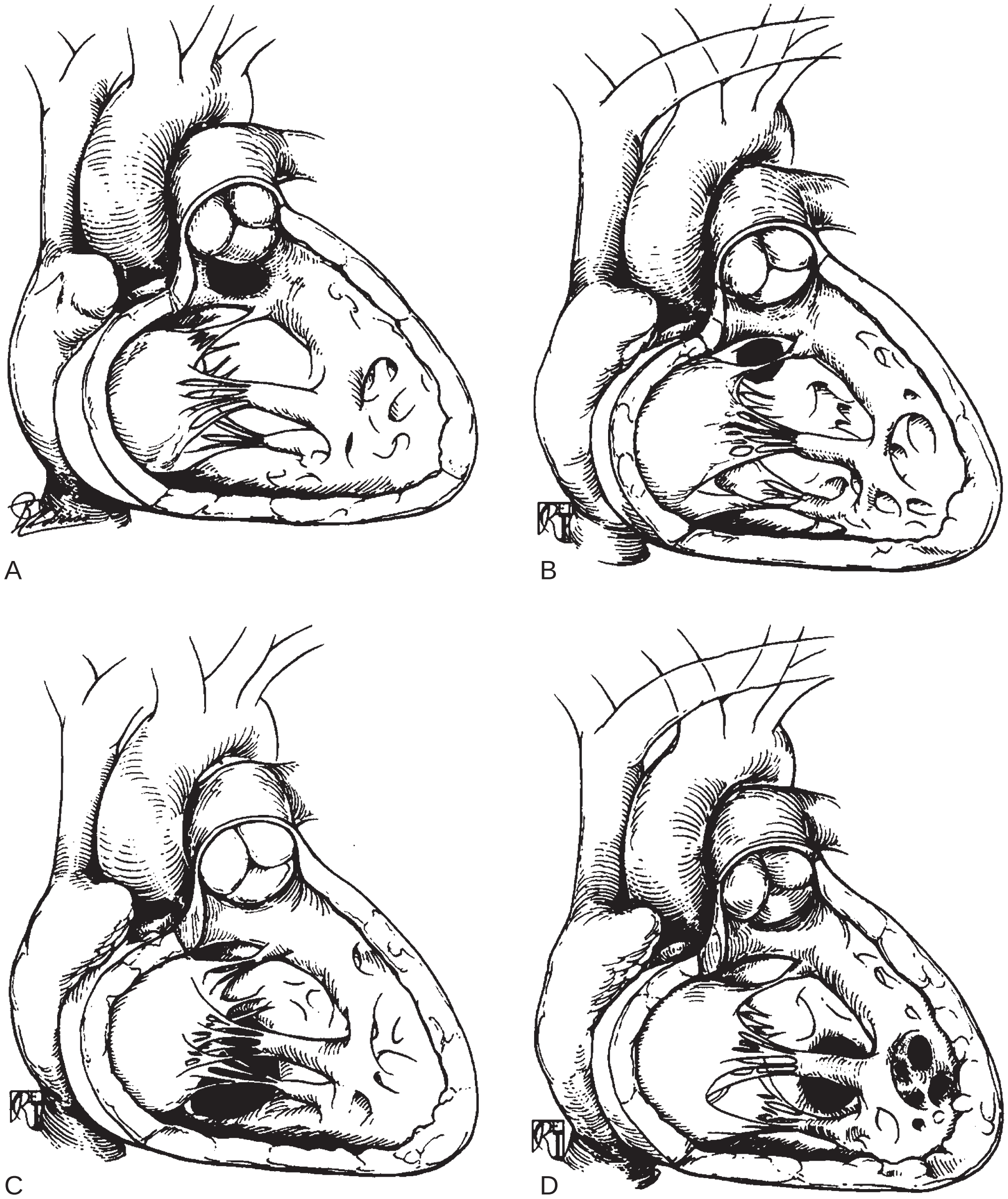



**FIGURE 127-10** Types of ventricular septal defects (VSDs) based on location. **A**, Outlet (supracristal, doubly committed subarterial). **B**, Perimembranous. **C**, Inlet. **D**, Trabecular (muscular). (From Mavroudis C, Backer CL, Jacobs JP: Ventricular septal defect. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

the first year of life.[38] Patients with large VSDs develop symptoms caused by congestive heart failure. Untreated, excessive pulmonary blood flow leads to pulmonary vascular obstructive disease by 1 to 2 years of age. Smaller VSDs may remain asymptomatic. In patients with outlet VSDs, proximity of the aortic valve may lead to prolapse of a valve cusp and aortic insufficiency.[39]

Signs of heart failure in infants with large VSDs include tachypnea, hepatomegaly, poor feeding, and failure to thrive. On examination, there is a holosystolic murmur at the left sternal border. The precordium is active. Usually, the murmur is louder with smaller defects. In patients with pulmonary vascular obstructive disease, there may be no murmur present but the pulmonary component of the second heart sound is prominent. Chest radiography shows increased pulmonary vascular markings and cardiomegaly. Electrocardiography is significant for right ventricular hypertrophy.

Patients with small VSDs have little shunting and are usually asymptomatic, having only a pansystolic murmur. Patients with moderate VSDs manifest symptoms and signs that are proportional to the degree of shunting.

Echocardiography is diagnostic in most cases. The anatomy can be accurately defined, and the presence of associated abnormalities can be excluded. Cardiac catheterization is used selectively in older children and adults with VSDs to determine pulmonary vascular resistance and assess reactivity to pulmonary vasodilators.

## MANAGEMENT

Treatment of a patient with a VSD depends on the size of the defect, type of defect, shunt volume, and pulmonary vascular resistance. In general, patients with large defects who

demonstrate intractable congestive heart failure (CHF) or failure to thrive should undergo early surgical repair. If the congestive symptoms can be moderated by medical therapy, surgery can be delayed to 6 months of age. Patients with moderate defects may be safely followed. If spontaneous closure has not occurred by school age, then surgery may be considered. Small VSDs with Qp/Qs less than 1.5 do not require closure. In these patients there is a small long-term risk of endocarditis, but this is minimized by appropriate antibiotic prophylaxis.[40] As noted previously, patients with outlet VSDs have a significant risk of developing aortic insufficiency secondary to leaflet prolapse; as a result, all outlet defects should be referred for closure.[41] Older children and adults with large VSDs who present late must undergo catheterization to evaluate the pulmonary vasculature. A fixed pulmonary vascular resistance greater than 8 to 10 Woods units/m$^2$ represents a contraindication to surgical closure of the VSD.

Surgical closure is performed through a median sternotomy (Fig. 127-11). Cardiopulmonary bypass is required, using bicaval cannulation. Following delivery of cardioplegia, a right atriotomy is performed. Exposure of the ventricular septum is achieved through the tricuspid valve. This provides access to perimembranous, inlet, and most outlet defects. Most trabecular defects may also be exposed in this fashion. Some outlet VSDs are best exposed via a pulmonary arteriotomy because the defect sits just beneath the valve. Trabecular VSDs located near the ventricular apex are notoriously difficult to expose, and an apical ventriculotomy (left or right) may be necessary. Once the defect is exposed, it is generally closed using a polytetrafluoroethylene patch and a running polypropylene suture, although other centers may prefer other patch material or an interrupted suture technique. Knowledge of the anatomy of the conduction tissue is critical when closing VSDs. The atrioventricular node is an atrial structure that lies in the apex of the triangle of Koch (formed by the coronary sinus, the tendon of Todaro, and the annular attachment of the septal leaflet of the tricuspid valve). The node then gives rise to the bundle of His, which penetrates the atrioventricular junction beneath the membranous septum. The bundle then bifurcates into right and left bundle branches, which descend along either side of the muscular ventricular septum. When a perimembranous VSD is present, the bundle of His traverses the posterior and inferior rim of the defect, generally on the left ventricular side. In this danger area, sutures must be placed superficially on the right ventricular side of the defect and a few millimeters away from the edge of the defect. The His bundle also tends to run along the posterior and inferior margin of inlet VSDs, whereas in outlet and trabecular defects, the conduction tissue is remote.

PA banding is a palliative maneuver that is designed to protect the pulmonary circulation from excessive flow in circumstances when the patient is not a candidate for a surgical closure, either due to associated illness or anatomic complexity (e.g., multiple trabecular VSDs). Placement of a PA band may be accomplished via sternotomy or thoracotomy. The band is tightened, and pressures are measured proximally and distally with a goal of achieving a distal pulmonary pressure of approximately one-half systemic. The band should then be secured to the adventitia of the main PA to prevent its migration. Distal migration may result in narrowing (and poor growth) of one or both branch pulmonary arteries, whereas proximal migration may lead to deformity of the

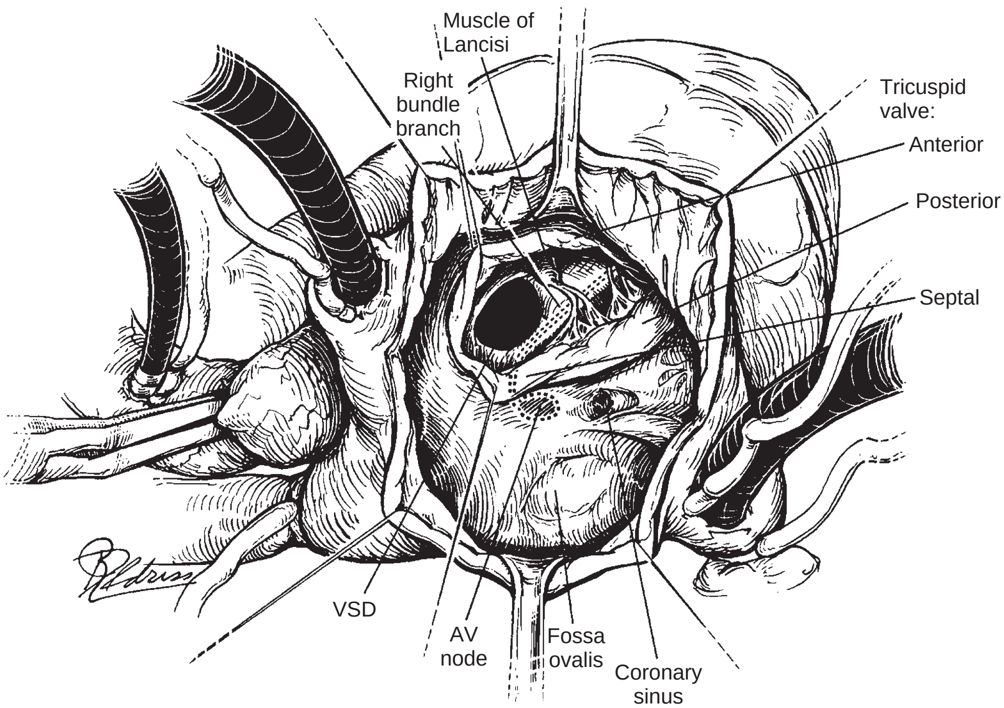



**FIGURE 127-11** Transatrial exposure of a perimembranous ventricular septal defect (VSD) as viewed by the surgeon. The septal and anterior leaflets of the tricuspid valve are retracted to expose the VSD. The conduction tissue is demonstrated by *dashed lines* leading from the atrioventricular (AV) node along the posterior and inferior margin of the VSD. When closing these defects, sutures are placed a few millimeters away from the edge of the defect on the right ventricular side of the septum to avoid conduction injury. (From Mavroudis C, Backer CL, Jacobs JP: Ventricular septal defect. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

pulmonary valve. Ultimately, when the patient is a candidate for VSD closure, the band must be removed. In most cases, a repair (scar resection and primary closure or patch repair) of the main PA will be necessary.

Recently, transcatheter technology has evolved and closure of some VSDs may be accomplished in the cardiac catheterization laboratory or by periventricular deployment without the use of cardiopulmonary bypass.[42,43] Device closure is optimal for large muscular defects with sufficient rims for securing the device. Periventricular closure allows the use of VSD device closure in smaller infants with symptomatic muscular VSDs with excellent results without the challenges of transvenous access in this population.[43] The use of devices for perimembranous VSDs remains limited by the risk of damage to the conduction system or impingement on the function of the tricuspid or aortic valves. A recent series demonstrated a 22% rate of complete heart block, which is prohibitively high in comparison with the surgical rate of complete heart block of less than 1%.[44]

### RESULTS

Repair of a VSD is associated with a mortality of approximately 1%.[45] The main complications include injury to the conduction tissue and injury to the tricuspid or aortic valves. Transient heart block may develop as a result of tissue swelling, but permanent heart block occurs in only 1% to 2% of cases.[45] Patients who develop heart block after surgery are observed for a period of 7 to 10 days. If normal conduction has not returned, then pacemaker implantation is indicated. Tricuspid insufficiency may be precipitated by annular distortion or chordal restriction by the VSD patch or sutures. The aortic valve may also be injured by inaccurate suturing (especially in perimembranous and outlet defects). A residual VSD may be observed in 5% of cases, and reoperation is indicated when significant shunting persists ($Qp/Qs > 1.5$). Intraoperative echocardiography is used routinely to identify valvar dysfunction and residual shunting.

## Atrioventricular Septal Defect

Atrioventricular septal defects (AVSD) represent a group of congenital abnormalities bound by a variable deficiency of the atrioventricular (AV) septum immediately above and below the AV valves. Other terms commonly applied to an AVSD include *atrioventricular canal defects, endocardial cushion defects,* and *atrioventricular communis.* These resulting septal defects are invariably associated with AV valve abnormalities. Atrioventricular septal defects include incomplete AVSDs, also termed *ostium primum atrial septal defects,* which have only a deficiency of the atrial septum immediately superior to the AV valves and two separate valve orifices. The far end of the spectrum encompasses complete AVSDs, with both an ASD and a VSD and a single common AV valve. AVSDs represent approximately 4% of congenital cardiac anomalies and are infrequently associated with other cardiac malformations. AVSDs comprise 30% to 40% of the cardiac abnormalities seen in patients with Down syndrome.[46]

The embryologic abnormality in AVSDs is the failure of the proper development of the endocardial cushions, which results in variable deficiency of the atrial and ventricular septa and malformation of the AV valves. Atrioventricular septal defects are generally categorized into incomplete and complete on the basis of the AV valve morphology. Incomplete, or partial, defects have two separate AV valve orifices (Fig. 127-12). The mitral valve in an incomplete AVSD is invariably associated with a cleft in the anterior leaflet. Although most incomplete AVSDs have no ventricular level shunting, the classification of AVSDs as complete and incomplete depends only on the valve anatomy, not on the presence or absence of a VSD. Incomplete defects without associated ventricular level shunting have also been termed *ostium primum ASDs,* whereas those with a VSD have been described as *intermediate* or *transitional AVSDs.* Complete AVSDs have a single common AV valve orifice resulting in a single five-leaflet valve overlying both the right and left ventricles (Fig. 127-13). Rastelli and colleagues[47] further subclassified complete AVSDs into types A, B, and C on the basis of the morphology of the superior bridging leaflet (SBL) of the common valve.

If both left and right AV valves equally share the common AV valve orifice, the AVSD is termed a *balanced defect.* Occasionally the orifice of the valve may be unbalanced, with one side being dominant. In marked right dominance, the left AV valve and left ventricle are hypoplastic and frequently coexist with other left-sided abnormalities including aortic stenosis, hypoplasia of the aorta, and coarctation. Conversely, marked left dominance is associated hypoplasia of the right ventricle, pulmonary stenosis or atresia, and tetralogy of Fallot.

The location of the conduction tissue is of importance in the surgical treatment of AVSDs because it is at risk during the repair. The AV node is displaced posteriorly and inferiorly toward the coronary sinus. The bundle of His courses anteriorly and superiorly to run along the leftward aspect of the crest of the VSD, giving off the left bundle branch before continuing as the right bundle branch.

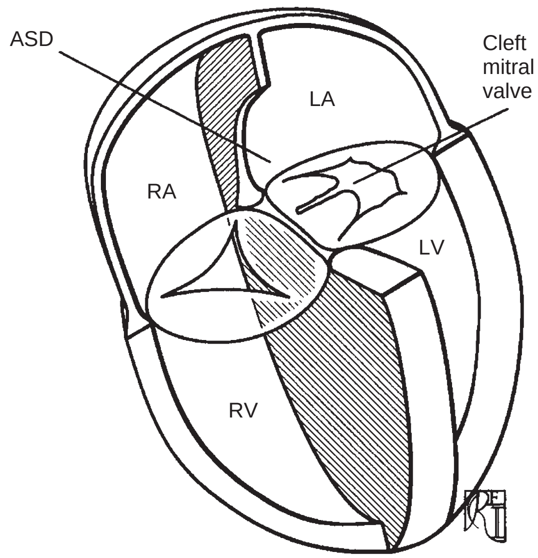



**FIGURE 127-12** Incomplete atrioventricular septal defect. ASD, primum atrial septal defect; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (From Backer CL, Mavroudis C: Atrioventricular canal defects. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, Philadelphia, Mosby, 2003.)

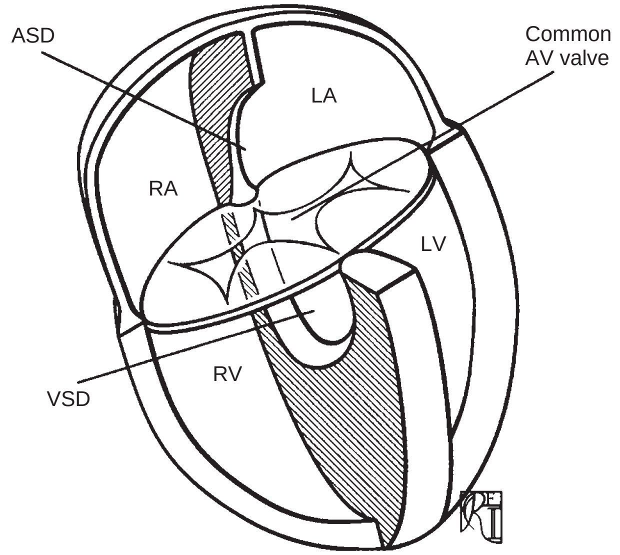



**FIGURE 127-13** Complete atrioventricular septal defect. ASD, primum atrial septal defect; AV, atrioventricular LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; VSD, inlet ventricular septal defect. (From Backer CL, Mavroudis C. Atrioventricular canal defects. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, Philadelphia, Mosby, 2003.)

Cardiac anomalies associated with AVSDs include a patent ductus arteriosus (10%) and tetralogy of Fallot (10%).[48] Important abnormalities of the left AV valve include single papillary muscle (parachute mitral valve) (2% to 6%) and double orifice mitral valve (8% to 14%).[49] A persistent left superior vena cava with or without an unroofed coronary sinus is encountered in 3% of patients with an AVSD. A double-outlet right ventricle (2%) significantly complicates or may even preclude complete surgical correction.[48] Left ventricular outflow tract obstruction from subaortic stenosis or redundant AV valve tissue occurs in 4% to 7%.[50,51] Associated transposition of the great arteries and left ventricular inflow obstruction have been reported rarely.[48,50]

## NATURAL HISTORY AND DIAGNOSIS

The predominant hemodynamic features of an AVSD are the result of left-to-right shunting at the atrial and ventricular levels. In the absence of ventricular level shunting, the hemodynamics and clinical presentation resemble that of a typical secundum ASD with right atrial (RA) and right ventricular (RV) volume overload. On physical examination, there is an active precordium, a pulmonary outflow murmur, and a fixed, widely split second heart sound. Electrocardiogram reveals a leftward axis, prominent P waves associated with atrial enlargement, and a prolonged PR interval. Chest radiograph generally shows mild cardiomegaly and increased pulmonary vascular markings. Echocardiography is diagnostic of the atrial septal defect, the absence of ventricular level shunting, and the presence of any AV valve abnormalities. Cardiac catheterization is only indicated in older patients or those manifesting physical or radiologic signs of decreased pulmonary blood flow. The decreased PA blood flow may be a result of pulmonary vascular disease or concurrent right-sided obstructive lesions. A fixed pulmonary vascular resistance of greater than 10 units/m$^2$ is a contraindication to surgical closure.

As with an uncomplicated ASD, the natural history of decades of chronic volume overload results in atrial dilatation and arrhythmias, ventricular dysfunction, and potentially pulmonary vascular disease. Therefore repair is indicated and generally undertaken by age 2 to 4 years.

Patients with a complete AVSD often have both atrial and ventricular level shunting. These patients generally present early in infancy with signs and symptoms of CHF. Moderate or greater left AV valve regurgitation may occur with a complete AVSD, worsening the clinical picture. On physical examination, the precordium is hyperactive, with auscultatory findings of a systolic murmur along the left sternal border, a high-pitched murmur at the apex from left AV valve regurgitation, and a mid-diastolic flow murmur across the common AV valve. Chest radiograph demonstrates significant cardiomegaly and pulmonary overcirculation. Electrocardiogram reveals biventricular hypertrophy, atrial enlargement, prolonged PR interval, leftward axis, and counterclockwise frontal plane loop. Echocardiography is diagnostic, defining the atrial and ventricular level shunting, valvular anatomy, and any associated anomalies. Cardiac catheterization should be performed for patients older than the age of 1 year, patients with signs or symptoms of increased pulmonary vascular resistance, or in select cases to further evaluate other associated major cardiac anomalies.

Up to 90% of untreated individuals with a complete AVSD develop pulmonary vascular disease by 1 year of age due to the large left-to-right shunt, potentially exacerbated by the associated AV valve regurgitation.[52] Patients with trisomy 21 tend to develop pulmonary vascular obstructive disease earlier than chromosomally normal infants due to small airway disease, chronic hypoventilation, and elevated $pCO_2$. Initial aggressive medical management is undertaken to relieve the symptoms of CHF. Elective surgical correction should be performed by age 3 to 6 months. Earlier intervention is indicated for failure of medical management.

## MANAGEMENT

The treatment of choice for an incomplete or complete AVSD is surgical repair. Currently, PA banding for palliation has a limited role in the management of these lesions. Indications for PA banding may include those patients with associated complex cardiac anomalies, functional single ventricle anatomy necessitating ultimate Fontan procedure, and poor clinical condition precluding major cardiac surgery.

A median sternotomy approach is employed, with routine conduct of cardiopulmonary bypass for the majority of patients. Repair of an incomplete AVSD with only atrial level shunting is similar to the approach employed for a secundum-type ASD.

There are two techniques widely employed for the repair of complete AVSDs, a one-patch technique and a two-patch technique. Regardless of which approach is selected, the goals are to close the ASD and VSD and to separate the common AV valve into two nonstenotic, competent valves. The cleft in the anterior leaflet of the mitral valve is generally closed to lessen the risk of long-term mitral regurgitation.[53–55]

For the two-patch technique, separate patches are used for the ASD and VSD (Fig. 127-14, *A*). For the one-patch

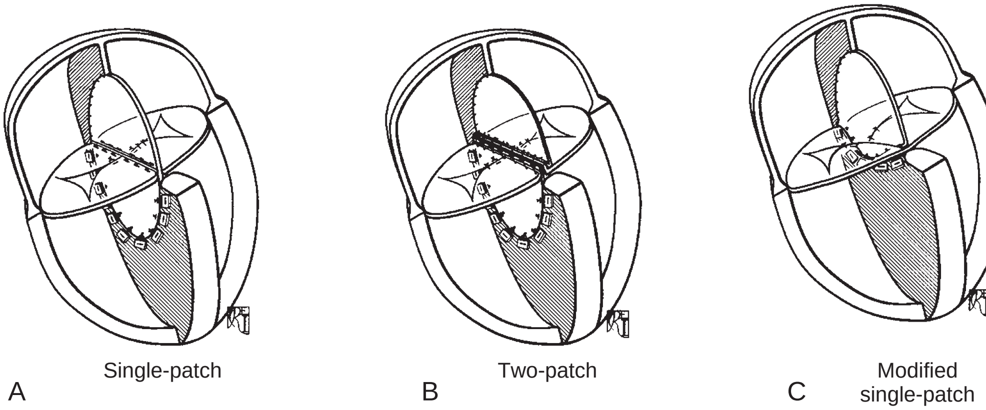



**FIGURE 127-14** Surgical repair of an atrioventricular septal defect using a single-patch **(A),** two-patch **(B),** and modified single-patch **(C)** technique. (From Backer CL, Mavroudis C. Atrioventricular canal defects. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, Philadelphia, Mosby, 2003.)

technique, the superior and inferior bridging leaflets are divided along a line separating them into right and left components. A single patch is used to close both the ventricular and atrial septal defects. The cut edges of the leaflets are then resuspended to the patch (see Fig. 127-14, *B*). For defects with a small VSD component, a modified single-patch technique may be employed. For this method, a single patch is sewn directly to the rim of the VSD, sandwiching the bridging leaflets between the patch and the crest of the VSD (see Fig. 127-14, *C*).

### RESULTS

Operative mortality is largely related to any associated cardiac anomalies and left AV valve regurgitation. Mortality for repair of uncomplicated incomplete AVSDs is 0% to 0.6%. The addition of left AV valve regurgitation increases mortality to 4% to 6%.[51,56] For complete AVSDs, the mortality without left AV valve regurgitation is approximately 5%, compared with 13% when significant degrees of regurgitation are present.[51]

The difference in operative mortality between patients with and without regurgitation underscores the importance of careful management of the left AV valve. In addition, the majority of reoperations after repair of AVSD are due to left AV valve regurgitation. Significant postoperative AV valve regurgitation occurs in 10% to 15% of patients, necessitating reoperation for valve repair or replacement in 7% to 12%.[53–55]

The incidence of permanent complete heart block is approximately 1%.[51,57] Heart block encountered in the immediate postoperative period may be transient due to edema or trauma to the AV node or bundle of His. However, right bundle branch block is common (22%).[57]

## Tetralogy of Fallot

Tetralogy of Fallot (TOF) was described by Etienne Fallot in 1888. The pathologic anatomy is frequently described as having four components: a malalignment ventricular septal defect, overriding aorta, pulmonary stenosis, and right ventricular hypertrophy (Fig. 127-15). The anatomy of tetralogy of Fallot has also been related to a single embryologic defect: anterior malalignment of the infundibular septum.[58]

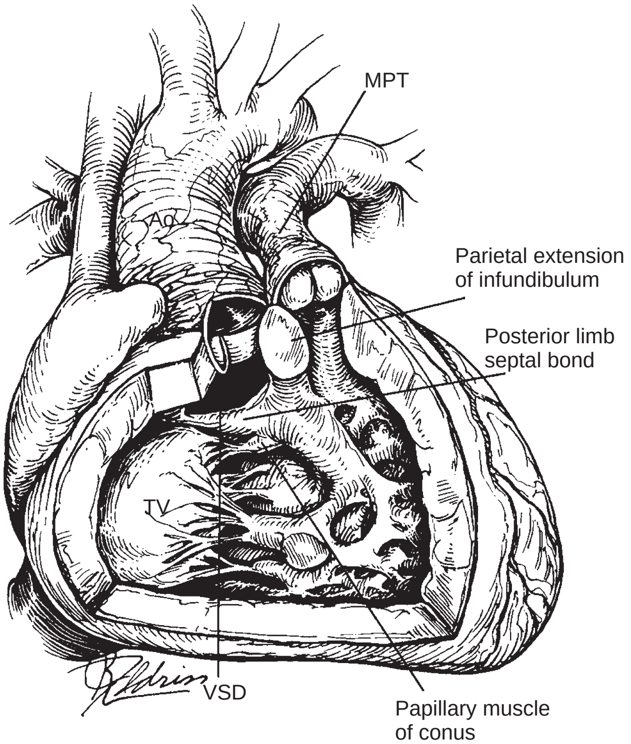



**FIGURE 127-15** Pathologic anatomy of tetralogy of Fallot. The ventricular septal defect (VSD) is nonrestrictive. The infundibular septum is maligned, leading to aortic override and crowding of the right ventricular outflow tract. Note the hypoplastic main pulmonary trunk (MPT). Ao, aorta; TV, tricuspid valve. (From Hirsch JC, Bove EL: Tetralogy of Fallot. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

The infundibular septum normally separates the primitive outflow tracts and fuses with the ventricular septum. Anterior malalignment of the infundibular septum creates a VSD due to failure of fusion with the ventricular septum and also displaces the aorta over the VSD and right ventricle. The malaligned infundibular septum crowds the right ventricular outflow tract, producing pulmonary stenosis and, secondarily, right ventricular hypertrophy. Prominent muscle bands also extend from the septal insertion of the infundibular septum to the right ventricular free wall and contribute to the obstruction

of the right ventricular outflow tract. The pulmonary valve is usually stenotic with thickened leaflets, which are bicuspid in 58% of cases.[59] Abnormalities of coronary artery anatomy may be present, with origin of the left anterior descending from the right coronary artery in 5% of cases. In 25% of cases, there is a right aortic arch. Associated defects may include ASD, complete AVSD, PDA, or multiple VSDs.

Tetralogy of Fallot is the most common cyanotic congenital heart defect. It occurs in 0.6 per 1000 live births and has a prevalence of 5% among all patients with congenital heart disease.[1]

## NATURAL HISTORY AND DIAGNOSIS

Patients with TOF develop cyanosis as a result of shunting from right to left across the ventricular septal defect. The degree of cyanosis is proportional to the degree of obstruction of the right ventricular outflow tract. There is a spectrum of severity, with some patients developing symptoms as neonates and others remaining asymptomatic. The occurrence of intermittent cyanotic spells is a well-known clinical feature of TOF. The etiology of spelling is still controversial but is clearly related to a transient imbalance between pulmonary and systemic blood flow. A spell may be triggered by hypovolemia, peripheral vasodilation (e.g., after a bath), or infundibular spasm. Spells have been reported in neonates but tend to occur most frequently between 3 and 18 months of age. Older children have been observed to spontaneously squat to terminate spells. The squatting position is thought to increase systemic vascular resistance, which thereby favors pulmonary blood flow.

Long-term complications of untreated TOF include clubbing of the fingers and toes, severe dyspnea on exertion, brain abscesses (secondary to right-to-left shunting), paradoxical embolization, and polycythemia (which may lead to cerebral thrombosis). Long-term survival is unlikely for most patients with untreated TOF.

Cyanosis is the most frequent physical examination finding. There is usually a normal first heart sound and a single second heart sound. A systolic pulmonary ejection murmur is present at the left upper sternal border. Older children and adults may exhibit clubbing. Chest radiography characteristically demonstrates a boot-shaped heart because of elevation of the cardiac apex from right ventricular hypertrophy. A right aortic arch may be evident. An echocardiogram shows right ventricular hypertrophy. Echocardiography is definitive, and catheterization is unnecessary in most cases.

## MANAGEMENT

The medical management of TOF is directed at the treatment and prevention of cyanotic spells. The spelling patient should be given oxygen and sedation, and acidosis, if present, should be corrected. Transfusion may be indicated in anemic infants. Alpha-agonists can be administered to increase systemic vascular resistance, which favors pulmonary blood flow. Some centers have used long-term therapy with beta blockers to reduce the incidence of cyanotic spells.

All patients with TOF should undergo surgical repair. In general, asymptomatic patients should be repaired electively between 4 and 6 months of age. Early repair is indicated for neonates with severe cyanosis, as well as for infants who have had a documented spell.[60]

Classically, the repair of TOF was performed in two stages. The first stage involved creation of a systemic-to-pulmonary shunt to relieve cyanosis. The second stage was a complete repair. Currently, one-stage complete repair is preferred by most centers. In some patients (such as those with multiple congenital anomalies, severe concurrent illness, or an anomalous coronary artery crossing a hypoplastic infundibulum), initial palliation with a shunt may still be indicated. The modified Blalock-Taussig shunt is the most common type of shunt used today and consists of an interposition graft (polytetrafluoroethylene) between the innominate or subclavian artery and the ipsilateral pulmonary artery. Creation of a shunt may be performed with or without the use of cardiopulmonary bypass.

Complete repair of TOF is performed using a median sternotomy and cardiopulmonary bypass with bicaval cannulation (Fig. 127-16). Via a transatrial approach, the muscle bundles obstructing the right ventricular outflow tract are divided; resection is rarely necessary. The VSD is closed using a patch. Depending on the status of the pulmonary valve, pulmonary valvotomy may be appropriate. In cases of severe hypoplasia of the pulmonary annulus or infundibulum, a right ventricular outflow tract transannular patch may be required to relieve obstruction (Fig. 127-17). Our philosophy is to minimize right ventricular incisions whenever possible in order to preserve right ventricular function. When an anomalous coronary artery crosses the right ventricular infundibulum, a transannular incision may be contraindicated; in these cases, placement of a conduit (cryopreserved homograft or bioprosthetic heterograft) between the right ventricle (via a separate ventriculotomy) and main PA may be necessary. Patients requiring a transannular patch will develop free pulmonary insufficiency. This is well tolerated in most infants, as long as the tricuspid valve is competent. As adults, these patients will develop right ventricular failure due to chronic pulmonary insufficiency and pulmonary valve implantation will be necessary.[61,62]

## RESULTS

The early mortality following repair of TOF is between 1% and 5%.[59,63] Long-term complications include recurrent obstruction of the right ventricular outflow tract, conduit failure, and development of right ventricular dysfunction due to chronic pulmonary insufficiency. Actuarial survival is 86% at 20 years with excellent functional status.[64]

# Transposition of the Great Arteries

Transposition of the great arteries (TGA) is a common congenital cardiovascular malformation in which there is ventriculoarterial discordance. This discordant anatomy is a result of the aorta arising from the morphologic right ventricle and the PA arising from the morphologic left ventricle (LV). Transposition of the great arteries is divided into *dextro* looped- or d-TGA, and *levo* looped- or l-TGA. The looping refers to the right or left looping of the heart during fetal

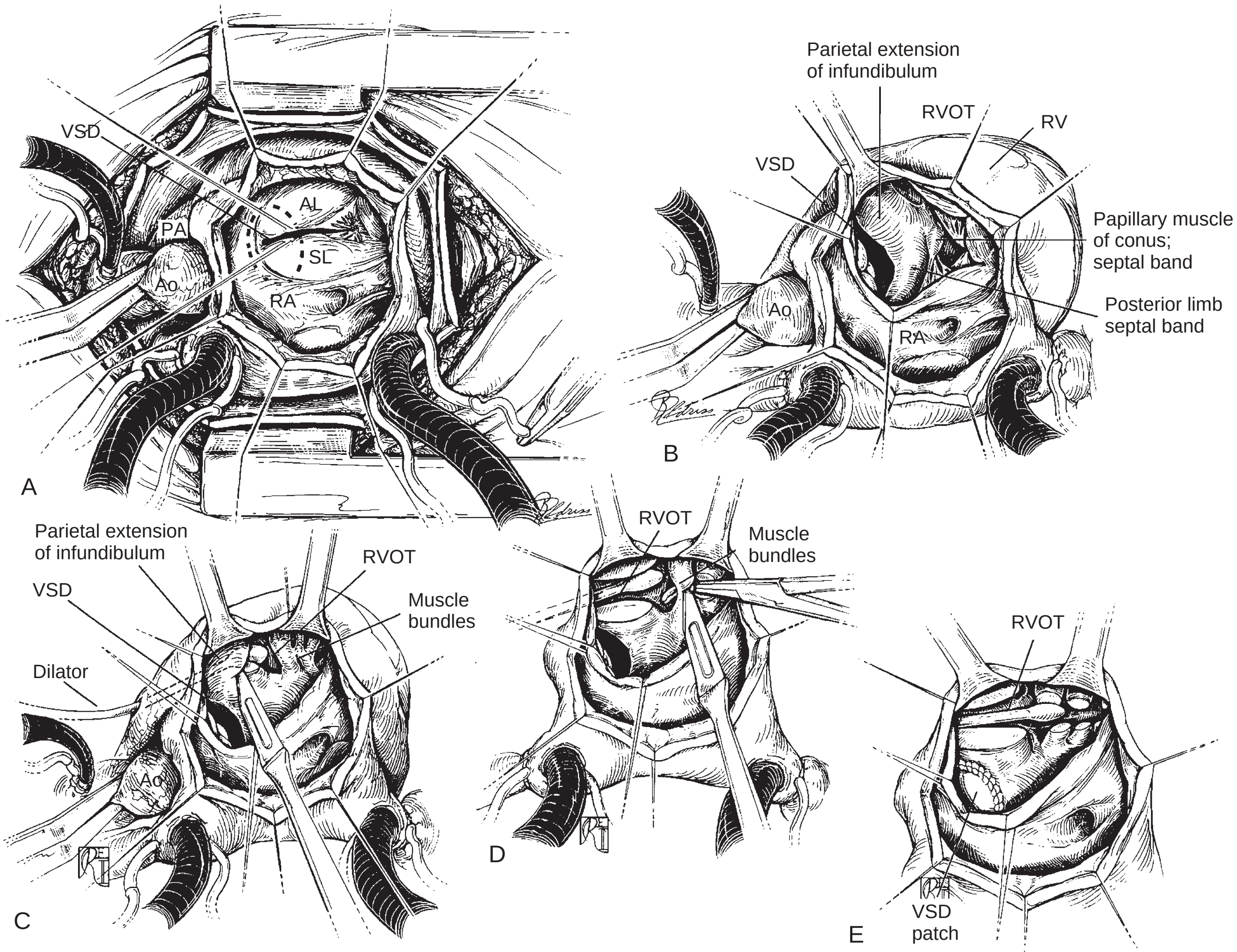



**FIGURE 127-16** Transatrial repair of tetralogy of Fallot. **A,** The location of the ventricular septal defect (VSD) is denoted by the *dashed line*. **B,** Stay sutures on the septal and anterior leaflets of the tricuspid valve allow for exposure of the VSD. **C** and **D,** Using a dilator to demonstrate the course of the right ventricular outflow tract (RVOT), hypertrophied muscle bundles may be divided or resected. **E,** The VSD is closed with a patch. AL, anterior leaflet of tricuspid valve; Ao, aorta; PA, pulmonary artery; RA, right atrium; SL, septal leaflet of tricuspid valve. (From Hirsch JC, Bove EL: Tetralogy of Fallot. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

development, which determines whether the atria and ventricles are concordant (right atrium attaches to right ventricle and left atrium attaches to left ventricle) or discordant. L-transposition of the great arteries is associated with both atrioventricular discordance (right atrium attaches to left ventricle and left atrium attaches to right ventricle) and ventriculoarterial discordance and is also termed *congenitally corrected TGA*. L-transposition of the great arteries is a rare variant of TGA and is beyond the scope of this chapter, which focuses on d-TGA.

d-Transposition of the great arteries is the most common cause of cyanosis in the infant and accounts for approximately 10% of all congenital cardiovascular malformations.[65] The defect can be subdivided into d-TGA with intact ventricular septum (IVS) (55% to 60%) and d-TGA with ventricular septal defect (VSD) (40% to 45%), one third of which are hemodynamically insignificant. Pulmonic stenosis (PS), causing significant left ventricular outflow tract obstruction, occurs rarely with an IVS and in approximately 10% of d-TGA/VSD.[66]

## NATURAL HISTORY AND DIAGNOSIS

Without intervention, d-TGA is universally fatal; 30% of neonates will die in the first week of life, 50% by the first month, 70% within 6 months, and 90% by 1 year.[67] Clinical characteristics depend on the degree of mixing and the amount of pulmonary blood flow (PBF). These factors relate to the specific anatomic subtype of d-TGA.

Neonates with d-TGA and IVS (or small VSD) have mixing limited to the atrial level and PDA. The ASD may be restrictive, and the PDA generally will close over the first days to week of life. As the degree of mixing decreases, the patient becomes increasingly cyanotic and will eventually suffer cardiovascular collapse. Fortunately, the majority of these neonates will manifest cyanosis early in life, which is recognized by a nurse or physician within the first hour in 56% and in the first day in 92%.[68]

In d-TGA with a large VSD, there is additional opportunity for mixing and increased PBF. The neonate with d-TGA/VSD

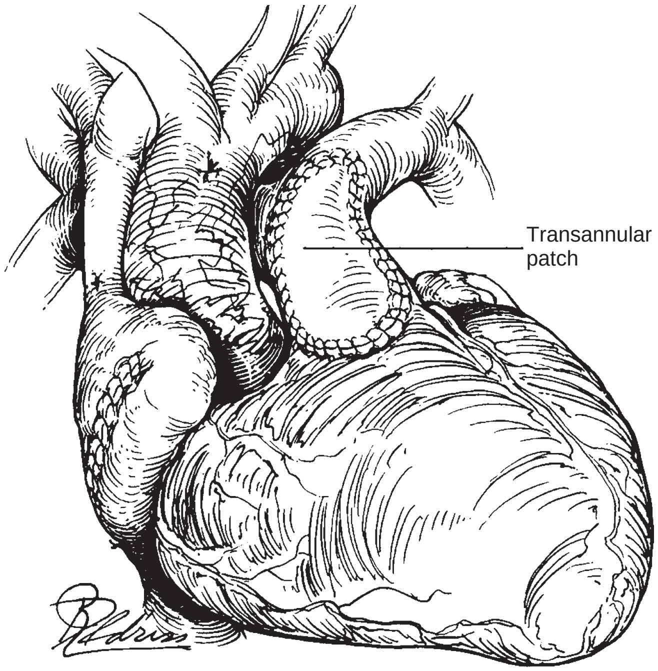



FIGURE 127-17 A transannular patch is used to enlarge a hypoplastic pulmonary annulus and main pulmonary trunk. (From Hirsch JC, Bove EL: Tetralogy of Fallot. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, 3rd ed. Philadelphia, Mosby, 2003.)

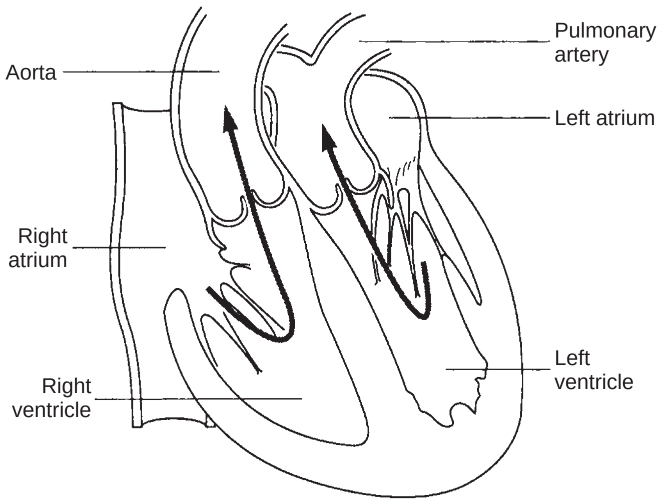



FIGURE 127-18 The anatomy of d-transposition of great arteries with intact ventricular septum. (From Bove EL, Lupinetti FM: Congenital heart disease and cardiac tumors. In Greenfield LJ, Mulholland MW, Oldham KT, Zelenock GB [eds]: Surgery: Scientific Principles and Practice. Philadelphia, JB Lippincott, 1993.)

may only manifest mild cyanosis, which may be initially overlooked. Generally within 2 to 6 weeks, signs and symptoms of congestive heart failure will emerge. Tachypnea and tachycardia become prominent, while cyanosis may remain mild. Auscultatory findings are consistent with congestive heart failure with increased PBF including a pansystolic murmur, third heart sound, mid-diastolic rumble, gallop, and narrowly split second heart sound with increased pulmonary component. Neonates with d-TGA and significant PS present with severe cyanosis at birth. Lesser degrees of PS will result in varying levels of cyanosis.

The diagnosis of d-TGA is generally suspected by the clinical presentation, or it may be seen on prenatal ultrasonography and fetal echocardiography. Chest radiograph reveals an egg-shaped heart with a narrow superior mediastinal shadow, mild cardiomegaly, and increased pulmonary vascular markings. Echocardiography is the diagnostic modality of choice. Diagnostic cardiac catheterization is rarely necessary in the current era.

## MANAGEMENT

With all forms of d-TGA, there is the need to maintain adequate mixing of oxygenated and deoxygenated blood between the right and left sides of the heart. The circulation in d-TGA is of two separate circuits, pulmonary and systemic, in parallel (Fig. 127-18). Without communication between the two sides of the heart, deoxygenated blood does not reach the lungs and oxygenated blood does not reach the systemic circulation. The majority of patients will require two levels of mixing until the time of repair to maintain adequate saturations. In d-TGA/IVS, this is achieved by maintaining a patent ductus arteriosus (PDA) with prostaglandin $E_1$ ($PGE_1$) infusion and ensuring an adequate atrial septal defect (ASD), which may require a balloon atrial septostomy. Occasionally, with d-TGA/VSD with mild or no PS, there will be adequate mixing at the atrial and ventricular levels to allow for discontinuation of $PGE_1$. In the presence of significant PS, $PGE_1$ will be necessary to provide sufficient pulmonary blood flow. These management strategies are used to palliate the patient until definitive surgical correction can be undertaken. In the absence of mitigating factors such as poor clinical condition preventing major open heart surgery, the current treatment of all forms of d-TGA is neonatal complete repair.

### d-Transposition of the Great Arteries Without Pulmonic Stenosis

The current treatment for d-TGA is an arterial switch operation (ASO). The repair is performed via a median sternotomy with standard techniques of cardiopulmonary bypass. The aorta and main PA are divided. The PA is translocated anterior to the aorta using the Lecompte maneuver, and the distal aorta is anastomosed to the proximal PA. The coronary arteries are removed from the aorta with buttons of adjacent artery and transferred to the proximal PA. The proximal aorta is reconstructed using a pantaloon-shaped patch of autologous pericardium and anastomosed to the distal PA. The ASD and, if present, the VSD are closed.

### d-Transposition of the Great Arteries with Ventricular Septal Defect and Pulmonic Stenosis

In the presence of significant PS, a Rastelli procedure is performed because an ASO will result in systemic (LV) outflow tract obstruction. The Rastelli operation uses the VSD to allow the LV to eject via the aorta. The PA is ligated and divided at the level of the pulmonary annulus. The VSD patch is constructed to incorporate both the VSD and the aortic valve, creating a tunnel from the LV to the aorta (Fig. 127-19). Right ventricle-to-PA continuity is established using a conduit from the RV infundibulum to the distal PA.

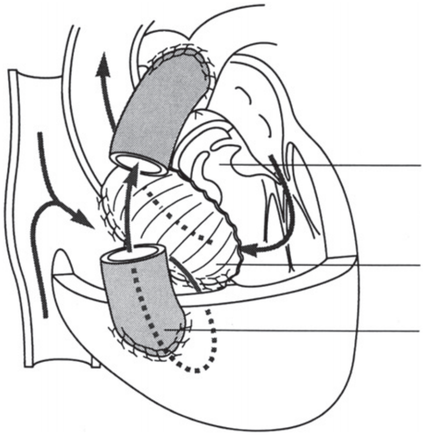



**FIGURE 127-19** The Rastelli procedure. (From Bove EL, Lupinetti FM: Congenital heart disease and cardiac tumors. In Greenfield LJ, Mulholland MW, Oldham KT, Zelenock GB [eds]: Surgery: Scientific Principles and Practice. Philadelphia, JB Lippincott, 1993.)

## RESULTS

Current hospital survival for the ASO ranges from approximately 90% to 98%.[66,69–72] In earlier eras, d-TGA/IVS had a lower mortality than d-TGA/VSD or d-TGA/VSD/PS; however, recent studies have neutralized this difference.[70,72] Long-term survival at 5 to 10 years and 15 years range from 88% to 93% and 86% to 88%, respectively.[69–71] The most common cause for reintervention is supravalvar pulmonic stenosis, occurring in 3.9% to 16%.[69,71] Late follow-up of arterial switch operation patients has led to increased concerns regarding coronary artery patency and neoaortic root dilation.[73]

A study of 101 patients undergoing a Rastelli operation over a 25-year period revealed a hospital mortality of 7%, with no deaths in the past 7 years of the study.[74] Actuarial survival at 5, 10, 15, and 20 years was 82%, 80%, 68%, and 52%.

# Single Ventricle and the Hypoplastic Left Heart Syndrome

A variety of congenital cardiovascular malformations may result in functional single ventricle anatomy, most commonly tricuspid atresia, pulmonary atresia, unbalanced atrioventricular septal defect, and hypoplastic left heart syndrome. The most common lesion is hypoplastic left heart syndrome (HLHS). There are approximately 1000 infants with HLHS born in the United States each year. It is the most common severe congenital heart defect, comprising 7% to 9% of all anomalies diagnosed within the first year of life.[75] All single ventricle lesions share the common physiology of only a single ventricle capable of supporting cardiac output. They also share the need for a two- or three-stage approach to reconstruction, ultimately resulting in a Fontan procedure. The goal of the initial procedure is to maintain adequate cardiac output and oxygen saturation while optimizing the patient for the ultimate Fontan procedure. Characteristics for an optimal Fontan candidate include good ventricular function, low PA vascular resistance, no outflow tract obstruction, and no significant atrioventricular or semilunar valve regurgitation. Another option to staged palliation is cardiac transplantation.

## NATURAL HISTORY AND DIAGNOSIS

The natural history of these lesions depends on the amount of pulmonary blood flow and the degree of systemic outflow tract obstruction. Patients with severely limited pulmonary blood flow or significant systemic outflow tract obstruction will succumb rapidly as the ductus arteriosus closes. Excessive pulmonary blood flow without systemic outflow tract obstruction will result in death due to pulmonary vascular obstructive disease, which develops at months to decades of age, depending on the degree of pulmonary overcirculation. Occasionally, patients may be "balanced" with an appropriate ratio of systemic and pulmonary blood flow, which in rare cases may allow survival into adulthood. The treatment of choice for all of these patients is still staged reconstruction to a Fontan procedure because even a perfectly balanced circulation leaves the heart volume overloaded and subject to ultimate failure. More commonly, this scenario simply allows the patient to avoid the need for an initial stage to control pulmonary blood flow in the neonatal period.

## MANAGEMENT

Due to the limited number of suitable donors, the uncertain effects of long-term immunosuppression, and the limited life span of transplanted hearts, the majority of centers have pursued a policy of staged reconstruction as the primary therapy for single ventricle lesions. Staged reconstruction involves a series of two or three procedures. An initial neonatal operation may or may not be necessary depending on the presence of systemic outflow tract obstruction or the need to limit or augment pulmonary blood flow. This is followed at 4 to 6 months of age by a bidirectional Glenn or hemi-Fontan procedure and the Fontan procedure at 18 to 24 months of age.

Because of the frequent prenatal detection of HLHS, its high morbidity and mortality, and the thought that it may be a consequence of critical aortic stenosis during development, there have been attempts at fetal ultrasound-guided balloon valvuloplasty in a few centers, with limited success thus far.

### Initial Palliation

Patients who do not have balanced systemic and PA flow ratios require an initial operation in the neonatal period. The goal of this first stage of reconstruction is to provide unobstructed blood flow to the systemic and coronary circulations, nonrestrictive pulmonary venous return, and a controlled amount of flow to the lungs. For patients with unobstructed systemic blood flow and excessive pulmonary blood flow, the PA may be banded or disconnected with the placement of a systemic to PA shunt to control the pulmonary overcirculation. For patients with unobstructed systemic blood flow and inadequate pulmonary blood flow, a systemic to PA shunt is placed. The most common single ventricle lesion, HLHS, results in systemic outflow tract obstruction and excessive pulmonary blood flow and requires an initial Norwood operation. During the Norwood procedure, the aorta is reconstructed, incorporating the proximal PA to allow the single right ventricle to eject via the aorta. A systemic to PA shunt or right ventricle

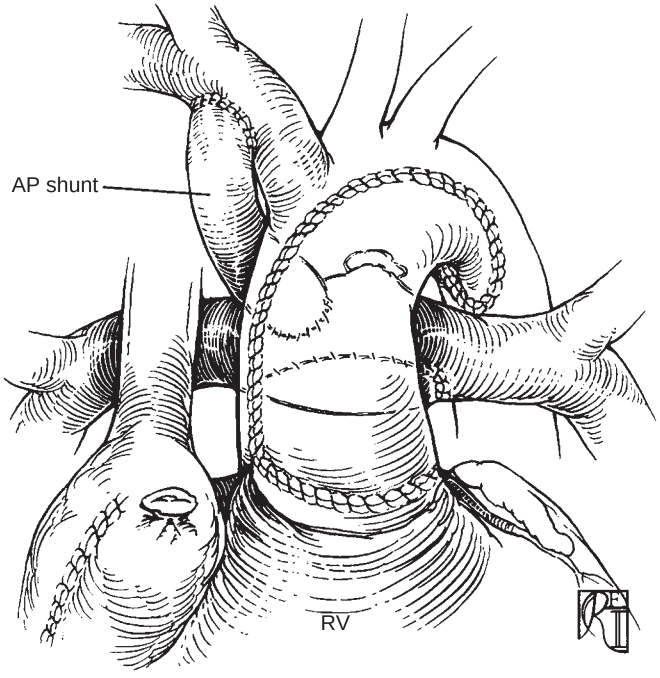



FIGURE 127-20 The completed Norwood procedure. AP, aortopulmonary; RV, right ventricle. (From Ohye RG, Mosca RM, Bove EL, et al: Hypoplastic left heart syndrome. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, Philadelphia, Mosby, 2003.)

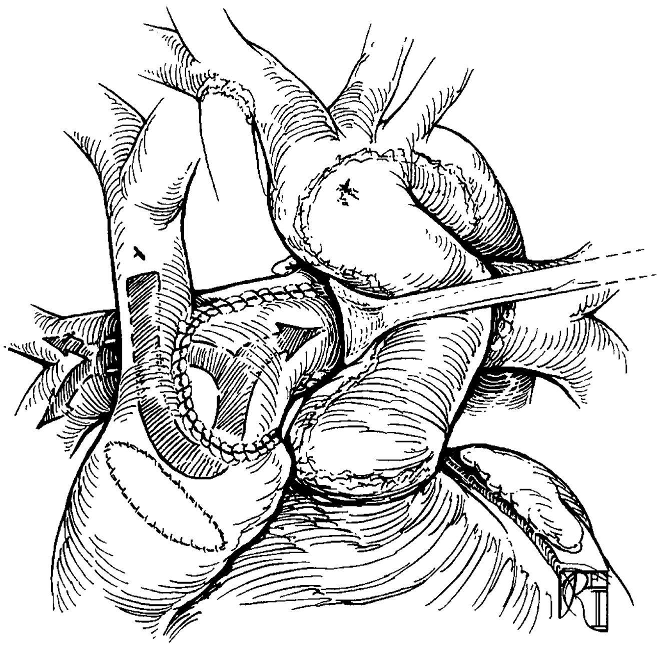


FIGURE 127-21 The completed hemi-Fontan procedure. (From Ohye RG, Mosca RM, Bove EL, et al: Hypoplastic left heart syndrome. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery, Philadelphia, Mosby, 2003.)

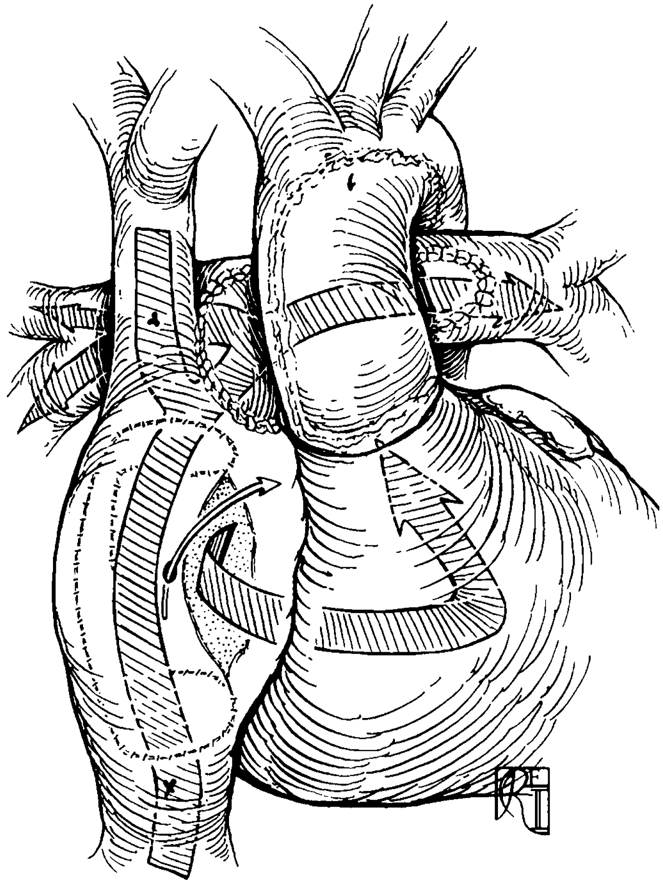


FIGURE 127-22 The completed Fontan procedure. (From Ohye RG, Mosca RM, Bove EL, et al. Hypoplastic left heart syndrome. In Mavroudis C, Backer CL [eds]: Pediatric Cardiac Surgery. Philadelphia, Mosby, 2003.)

to PA conduit is then placed to provide PA blood flow (Fig. 127-20). In response to the high mortality associated with the Norwood procedure at lower volume centers, a hybrid procedure has been introduced. It involves placement of a patent ductus arteriosus stent and bilateral PA bands via a median sternotomy in the catheterization laboratory. This approach has produced improved early results with long-term results still pending.[76] This approach delays the complex aortic arch reconstruction to the second stage.

### Bidirectional Glenn or Hemi-Fontan Procedure

In order to minimize the period of time during which the right ventricle is subject to volume overload, the hemi-Fontan operation or a bidirectional Glenn anastomosis (BDG) is typically performed between 4 to 6 months of age. The BDG entails removing the systemic to PA shunt and connecting the superior vena cava (SVC) directly to the right PA by an end-to-side anastomosis. The pulmonary blood flow after this second stage is provided solely by the SVC. The hemi-Fontan is a modification of the bidirectional Glenn procedure. The hemi-Fontan involves a side-to-side connection between the superior vena cava/right atrial junction and the pulmonary arteries, routine augmentation of the branch pulmonary arteries, and temporary patch closure between the pulmonary arteries and the right atrium (Fig. 127-21).

### Fontan Procedure

The completion of the Fontan procedure is usually performed at 18 to 24 months of age. The Fontan technique that we have employed for HLHS anatomy is the total cavopulmonary connection with a lateral tunnel (Fig. 127-22). During the Fontan procedure, the inferior vena caval venous return is directed to the pulmonary artery. Other centers use an extracardiac

conduit from the IVC to the right pulmonary artery. Of significance to pediatric surgeons, a Fontan procedure may lead to an increased venous pressure in the IVC, which may in turn cause ascites in the early postoperative period, leading to respiratory compromise. Although this has become less frequent with fenestrated Fontans, peritoneal drainage catheters may be required for several days postoperatively in some patients.

### RESULTS

Recently, tremendous strides have been made in the outcomes for patients with single ventricle anatomy. Most notably, survival for patients with HLHS, universally fatal only 2 decades ago, has drastically improved. The highest risk stage of the repair remains the Norwood operation. During the 1990s, the hospital survival for the Norwood procedure across the United States was approximately 40%.[77] Currently, several select centers are reporting hospital survivals of approximately 90% or greater.[78–81] Reported survival for the hemi-Fontan and Fontan procedures has been excellent at 98% for both operations.[82–84]

## Vascular Rings and Slings

Vascular rings comprise a spectrum of vascular anomalies of the aortic arch, pulmonary artery, and brachiocephalic vessels. The clinically significant manifestation of these lesions is a varying degree of tracheoesophageal compression. These vascular anomalies can be divided into complete vascular rings and partial vascular rings. Complete vascular rings can be divided into double aortic arch and right aortic arch with retroesophageal left ligamentum arteriosum. These two categories can be further subdivided on the basis of the specific anatomy (Table 127-1). Incomplete vascular rings include aberrant right subclavian artery, innominate artery compression, and PA sling. Other rare variations, which have been described, include left aortic arch with right descending aorta and right ligamentum and left aortic arch with aberrant right subclavian artery and right ligamentum. The incidence of clinically significant vascular rings is 1% to 2% of all congenital heart defects.

Vascular rings and pulmonary slings have been described in conjunction with other cardiac defects including tetralogy of Fallot, atrial septal defect, branch PA stenosis, coarctation, atrioventricular septal defect, ventricular septal defect, interrupted aortic arch, and aortopulmonary window. Significant associated cardiac anomalies occur in 11% to 20% of patients with a vascular ring.[83,85,86] A right aortic arch is generally associated with a greater incidence of coexisting anomalies. Pediatric surgeons should be aware that arch anomalies and aberrant subclavian arteries are more common in children with esophageal atresia, even in the absence of cardiac malformations.

By the end of the fourth week of embryonic development, the six aortic or branchial arches have formed between the dorsal aortae and ventral roots. Subsequent involution and migration of the arches results in the anatomically normal or abnormal development of the aorta and its branches. The majority of the first, second, and fifth arches regress. The third arch forms the common carotid artery and proximal internal carotid artery. The right fourth arch forms the proximal right subclavian artery. The left fourth arch contributes to the portion of the aortic arch from left carotid to left subclavian arteries. The proximal portion of the right sixth arch becomes the proximal portion of the right pulmonary artery, while the distal segment involutes. Similarly, the proximal left sixth arch contributes to the proximal left pulmonary artery, and the distal sixth arch becomes the ductus arteriosus (Fig. 127-23).

The PA is formed from two vascular precursors, as well as through a combination of angiogenesis, the de novo development of new blood vessels, and vasculogenesis, the budding and migration of existing vessels. As stated earlier, the proximal pulmonary arteries are based on the sixth arches, whereas the primitive lung buds initially derive their blood supply from the splanchnic plexus. Ultimately, these two segments of the PA join to form the vascular network of the lung parenchyma (Fig. 127-24).

**TABLE 127-1**
**Anatomic Classification and Distribution of Vascular Anomalies**

| *Anomaly Prevalence* | % |
|---|---|
| Complete vascular rings | 65-82 |
| Double aortic arch | 38-55 |
| Right dominant | 73-81 |
| Left dominant | 15-20 |
| Co-dominant | 3-11 |
| Right arch, left ligamentum/ductus | 24-55 |
| Aberrant left subclavian | 65-92 |
| Mirror-image branching | 8-35 |
| Right ligamentum | 0-3 |
| Incomplete vascular rings | 14-29 |
| Innominate artery compression | 80-87 |
| Aberrant right subclavian | 13-20 |
| Pulmonary sling | 2-9 |

From Ohye RG, Wild LC, Mutabagani K, Bove EL: Vascular rings and slings. In Franco KL, Putman JB (eds): Advanced Therapy in Thoracic Surgery. Hamilton, Ontario, BC Decker, 2004.

### NATURAL HISTORY AND DIAGNOSIS

Children with a complete vascular ring generally present within the first weeks to months of life. Typically, children with a double aortic arch present earlier in life than those with a right arch and retroesophageal left ligamentum. In the younger age group, respiratory symptoms predominate, as liquids are generally well tolerated. Respiratory symptoms may include stridor, nonproductive cough, apnea, or frequent respiratory infections. The cough is classically described as "seal bark" or "brassy." These symptoms may mimic asthma, respiratory infection, or reflux, and children with vascular rings are often initially misdiagnosed. With the transition to solid food, dysphagia becomes more apparent.

The presentation of a patient with an incomplete vascular ring is variable. Children with innominate artery compression usually present within the first 1 to 2 years of life with respiratory symptoms. Although aberrant right subclavian artery is the most common arch abnormality, occurring in approximately 0.5% to 1% of the population, it rarely causes symptoms. Classically, when symptoms do occur, they present in the seventh and eighth decade, as the aberrant vessel becomes

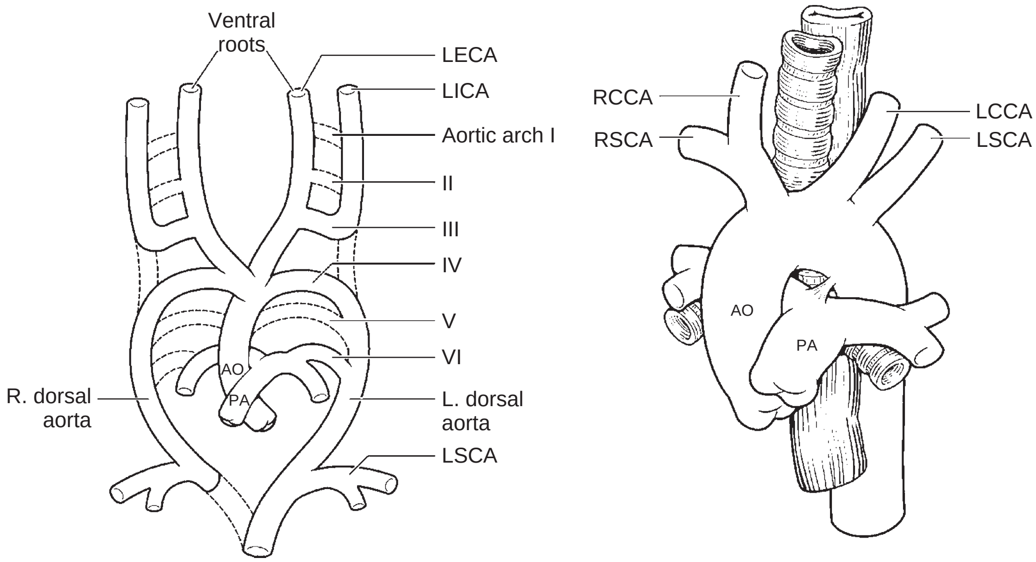



**FIGURE 127-23** Normal aortic arch development. AO, aorta; DA, ductus arteriosum; LCCA, left common carotid artery; LECA, left external carotid artery; LICA, left internal carotid artery; LSCA, left subclavian artery; PA, pulmonary artery; RCCA, right common carotid artery; RSCA, right subclavian artery. (From Ohye RG, Wild LC, Mutabagani K, Bove EL: Vascular rings and slings. In Franco KL, Putman JB [eds]: Advanced Therapy in Thoracic Surgery. Hamilton, Ontario, BC Decker, 2004.)

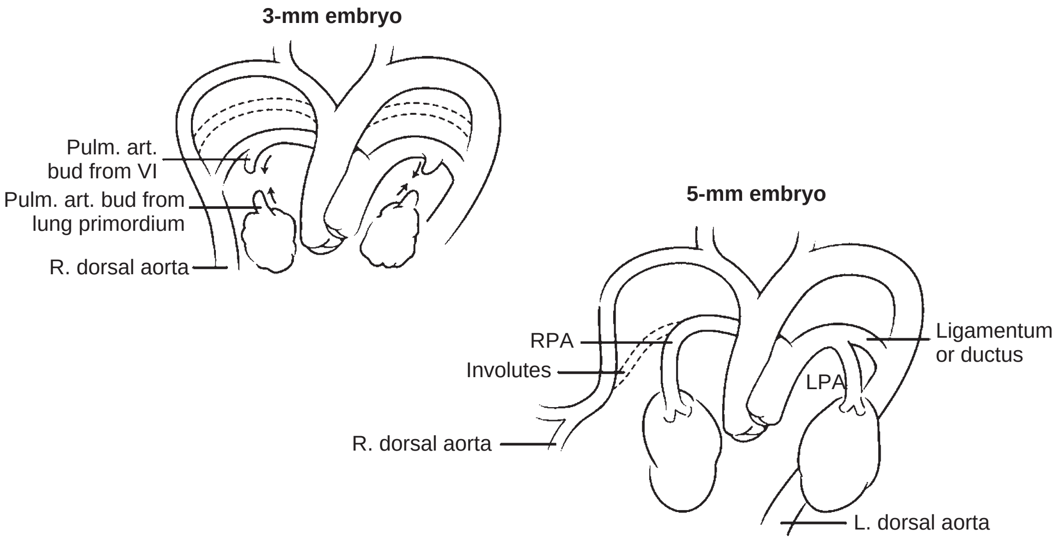



**FIGURE 127-24** Normal pulmonary artery development. LPA, left pulmonary artery; RPA, right pulmonary artery. (From Ohye RG, Wild LC, Mutabagani K, Bove EL: Vascular rings and slings. In Franco KL, Putman JB [eds]: Advanced Therapy in Thoracic Surgery. Hamilton, Ontario, BC Decker, 2004.)

ectatic and calcified, causing *dysphagia lusoria* due to impingement of the artery on the posterior esophagus. An aberrant right subclavian rarely causes symptoms, except when it is of an abnormally large caliber or associated with tracheomalacia.

Children with PA slings generally present with respiratory symptoms within the first few weeks to months of life. As with complete rings, respiratory symptoms may include stridor, nonproductive cough, apnea, or frequent respiratory infections and may mimic other conditions leading to misdiagnosis. PA slings are associated with complete tracheal rings in 30% to 40% of patients, leading to focal or diffuse tracheal stenosis.[87]

The methods for diagnosing a vascular ring are variable due to the variability in presentation and the spectrum of diagnostic tests available. A child with a presumptive diagnosis of asthma or tracheomalacia may be referred to a pulmonologist, and a diagnosis of vascular ring made or suspected initially by chest radiograph and bronchoscopy. In some situations, the diagnosis is made by echocardiography during evaluation for concurrent cardiac defects. Regardless, the diagnosis generally begins with a chest radiograph. Complementary studies may include barium esophagogram, CT, MRI, and bronchoscopy. CT, MRI, and bronchoscopy are important modalities to define the tracheal anatomy in a patient with a PA sling. Echocardiography may be diagnostic and is used to rule out other cardiac anomalies. Tracheograms and cardiac catheterizations, which have been used extensively in the past, are rarely indicated in the current era.

## MANAGEMENT

### Complete Vascular Rings

***Double Aortic Arch*** A double aortic arch occurs when the distal portion of the right dorsal aorta fails to regress (Fig. 127-25). The two arches form a complete ring, encircling the trachea and esophagus. The right arch is dominant in the majority of cases, followed by left dominant, with co-dominant arches being the least common (Table 127-1). The left and right carotid and subclavian arteries generally arise from their respective arches. The ligamentum arteriosum and descending aorta usually remain on the left.

The approach to repair of a double aortic arch is via a left posterolateral thoracotomy. The procedure can easily be accomplished through a limited, muscle-sparing incision through the third or fourth intercostal space. The lung is retracted anteriorly and inferiorly, exposing the posterior mediastinum. The pleura is incised, after identifying the vagus and phrenic nerves. The ligamentum or ductus arteriosum is divided while preserving the recurrent laryngeal nerve. The nondominant arch is then divided between two vascular clamps at the point where brachiocephalic flow is optimally preserved. If there is concern regarding the location for division, the arches can be temporarily occluded at various points while monitoring pulse and blood pressure in each limb. If there is an atretic segment, the division is done at the point of the atresia. Dissection around the esophagus and trachea in the regions of the ligamentum/ductus and nondominant arch allows for retraction of the vascular structures and lysis of any residual obstructing adhesions.

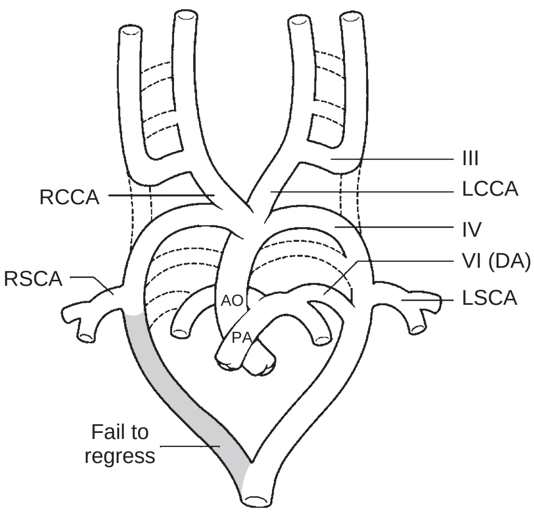
***Right Aortic Arch with Left Ligamentum Arteriosum*** There are three anatomic variations for a right arch with a left ligamentum, which cause a complete vascular ring. If the left fourth arch regresses between the aorta and left subclavian, a right aortic arch with aberrant left subclavian artery results. The ligamentum arteriosum is retroesophageal, bridging the left PA and aberrant left subclavian, forming a complete vascular ring (Fig. 127-26). If the left fourth arch regresses after the origin of the left subclavian artery, but before the arch reaches the dorsal aorta to communicate with the left sixth arch (which becomes the ductus arteriosum), there is mirror-image branching. The retroesophageal ligamentum arteriosum arises directly from the descending aorta, or from a Kommerell diverticulum off of the descending aorta, forming the complete ring (Fig. 127-27). If communication is maintained between the left fourth and sixth arches, there is mirror image branching with the ligamentum arising from the anterior and mirror image left subclavian and a ring is not formed (Fig. 127-28).

The surgical approach for a right aortic arch with retroesophageal left ligamentum arteriosum is the same as for a double arch. The ligamentum is divided, and any adhesions around the esophagus and trachea are lysed. Rarely, the Kommerell diverticulum has been reported to cause compression even after division of the ligamentum. As such, it may be prudent to resect or suspend the diverticulum posteriorly to the prevertebral fascia, if it is particularly prominent.

### Incomplete Vascular Rings

***Innominate Artery Compression*** In innominate artery compression syndrome, the aortic arch and ligamentum are in their normal leftward position; however, the innominate artery arises partially or totally to the left of midline (Fig. 127-29). As the artery courses from left to right anterior to the trachea, it causes tracheal compression. The symptoms of innominate artery compression may be mild to severe. With mild symptoms and minimal tracheal compression on bronchoscopy, children can be observed expectantly because the symptoms may resolve with growth. Indications for surgery include apnea, severe respiratory distress, significant stridor, or recurrent respiratory tract infection.

Several approaches for the correction of innominate artery compression syndrome have been described. These include simple division, division with reimplantation into the right side of the ascending aorta, and suspension to the overlying sternum. Suspension is currently the most widely used



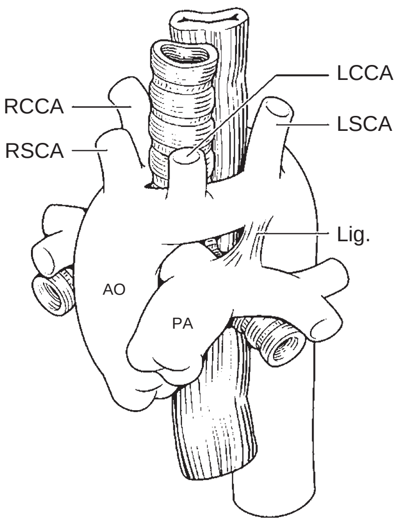




**FIGURE 127-25** Formation of a double aortic arch. AO, aorta; DA, ductus arteriosum; LCCA, left common carotid artery; Lig., ligamentum arteriosum; LSCA, left subclavian artery; PA, pulmonary artery; RCCA, right common carotid artery; RSCA, right subclavian artery. (From Ohye RG, Wild LC, Mutabagani K, Bove EL: Vascular rings and slings. In Franco KL, Putman JB [eds]: Advanced Therapy in Thoracic Surgery. Hamilton, Ontario, BC Decker, 2004.)

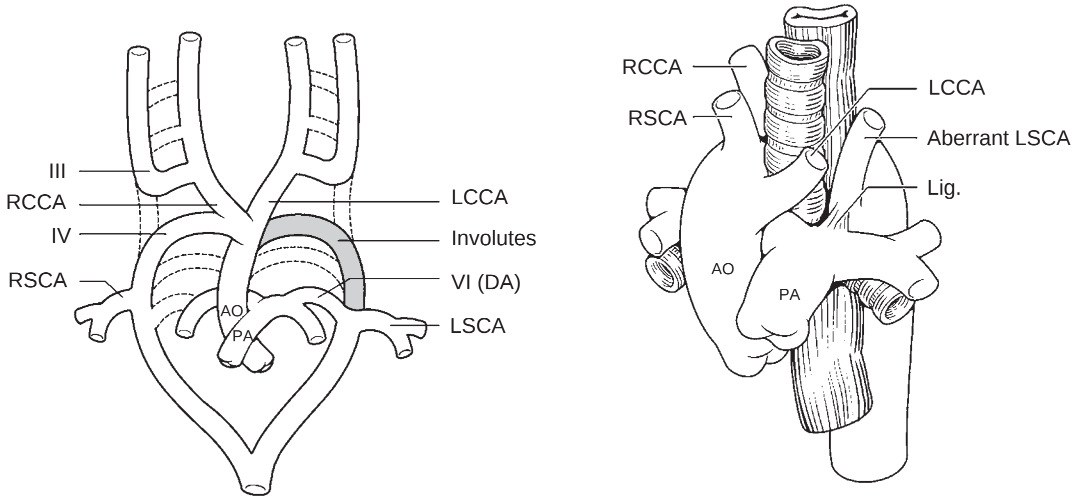



**FIGURE 127-26** Formation of a right aortic arch with aberrant left subclavian and retroesophageal left ligamentum arteriosum. AO, aorta; DA, ductus arteriosum; LCCA, left common carotid artery; Lig., ligamentum arteriosum; LSCA, left subclavian artery; PA, pulmonary artery; RCCA, right common carotid artery; RSCA, right subclavian artery. (From Ohye RG, Wild LC, Mutabagani K, Bove EL: Vascular rings and slings. In Franco KL, Putman JB [eds]: Advanced Therapy in Thoracic Surgery. Hamilton, Ontario, BC Decker, 2004.)

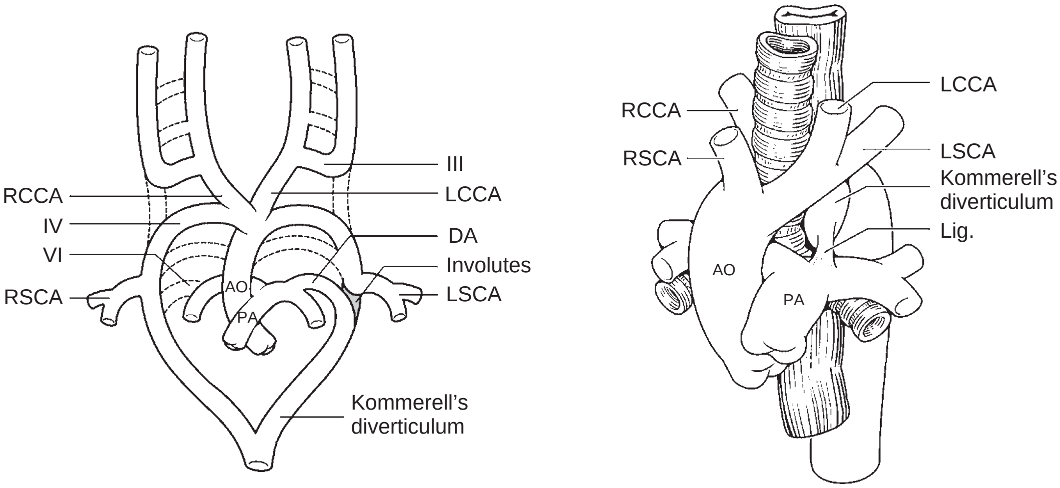



**FIGURE 127-27** Formation of a right aortic arch with mirror image branching and retroesophageal left ligamentum arteriosum. AO, aorta; DA, ductus arteriosum; LCCA, left common carotid artery; Lig., ligamentum arteriosum; LSCA, left subclavian artery; PA, pulmonary artery; RCCA, right common carotid artery; RSCA, right subclavian artery. (From Ohye RG, Wild LC, Mutabagani K, Bove EL: Vascular rings and slings. In Franco KL, Putman JB [eds]: Advanced Therapy in Thoracic Surgery. Hamilton, Ontario, BC Decker, 2004.)

technique. Exposure is obtained through a limited left anterior, right anterior, or right inframammary anterolateral thoracotomy. Once the innominate artery is exposed, no dissection of the artery is undertaken. By not performing a circumferential dissection of the innominate artery, the suspension of the vessel will also pull up on the anterior trachea. Pledgeted polypropylene sutures are passed partial thickness through both the innominate artery and the aorta at the origin of the innominate. Temporary distraction on the sutures under bronchoscopic guidance aids in the optimal placement of the sutures in the vessels and overlying sternum. Once satisfactory establishment of tracheal patency is confirmed by bronchoscopy, the sutures are brought through the sternum and secured. The operation is essentially the same as an aortopexy done to relieve severe localized tracheomalacia associated with esophageal atresia (see Chapter 69).

***Left Aortic Arch with Aberrant Right Subclavian Artery*** An aberrant right subclavian artery occurs when there is regression of the right fourth arch between the right common carotid and right subclavian arteries (Fig. 127-30). The right subclavian then arises from the leftward descending aorta, laying posterior to the esophagus as it crosses from left to right. Although the artery can compress the esophagus posteriorly, it is rarely the cause of symptoms in children. Surgical treatment involves simple division via a left posterolateral thoracotomy. Rarely, reimplantation or grafting from the right carotid or aortic arch may be necessary. More significantly, any vascular ring or sling that goes around the esophagus should be a contraindication to long-term nasogastric tubes or any esophageal stent (as may be used in the postoperative management of patients with esophageal atresia), because of the risk of arterio-esophageal fistula.

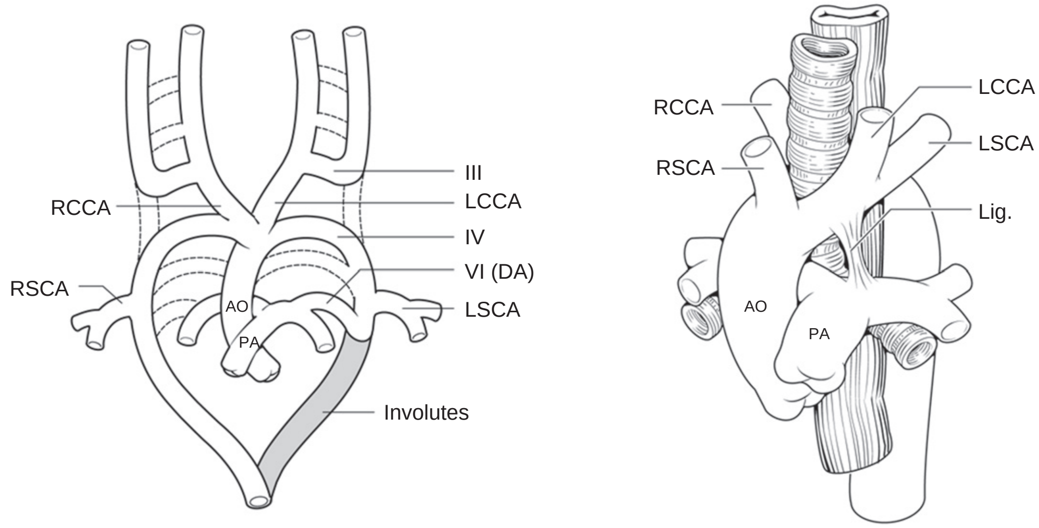



**FIGURE 127-28** Formation of a right aortic arch with mirror imaging branching and left ligamentum arteriosum, which does not form a vascular ring. AO, aorta; DA, ductus arteriosum; LCCA, left common carotid artery; Lig., ligamentum arteriosum; LSCA, left subclavian artery; PA, pulmonary artery; RCCA, right common carotid artery; RSCA, right subclavian artery. (From Ohye RG, Wild LC, Mutabagani K, Bove EL: Vascular rings and slings. In Franco KL, Putman JB [eds]: Advanced Therapy in Thoracic Surgery. Hamilton, Ontario, BC Decker, 2004.)

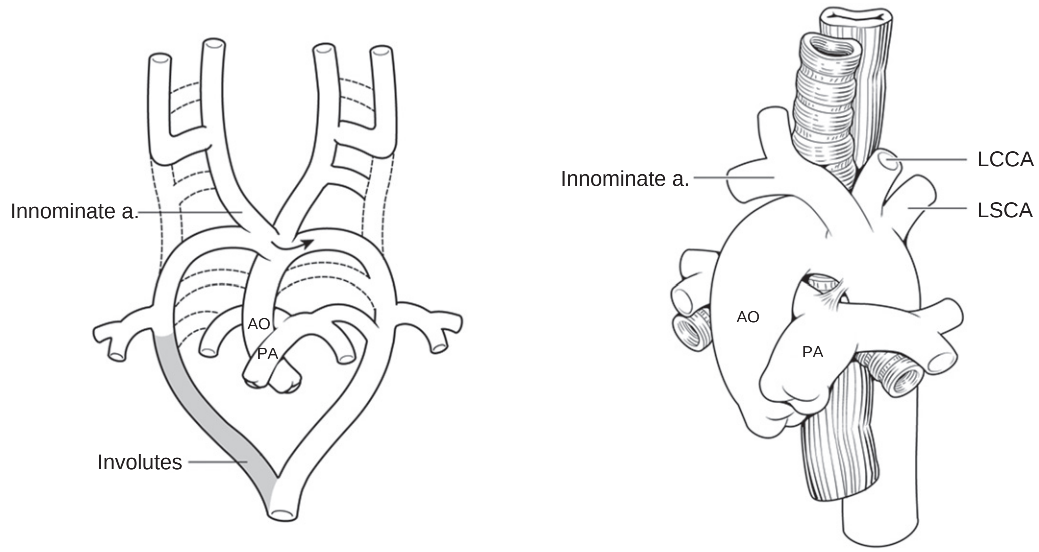



**FIGURE 127-29** Embryologic origin of innominate artery compression syndrome. AO, aorta; LCCA, left common carotid artery; LSCA, left subclavian artery; PA, pulmonary artery. (From Ohye RG, Wild LC, Mutabagani K, Bove EL: Vascular rings and slings. In Franco KL, Putman JB [eds]: Advanced Therapy in Thoracic Surgery, Hamilton, Ontario, BC Decker, 2004.)

### Pulmonary Artery Sling

Normally, the right and left sixth aortic arches contribute to the proximal portions of their respective pulmonary arteries. If the proximal left sixth arch involutes and the bud from the left lung migrates rightward to meet the right pulmonary artery, a PA sling is formed (Fig. 127-31). PA slings are associated with complete tracheal rings and tracheal stenosis in 30% to 40% of patients.[87] Origin of the right upper lobe bronchus from the trachea has been reported in frequent association with PA sling.[88]

Initial attempts at the repair of a PA sling involved reimplantation after division of the left pulmonary artery (LPA) and translocation of the trachea without cardiopulmonary bypass. These early reports had a high incidence of LPA thrombosis. This has led some authors to advocate division of the trachea and translocation of the LPA. This approach would seem sensible if the trachea were being divided in the course of tracheal reconstruction. However, currently most authors advocate the reimplantation of the LPA, which has resulted in excellent results.[89,90] The procedure is done via a median sternotomy on cardiopulmonary bypass to ensure optimal visualization of the repair. Aortic cross clamping is not necessary. The LPA is divided from the RPA, translocated anterior to the trachea, and reimplanted into the main pulmonary artery.

Any necessary reconstruction of the trachea is done concurrently with bronchoscopic assistance. Many techniques for tracheal reconstruction have been described, the most

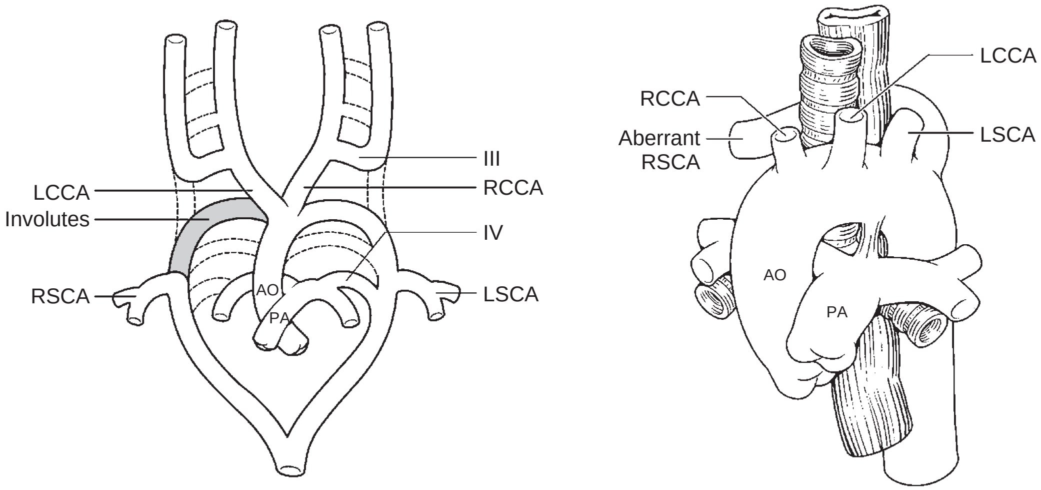



FIGURE 127-30 Formation of a left aortic arch with aberrant right subclavian artery. LCCA, left common carotid artery; LSCA, left subclavian artery; RCCA, right common carotid artery; RSCA, right subclavian artery. (From Ohye RG, Wild LC, Mutabagani K, Bove EL: Vascular rings and slings. In Franco KL, Putman JB [eds]: Advanced Therapy in Thoracic Surgery, Hamilton, Ontario, BC Decker, 2004.)

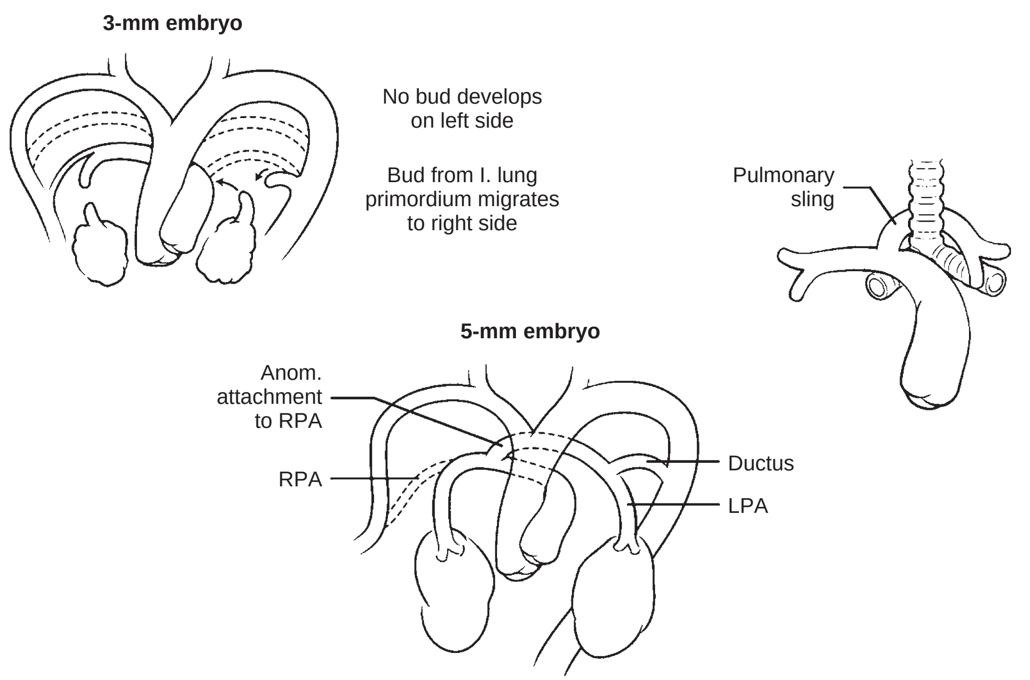



FIGURE 127-31 Formation of a pulmonary artery sling. LPA, left pulmonary artery; RPA, right pulmonary artery. (From Ohye RG, Wild LC, Mutabagani K, Bove EL: Vascular rings and slings. In Franco KL, Putman JB [eds]: Advanced Therapy in Thoracic Surgery, Hamilton, Ontario, BC Decker, 2004.)

common of which are resection with primary reanastomosis and sliding tracheoplasty for short segment stenosis and rib cartilage or pericardial patch for long areas of narrowing.

## Vascular Rings Requiring a Right Thoracotomy

More than 95% of vascular rings without concurrent cardiac defects can be performed through a left thoracotomy. A right thoracotomy is indicated for the rare cases where there is a right ligamentum arteriosum. A right ligamentum occurs in the setting of a left aortic arch with right descending aorta, where the ligamentum bridges from the descending aorta to the right PA, forming a complete ring. Right ligamentum arteriosum has also been described with a left aortic arch with aberrant right subclavian artery. In this case, the ligamentum may arise from the aberrant subclavian artery, a diverticulum off of the arch, or directly from the left arch to the right pulmonary artery. In addition, a double aortic arch with an atretic segment proximal to the right carotid artery is more easily divided through a right thoracotomy. The approach to these anomalies is the same as for a left-sided ring division, with the caveat that the right recurrent laryngeal nerve will loop around the right ligamentum.

## Video-Assisted Thoracoscopic Surgery

We and Burke and colleagues have repaired vascular rings using video-assisted thoracoscopic surgery (VATS) both with[91] and without[92] robotic assistance. Candidates for thoracoscopic division in both series were limited to those patients requiring

only the division of nonpatent vascular structures. There were no operative deaths, and all procedures were completed by VATS. In general, VATS is used for patients greater than 15 kg due to current size limitations of the instruments.[93]

## RESULTS

Mortality for the repair of a vascular ring is 0.5% to 7.6%, with improved survival occurring in more recent series.[83,85,88,94] The majority of deaths are related to other cardiac defects or respiratory infection and failure. Backer and colleagues[89] reported a series of 16 patients repaired using LPA division and reimplantation for PA sling, all of whom also required tracheal reconstruction. There were no operative mortalities and one late death due to respiratory complications. The major source of morbidity, as well as mortality, in this and other series is related to the tracheal reconstruction.[89,90]

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 128

# Management of Neural Tube Defects, Hydrocephalus, Refractory Epilepsy, and Central Nervous System Infections

Jodi L. Smith

## Neural Tube Defects

Neurulation, one of the earliest and most crucial events in human development, generates the neural tube (NT), the rudiment of the entire adult central nervous system (CNS) (i.e., the brain and spinal cord [SC]). The NT forms during primary and secondary neurulation. Primary neurulation involves the formation of a neural plate (NP) and the subsequent morphogenetic movements that transform it into an NT. Secondary neurulation involves the formation of an epithelial cord (i.e., the medullary cord) and its subsequent cavitation to form an NT. In humans, the brain and SC as far caudally as the S2 level form by primary neurulation, whereas the SC caudal to the S2 level and the filum terminale form by secondary neurulation. For more than a century, investigators have used many different animal models and experimental paradigms to ascertain the mechanisms underlying primary and secondary neurulation. When these processes go awry in humans, neural tube defects (NTDs) result. NTDs are among the most common of all human birth defects, with incidence rates varying from less than 1 to more than 6 per 1000 pregnancies around the world and affecting about 3000 pregnancies per year in the United States.[1,2,2a] These complex congenital malformations occur when the NT, which ultimately forms the brain and SC, fails to close during the first few weeks of embryonic development. NTDs are commonly classified as open or closed on the basis of the presence or absence of exposed neural tissue. In open NTDs, which occur as a consequence of failed primary neurulation, the NT and its membranous coverings are abnormal and are exposed at birth through a defect in the skull or spine. In closed NTDs, which occur because of faulty secondary neurulation, the NT and its membranous coverings are abnormal but the overlying skin is intact. Open NTDs, which occur more frequently than closed NTDs, include anencephaly, spinal rachischisis or spina bifida aperta/cystica (i.e., myeloschisis, myelomeningocele, and meningocele), and encephalocele. Closed NTDs include spina bifida occulta; lipomatous malformations (e.g., lipomas and lipomyelomeningoceles); split cord malformations (diastematomyelia, diplomyelia); neurenteric cysts; dermal sinuses; tethered SC; and sacral agenesis (caudal regression). Anencephaly, or absence of the brain, is invariably fatal and results when the cephalic part of the NT fails to close. Infants born with this condition typically die at birth or within the first few days after birth. Spina bifida cystica (i.e., myeloschisis, myelomeningocele, and meningocele) results from incomplete development of the NT more caudally, with protrusion of the malformed neural tissue, meninges, or both through an opening in the vertebral arches, muscle, and skin (Fig. 128-1). Open NTDs range in severity from craniorachischisis, in which the entire NT remains open, to a lesion limited to a single vertebral level. Of the open NTDs, myelomeningocele is the most common and the most severe birth defect compatible with survival.[3] Recent studies have suggested that periconceptional folic acid supplementation reduces the occurrence and recurrence risk of NTDs by 50% to 70%[4,5]; however, these serious birth defects continue to affect approximately 1 per 1000 live-born infants. In other words, including pregnancies that are electively terminated, approximately 4000 pregnancies per year, or 11 to 12 pregnancies per day, in the United States are affected by an NTD. These devastating birth defects are associated with fetal wastage, infant mortality, lifelong disability, and substantial health care costs. To eradicate NTDs, we must continue to advance our understanding regarding the cellular and molecular mechanisms responsible for normal NT formation through dedicated research efforts.

### EMBRYOLOGY

Most of what we already know about the mechanisms that comprise normal human NT formation comes from extensive descriptive studies on both human and nonhuman embryos and from experimental studies on nonhuman animal models

FIGURE 128-1 Three-hour-old male infant with an L5-S1 myelomeningocele diagnosed prenatally by ultrasound.

such as the chick and mouse, from which much of our current understanding of neurulation is derived. Such studies, which provide insight into the mechanisms underlying early human neural development, have revealed that primary neurulation occurs in four spatially and temporally overlapping stages: (1) formation of the NP, (2) shaping of the NP, (3) bending of the NP, and (4) fusion of the neural folds (Fig. 128-2, *A* to *E*).[6,7] The important stages in embryologic development are further summarized in Figures 128-3 and 128-4.[6–9]

For many years, neurulation was viewed as a simple, intrinsic force-driven, all-or-none process in which the NP either rolled up into a tube or did not. Moreover, a change in neuroendocrine (NE) cell shape from column-like to wedgelike by contraction of apical microfilaments was the intrinsic force proposed to drive this process. However, through more recent advances in research we now know that this "traditional view of neurulation" is incorrect. Instead, neurulation is a highly complex, multifactorial process that requires not only intrinsic forces generated by NE cells but also extrinsic forces generated by epidermal ectoderm cells, with the intrinsic and extrinsic forces acting in concert.[6,7]

A "multifactorial model of neurulation" has been proposed to explain how intrinsic and extrinsic morphogenetic forces generated by fundamental cell behaviors such as changes in cell shape, position, and number interact during neurulation to transform a flat pseudostratified sheet of ectodermal cells, the NP, into an elongated NT, the precursor of the entire adult CNS.[7] According to this model, intrinsic forces generated by elongation, rearrangement, and nonrandomly oriented rostrocaudal division of NE cells drive shaping of the NP and intrinsic forces generated by NE cell wedging drive furrowing of the NP. Extrinsic forces are generated by changes in epidermal ectoderm cell shape from low cuboidal to squamous, rearrangement of epidermal ectoderm cells with caudal-to-medial convergent extension, and nonrandomly oriented rostrocaudal and mediolateral cell division. Such changes in epidermal ectoderm cell behavior drive rostrocaudal lengthening of the epidermal ectoderm, as well as medial epidermal ectoderm expansion, which in turn drives neural fold elevation, convergence, and fusion. Failure of this process at any step along the way presumably will generate a neural tube defect.

## EPIDEMIOLOGY

The incidence of spina bifida is estimated at one to two cases per 1000 population, with certain populations having a significantly higher incidence based on genetic predilection. There is also a marked geographic variation in incidence.

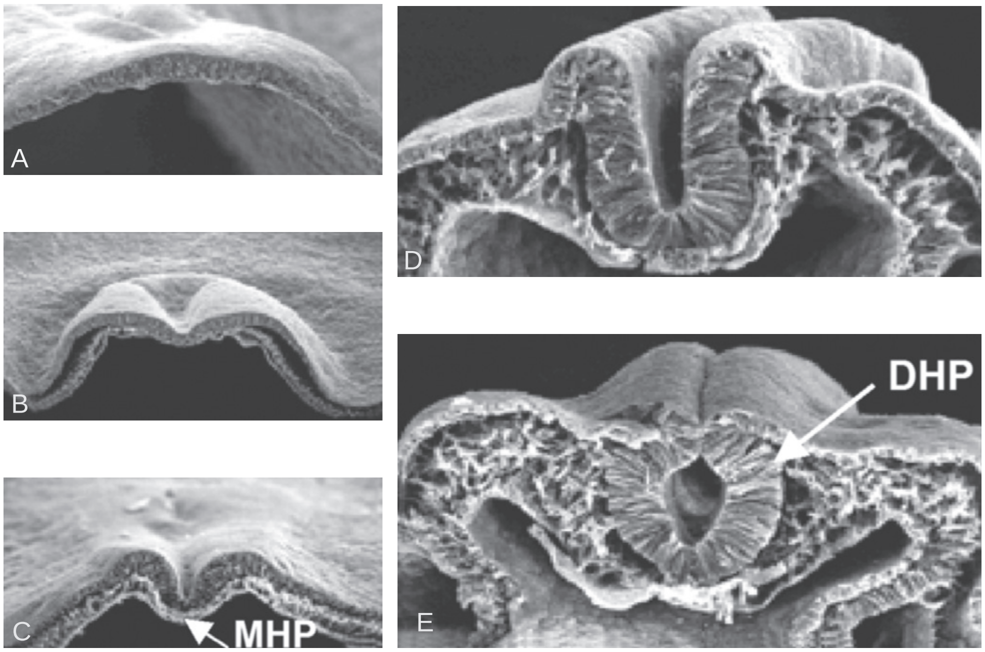


FIGURE 128-2 **A-E,** Scanning electron micrographs of transverse sections through the chick blastoderm demonstrating the four stages of primary neurulation—formation, shaping, and bending of the neural plate and fusion of the neural folds. During primary neurulation, the neural tube, the precursor of the entire adult central nervous system, develops from the ectodermal flat neural plate. DHP, dorsolateral hinge point; MHP, median hinge point. (Modified from Smith JL, Schoenwolf GC: Neurulation: Coming to closure. Trends Neurosci 1997;20:510.)

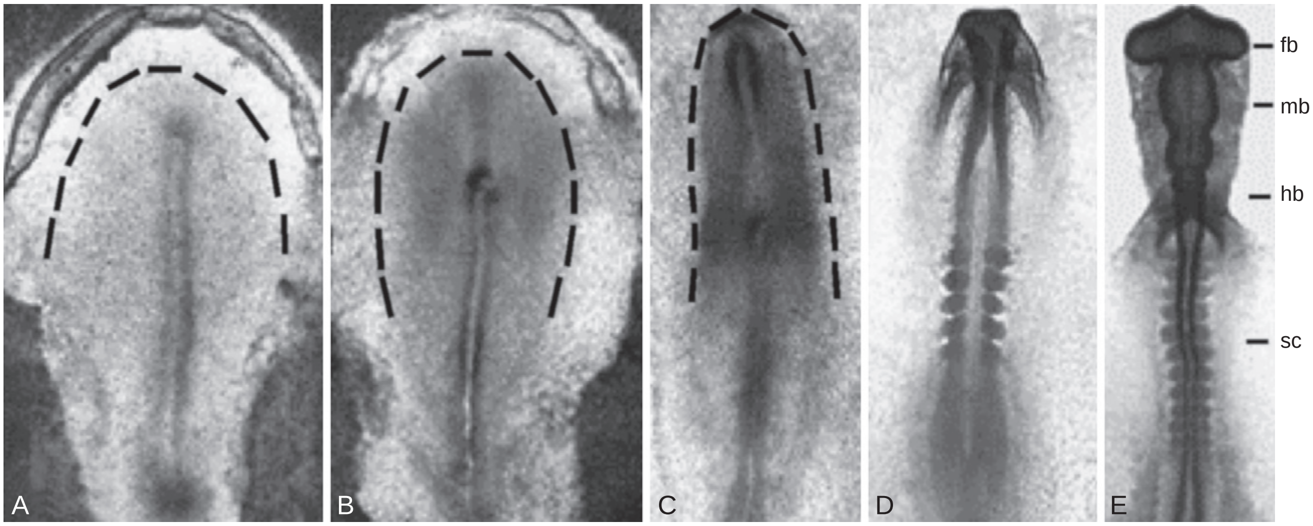


**FIGURE 128-3** Light micrographs of dorsal views of chick blastoderms at Hamburger and Hamilton stages 4 to 10+.[183] **A,** Flat neural plate (stage 4) shortly after its formation. **B,** Flat neural plate with a notochord (head process; stage 5). **C,** Neural groove stage (stage 6) showing rostrocaudal lengthening and mediolateral narrowing characteristic of shaping of the neural plate. The broken line in **A** to **C** indicates approximate rostrolateral boundaries of the neural plate. **D,** Incipient neural tube (stage 8+). **E,** Definitive neural tube (stage 10+). fb, forebrain; hb, hindbrain; mb, midbrain; sc, spinal cord. (Modified from Smith JL, Schoenwolf GC: Neurulation: Coming to closure. Trends Neurosci 1997;20:510.)

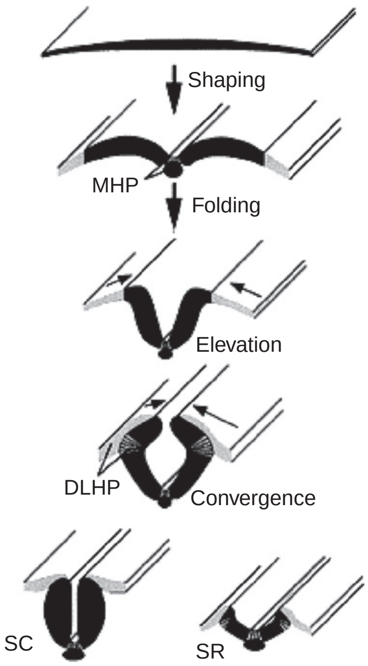


**FIGURE 128-4** Schematic diagram illustrating the major morphogenetic events of primary neurulation at the future midbrain/hindbrain level and differing morphologies at the spinal cord (*SC*) and sinus rhomboidalis (*SR*) levels. DLHP, dorsolateral hinge point; MHP, median hinge point. (Modified from Smith JL, Schoenwolf GC: Neurulation: Coming to closure. Trends Neurosci 1997;20:510.)

For instance, the highest rates occur in parts of the British Isles, mainly Ireland and Wales, where the incidence of myelomeningocele is as high as three to four cases per 1000 population and the incidence of anencephaly is more than six cases per 1000 population for both live births and stillbirths. In the United States, the prevalence is declining, with African Americans having a rate of 0.1 to 0.4 per 1000 live births versus 1 per 1000 live births in the white population. The two main reasons for the decline of NTDs in the United States are pregnancy termination and periconceptional use of folic acid. Finally, the risk of giving birth to a second child with an NTD in the United States is 1% to 3%.

## ETIOLOGY

The precise etiology and specific genes responsible for the generation of NTDs such as myelomeningocele have not yet been elucidated. The cause of such defects is probably multifactorial, with both genetic and environmental factors playing a role. Besides problems occurring during neurulation that prevent NT closure, problems in the postneurulation period (e.g., as a result of exposure of the unprotected nervous system to amniotic fluid) may also have a deleterious effect on NT development and subsequent neural function. In addition, numerous teratogens have been implicated in the etiology of NTDs. Of all the teratogens evaluated thus far, carbamazepine, valproic acid, and folic acid deficiency have been most strongly tied to the development of NTDs. In support of this association, periconceptional folic acid supplementation has been shown to reduce the occurrence and recurrence risks of NTDs,[4,5] suggesting that NTDs result, at least in part, from folic acid deficiency. However, the precise role of folic acid in preventing NTDs remains unclear. Nevertheless, the U.S. Public Health Service made a strong recommendation in September 1992 that all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing the risk of having a pregnancy affected with an NTD. Furthermore, valproic acid (a known folate antagonist), if taken during pregnancy, results in a 1% to 2% estimated risk of having a child with an NTD.

## PATHOLOGY

The two most common types of NTDs seen with spina bifida aperta or cystica are myelomeningocele and meningocele. Myelomeningocele, the most common NTD compatible with

life, consists of an open neural placode surrounded by an intermediate zone of thin epithelium, which in turn is surrounded by normal skin (see Fig. 128-1). The dorsal (i.e., exposed) surface of the neural placode constitutes the everted interior of the NT and is continuous with the central canal of the SC rostrally. In contrast, the ventral surface constitutes the outside of what should have been a closed NT. Ventral or motor roots exit from the ventral surface of the placode just lateral to the midline on both sides; dorsal or sensory roots enter the periphery of the placode lateral to the motor roots. An arachnoid sac and subarachnoid space underlie the neural placode, and the junction between the skin and dura underlies the skin within a few millimeters from the skin edge. Subjacent to the dura is an epidural space that contains fat. The spinous processes are absent, and the paraspinous muscle masses, hypoplastic laminae, and pedicles are everted. In most cases, the SC rostral to the neural placode is normal; however, additional anomalies such as a split cord malformation (i.e., diastematomyelia), arteriovenous malformation, epidermoid, or lipoma may be present. In addition, most neonates with myelomeningocele have associated neurologic malformations such as hydrocephalus and Chiari II malformation (deformity of the hindbrain, cervical SC, and craniovertebral junction), as well as orthopedic anomalies of their lower extremities and urogenital anomalies caused by involvement of the sacral nerve roots. A meningocele is a skin-covered anomaly characterized by herniation of just the meninges through a dorsal bony defect (spina bifida). However, unlike myelomeningocele, the SC and nerve roots do not herniate into the skin-covered dural sac and neonates with these lesions typically do not have associated neurologic malformations.

## DIAGNOSIS OF NEURAL TUBE DEFECTS

Open NTDs such as anencephaly and myelomeningocele can be diagnosed prenatally by measuring alpha-fetoprotein (AFP) in the amniotic fluid or maternal bloodstream. AFP, the major serum protein in early embryonic life, can leak into the amniotic fluid from an open NTD. The first step in prenatal screening for open NTDs is drawing blood to measure maternal serum AFP between 15 and 20 weeks of gestation. A patient-specific risk is then calculated on the basis of gestational age and AFP level. For example, at an estimated gestational age of 20 weeks, a maternal serum AFP concentration higher than 1000 ng/mL would be consistent with the diagnosis of an open NTD. Measurement of maternal serum AFP is more than 75% accurate in detecting an open NTD when gestational age is greater than 15 weeks. If the diagnosis is uncertain with maternal serum AFP, an amniotic AFP level can be obtained, which will detect approximately 98% of all open NTDs. Moreover, fetal ultrasound can detect open and sometimes closed NTDs prenatally, especially in the hands of a skilled ultrasonographer. If the diagnosis of myelomeningocele is made prenatally, the parent or parents undergo extensive prenatal counseling and cesarean delivery is planned.

## EVALUATION AND TREATMENT

Neonates with myelomeningocele have a saclike protrusion containing a neural placode bathed in cerebrospinal fluid (CSF) (see Fig. 128-1). The size of the sac on the child's back at the time of birth depends on the amount of CSF that has collected ventral to the neural placode. These children may also have other associated CNS abnormalities including Chiari II malformation, hydrocephalus, syringomyelia, brainstem malformations, agenesis of the corpus callosum, and polymicrogyria. Shortly after birth, a thorough physical examination is performed that includes measurement of head circumference and assessment of general vigor (especially cry and suck); anal sphincter function (anocutaneous reflex or anal wink); upper and lower extremity motor and sensory function; the site, level, and size of the myelomeningocele defect; and whether or not the defect is leaking CSF. In addition, the neonate should be evaluated for signs and symptoms of hydrocephalus and brainstem compression (i.e., Chiari II malformation), as well as for associated orthopedic deformities such as clubfeet and kyphoscoliosis.

Before repair, the neonate is kept prone to prevent rupture of the sac and avoid trauma to the neural placode. In addition, the myelomeningocele defect should be covered with sterile saline-soaked gauze to prevent desiccation of the exposed neural tissue. The gauze, in turn, should be covered with a plastic wrap to prevent heat loss.[3] An intravenous catheter is placed, and broad-spectrum antibiotics are administered to reduce the risk of CNS infection. Head ultrasonography or computed tomography (CT) is performed to evaluate the extent of ventricular enlargement and determine the need for shunt placement. Initially, the ventricles may be normal or only slightly enlarged. However, after the NTD is closed, the ventricles often enlarge. The incidence of hydrocephalus associated with myelomeningocele ranges from 80% to 95%.

A myelomeningocele is typically closed within 24 to 72 hours following birth unless the infant has associated medical conditions that prevent administration of a general anesthetic or surgery.[10] The goal of surgery is to close the neural placode into an NT to establish a microenvironment conducive to neuronal function.[11] Closure involves (1) separation of the neural placode from the intermediate zone of epithelium and reconstruction of the placode into a tube with preservation of all neural tissue; (2) separation of the dura from the epidural space at the lateral margins of the defect and closure of the dura in a watertight but patulous fashion around the newly created NT; (3) surgical correction of any significant kyphotic deformity; (4) mobilization and midline approximation of the paraspinal muscles and fascia; and (5) tension-free closure of the skin in the midline, which often requires mobilization of the skin and subcutaneous tissue from the underlying fascia rostrally, caudally, and bilaterally.

Common postoperative complications include CSF leak, wound-healing problems, and tethered SC. The incidence of CSF leak may be reduced by careful closure of the dura and by placement of a shunt to treat associated hydrocephalus. Wound-healing problems may occur, especially in patients with large myelomeningoceles, and can be managed by keeping the patient prone and performing moist-to-dry dressing changes. Currently, no techniques are available to reduce the incidence of SC tethering after myelomeningocele repair.

### Fetal Surgery for the Treatment of Neural Tube Defects

Intrauterine repair of myelomeningocele has been advocated as a means of improving the neurologic outcome and reducing hindbrain herniation in infants with myelomeningocele. This is based on the idea that secondary damage and resultant

disability, which may occur when exposed neural tissue is in contact with amniotic fluid, may be reduced or even completely eliminated by closing the defect as early as possible in utero. Moreover, halting CSF loss by in utero closure of the neural placode may reverse some of the potentially devastating neurologic sequelae of NTDs such as shunt-dependent hydrocephalus and Chiari II malformation, by reducing hindbrain herniation.

A single-institution, nonrandomized observational study conducted between 1990 and 1999 compared outcomes including the requirement for ventriculoperitoneal shunt placement, obstetric complications, gestational age at delivery, and birth weight in 29 patients who underwent intrauterine myelomeningocele repair between 24 and 30 weeks of gestation with 23 lesion-matched controls who underwent standard postnatal repair.[12] The results of this study suggested that intrauterine repair decreased the incidence of hindbrain herniation and shunt-dependent hydrocephalus. However, this study also demonstrated an increased risk of oligohydramnios and admission to the hospital for preterm uterine contractions, an earlier estimated gestational age at delivery (33.2 vs. 37.0 weeks), and a smaller birth weight (2171 vs. 3075 g) in patients who underwent intrauterine repair. Other problems with this study included relatively short follow-up times, small sample size, varied selection criteria, and lack of a comparable control group of children with myelomeningocele who did not undergo intrauterine repair.

Thus, the study by Bruner and others[12] provided preliminary evidence that suggested that intrauterine myelomeningocele repair may decrease the incidence of hydrocephalus and reduce the severity of hindbrain herniation (including the incidence of Chiari II malformation). However, this study also showed that intrauterine repair involved substantial risks not associated with standard postnatal repair. Moreover, another study demonstrated that intrauterine repair between 20 and 28 weeks of gestation did not statistically improve lower extremity function when compared with lower extremity function in patients undergoing postnatal closure.[13] For the risks and benefits of intrauterine repair to be more clearly established, a multicenter, prospective, randomized controlled trial of intrauterine and conventional therapies, the management of myelomeningocele study (MOMs), was funded by the National Institutes of Health.[14–16] The MOMs trial began in 2003 and was carried out at three hospitals in the United States. In this trial, fetuses were randomized to surgery at 19–25 weeks of gestation or to standard postnatal repair. The primary objective of the trial was to ascertain whether intrauterine repair of myelomeningocele at 19 to 25 weeks of gestation improved outcome as measured by death or the need for a shunt by one year of life.[15] Other outcomes included a composite of mental development and motor function at 30 months, the degree of Chiari II malformation, and maternal morbidity. The trial was stopped for efficacy of prenatal surgery after 183 of a planned 200 patients were recruited, and the results of the study were based on 158 patients whose children were evaluated at 12 months. This study provided evidence that prenatal repair of myelomeningocele reduced the need for shunting and improved motor outcomes at 30 months when compared with standard postnatal repair. However, in contrast to postnatal repair, prenatal surgery was associated with an increased risk of preterm delivery, as well as uterine dehiscence at delivery.

### Associated Anomalies

Children with myelomeningocele often have other anomalies of the CNS that require attention. For example, more than 90% of children with myelomeningocele have a Chiari II malformation and hydrocephalus. Chiari II malformation is a complex deformity involving the calvarium, dura, and hindbrain. The spectrum of abnormalities observed in Chiari II malformation includes a lacunar skull (i.e., thinning and scalloping of the calvaria producing a "copper-beaten" appearance), small posterior fossa, low-lying transverse sinuses and torcular Herophili, fenestrated falx, heart-shaped tentorial incisura with upward herniation of the cerebellum, medullary kinking, beaking of the tectal plate, prominence of the massa intermedia, enlargement of the suprapineal recess, elongation of the fourth ventricle, syringomyelia, and downward displacement of the cerebellar vermis, fourth ventricle, medulla, and pons through the foramen magnum (Fig. 128-5, *A* and *B*). Neonates with symptomatic Chiari II malformation commonly have inspiratory stridor, apnea, dysphagia or nasal regurgitation, aspiration, weak or absent cry, weakness/spasticity in the upper or lower extremities (or both), and opisthotonic posturing. Older children and adolescents have a more insidious manifestation consisting of syncopal episodes, nystagmus, oscillopsia, lower cranial nerve palsies, hyperreflexia, and spastic quadriparesis. Radiologic diagnosis of Chiari II malformation is best made by brain magnetic resonance imaging (MRI).Treatment of patients with symptomatic Chiari II malformation (i.e., those with signs and symptoms of brainstem compression) involves decompression of the posterior fossa or cervical SC, or both, which can be surgically challenging because the torcular Herophili and transverse sinuses are low lying (i.e., near the foramen magnum), the cerebellum is often adherent to the medulla, and the fourth ventricle is displaced caudally and dorsally. Before subjecting the patient to a Chiari decompression, one must make certain that the patient has a functioning shunt because shunt malfunction can produce signs and symptoms of brainstem compression similar to those observed in a Chiari II malformation. When evaluating shunt function, it is important to remember that CT findings can be misleading because the ventricles may remain small or fail to show an increase in size despite a high-grade shunt obstruction. Therefore a shunt tap, radionuclide shunt injection, or shunt exploration should be performed to evaluate shunt function before decompressing a Chiari II malformation in a patient with myelomeningocele. Unfortunately, many patients fail to respond to surgical decompression of their Chiari II malformation. This is thought to be related at least in part to the possibility that their symptoms arise from incomplete formation of the brainstem nuclei rather than to brainstem compression from the Chiari II malformation.[17]

Hydrocephalus, which is discussed in this chapter in greater detail later, is present in 80% to 95% of children with myelomeningocele. Factors contributing to the development of hydrocephalus in this patient population include the Chiari type II malformation, aqueductal stenosis, fourth ventricle outlet obstruction, anomalous venous drainage in the posterior fossa caused by compression of the dural venous sinuses, open myelomeningocele with associated CSF leak, and the presence of other CNS malformations. Hydrocephalus is usually treated with a ventriculoperitoneal shunt, which diverts CSF from the brain to the peritoneal cavity for reabsorption.


**FIGURE 128-5** Five-year-old girl with myelomeningocele repaired in utero. **A,** Sagittal brain magnetic resonance image (MRI) showing a Chiari II malformation with upward herniation of the cerebellum and tectal plate beaking (*asterisk*), as well as downward displacement of the cerebellar tonsils through the foramen magnum (*arrow*). **B,** Sagittal spine MRI showing syringomyelia extending from C5 to L2 (*upper arrow*). The spinal cord and conus end at L4 (*lower arrow*), consistent with a tethered spinal cord.

A shunt may be placed at the time of myelomeningocele closure in patients with severe symptomatic hydrocephalus with associated macrocrania and massive ventriculomegaly apparent at birth or several days later under separate anesthesia to reduce the risk of shunt infection. CSF diversion is indicated in patients with rapidly progressive hydrocephalus and in those manifesting acute neurologic change such as stridor, swallowing dysfunction, or central apnea, with or without significant change in the size of the ventricles.[3]

## OCCULT SPINAL DYSRAPHISM-CLOSED NEURAL TUBE DEFECTS

During secondary neurulation, the caudal part of the NT develops from the tail bud, a mesenchymal mass of cells derived from remnants of the cranial part of the primitive streak. Secondary neurulation occurs in three stages: (1) formation of the medullary cord from the tail bud; (2) cavitation of the central aspect of the medullary cord, which results in the formation of multiple lumina; and (3) coalescence of the lumina into a single, central cavity surrounded by a peripheral layer of radially oriented medullary cord cells.[18] When secondary neurulation goes awry, closed NTDs result in which the overlying skin is intact but the caudal NT and its membranous coverings develop abnormally. Developmental anomalies of the caudal SC include spina bifida occulta; tight or thickened filum terminale; split cord malformations (also known as *diastematomyelia, diplomyelia*); neurenteric cysts; dermal sinuses; sacral agenesis/caudal regression; and lipomatous malformations such as lumbosacral lipoma, leptomyelolipoma, lipomyelomeningocele, and fatty filum. Such anomalies may lead to SC tethering, which, in turn, can cause progressive neurologic deterioration secondary to traction on the conus medullaris and resultant ischemic injury.[19]

Cutaneous stigmata are often found in association with occult spinal dysraphism and thus serve as markers for SC tethering, especially when they occur above the gluteal cleft. Such skin lesions include lumbosacral hypertrichosis (i.e., hairy patch), dermal sinus tract, sacral dimple, capillary hemangioma, caudal appendage, and subcutaneous lipoma. Patients with one or more of these lesions above the gluteal cleft should undergo further evaluation including a full spine MRI to look for SC tethering. In contrast, a skin lesion such as a dimple or pit below the gluteal cleft most likely represents a benign, nonneurologic finding that requires no further workup.

Besides cutaneous stigmata, children with tethered cord syndrome and occult spinal dysraphism frequently have (1) dysraphic posterior spinal elements and vertebral abnormalities; (2) orthopedic abnormalities such as scoliosis, lower extremity atrophy or asymmetry, and foot deformities; (3) progressive neurologic dysfunction such as lower extremity weakness, loss of sensation, radiculopathy, spasticity, hyperreflexia, and abnormal gait; (4) urologic dysfunction such as neurogenic bladder and urinary incontinence; and (5) bowel dysfunction. In addition, there is a high incidence of caudal SC abnormalities and associated SC tethering in patients with anorectal and urogenital malformations including cloacal exstrophy, persistent cloaca, penoscrotal transposition,

imperforate anus, the Currarino syndrome, and the VATER/VACTERL association (vertebral defects, imperforate anus, tracheoesophageal fistula with esophageal atresia, and radial and renal dysplasia with or without cardiac and limb abnormalities).[20] Although the explanation for the simultaneous development of cloacal and caudal SC malformations remains unknown, it is likely related at least in part to the intimate temporospatial relationship of urogenital, anorectal, and caudal NT development. Because of the high incidence of coexistent malformations and SC tethering, patients with anorectal and urogenital malformations should undergo a routine screening lumbosacral spine ultrasound or MRI to evaluate for asymptomatic tethering of the SC.

Lipomatous SC malformations such as fatty filum, lipomyelomeningocele, and leptomyelolipoma cause tethering of the SC and are the most common types of closed NTDs requiring neurosurgical treatment.[19,21,22] A fatty filum consists of a short, thickened filum terminale in which there is partial or complete fatty infiltration. A lipomyelomeningocele consists of a skin-covered subcutaneous lipoma that extends through a defect in the lumbosacral fascia, lamina, dura, and pia into a low-lying SC. Leptomyelolipoma, a type of lipomyelomeningocele, consists of a conus lipoma. Most children with lipomatous malformations have intact neurologic function at birth and are brought to medical attention for evaluation of a subcutaneous lipoma or other cutaneous stigmata as described earlier.

The natural history of tethered SC is that of progressive neurologic deterioration with deficits in sensory, motor, bowel, and bladder function arising during periods of rapid growth and weight gain.[21] As a consequence, early prophylactic untethering is recommended for all patients to stabilize neurologic function and prevent irreversible injury. Surgery involves microsurgical technique with monitoring of anal sphincter electromyography and somatosensory evoked potentials. Intraoperative stimulation of nerve roots helps distinguish functional from nonfunctional roots. In the case of a fatty filum, surgical treatment consists of a partial laminectomy at L4-L5 or L5-S1 through a short posterior midline incision and opening of the dura in the midline to expose the filum. After stimulating the filum to ensure that no neural function is present, the filum is sectioned at the rostral and caudal ends of the exposure and the intervening segment is sent to pathology for evaluation. In the case of lipomyelomeningocele or leptomyelolipoma, surgical treatment involves detaching the subcutaneous lipoma from the SC or conus lipoma at the point where it emerges through the defect in the lumbosacral fascia. It is unnecessary to resect the subcutaneous fatty mass completely because doing so can result in devascularization of the overlying skin, which in turn can compromise wound healing.[22] A laminectomy is performed rostral to the dural defect to identify normal anatomy, followed by careful dissection progressively more caudally to the region where the lipoma traverses the dural defect and enters the SC or conus. Subsequent steps include (1) releasing the conus from its attachments to the lipoma, leptomeninges, and dura; (2) decompressing the SC and conus by debulking the intramedullary lipomatous mass with the laser or ultrasonic aspirator; (3) sectioning the filum; (4) closing the dura in a watertight but patulous fashion; and (5) closing the paraspinal muscles, lumbosacral fascia, and skin using meticulous technique. Surgery-related complications include anesthesia-related risks, worsening of neurologic or urologic function (or both), CSF leak, and infection.

Other types of occult spinal dysraphism include split cord malformations (a.k.a. diastematomyelia), dermal sinus tracts, and neurenteric cysts. In split cord malformations, the SC is split into two halves in the sagittal plane, with each hemicord residing either together in a single dural tube (type I malformation) or in separate dural tubes (type II malformation).[23] A hairy patch usually overlies the region of the split cord malformation, and tethering of the SC may occur as a consequence of a thickened filum or a midline bony spur, or both, in the case of type II malformations or dorsal tethering bands/fibrous median septum between the dura and hemicords in the case of type I malformations. To prevent neurologic and urologic deterioration, the SC is untethered by first resecting the midline bony spur or sectioning the dorsal bands/fibrous septum between the dura and hemicords followed by sectioning of the filum.

Dermal sinus tracts often present in childhood with cutaneous findings, neurologic deficits, or infectious or chemical meningitis, or any combination of these findings.[24,25] Dermal sinus tracts represent remnants of incomplete NT closure, developing as a consequence of localized failure of dysjunction, the process whereby the surface ectoderm and dermal elements separate from the neuroectoderm. Failure of dysjunction generates an epithelial-lined tract that extends from an opening on the surface of the skin to the fascia, dura, or SC. Dermal sinus tracts can be found anywhere along the midline of the neuraxis and may be associated with drainage of CSF, intradural dermoid or epidermoid cysts, split cord malformations,[23] and tethering of the SC. Skin lesions associated with dermal sinus tracts are typically found in the lumbodorsal midline rostral to the gluteal cleft and include a dimple, pit, capillary hemangioma, hairy patch, skin tag, and subcutaneous lipoma. In the case of a dimple or pit, there may be drainage of cyst contents or CSF or local signs of infection such as erythema or induration. MRI is the neurodiagnostic tool of choice because it enables visualization of the dermal sinus tract and associated pathology such as a tethered SC, inclusion tumor, syrinx, or split cord malformation. However, some dermal sinus tracts may not be well visualized on MRI if they are small or out of the plane of imaging.[24] Hence if a patient has a cutaneous finding overlying the midline neuraxis that is above the gluteal cleft, surgical exploration may be warranted even if the MRI appearance is normal. Treatment consists of complete excision of the dimple and tract, intradural exploration with resection of any intradural connections or masses, and untethering of the SC. Timely diagnosis and appropriate surgical intervention with intradural exploration are essential in preventing infection including meningitis and preserving or improving neurologic function.

Spinal neurenteric cysts are rare congenital malformations lined by alimentary tract mucosa.[19] They form as a consequence of a persistent abnormal connection between the primitive ectoderm and endoderm[26] and are often accompanied by vertebral abnormalities and other forms of occult spinal dysraphism such as split cord malformation, lipoma, dermal sinus tract, and tethered SC. Patients with spinal neurenteric cysts may have cutaneous stigmata or signs of SC compression such as pain and neurologic deficits. Treatment involves complete excision of the neurenteric cyst, as well as appropriate surgical management of other associated congenital abnormalities including untethering of the SC. Gross total resection is essential because there is a high incidence of cyst recurrence associated with subtotal resection of neurenteric cysts.[26]

In patients with occult spinal dysraphism and tethered SC who have undergone an untethering procedure, progressive neurologic or urologic deterioration may signal recurrent tethering of the SC, which can occur in up to 15% of patients.[27] Therefore long-term neurologic and urologic follow-up is warranted to determine patients who may benefit from reoperation.

### OUTCOME AND PROGNOSIS

Treatment of NTDs has evolved over the past 50 years. Previously, neonates with NTDs either were left untreated or were treated selectively; however, most of them died of meningitis, hydrocephalus, and/or sepsis. In contrast, during the past 3 decades, neonates with NTDs have received prompt, aggressive treatment in almost all pediatric centers in the North America. Such treatment including early closure of open NTDs and aggressive shunting of hydrocephalus leads to survival with nearly normal intelligence in many patients.

Initial closure of an open NTD is just the beginning of the medical care typically required. In general, such patients require frequent and consistent follow-up in a comprehensive multidisciplinary clinic where they can be evaluated by a team of pediatric specialists. The team would include a developmental pediatrician, neurosurgeon, urologist, orthopedic surgeon, physiatrist, physical therapist, occupational therapist, nurse, and nutritionist. The multidisciplinary team approach is critical to the ultimate success and long-term management of these patients. With proper medical care, children with open NTDs can lead active and productive lives. For example, in a 20- to 25-year follow-up study of children with open spina bifida who were treated aggressively in a nonselective, prospective manner, these children entered college in the same proportion as the general population and many were actively employed.[28] With aggressive treatment and a multidisciplinary clinical approach, long-term survival into adulthood and advanced age is now common.

The goal of treating children with myelomeningocele is to maintain stable neurologic functioning throughout their lifetime.[3] Neurosurgeons must always be on the alert for neurologic deterioration in children and adults with myelomeningocele. Besides shunt malfunction, the most common cause of neurologic deterioration is symptomatic SC tethering in which there is tension on the SC resulting from fixation of the SC due to adhesions between the previously exposed neural tissue and the surrounding tissues. In almost all patients with myelomeningocele, the SC is low lying and ends in the lumbar or sacral region. This may be observed in patients without any new neurologic complaints. However, symptomatic tethering of the SC develops in at least 20% of all patients with myelomeningocele despite careful surgical closure of the original neural placode. Such patients often have one or more of the following signs/symptoms: gait difficulty, back pain, leg weakness, sensory loss, a new foot deformity, a change in urodynamic data, or urinary incontinence. When one or more of these signs/symptoms occur in patients with shunted hydrocephalus, the shunt must be evaluated first to confirm that it is functioning appropriately. After this has been established, surgery is performed to free the neural placode and nerve roots from the dorsal surface of the dura and thereby untether the SC. In contrast, asymptomatic patients who demonstrate SC tethering on routine MRI do not require reoperation.

## Hydrocephalus

Hydrocephalus is a common pediatric disorder in which there is an increase in CSF volume, which in turn causes enlargement of the ventricles, thinning of the cortical mantle (Fig. 128-6), and elevation of intracranial pressure (ICP). The incidence of congenital hydrocephalus is approximately 0.9 to 1.8 per 1000 births,[29] and the mortality rate is approximately 1% per year. To prevent neurologic deterioration associated with increased ICP, CSF diversion is required. Treatment with CSF diversion techniques such as valve-regulated CSF shunt systems and endoscopic third ventriculostomy increases life expectancy in pediatric patients with hydrocephalus and improves their intellectual outcome.

Hydrocephalus results from a disparity between CSF production and absorption. Most cases of hydrocephalus occur as a consequence of impaired CSF absorption. The exception to this rule is hydrocephalus in patients with a choroid plexus papilloma, which results, at least in part, from overproduction

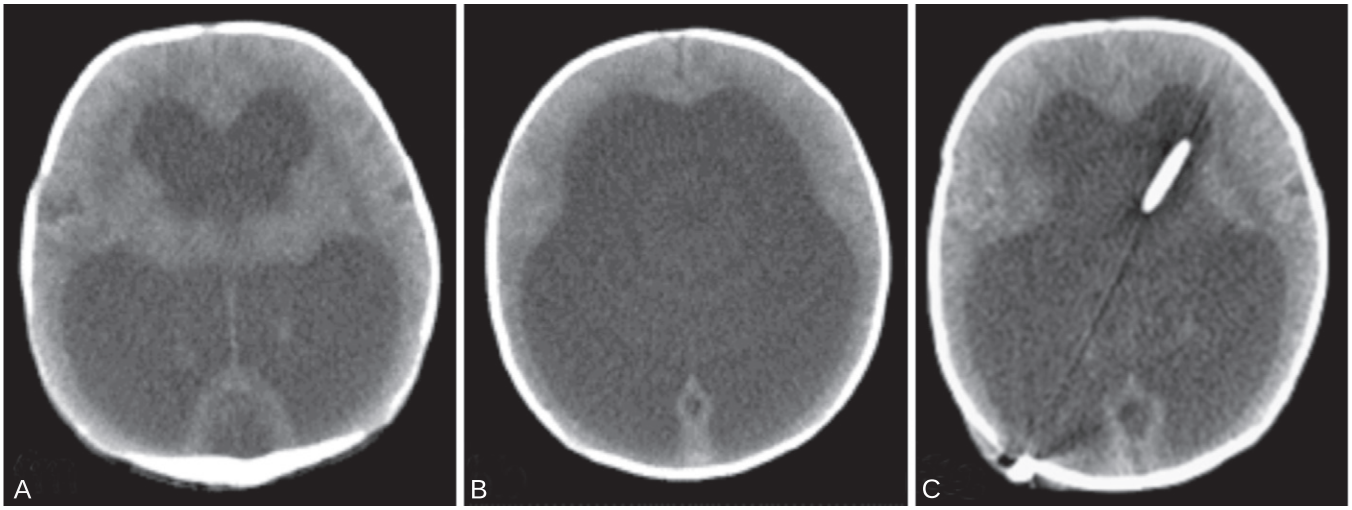


**FIGURE 128-6** One-day-old girl with severe obstructive hydrocephalus secondary to congenital aqueductal stenosis. **A** and **B,** Head computed tomography (CT) scan showing severe ventriculomegaly. **C,** Head CT scan 1 day after shunt placement.

of CSF. Increased CSF volume secondary to impaired absorption or increased production (or both) leads to progressive ventricular dilatation. In some children, CSF absorption can occur through alternative pathways, thereby resulting in stabilization of their ventricular enlargement. This, in turn, leads to arrested or compensated hydrocephalus. In support of this, a detailed analysis of the natural history of unoperated hydrocephalus has shown that arrest of the progressive ventricular enlargement eventually occurs in up to 45% of children with hydrocephalus.[30] Children with compensated hydrocephalus do not require CSF diversion; however, many factors such as fever and infection can cause sudden decompensation of the hydrocephalus and elevated ICP. Therefore children with suspected shunt-independent "compensated" or "arrested" hydrocephalus must be monitored closely for signs and symptoms suggesting decompensation such as headaches, vomiting, ataxia, and visual symptoms.

Formation of CSF is an energy-dependent, ICP-independent process that requires carbonic anhydrase and occurs at a rate of approximately 450 mL/day, or 0.3 mL/min. Choroid plexus in the lateral, third, and fourth ventricles produces 50% to 80% of the CSF; the remaining 20% to 50% of CSF is produced by the ventricular ependyma and brain parenchyma as a byproduct of cerebral metabolism. CSF flows in a caudal direction through the ventricular system and exits by way of the foramina of Luschka and Magendie into the cortical and spinal subarachnoid space. CSF then travels through the tentorial incisura, passes over the hemispheric convexity, and is absorbed into the venous system at the level of the arachnoid villi.

CSF absorption is an energy-independent process that occurs predominantly by bulk flow through the arachnoid villi, which represent the interface between the cortical subarachnoid space and the intradural venous sinuses. The rate of CSF absorption depends on a pressure gradient from the subarachnoid space across the arachnoid villi to the venous space in the dural venous sinuses. When ICP is normal (i.e., 7 cm $H_2O$ or 5 mm Hg), CSF is produced at a rate of 0.3 mL/min but no CSF absorption occurs. When ICP increases, CSF absorption occurs in direct proportion to the increase in ICP. Other pathways for CSF absorption have been proposed. Such pathways including the lymphatic system, nasal mucosa, paranasal sinuses, and the nerve root sleeves of cranial and spinal nerves are probably recruited for CSF absorption when ICP is elevated; however, definitive evidence for these alternative pathways is currently lacking.

Obstruction of CSF flow at any point along the ventricular pathway or impaired absorption of CSF generates increased intraventricular pressure, which in turn results in progressive dilatation of the ventricular system proximal to the block. The pathologic effects of ventricular obstruction or impaired CSF absorption include ventricular dilatation, which is often more pronounced initially in the occipital horns, thinning of the cortical mantle, disruption of the ependymal membrane, transependymal absorption of CSF into the periventricular white matter, white matter injury and scarring, elevation of ICP, brain herniation, coma, and ultimately, death.

## ETIOLOGY

The etiology of hydrocephalus depends on the site of the obstruction of CSF flow. If the obstruction is proximal to the arachnoid villi, there is selective enlargement of the ventricles proximal to the obstruction and the resultant hydrocephalus is termed *noncommunicating* or *obstructive hydrocephalus*. For example, obstruction of the aqueduct of Sylvius results in enlargement of the lateral and third ventricles out of proportion to the fourth ventricle. In contrast, when the block is at the level of the arachnoid villi and CSF absorption is impaired, the lateral, third, and fourth ventricles become dilated and the volume of CSF in the subarachnoid space is increased. The resultant hydrocephalus is referred to as *communicating* or *nonobstructive hydrocephalus*. Of note, hydrocephalus ex vacuo, a condition in which the ventricles become enlarged as a consequence of cerebral atrophy, is not true hydrocephalus.

Obstructive hydrocephalus can be caused by blockage at the foramen of Monro. Common causes include congenital atresia or stenosis; intracranial cysts such as arachnoid cysts within the subarachnoid space or ventricle, porencephalic cysts within the brain adjacent to the ventricle, and colloid cysts; tumors such as hypothalamic gliomas, craniopharyngiomas, and subependymal giant cell astrocytomas; and cavernous malformations. Obstruction at the level of the aqueduct of Sylvius is another common cause of obstructive hydrocephalus (see Fig. 128-6). Causes of aqueductal obstruction include upward herniation of the cerebellum through the tentorial incisura in patients with myelomeningocele and associated Chiari II malformation, vein of Galen vascular malformations, gliosis of the aqueduct from infection or hemorrhage, tumors of the pineal region, and tectal plate gliomas. In addition, obstructive hydrocephalus can occur as a consequence of fourth ventricle outflow obstruction from posterior fossa and fourth ventricle tumors such as medulloblastomas, ependymomas, and pilocytic astrocytomas; a Dandy-Walker malformation, in which there is a large posterior fossa cyst that communicates with an enlarged fourth ventricle, as well as atresia of the outlet foramina (i.e., lateral foramina of Luschka and midline foramen of Magendie); and a Chiari II malformation, in which there is herniation of the fourth ventricle through the foramen magnum because of a small posterior fossa.

In communicating or nonobstructive hydrocephalus, the block can occur at the level of the basal cisterns. When this occurs, CSF is blocked between the spinal and cortical subarachnoid spaces and cannot reach the arachnoid villi for absorption. As a consequence, the lateral, third, and fourth ventricles become dilated. Common causes include congenital infections; meningitis from acquired pyogenic, tuberculous, and fungal infections; subarachnoid hemorrhage from aneurysm rupture, a vascular malformation, or trauma; intraventricular hemorrhage associated with a germinal matrix hemorrhage in a preterm infant; basal arachnoiditis; leptomeningeal carcinomatosis; neurosarcoidosis; and tumors producing high protein levels in the CSF. The block can also occur at the level of the arachnoid villi from occlusion or atresia of the arachnoid villi, which results in dilatation of the subarachnoid space and ventricles. Furthermore, the block can occur at the level of the dural venous sinus from venous outflow obstruction. Such a block can be seen in patients with achondroplasia or multisutural craniosynostosis who have stenosis of the jugular foramina, in patients with high right atrial pressure from congenital heart disease, and in those with thrombosis of the dural venous sinuses or superior vena cava. Venous outflow obstruction causes increased venous pressure, which in turn results in decreased drainage of cortical veins,

increased cerebral blood volume, elevated ICP, increased brain stiffness, and decreased CSF absorption. In infants with an open anterior fontanelle and cranial sutures, increased venous pressure and decreased CSF absorption result in macrocephaly, with splitting of the cranial sutures and ventricular enlargement. In contrast, when the cranial sutures and anterior fontanelle are closed, the elevated venous pressure produces venous engorgement, which in turn raises ICP. In such patients the ventricular system is compressed despite decreased CSF absorption, and the clinical entity known as *pseudotumor cerebri* is produced.

Maximal hydrocephalus is characterized by extreme ventricular enlargement with only a thin rim of cortical mantle, the presence of background cortical activity throughout the brain on electroencephalography (EEG), and at least some restitution of the cortical mantle with CSF diversion (see Fig. 128-6). In contrast, hydranencephaly is a condition in which the intracranial cavity is filled with CSF instead of brain because of a total or nearly total loss of brain tissue supplied by the anterior and middle cerebral arteries bilaterally (Fig. 128-7). The cranial vault and meninges remain intact along with the thalamus, brainstem, and a small amount of occipital lobe supplied by the posterior cerebral artery. The most common causes of hydranencephaly are bilateral internal carotid artery infarcts and infection. Cortical activity is absent on EEG. Such infants cry, suck, and feed; they are typically hyperirritable; they retain primitive reflexes; and rarely progress beyond spontaneous vowel production or a social smile. CSF shunting may be performed to control head size in the face of progressive head enlargement; however, shunting does not improve neurologic function or reduce hyperirritability.

## CLINICAL FEATURES

In infants, hydrocephalus results in irritability, lethargy, failure to thrive (with or without vomiting), delayed development, apnea, bradycardia, hyperreflexia, hypertonia, increasing head circumference, bulging anterior fontanelle, splaying of the cranial sutures, thin scalp with distended scalp veins, frontal bossing, impaired upward gaze with eyelid retraction (i.e., "setting sun" sign from pressure on the tectal plate), decreased levels of consciousness, and papilledema, as well as third, fourth, and sixth nerve palsies. In older children with a rigid cranial vault, hydrocephalus can cause headache (especially in the morning), nausea, vomiting, lethargy, papilledema, deterioration in vision, decline in cognitive function or behavior, memory problems, decreased attention span, worsening of school performance, gait changes, upgaze palsy, diplopia (especially from sixth nerve palsy), and seizures.

## RADIOLOGIC FEATURES OF HYDROCEPHALUS

Plain skull films from patients with hydrocephalus often demonstrate a beaten-copper appearance and splitting of the coronal sutures. CT and MRI frequently reveal dilated temporal horns; obliteration of the sylvian and interhemispheric fissures, sulci, and basilar cisterns; ballooning of the frontal horns and third ventricle; upward bowing or atrophy of the corpus callosum, or both; and periventricular edema related to transependymal absorption of CSF.

Benign external hydrocephalus (also known as *benign extra-axial fluid of infancy*), a condition that rarely requires CSF diversion, is characterized by enlargement of the anterior cortical subarachnoid spaces (i.e., sulci and cisterns) bilaterally; normal or mildly dilated ventricles; a prominent pulsatile anterior fontanelle; and progressive enlargement of head circumference, with crossing of percentile lines when head circumference is plotted with respect to age. Infants with benign external hydrocephalus have large heads and may demonstrate slight delays in motor development related to their large head size. The etiology of this clinical entity is unclear; however, defective CSF absorption has been proposed. Frequently, the family history is significant for large heads. At approximately 12 to 18 months of age, the enlarging head circumference tends to plateau, which allows the child's body growth to catch up with head growth, and the hydrocephalus typically resolves spontaneously by 2 years of age without a need for shunting. Although shunting is not usually required, these children should be monitored closely with serial head circumference measurements and head CT or ultrasound to evaluate for abnormal ventricular enlargement.

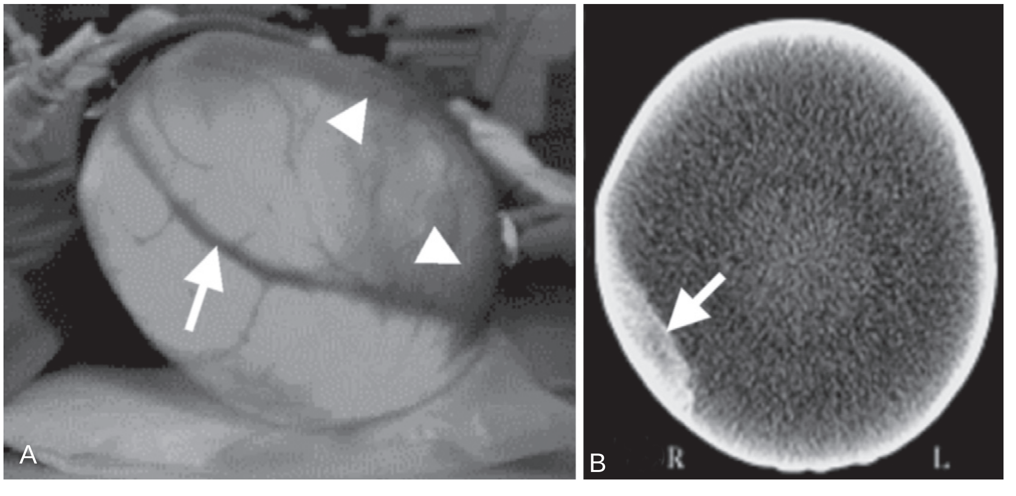


**FIGURE 128-7** Two-day-old girl with hydranencephaly. **A,** Transcranial illumination showing the superior sagittal sinus (*arrow*) and a scant amount of right inferior temporal and occipital cortex (*arrowheads*). **B,** Head computed tomographic scan shortly after birth revealing a scant amount of right cerebral cortex posteriorly (*arrow*). The cerebral hemispheres are replaced almost entirely by cerebrospinal fluid.

## MANAGEMENT

The goal of treatment is to achieve optimum neurologic function and prevent or reverse neurologic damage caused by distortion of the brain from ventricular enlargement. The best predictor of a good outcome is postoperative reconstitution of the cerebral mantle to at least 2.8 cm.[31] This is more likely to occur if a symptomatic hydrocephalic infant undergoes shunting by 5 months of age. The treatment of hydrocephalus is surgical, and the type of surgery depends on the cause of the hydrocephalus. For example, in patients with obstructive hydrocephalus, surgery is performed to remove the obstruction (e.g., tumor). In patients with communicating hydrocephalus or obstructive hydrocephalus in which the obstruction cannot be removed, CSF is shunted from the site of its secretion within the ventricle proximal to the obstruction to a distal site capable of reabsorption. The most commonly used distal sites include the peritoneal cavity, right atrium, pleural cavity, gallbladder, bladder/ureter, and basilar cisterns (i.e., third ventriculostomy). The preferred site for the distal catheter is the peritoneal cavity (i.e., ventriculoperitoneal shunt), unless there is a problem with absorption or abdominal sepsis. When abdominal abnormalities such as extensive postsurgical abdominal adhesions, peritonitis, morbid obesity, and necrotizing enterocolitis are present in preterm infants, a ventriculoatrial shunt is the treatment of choice. Alternatively, if the peritoneum and atrium are not available, a ventriculopleural shunt can be placed in children who are 7 years of age or older.

CSF shunt systems consist of at least three components: a ventricular catheter, which is usually placed in the occipital or frontal horn of the lateral ventricle (see Fig. 128-6, *C*); distal shunt tubing to drain CSF into a distal site for reabsorption; and a valve. Conventional differential pressure shunt valves control unidirectional CSF flow by opening at a fixed pressure differential across the valve. This pressure differential is determined by the characteristics of the valve and is designated as low, medium, or high (typically 5, 10, and 15 cm $H_2O$, respectively). Once the valve is open, it provides little resistance to CSF flow. Consequently, the gravitational effects of an upright posture can lead to high CSF flow rates, which in turn can generate a large negative ICP, a process referred to as "siphoning."

Because siphoning can result in slit ventricles, which in turn are associated with a higher incidence of proximal shunt obstruction, some shunt valves have been designed to limit excess CSF flow, particularly in the upright position.[32] For example, the Delta valve (Medtronic PS Medical, Goleta, CA) is a standard diaphragm-type, differential pressure shunt valve with an integral siphon control device to diminish overdrainage in upright positions. The Orbis-Sigma valve (Cordis, Miami) contains a variable-resistance, flow-limiting component that limits excess CSF flow by progressively narrowing the flow orifice with increasing pressure. Although use of these valves has been advocated as a means of preventing overdrainage and improving treatment results, a randomized trial comparing three different shunt valve designs (i.e., standard differential pressure valve, Delta valve, and Orbis-Sigma valve) in the treatment of children with newly diagnosed hydrocephalus showed no significant difference in shunt failure rates among the valves tested.[33] Currently, there are also three types of programmable differential pressure shunt valves available for use. Such valves, which allow the pressure setting to be altered after implantation, are commonly used in the treatment of pediatric hydrocephalus. Despite the vast array of shunt systems available to treat hydrocephalus, no prospective, randomized, controlled, double-blind, multicenter trial has ever proved a particular shunt system to be more effective than any other.

Ventriculoperitoneal shunting is commonly used to treat childhood hydrocephalus. Placement of a ventriculoperitoneal shunt is performed under general anesthesia after prophylactic intravenous antibiotics are administered. The role of antibiotic prophylaxis has been studied by meta-analysis, and antibiotic coverage is recommended.[34,35] The head of the patient is positioned on a gel donut at the top edge of the operating table in close proximity to the surgeon and turned to the side opposite the shunt insertion. The neck and trunk are extended with a gel roll under the shoulders to assist subcutaneous tunneling of the shunt. Skin incisions are delineated before skin preparation, depending on the desired location of the burr hole for placement of the ventricular catheter (e.g., frontal or occipital). A meticulous skin preparation (e.g., with povidone-iodine scrub and paint solution or chlorhexidine 2% in 70% alcohol) is performed, and the incisions are marked again. The abdominal incision is typically marked in the right upper quadrant or in the midline approximately two to three fingerbreadths below the xiphoid process. Surgical drapes including an iodine-impregnated sterile adhesive drape are placed over the incisions and tunneling site. A curvilinear incision is made in the scalp overlying the proposed burr hole site, and the scalp is retracted. The pericranium is opened at the base of the incision, and a burr hole is drilled. The dura, arachnoid, and pia are then coagulated and opened.

Next, the abdominal incision is opened and entrance into the peritoneal cavity is achieved and confirmed by gently probing the opening into the peritoneal cavity. A shunt tunneling device is then used to create a subcutaneous tunnel extending between the two incisions. The shunt components are removed from their sterile packages just before shunt placement and placed into antibiotic solution. The distal shunt system including the valve is passed within the subcutaneous tunnel, and the proximal and distal ends of the shunt are covered with sponges soaked in antibiotic solution. Care is taken to prevent contact of the shunt tubing with the skin during this portion of the procedure. After this, the ventricular catheter is passed on a wire stylet into the ventricle. Intraoperative ultrasound or ventricular endoscopy, or both, can be used to accurately place the catheter within the ventricle. Ventriculoscopy can also be used to fenestrate intraventricular cysts and provide communication between loculated ventricles.

Once the catheter is in the ventricle and CSF flow has been confirmed, the catheter is cut to the desired length, guided by measurements obtained from the preoperative head CT scan, and then connected to the distal shunt system, usually by way of a reservoir. Silk ties (2-0 or 3-0) are used to secure the catheter to the reservoir. After this, the distal shunt tubing is evaluated for CSF flow. Once confirmed, the distal shunt tubing is passed into the peritoneal cavity; it should pass freely without resistance. The incisions are then irrigated with antibiotic solution, closed in a meticulous, two-layered fashion with good approximation of the skin edges, and covered with sterile dressings.

## COMPLICATIONS OF SHUNT MANAGEMENT

Most children are shunt dependent after shunt implantation. Consequently, children with shunts require lifelong follow-up to make certain that their shunt is functioning adequately,

especially in light of the high incidence of failure over the life of a shunt. For example, in a previous retrospective study in which 1719 hydrocephalic children were evaluated in an attempt to understand why shunts fail,[36] the actuarial probability of the occurrence of shunt failure was 70% at 10 years after the initial shunt insertion, with the highest risk for shunt failure occurring in the immediate postoperative period (i.e., a 30% risk of shunt failure during the first year and a 2% to 5% risk per year thereafter). In addition, the actuarial probability of the occurrence of a shunt infection was 9% over the same 10-year period and the time of shunt failure varied significantly according to the cause of the shunt failure. Other studies have reported shunt failure rates of approximately 40% within the first year for standard CSF shunts implanted for the treatment of pediatric hydrocephalus.[37,38] Moreover, in a randomized trial of CSF shunt valve design,[33] the shunt failure rate was 40% at 1 year and 60% at 2 years and the infection rate was 8% in the hands of experienced pediatric neurosurgeons working in centers where many shunts are implanted each year.

CSF shunt systems malfunction due to three main factors: (1) mechanical failure, (2) infection, and (3) overdrainage or underdrainage (i.e., "functional" failure). Proximal obstruction (i.e., obstruction of the ventricular catheter) is the most frequent cause of mechanical shunt failure.[36] Other causes include obstruction of the distal catheter or any accessory part of the shunt (e.g., antisiphon device); formation of a peritoneal pseudocyst, which is usually associated with infection and causes obstruction of the peritoneal catheter; ascites resulting from failure of intraperitoneal reabsorption of CSF; fracture of the shunt tubing; disconnection of the shunt at a junction point of shunt components (e.g., proximal or distal to a straight connector); migration of the shunt; inadequate length of the distal catheter; improper proximal or distal catheter placement; infection; and overdrainage, which can lead to the formation of subdural fluid collections, slit ventricles, craniosynostosis, or intracranial hypotension. In a study by Sainte-Rose and colleagues,[36] two thirds of the shunt failures were due to obstruction or fracture, with obstruction responsible for 56.1% of shunt failures and fractures occurring almost exclusively at sites of connectors. Moreover, they found that a significantly higher percentage of shunt failure was due to proximal obstruction in patients with slit ventricles than in those with normal or enlarged ventricles and to distal obstruction in patients with slit-ended peritoneal catheters than in those with open-ended catheters.

Repeated shunt failures are common in pediatric patients and are associated with significant morbidity and occasionally death. A prospective, single-institution, observational study designed to identify risk factors predisposing pediatric patients to repeated shunt failures[39] revealed that the timing of the previous shunt procedure is significant, with shunt revisions performed within less than 6 months from the time of the preceding implantation having a significantly increased risk for failure. Furthermore, in this study the age of the patient at the time of first shunt insertion was a significant risk factor for subsequent shunt failure, with patients younger than 40 weeks and those between 40 weeks and 1 year of age at the time of shunt insertion having a higher risk for subsequent shunt failure than those older than 1 year. With respect to the effect of the cause of hydrocephalus on repeated shunt failure, this study showed a higher risk for recurrent shunt failure in patients with intraventricular hemorrhage, meningitis, and tumor. Finally, concurrent surgical procedures also increased the risk for shunt failure in this study.

In most cases of shunt malfunction, the diagnosis is obvious because the child has acute and overt signs and symptoms of elevated ICP such as irritability, headache, vomiting, and lethargy and will progress to stupor, coma, and death if the shunt is not revised promptly. In the study by Sainte-Rose and colleagues,[36] there was a 1.05% mortality rate directly related to shunt failure. Alternatively, some children with shunt failure will have more subtle signs of deterioration such as a decline in school performance, change in attention span, or change in behavior. These "subtle deteriorators" often demonstrate a gradual increase in ventricular size over time and may have a marked increase in ventricular size at the time of presentation. In contrast, acute deteriorators often have only a slight increase in ventricular size. When a child has a suspected shunt malfunction, a head CT is performed to evaluate for interval enlargement of the ventricles. This must be compared with a previous scan obtained when the patient was doing well. A shunt series is also performed to look for continuity of the shunt, especially at sites of connectors, the position of the ventricular catheter or catheters, and the length of the distal shunt tubing.

When a shunt malfunction is suspected, the site of shunt failure must be determined. The most common cause of shunt failure is obstruction of the ventricular catheter by choroid plexus, glial tissue, connective tissue, leptomeninges, ependyma, or brain tissue (or any combination of these tissues), especially in patients with slitlike ventricles.[36] Proximal obstruction is typically associated with precipitous development of intracranial hypertension, which necessitates immediate shunt revision. To reduce the incidence of proximal catheter obstruction, surgeons attempt to place the ventricular catheter with the use of external anatomic landmarks either within the frontal horn of the lateral ventricle anterior to the foramen of Monro or within the occipital horn to keep the catheter away from choroid plexus.[36] With the introduction of fiberoptic endoscopes in the early 1990s, surgeons began using ventricular endoscopy to insert the ventricular catheter away from choroid plexus under direct visualization. Although evidence from uncontrolled series suggested that endoscopic insertion of the ventricular catheter decreased the incidence of shunt failure,[40] a multicenter randomized trial evaluating time to first shunt failure after endoscopic versus nonendoscopic placement of the ventricular catheter in children with hydrocephalus showed no reduction in the incidence of shunt failure with endoscopically assisted placement of the ventricular catheter.[41] However, in this trial, ventricular catheters that were thought by surgeons to be placed away from choroid plexus at the time of shunt insertion were actually found to be located away from choroid plexus on postoperative imaging studies only two thirds of the time in both endoscopic and nonendoscopic insertions. This suggests that the endoscope did not help achieve the goal of placing ventricular catheters away from choroid plexus in this trial. However, a secondary analysis of catheter position in this trial did demonstrate a reduced incidence of shunt failure when the ventricular catheter was positioned away from choroid plexus on the basis of postoperative imaging studies.

Distal shunt malfunctions can occur as a consequence of shunt fracture, inadequate length of the distal shunt tubing, shunt infection, and impaired absorption of CSF at the distal site. Shunt tubing is made of silicone elastomers, which can calcify and break over time. Breakage often occurs above the clavicle, where there is increased motion, or in the region of a connector. Consequently, a shunt series (i.e., anteroposterior and lateral skull, chest, and abdominal radiographs) should be evaluated carefully to look for discontinuity in the shunt system, particularly at sites of connectors. If a shunt fracture is found, the shunt should be revised. The shunt series can also detect whether the distal shunt tubing is too short and a distal lengthening procedure is necessary.

Shunt infection can also cause a distal shunt malfunction and is the second leading cause of shunt failure after mechanical obstruction. With each shunt operation, there is a 2% to 8% incidence of shunt infection,[33] with 5% to 15% of shunts becoming infected over the life of a shunt. The consequences of shunt infection are devastating and can include intellectual and focal neurologic deficits, enormous health care costs, and death. Most shunt infections occur within the first 6 months after a shunt operation,[34] with approximately 70% of shunt infections diagnosed within the first month after surgery and 90% by 6 months. The most common pathogens are staphylococci (*Staphylococcus epidermidis,* 40%; *Staphylococcus aureus,* 20%). Others include coryneforms, streptococci, enterococci, aerobic gram-negative rods, and yeasts. Although shunt infections can occur after 6 months, they are rare and almost always result from indolent bacteria that are a normal part of skin flora, such as *S. epidermidis* or *Propionibacter acnes.* The fact that most shunt infections occur as a consequence of contamination with the patient's own skin flora underscores the need for meticulous attention to surgical technique at the time of shunt insertion.

Shunt infections can range from isolated wound infections and colonization of the shunt tubing to ventriculitis, peritonitis, and an infected pseudocyst. Risk factors implicated in shunt infection include young age of patient, poor skin condition, prolonged surgery, an open NTD, CSF leakage from an incision or wound breakdown postoperatively, increased number of shunt revisions, and concomitant infection. Patients with a shunt infection typically have a low-grade fever (i.e., between 100° F and 102° F) or evidence of shunt malfunction. However, they can also manifest signs of meningitis, ventriculitis, peritonitis, or cellulitis, or any combination of such signs. Symptoms include irritability, headache, nausea and vomiting, lethargy, decreased appetite, abdominal pain, erythema and tenderness along the shunt tract, photophobia, and neck stiffness. A head CT may or may not show a change in ventricular size. It is important for pediatric surgeons to be aware that shunt infection may present only as an acute surgical abdomen, often mimicking appendicitis.[40a]

If shunt infection is suspected, the patient should undergo a radiologic evaluation that includes a shunt series and a head CT scan. The shunt series provides information regarding the continuity of the shunt tubing and location of the shunt reservoir for tapping, possible sources of shunt-related problems, and other potential sources of infection such as pneumonia. The head CT reveals ventricular catheter location, size, and contents including loculations and purulent fluid collections, which can be seen in cases of severe gram-negative ventriculitis. If the patient complains of abdominal pain or abdominal distention is present, an abdominal CT or ultrasound should be performed to evaluate for a CSF pseudocyst. In addition, a peripheral white blood cell count and blood cultures should be obtained because patients with shunt infections often have leukocytosis and positive blood cultures. Finally, a multisystem fever workup should be performed to evaluate for concurrent infections.

If the initial evaluation suggests possible shunt infection, a shunt tap is performed to obtain CSF for study. To do this, the area over the shunt reservoir is shaved and prepared with povidone-iodine or chlorhexidine solution. A 25-gauge butterfly needle is then passed percutaneously into the reservoir using sterile technique. Proximal and distal shunt flow dynamics are evaluated, and CSF is obtained and sent for cell count and differential, protein, glucose, Gram stain, and culture and sensitivity studies. Broad-spectrum intravenous antibiotics are then started.

If CSF studies demonstrate a shunt infection (i.e., isolation of bacteria in CSF obtained from the shunt tap, elevated neutrophils and protein in CSF, or decreased CSF glucose), the entire shunt is removed and an external ventricular drain and central venous line are placed. The patient is treated with the appropriate systemic antibiotics (i.e., antibiotics that have good activity against the isolated organism and adequate CSF penetration) until the shunt infection has cleared, at which time a new shunt may be placed. Monitoring of CSF during treatment is essential. At present, significant variation exists in the duration of antibiotic therapy, with treatment regimens ranging from 2 days to 3 weeks.[42] Studies are currently under way to determine the most effective duration of antibiotic therapy in an effort to shorten hospitalization and minimize complications without sacrificing efficacy. It is the practice at the author's institution to treat with antibiotics until at least two consecutive CSF cultures, at least 48 hours apart, are negative and the inflammatory component of the infection has resolved. Aside from the practical problems associated with their treatment, shunt infections have been linked to an increase in the development of loculated CSF compartments, impaired intellectual outcome (with as high as an 8- to 10-point decrease in IQ), an increased risk for seizures, and an increased mortality rate.[34]

Shunt overdrainage, or "overshunting," can also be associated with shunt failure. Most shunts with differential pressure valves will overdrain regardless of whether the valve pressure is high or low.[32] Overdrainage can lead to the formation of subdural hematomas, a low-ICP syndrome, or slit ventricle syndrome. Subdural hematomas result from the tearing of bridging veins as the ventricles collapse and the cortical surface pulls away from the dura. Although they often resolve without treatment, symptomatic or progressive subdural hematomas from overshunting may require a reduction in the degree of shunting to allow the ventricles to re-expand and the subdural space to become obliterated. Alternatively, drainage of the subdural space either by placing burr holes or by shunting the subdural space with a low-pressure valve may be required. Overshunting can also lead to an intracranial hypotension syndrome with symptoms such as headache, nausea, vomiting, tachycardia, and lethargy that are sensitive to changes in position. In such patients, overdrainage occurs when the patient assumes an upright position. This produces a negative ICP, which in turn leads to intense postural headaches that are relieved by recumbency.[43,44] If symptoms

persist and are frequent or recurrent enough to interfere with daily activities, especially school, the shunt should be revised by placing a higher-resistance valve or adding an antisiphon device, or both.

Overshunting can also lead to the formation of slitlike ventricles. Ventricles commonly become small or slitlike after placement of a shunt. In a previous retrospective study, slit ventricles developed in 80% of the total population of shunted patients.[32] Interestingly, 88.5% of the patients in whom slitlike ventricles developed were completely asymptomatic. Moreover, of the 11.5% of patients with slit ventricles who were symptomatic, only 6.5% required surgical intervention. Symptomatic slit ventricle syndrome occurs infrequently and is associated with intermittent episodes of vomiting, headache, and lethargy. Patients with symptomatic slit ventricle syndrome tend to have small ventricles, diminished extraventricular CSF spaces, a thick skull, and no room for intracranial accumulation of CSF. In this syndrome the ventricular walls collapse around the ventricular catheter, which becomes obstructed, and the shunt fails to drain.[32] Eventually, intraventricular pressure builds up, the ventricles dilate slightly, and the shunt begins to drain. These patients often experience acute neurologic deterioration related to waves of elevated ICP that occur during periods of intermittent shunt obstruction. Moreover, because of the tight intracranial space in these patients, there is no room for any increase in intracranial volume including cerebral blood volume. Consequently, any event that leads to cerebral vasodilatation such as migraine headaches or to an increase in cerebral blood flow such as exercise or playing outside in the hot summer sun will cause symptoms of elevated ICP.[32] Patients with slit ventricle syndrome become symptomatic early in the phase of shunt obstruction, and head CT scans obtained in symptomatic patients frequently reveal no change in ventricular size when compared with their usual slitlike state.

Patients with acute neurologic deterioration in the face of a functioning shunt may benefit from treatment with medications such as furosemide (Lasix) or acetazolamide (Diamox) to lower ICP until the elevated pressure waves subside. Some patients may also benefit from taking antimigraine medications such as cyproheptadine (Periactin) or propranolol (Inderal). If symptoms persist despite conservative treatment, surgical intervention may be necessary. Such interventions include ventricular catheter revision, shunt valve upgrade to increase resistance, addition of an antisiphon or flow control device, decompressive subtemporal craniectomy ipsilateral to the ventricular catheter, or any combination of these interventions. ICP monitoring is useful to differentiate between high-pressure headaches caused by waves of elevated ICP in the face of a functioning shunt and low-pressure headaches caused by negative ICP in patients with true overdrainage.[45] ICP monitoring can also be helpful in identifying children with normal ICP physiology who are having headaches unrelated to shunt function.

Trapping of the fourth ventricle can occur in children with chronic shunting of the lateral ventricles, especially in those with a history of posthemorrhagic hydrocephalus from intraventricular hemorrhage related to prematurity, postinfectious hydrocephalus, or repeated shunt infections/ventriculitis. In this condition, overdrainage of CSF leads to slit ventricles, aqueductal narrowing, or both. When aqueductal stenosis occurs, the fourth ventricle does not communicate with the third ventricle. Likewise, the fourth ventricle does not communicate with the basilar cisterns because of occlusion of the outlets (i.e., foramina of Luschka and Magendie). Production of CSF by choroid plexus in the trapped fourth ventricle results in progressive ventricular enlargement, which may lead to headache, swallowing difficulty, lower cranial nerve palsies, ataxia, lethargy, spastic quadriparesis, and nausea/vomiting. Infants may have apneic spells and bradycardia. In symptomatic patients, the isolated fourth ventricle can be shunted with a separate shunt system or by adding a fourth ventricular catheter into an existing supratentorial shunt system above the valve. However, as the fourth ventricle is decompressed with CSF drainage, the brainstem moves posteriorly into a more normal position and the catheter can injure the brainstem.[46] In addition, approximately 40% of patients require a shunt revision within 1 year.[47] Alternatively, a suboccipital craniotomy with open fenestration of the fourth ventricle to the subarachnoid space and basal cisterns may be performed with or without placement of a shunt from the fourth ventricle to the spinal subarachnoid space.[48,49] Endoscopic aqueductoplasty and interventriculostomy with stent placement have also been proposed as treatment options to reestablish communication between the supratentorial ventricular system and the isolated fourth ventricle.[50]

## ENDOSCOPIC THIRD VENTRICULOSTOMY—AN ALTERNATIVE TO SHUNTING

Endoscopic third ventriculostomy (ETV) can be performed to treat certain types of obstructive hydrocephalus such as primary untreated aqueductal stenosis from tectal plate and pineal region tumors. This technique eliminates the need for a shunt and thereby avoids the complications associated with shunting. It is contraindicated in patients with communicating hydrocephalus, and the success rate is poorer in patients younger than 1 year of age. The highest success rate occurs in older children and adults with acquired obstructive hydrocephalus, with approximately 70% of patients achieving shunt independence.[51,52] In contrast, in children younger than 3 years of age, the success rate has traditionally been poorer, ranging from 40% to 50%. However, in a more recent study, the outcome of ETV was analyzed in patients younger 2 years of age.[53] ETV was successful in 71.4% of procedures in children younger than 2 years of age and in 75% of procedures in infants. The results of this study suggested that success of ETV in infants and young children depends primarily on the thickness of the floor of the third ventricle and the patient's age at the time they initially manifested their hydrocephalus. The success rate is also lower in patients with preexisting pathology such as a tumor, previous shunt, prior subarachnoid hemorrhage, previous whole-brain irradiation, and significant scarring of the third ventricle floor, with as little as 20% of third ventriculostomies remaining patent in such patients.[53]

ETV is performed through a frontal burr hole that is made approximately 2.5 to 3 cm lateral to the midline, just anterior to the coronal suture.[52] A peel-away sheath is passed through the foramen of Monro to protect bordering structures from damage caused by repeated passage of the endoscope. A rigid endoscope is passed by way of the peel-away

sheath through the foramen of Monro into the third ventricle, and the floor of the third ventricle is fenestrated in the midline just anterior to the cleavage plane of the mammillary bodies, which delineate the posterior border of the third ventricular floor. The fenestration is then dilated with a 2-Fr Fogarty balloon catheter by means of repeated inflation and deflation of the balloon. The endoscope is then passed through the fenestration into the interpeduncular cistern to evaluate the arachnoid membranes and make certain there are no redundant arachnoid membranes impeding CSF flow into the subarachnoid cistern.

Complications related to ETV include failure to complete the procedure for technical reasons, which has been reported in up to 26% of patients,[54] hemorrhage secondary to vascular injury,[55] cardiac arrest, diabetes insipidus, the syndrome of inappropriate antidiuretic hormone secretion, subdural hematoma, meningitis, cerebral infarction, transient third and sixth nerve palsies, and disturbances in short-term memory.[54,55] Risks of ETV include infection; injury to adjacent neural structures (e.g., hypothalamus, pituitary gland, optic chiasm); and arterial injury with intraoperative rupture or delayed hemorrhage related to traumatic aneurysm formation. In a small number of patients, delayed closure of the ETV has been described related to scar formation or metastatic tumor seeding.[56] In patients with recurrent symptoms of intracranial hypertension, cine-MRI can be performed to assess the patency of the third ventriculostomy by evaluating CSF flow across the floor of the third ventricle. If the floor of the third ventricle is no longer patent, endoscopic exploration with an attempt at repeat fenestration is reasonable. If postoperative scarring precludes safe repeat fenestration of the third ventricular floor, a ventricular shunt system should be placed.

Late rapid deterioration is an infrequent but deadly complication of ETV in which deterioration can occur long after the ETV becomes occluded.[57] It is imperative that patients and caregivers be counseled about this potential complication. As a means of avoiding this type of complication, the author places a permanent ventricular access device in patients undergoing ETV.

### OUTCOME AND PROGNOSIS

The natural history of untreated hydrocephalus is poor. In one study, 50% of children with untreated hydrocephalus died before 3 years of age[58] and only 20% to 23% reached adult life. Of the survivors, only 38% had normal intelligence.[30] The development of CSF diversion techniques has improved the prognosis for children with hydrocephalus. Many patients with shunted hydrocephalus have normal intelligence and participate in all aspects of social life, with cognitive development and life expectancy determined primarily by the nature of the underlying condition. Overall, about 50% to 55% of shunt-dependent children will achieve an IQ greater than 80, with verbal cognitive skills being superior to nonverbal ones.[59–61] Not surprisingly, epilepsy appears to be an important predictor of poor intellectual outcome in children with shunted hydrocephalus, with an IQ higher than 90 occurring in 66% of children without epilepsy versus in 24% of children with epilepsy.[62] Unfortunately, repeated shunt complications in pediatric patients with hydrocephalus carry significant morbidity.

## Epilepsy Surgery in Children

Epilepsy is a common childhood disorder.[63] It affects approximately 0.5% to 1% of the population in the United States and Canada,[63–65] and up to 50% of epilepsy cases begin before 5 years of age.[63,66] Children with epilepsy are usually managed with antiepileptic medications initially. However, 20% to 25% of children with epilepsy have inadequate control of their seizures with pharmacotherapy[67,68] and it is now recognized that seizures starting in childhood that are caused by a known structural lesion and are not controlled by medication rarely remit spontaneously as the child matures.[69] Repeated seizures and the side effects of seizure medications have a negative impact on the developing brain and can lead to severe impairment of neurocognitive function.[69–75] Moreover, recurring seizures can have a negative impact on a child's education as a consequence of learning difficulties and the associated psychosocial effects such as poor peer relationships, behavioral difficulties, poor school performance, depression, anxiety, and poor self-esteem.[73,76,77] Because refractory epilepsy in childhood is a progressive, debilitating condition associated with eventual deterioration in both intellectual and behavioral function, aggressive treatment is warranted. Seizure surgery provides an effective alternative therapeutic option for children who suffer from intractable seizures. The goal of surgery is to remove the seizure focus as completely as possible without creating a new neurologic deficit or worsening an existing one.

Epilepsy surgery is indicated when (1) a child's seizures persist despite an adequate trial of at least two appropriate anticonvulsants, alone or in combination, with each drug pushed to the maximum tolerated dosage; (2) the seizures significantly reduce the child's quality of life; (3) there is a unilateral seizure focus that can be reliably and reproducibly identified; and (4) resection of the seizure focus does not cause unacceptable neurologic deficits.[69,78–80] A preoperative workup is initiated as soon as a child fails medical therapy because early operative intervention is paramount to a good functional outcome.[69,80,81]

### PREOPERATIVE EVALUATION

The primary objective of the preoperative evaluation is to identify the area of seizure onset (i.e., the seizure focus) and its relationship to eloquent cortex.[69,74] This begins with noninvasive characterization of the seizure syndrome and optimization of medical management. Patients undergo a thorough neurologic history and physical examination, baseline EEG, and high-resolution brain MRI with thin coronal cuts through the temporal lobe (e.g., three-dimensional spoiled gradient echo [3D-SPGR] scan), fluid-attenuated inversion recovery (FLAIR) sequences, and MR spectroscopy. EEG can provide important information by confirming the presence of an epileptogenic focus, by helping to characterize the seizures and epilepsy syndrome, and by localizing the seizure focus.[82] Helpful localizing features on EEG include focal slowing, focal attenuation of fast activity, and focal epileptiform discharges (e.g., spikes or sharp waves). A good prognostic indicator for success with focal resective surgery is the presence of a single focus of epileptiform activity.[82] The MRI is evaluated for focal structural abnormalities (e.g., cytoarchitectural) or

abnormal lesions (e.g., neoplastic) that could be causing the child's seizures. The presence of a focal abnormality on MRI, especially when it corresponds to the location of seizure onset on EEG, increases confidence that the epileptogenic region has been identified and also increases the likelihood of achieving seizure control with surgery.[80,82,83,] Structural abnormalities that can be visualized on MRI and that are associated with medically refractory seizures include low-grade tumors such as a ganglioglioma (Fig. 128-8), dysembryoplastic neuroepithelial tumor (DNET), astrocytoma, oligodendroglioma, and pleomorphic xanthoastrocytoma; developmental abnormalities such as cortical dysplasia and focal neuronal migration abnormalities (e.g., gray matter heterotopia); vascular malformations such as cavernomas and arteriovenous malformations; secondary post-traumatic or postischemic encephalomalacia lesions; and mesial temporal sclerosis.[82]

If the initial evaluation suggests a possible seizure focus, additional studies are performed to define the seizure focus further including prolonged video-EEG monitoring with surface (i.e., scalp) electrodes, functional neuroimaging studies (positron emission tomography [PET] or single-photon computed emission tomography [SPECT], or both), and neuropsychological testing, with or without intracarotid injection of sodium amobarbital (i.e., Wada testing). Prolonged video-EEG monitoring involves the simultaneous recording of brain activity and clinical behavior and is the cornerstone of the presurgical evaluation.[82,84] It combines simultaneous EEG recording via scalp electrodes with a synchronized, continuous real-time audio/video recording of a child's typical seizures and thereby enables lateralization and localization of the child's seizure focus. When a temporal focus is suspected, sphenoidal electrodes can be placed to record activity from the mesial temporal lobes. In addition, antiepileptic medications can be withdrawn gradually while continuously monitoring for seizures until several of the child's "habitual events" are recorded. In the majority of cases, the video-EEG study enables one to determine whether a patient has epilepsy, whether the patient has partial or generalized seizures, and where the partial seizures arise.[78,80] When considering a child for epilepsy surgery, the ideal circumstance is to find that the seizures are highly stereotyped on EEG and that all seizures arise from the same region.[80]

Occasionally, video-EEG recording will demonstrate the presence of independent, bilateral seizure onset, especially in children with epilepsy secondary to multifocal abnormalities, as seen in tuberous sclerosis.[85] In such cases a child may still be considered a candidate for epilepsy surgery if a majority of the seizures come from one side; however, complete seizure control may not be possible.[80] Additionally, in children with tuberous sclerosis complex who have multiple and oftentimes bilateral epileptogenic tubers, a novel surgical approach has been proposed using multistaged and bilateral invasive intracranial monitoring to identify both primary and secondary epileptogenic zones.[86,87] In contrast to the typical epilepsy surgery approach where electrodes are placed to map the location of seizure onset during the first operative stage and surgical resection follows during the second stage, the multistaged approach involves resection of the primary seizure focus during the second operative stage followed by replacement of the electrodes during that same stage to determine whether a second epileptogenic region requires resection at the third and final stage. With such an approach, multiple

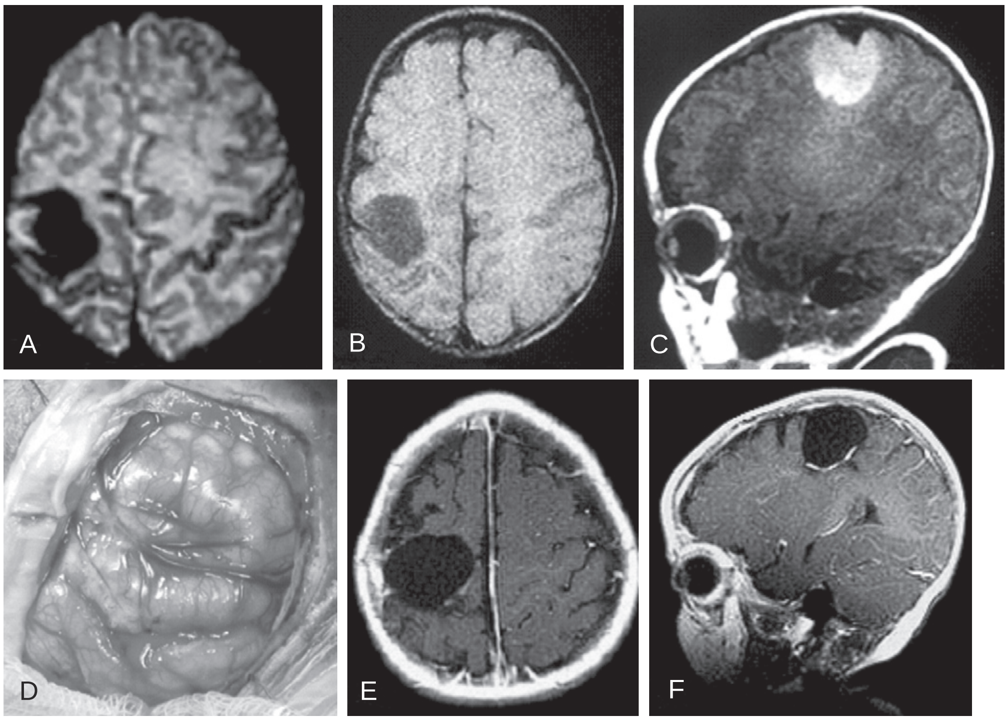


**FIGURE 128-8** Three-month-old girl with 30 to 60 seizures per day on three anticonvulsants. **A** to **F,** Brain magnetic resonance image (MRI) showing a 2.5 × 2.5 × 2-cm right posterior frontal mass. Preoperative video electroencephalographic studies localized her seizures to the region of the abnormality on MRI. She underwent complete resection of the mass and adjacent epileptogenic zone, which was localized via intraoperative electrocorticography. The final pathology was a ganglioglioma. She is now 33 months of age with no evidence of tumor recurrence, has mild residual spastic left hemiparesis, and is completely seizure free and off all anticonvulsants.

or bilateral seizure foci have been successfully resected to achieve good seizure control, suggesting that multiple or bilateral seizure foci are not necessarily a contraindication to surgery in selected patients. However, long-term follow-up is necessary to determine the durability of the effects of this novel surgical approach.

Functional neuroimaging with PET[88–90] and SPECT[91] also provides valuable localizing information by detecting generalized and focal functional brain abnormalities. This information can then be compared with the electrophysiologic dysfunction observed on EEG and the anatomic abnormalities on MRI. PET is a noninvasive functional imaging study that measures regional cerebral glucose utilization or metabolism by determining the extent of uptake of the radionuclide [$^{18}$F]deoxyglucose (FDG). Interictally, an epileptic focus is seen on PET as an area of glucose hypometabolism. This study is especially helpful in localizing focal areas of cortical dysplasia, mesial temporal sclerosis, and other structural abnormalities that correspond to surface EEG localization of epileptogenic regions. SPECT is another noninvasive functional imaging study that measures regional cerebral blood flow by using perfusion radiotracers such as technetium Tc 99m hexamethylpropyleneamine oxine ($^{99m}$Tc-HMPAO). It provides a snapshot of local cerebral blood flow at a specific point in time.[70] Between seizures, a seizure focus is hypometabolic and receives less blood flow. Consequently, relative hypoperfusion is observed in this region on a SPECT scan.[92] In contrast, hyperperfusion is observed in the region of the seizure focus on an ictal SPECT study if the tracer is injected at the time of seizure onset because local blood flow to the seizure focus increases significantly during a seizure as a consequence of increased metabolic demands. Ictal SPECT is more reliable than interictal SPECT in localizing the epileptogenic zone,[93–95] and ictal SPECT is more feasible than ictal PET because, unlike the ictal PET scan, which must be performed shortly after the tracer is given, the ictal SPECT scan can be performed at a convenient time after the tracer is injected.[105] Functional imaging studies such as PET and SPECT have reduced the need for invasive intracranial monitoring in children by up to 90%.[88,93,94]

Another important component of the presurgical evaluation is the identification of areas of brain function relative to the location of the seizure focus. This helps predict the risks associated with removal of the seizure focus. Neuropsychological testing plays an important role in this part of the presurgical evaluation.[82] Such testing can provide lateralizing and localizing information by identifying areas of neurologic dysfunction that correlate with the patient's underlying lesion.[96] For example, patients with seizures arising from their dominant temporal lobe may have deficits in verbal memory or language acquisition, whereas deficits in visuospatial memory suggest seizure onset in the nondominant temporal lobe. Significant deficits in both verbal and visuospatial memory suggest bilateral temporal lobe damage and probable bilateral seizure foci. In addition, preoperative neuropsychological testing can help predict the prognosis for cognitive functioning after surgery and can be used as a baseline to monitor disease progression, successful therapy, and the adverse effects of treatment.[70,82] Moreover, postoperative neuropsychological testing can be performed to identify residual or resultant cognitive deficits and to assist in planning psychoeducational interventions to address any impairments.

Intracarotid amobarbital injection (i.e., Wada testing) can also be used, especially in older children, to determine which cerebral hemisphere is dominant for language and to ascertain the relative contributions of each cerebral hemisphere to memory function.[70,78,97,98] During this study, a cerebral angiogram is performed and amobarbital is injected into each internal carotid artery individually. Intracarotid injection of amobarbital results in arrest of ipsilateral cerebral function, which mimics the effect of surgical removal of the ipsilateral cerebral hemisphere. A successful injection is demonstrated by contralateral hemiparesis and ipsilateral slowing of the EEG. Speech and memory are then tested to determine whether the hemisphere contralateral to a planned resection can adequately support language and memory function. Wada testing is the most reliable means of ascertaining lateralization of language dominance and assessing residual memory capacity after temporal lobectomy; however, it is often difficult to perform in young children because it is necessary for them to be awake and cooperative.

Results from the preoperative investigation determine whether a patient is a candidate for epilepsy surgery or whether additional studies are required to more accurately pinpoint the location of the seizure focus and areas of eloquent cortex. The results of the presurgical studies are reviewed in a multidisciplinary clinical conference attended by epileptologists, neurosurgeons, neuroradiologists, neuropsychologists, and other members of the epilepsy surgery team to determine whether the patient is a candidate for surgery. The pediatric neurosurgeon discusses the risks and benefits of surgery, determines the surgical approach, and makes the final decision on whether or not to proceed.[82] Results obtained from video-EEG, MRI, and PET are typically given the strongest consideration,[78] and surgery is recommended when there is a clearly defined focal area of seizure onset that is consistent with EEG, radiographic, neuropsychological, and clinical evidence.[79] The likelihood of a successful outcome from seizure surgery increases with the number of independent elements that converge toward a single localization.[78,95,99,100]

In some patients surgery appears to be a good option, but the data are inconclusive or discordant. Such patients include those with normal or nonlocalizing imaging studies and a video-EEG that regionalizes the seizure onset without sufficiently localizing it, patients with a seizure focus that is more extensive than the structural lesion observed on imaging studies, and those with a seizure focus in the vicinity of eloquent cortex. For these patients, prolonged, invasive intracranial EEG monitoring may be required to obtain more precise localizing information.[78,79,101–104] Intracranial EEG monitoring has the following advantages: (1) it helps define the boundaries of the epileptogenic zone around the lesion, which in turn guides the extent of resection; (2) it helps determine whether children with multiple structural lesions and multifocal interictal spike discharges are surgical candidates by ascertaining whether their seizures arise from a single operable epileptogenic zone; and (3) it enables mapping of areas of eloquent cortex that are contiguous to the seizure focus to determine whether resection of the seizure focus can be performed safely without creating new deficits or worsening existing ones.

This technique involves placing surface electrodes such as grid and strip electrodes embedded in a thin pliable sheet of plastic, directly onto the cortical surface through a craniotomy

and dural opening in the case of subdural grids or through burr holes in the case of subdural strips.[105] Before closing the dura, an ICP monitor can be placed in patients with subdural grids to assist postoperative monitoring and management of elevated ICP related to grid placement. ICP monitoring is particularly beneficial in the case of a prolonged postictal state because it can help differentiate postictal lethargy from neurologic deterioration as a result of hemorrhage or edema.[79] In addition, the strips and grids are sutured to the dura to minimize the risk of postoperative movement and the electrode leads are tunneled to a distant exit site to minimize the risk of infection. Duraplasty is performed in cases in which the subdural space must be enlarged to accommodate the electrodes, the bone flap is replaced loosely, and the scalp incision is closed in a two-layered fashion. The skin around the exiting leads is closed tightly to avoid a CSF leak, and the leads are secured to the scalp with 4-0 nylon suture to minimize movement of the electrodes. If necessary, multicontact depth electrodes can be placed stereotactically with a frame-based system to achieve accurate EEG recordings from structures located deep to the cortical surface. Depth electrodes survey restricted areas of cortex and are not helpful in delineating large epileptogenic zones. However, monitoring with depth electrodes can be advantageous in children when the seizures are thought to arise from mesial temporal lobe structures such as the hippocampus and amygdala, but the side of origin is uncertain.[102]

After implanting the surface electrodes, a postoperative skull radiograph is obtained to document electrode position, prophylactic intravenous antibiotics and low-dose corticosteroids are administered, and continuous video-EEG monitoring is performed. The child is monitored until several typical seizures are recorded. Once an adequate number of the child's typical seizures have been recorded, cortical stimulation studies are carried out to map functional cortex and induce auras or seizures that can be of further help in localizing the seizure focus.[70,78,79] A surgical plan is then formulated on the basis of the electrical, structural, and functional data, and the child is taken back to the operating room, where the craniotomy is reopened and the planned resection is performed. A repeat skull radiograph is performed before the second operation and compared with the initial skull film to document electrode position and evaluate for electrode movement. Occasionally, an epileptogenic focus cannot be found or resection of the epileptogenic focus may lead to an unacceptable neurologic deficit. In such cases, the subdural electrodes are removed and the craniotomy is closed without performing resective surgery.[79]

Although intracranial EEG monitoring can help determine the feasibility and safety of epilepsy surgery, it is an invasive procedure associated with a number of possible risks including hemorrhage, infection, CSF leak, electrode migration, increased ICP, and even death.[104,106] The complication rate for strips is 1% to 3%,[107] whereas that for depth electrodes is 3% to 10%.[108] Complications occur more commonly with grids than with strips. The risk of infection increases with the duration of invasive monitoring and may be decreased by administering prophylactic intravenous antibiotics. In many cases, extraoperative electrode grid placement is unnecessary.[102,103,109] Instead, intraoperative electrocorticography can be carried out at the time of surgery to define the precise limits of the cortical resection on the basis of the location of interictal spike discharges, differences in background EEG patterns, and identification of critical functional cortex (e.g., primary sensorimotor cortex) by intraoperative somatosensory evoked potentials.[102,110]

## TYPES OF EPILEPSY SURGERY

Three main types of surgery are used to treat intractable seizures in children: (1) resections, in which the epileptogenic cortex is removed; (2) disconnections, in which critical pathways involved in the propagation of epileptiform discharges are interrupted; and (3) implantations, in which electrical stimulation is used.[74,82,111] The type of surgery performed is determined by the results of the presurgical workup.

### Resection Surgery

Specific types of resection surgery include anterior temporal lobectomy with amygdalohippocampectomy for intractable complex partial seizures; extratemporal resections for nonlesional epilepsy[79]; multilobar, lobar, and focal cortical resections for intractable seizures caused by structural lesions such as cortical malformations, intracerebral hamartomas, tumors (see Fig. 128-8), and vascular malformations[74]; and hemispherectomy, the extreme of resection surgery, which involves either complete removal (anatomic) or isolation (functional) of the abnormal cerebral hemisphere and is reported to be one of the most successful of all operations for the relief of epilepsy.[111–113] Hemispherectomy is reserved for patients who have severe damage to one hemisphere and a relatively intact contralateral hemisphere. It is particularly effective in children with severe unilateral motor seizures who already have contralateral hemiparesis and hemianopsia. Candidates for hemispherectomy include patients with Rasmussen syndrome,[114] Sturge-Weber syndrome,[115] hemimegalencephaly,[116] diffuse hemispheric cortical dysplasia, infantile hemiplegia, and cerebral infarction. When the presurgical workup reveals that a child's seizures are arising from the entire hemisphere and that hemisphere is removed with sparing of the ipsilateral basal ganglia (anatomic hemispherectomy) or disconnected with removal of less cortical tissue (functional hemispherectomy or hemispherotomy), 75% to 80% of patients have a marked reduction (80% or more) in seizure frequency with improvement in cognitive function.[74,114,117,118]

Temporal lobe epilepsy (TLE) is the most common localization-related epilepsy in adult and adolescent surgical candidates but is less common than extratemporal epilepsy in infants and children.[119,120] In TLE, patients generally experience complex partial seizures with oral and gestural automatisms, which may be preceded by an aura.[78] Although the most common cause of TLE in adults and adolescents is mesial temporal sclerosis, such is not the case for infants and children.[121,122] Instead, TLE in this age group is more commonly caused by congenital abnormalities in cerebral development such as cortical dysplasia, low-grade neoplasms, and vascular malformations.[81,123] In patients with lesion-related TLE, which occurs as a result of a temporal lobe mass, the source of the seizures is not generally the lesion itself but the margins around the lesion[124] and a successful outcome in such patients depends on adequately defining the extent of the epileptogenic zone around the lesion and resecting this region along with the lesion.

When the results of diagnostic studies indicate that the seizures are arising from a single temporal lobe, surgery is recommended. Both the lateral neocortex and the medial basal portion of the temporal lobe can cause temporal lobe seizures in children.[69,70] The medial basal portion of the temporal lobe consists of the fusiform and parahippocampal gyri and the amygdalohippocampal complex. Several surgical approaches have been described for resecting epileptic foci arising from the medial temporal lobe in children with medically refractory mesial TLE of unilateral origin.[74] For example, an anterior temporal lobectomy with amygdalohippocampectomy can be performed.[70,111,125] This two-step approach involves the initial removal of approximately 3.5 cm of anterolateral temporal lobe (measured with a ruler from the temporal tip along the middle temporal gyrus) below the superior temporal gyrus with a subpial dissection technique. This results in exposure of the temporal horn and mesial temporal lobe structures including the hippocampus, amygdala, and parahippocampal gyrus. The mesial structures are then removed by subpial dissection under the operating microscope, with the posterior limit of the dissection extending to the level of the tectal plate. In children with medically refractory mesial TLE of unilateral origin, removal of the affected mesial temporal lobe, with complete removal of the medial temporal structures, has a greater than 75% chance of significantly reducing a child's seizures or rendering a child seizure free off medication.[69,70,74,81,126]

Extratemporal epilepsy is found more frequently than TLE in pediatric epilepsy surgery candidates.[119] The epileptiform abnormalities can be frontal, parietal, or occipital and are often poorly localized.[127–129] Moreover, it is not uncommon for more than one lobe to be involved in children with intractable epilepsy.[79] When the seizure focus is outside the temporal lobe and is not associated with a lesion on imaging studies (nonlesional, extratemporal epilepsy), patients often require invasive intracranial monitoring and stimulation studies to define and accurately localize the seizure focus, as well as to map areas of eloquent brain function relative to the epileptogenic cortex.[78,79] Such seizures may be clinically silent and suggest a parietal or lateral frontal focus, complex partial and suggest a frontal lobe focus, or associated with amaurosis and suggest an occipital lobe focus. Resection margins are defined on the basis of the epileptogenic gyri identified during preoperative intracranial monitoring and stimulation studies with implanted subdural electrodes, as well as by intraoperative electrocorticography and functional cortical mapping. Corticectomy is then carried out under the operating microscope, and the entire epileptogenic focus is resected en bloc using a subpial dissection technique. Roughly two thirds of children with extratemporal (both lesional and nonlesional) epilepsy derive significant improvement from surgical intervention.[130,131]

The risks associated with resection procedures are generally related to the area or areas of brain resected and include visual field cuts (e.g., contralateral superior quadrantanopsia or "pie-in-the-sky" defect caused by an injury to Meyer loop/optic radiation during posterior temporal lobe resection), manipulation hemiplegia, speech and memory deficits, stroke from injury to nearby blood vessels (e.g., sylvian branches of the middle cerebral artery during temporal lobectomy), and cranial nerve palsies (e.g., injury to the third nerve during resection of the hippocampus). The incidence of major complications such as stroke or paresis ranges from 2% to 5%.[131,132]

## Disconnection Surgery

Resection of an epileptogenic focus is the mainstay of epilepsy surgery. However, in some children, the epileptogenic area is in a functionally critical cortical region (e.g., sensorimotor, language, or visual cortex, or more than one of these regions) and cannot be resected safely. Such children may be candidates for disconnection surgery—surgery in which the seizure focus is isolated from the rest of the brain.[111] For example, if the presurgical workup reveals that a child has a seizure focus in an area of eloquent brain such as the motor cortex, resection of the focus might cause unacceptable deficits such as contralateral paralysis or weakness. To prevent this, children with seizures arising in eloquent cortex can undergo a type of "disconnection" procedure called *multiple subpial transection*.[79,111,133] The efficacy of this type of surgery is based on the observation that normal cortical function is transmitted vertically, whereas seizures are transmitted through horizontal pathways. A small ball-tipped probe is used to transect the horizontal fibers in regions of eloquent cortex, thereby interrupting the horizontal spread of the ictal discharge without damaging the vertical columns of functional cortex. The cuts are made within the superficial convexity of the cortex under direct vision through the operating microscope, with each cut occurring at a right angle to the long axis of the gyrus at 5-mm intervals in a parallel fashion until the entire epileptogenic zone has been covered. With this technique, selected patients can achieve a substantial reduction in seizure frequency, without sustaining any persistent neurologic deficits. In extratemporal epilepsy, seizure control with multiple subpial transection is comparable with that achieved with resective surgery.[134]

Corpus callosotomy is another type of disconnection surgery that can be performed in the absence of an identifiable seizure focus or in the presence of multiple foci. During this procedure, the anterior two thirds or the entire corpus callosum is sectioned through a bifrontal craniotomy approach.[23,74,135] It is typically reserved for patients who have symptomatic generalized epilepsy with multiple seizure types and foci of epileptogenicity, as well as some degree of developmental delay or mental retardation.[78,82] Sectioning the corpus callosum results in separation of the cerebral hemispheres and prevents rapid bilateral generalization of epileptic discharges. Candidates for operative intervention include patients with atonic seizures ("drop attacks") who are prone to violent falls and closed head injuries and patients with Lennox-Gastaut syndrome. In appropriate patients, this type of procedure can be effective. For example, in patients with atonic seizures, up to 80% may experience complete or nearly complete cessation of attacks.[82] However, rarely do seizures totally remit, and patients with absence or myoclonic seizures either derive no benefit or experience an inconsistent response with corpus callosotomy. In addition, corpus callosotomy is associated with a number of possible adverse effects, some of which can be quite devastating, including language disturbances (e.g., complete mutism vs. slowness in initiating speech), weakness, increased frequency or intensity of partial seizures, and a disconnection syndrome. This syndrome, which can occur in patients with a dominant left hemisphere, consists of left tactile anomia, left-sided dyspraxia, pseudohemianopsia, right-sided anomia for smell, impaired spatial synthesis of the right hand resulting in difficulty copying complex figures, decreased spontaneity of speech, and incontinence.[74]

***Outcome*** Successful outcome from epilepsy surgery depends on (1) proper and timely patient selection guided by a thorough presurgical evaluation; (2) good correlation among clinical, electrophysiologic, and neuroradiologic data; (3) complete or nearly complete resection of the seizure focus; and (4) lack of surgery-related injury. Patients undergo routine EEG, MRI, and neuropsychological testing postoperatively and are graded in terms of percentage of seizure reduction and length of time since surgery. Results from preoperative neuropsychological testing can also be compared with those from postoperative testing to ascertain the effects of surgery on the child's behavior and cognition. In this manner, postoperative neuropsychological testing can help identify residual or resultant cognitive deficits and assist in planning psychoeducational interventions to address these deficits. Patients continue taking anticonvulsants for 1 to 2 years postoperatively. Those who are seizure free at that time, with a relatively benign-appearing EEG, are gradually weaned from their seizure medications.

Some studies have shown that outcome after epilepsy surgery (especially in the case of multilobar, lobar, and focal cortical resections for intractable seizures caused by structural lesions) is related to the pathology and location of the lesion.[74,82] Structural lesions associated with intractable epilepsy in children include developmental lesions such as focal cortical dysplasia and hamartomas; vascular lesions such as cavernomas and arteriovenous malformations; low-grade tumors such as DNET, ganglioglioma, ganglioneuroma, astrocytoma, pleomorphic xanthoastrocytoma, and oligodendroglioma; ischemic or hypoxic lesions; traumatic lesions; and mesial temporal sclerosis.[74,82] With focal cortical dysplasia, an important cause of intractable epilepsy in children, the outcome after surgical intervention is good within the first 2 years after surgery; however, the percentage of patients who remain seizure free declines over time. For example, in one series,[136] although 65% of patients with cortical dysplasia were seizure free at 2 years, only 40% remained seizure free at 5 years and just 33% were seizure free at 10 years. In another series with a mean follow-up period of 3.6 years, children with cortical dysplasia had seizure-free rates of 52%.[137] With mesial temporal sclerosis, a relatively rare pathologic entity in children, seizure-free rates are excellent for the vast majority of children and adolescents, with surgical results comparable with those observed in adults.[136,137] A DNET is a benign cortical tumor that has cystic or microcystic components and is frequently associated with cortical dysplasia.[82] In contrast to cortical dysplasia, the epileptogenic area associated with a DNET resides within the cortex immediately adjacent to the lesion rather than within the DNET itself.[138] Total resection of these lesions, aided by preresection electrocorticography to identify adjacent epileptogenic cortex, can result in complete seizure freedom in about 75% of patients.[139] In patients with ganglioglioma who have seizures (see Fig. 128-8), complete surgical resection is the preferred management and the most important factor predicting a seizure-free outcome,[140] with about 78% of patients becoming seizure free off anticonvulsants.[141]

The goal of surgical management is complete elimination of seizures or excellent seizure control with seizure medications and an improvement in the child's long-term cognitive, behavioral, and social development. Surgical treatment of epilepsy in children can reduce seizure frequency and limit the cognitive and psychologic impairment that often occurs as a consequence of chronic uncontrolled seizures. However, surgical intervention must be timed appropriately to enable children to develop their maximal potential and reach their educational, vocational, and social goals.[82]

As with any surgical procedure, epilepsy ablative procedures are not risk free and the risk of creating a new permanent neurologic deficit or worsening an existing deficit must be balanced against the potential benefit of completely eliminating a patient's seizures or significantly reducing the frequency of seizures. Risks of epilepsy surgery include removal of or injury to eloquent cortex; injury to projection fibers, association fibers, or commissural fibers underlying the cortical resection; injury to the Meyer loop causing a contralateral "pie-in-the-sky" visual field defect; injury to vessels in the area of the resection causing ischemic damage or stroke in the corresponding areas of vascular distribution; and injury to nearby cranial nerves. Despite the risks of the procedure, early surgical intervention in appropriate cases can arrest progressive deleterious changes in the developing brain including progressive psychologic and intellectual impairment, allow for optimum brain development, reduce the undesirable side effects of medical therapy, and allow many children with seizures to lead normal, productive lives. Currently, surgery is the only therapy that offers the chance of a cure and early identification of appropriate surgical candidates by means of a comprehensive preoperative evaluation is paramount to achieving a successful outcome.[82]

## Vagus Nerve Stimulation

Vagus nerve stimulation by means of the implantable NeuroCybernetic Prosthesis (NCP; Cyberonics, Houston) is a relatively recent development in the surgical treatment of childhood epilepsy and is gaining increasing popularity as an effective treatment option for children with drug-resistant epilepsy who have failed medical therapy and are not candidates for resection or disconnection procedures. Such children often have many generalized or focal seizures (or both) every day that arise from multiple areas on both sides of the brain, and they are not candidates for or have already failed previous cortical resection. The FDA limits its use to patients older than 12 years of age; however, it is also commonly used in children younger than 12 years of age because earlier control of seizures generally results in improved long-term outcomes.

Placement of a vagal nerve stimulator involves wrapping helical, platinum, bifurcated ribbon electrodes around the left vagus nerve in the cervical region and connecting the bifurcated helical lead to a pulse generator, which in turn is inserted into a subcutaneous or submuscular pocket in the left pectoral region.[111,142] Together, they deliver intermittent electrical stimulation to the left cervical vagus nerve—usually for 30 seconds every 5 minutes. Electrical impulses, which travel to the cerebral cortex by way of ascending sensory nuclei (e.g., nucleus tractus solitarius), exert widespread effects on neuronal excitability throughout the CNS.[143] Although it has been postulated that these rostral impulses stop seizure activity by disrupting the abnormal electrical activity caused by abnormal

groups of neurons firing in an uncontrolled synchronous fashion, the exact mechanism of seizure modulation remains unknown.[64,144,145]

The pulse generator has eight programmable parameters that are adjusted noninvasively through the skin by a telemetry programming wand controlled by a hand-held computer. The stimulation parameters are adjusted according to patient tolerance and seizure frequency, and seizure medications are weaned as tolerated. An additional benefit of vagus nerve stimulation is the ability to control seizure activity with the use of a hand-held magnet. For example, at the beginning of an aura or seizure, the patient or a family member may pass a hand-held magnet across the chest pocket where the generator resides. This triggers a train of stimulation superimposed on the baseline output that can attenuate or even abort an impending seizure.[143] Other advantages of vagus nerve stimulation include guaranteed treatment compliance, sustained efficacy over time,[146] and global improvement in quality of life and cognitive function.[143] Adverse effects of vagus nerve stimulation can occur and include hoarseness, throat pain, cough, dyspnea, and paresthesias. Such effects tend to occur intermittently, concomitantly with stimulus delivery, and are typically transient.[146,147] Surgical complications of vagus nerve stimulation are rare and include left vocal cord injury, lower facial paresis, bradycardia, and infection requiring explantation in 1.1%.[143] Although the vagus nerve is the principal efferent component of the parasympathetic nervous system, vagus nerve stimulation by the NCP system has not been shown to adversely influence pulmonary function, gastrointestinal motility, or secretion.[147] Nevertheless, there is a case report in the literature of bradyarrhythmia, perfectly correlated with VNS stimulation periods, which suddenly occurred 2 years and 4 months after VNS implantation in a pediatric patient who presented with syncope-like episodes.[148]

Previous studies have shown that children and adolescents with medically and surgically refractory epilepsy derive substantial benefit from vagus nerve stimulation, with many patients achieving a significant reduction in seizure frequency and some being able to reduce the number of anticonvulsants.[149,150] Patients with idiopathic epilepsy, as well as those with seizures arising from a structural etiology, are considered appropriate candidates.[143] In particular, vagal nerve stimulation has been shown to be highly effective in patients with Lennox-Gastaut syndrome, with five of six children in one series achieving a 90% reduction in seizure frequency.[151] Moreover, use of the magnet in pediatric patients has been shown to reduce seizure duration in some patients and improve postictal lethargy in others.[150] In a previous retrospective analysis of seizure frequency and quality of life in pediatric patients with medically refractory epilepsy,[150] 29% of children achieved a greater than 90% reduction in seizure frequency, 39% had a 50% to 90% reduction, and 13% had less than a 50% reduction with vagus nerve stimulation. When compared with the efficacy in adult patients, multiple studies have shown an equivalent or slightly higher response rate in children with about 45% to 55% of patients deriving a greater than 50% reduction in seizure frequency. Moreover, there is a suggestion that these patients also showed significant improvement in quality of life measures.[152–156] Although complete seizure control is possible with vagus nerve stimulation, the likelihood of complete control is low.[143]

# Suppurative Central Nervous System Infections

Suppurative infections of the CNS include intracranial infections such as brain abscess, subdural empyema, epidural abscess, osteomyelitis of the skull, Pott puffy tumor, and acute pyogenic meningitis,[157] as well as intraspinal infections such as SC abscess, spinal epidural abscess, diskitis, and vertebral osteomyelitis. Intracranial infections can be life threatening and must be considered in the differential diagnosis in children with fever, headache, and cranial wounds or sinus disease. Similarly, intraspinal infections can result in devastating neurologic impairment, especially if the diagnosis is delayed, and must be considered in the differential diagnosis in children with back pain, spinal tenderness, and fever. The remainder of this chapter discusses suppurative CNS infections.

## INTRACRANIAL INFECTIONS

Suppurative processes in the epidural and subdural spaces and brain parenchyma are classic neurosurgical complications of otorhinologic, middle ear, and post-traumatic infections, as well as immunosuppression, and they commonly manifest as neurosurgical emergencies.[158] An epidural abscess refers to suppuration in the epidural space between the dura and calvaria or skull base, a subdural empyema refers to suppuration in the subdural space between the dura and arachnoid, and a brain abscess refers to a circumscribed focus of suppurative tissue necrosis within the brain parenchyma.

### Incidence

The reported incidence of intracranial infections in children remains low. In busy pediatric neurosurgical centers, the incidence of an isolated epidural abscess is about one case per year and that of a subdural empyema is one to two cases per year.[159,160] The incidence of brain abscess is less than one to three cases per year.[158] Although intracranial infections are relatively uncommon in children, they can be rapidly fatal if not recognized promptly and managed appropriately. Successful treatment requires early diagnosis, guided by CT or MRI (or both), aggressive antibiotic therapy, and timely and adequate surgical intervention targeted to maximal areas of suppuration. Response to treatment must also be monitored neuroradiographically to ensure that the infection is resolving.

### Etiology

Intracranial infections occur as a consequence of (1) direct extension from contiguous infection, such as paranasal sinusitis, otitis media, or mastoiditis, or propagation through venous channels; (2) direct inoculation of the brain after penetrating cranial trauma or a neurosurgical procedure; and (3) hematogenous spread from a distant focus of infection. Contiguous infection in the paranasal sinuses, mastoid air cells, orbit, or skull is the most commonly reported cause of suppuration in the epidural space.[161] Epidural abscess can also occur as a complication of a congenital dermal sinus, trauma (especially penetrating wounds), craniotomy, application of skull pins or tongs, and paranasal sinus and skull base operative procedures.[162] Subdural empyema commonly occurs as a result of infection in the frontal and ethmoidal sinuses, middle ear, and mastoid air cells.[163,164] Other causes of subdural

empyema include spread from contiguous infections of the scalp, subgaleal space, calvaria, or epidural space (or any combination of these regions); meningitis; hematogenous infection of a preexisting subdural effusion or hematoma[165]; rupture of a parenchymal brain abscess into the subdural space; and subdural puncture or subdural shunt placement.

In the pediatric population, the most common cause of brain abscess is direct or indirect spread from infection in the paranasal sinuses, middle ear, and teeth.[166] In adolescent boys, frontal lobe abscess is a relatively common complication of acute frontal sinusitis.[158] In children with congenital heart defects or pulmonary right-to-left shunt disease, hematogenous spread from remote sources of infection such as pulmonary infections, cutaneous infections, osteomyelitis, and bacterial endocarditis remains an important pathogenic mechanism of brain abscess formation.[167] In neonates, bacterial meningitis caused by *Citrobacter, Proteus, Serratia,* or *Enterobacter* is complicated by the formation of brain abscesses in a high percentage of patients.[168] Moreover, direct inoculation of the brain after penetrating cranial trauma, penetrating wounds of the orbit, compound skull fractures, scalp wounds, facial sepsis, CSF fistula, and post-traumatic meningitis can lead to the development of brain abscesses in children. The location of the abscess is dependent on the portal of entry. For example, otogenic abscesses or those resulting from mastoiditis often develop in the temporal lobe or cerebellar hemisphere adjacent to the infected ear or mastoid air cells, paranasal sinusitis commonly gives rise to abscess formation in the frontal lobe, and brain abscesses arising from hematogenous spread tend to occur in the distribution of the middle cerebral artery.

Aerobic organisms commonly isolated from suppurative intracranial infections include *Staphylococcus, Streptococcus, Enterobacteriaceae,* and *Haemophilus.* Anaerobic organisms include *Bacteroides, Peptostreptococcus, Fusobacterium, Veillonella, Propionibacterium,* and *Actinomyces.* In many cases, culture of pus obtained from intracranial infections reveals multiple organisms including both anaerobic and aerobic organisms.[158] However, in some cases, no organisms are isolated despite proper handling of specimens. With regard to the causative organisms, the bacteriologic diagnosis often points to the source of the intracranial infection. For example, aerobic or anaerobic streptococci (or both) are often cultured from intracranial infections complicating paranasal sinus infection, gram-negative organisms such as *Bacteroides* and *Haemophilus* are cultured from intracranial infections complicating otogenic infections, and *S. aureus* is cultured from intracranial infections complicating compound skull fractures and neurosurgical procedures. Fungal organisms such as *Candida, Aspergillus, Nocardia,* and *Cryptococcus* commonly cause intracranial infections in children who are immunologically suppressed after organ transplantation or chemotherapy or who have impaired host defenses.[169]

## Pathogenesis

Spread of infection from the paranasal sinuses, mastoid air cells, or middle ear to the epidural and subdural spaces or to the brain parenchyma occurs as a consequence of infective thrombophlebitis of the diploic vessels or nutrient vessels that supply the outer layer of the dura.[158] Once infection enters the diploic space, it spreads rapidly through this space to involve widespread areas of the skull. Occasionally, a subperiosteal abscess (Pott puffy tumor) forms as a result of the osteomyelitis and leads to swelling of the overlying scalp (Fig. 128-9). Once the inflammatory process reaches the subdural space, it can spread rapidly throughout the subdural space because this space is in continuity over the surface of the brain, on each side of the falx and tentorium, and through the foramen magnum with the spinal subdural space. Direct exposure of the brain to subdural infection can lead to occlusion of cortical veins and septic thrombophlebitis. This, in turn, can cause

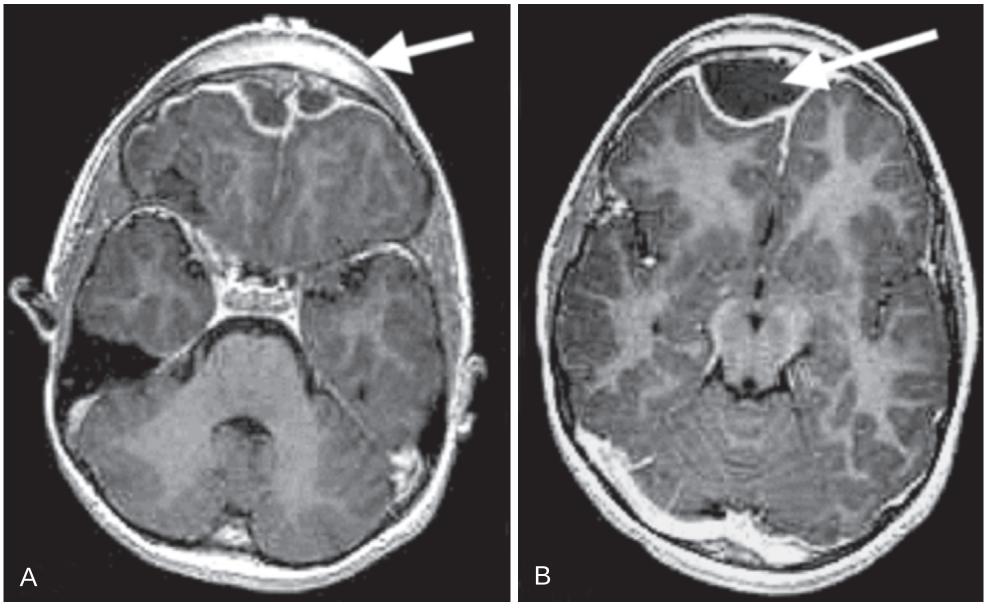


**FIGURE 128-9** **A** and **B,** Axial magnetic resonance images from a 5-year-old boy with a history of strep throat, treated with 2 weeks of oral antibiotics, followed by fever, malaise, headaches, progressive swelling in the midline of his forehead, vomiting, and lethargy. A frontal subperiosteal abscess (i.e., Pott puffy tumor; **A,** *arrow*) and an epidural abscess (**B,** *arrow*) are evident. He was managed by surgical evacuation and aggressive antibiotic therapy; the bone flap was left in place. The infection resolved completely with no neurologic sequelae.

cerebral infarction and edema, and the edema can produce significant mass effect and associated brain compression and herniation.

A brain abscess develops as a consequence of seeding of bacteria in areas of preexisting necrosis or direct traumatic injury, hemorrhage, or infarction from septic thrombophlebitis. Once a nidus of bacteria is established within the brain parenchyma, the organisms produce an acute inflammatory response that results in polymorphonuclear infiltration and edema. The central area eventually undergoes necrosis and liquefaction and becomes surrounded by a peripheral zone of inflammatory cells, neovascularization, and fibroblasts.[158] The fibroblasts, in turn, create a dense collagenous capsule that is surrounded by edema and reactive gliosis. An abscess with its surrounding edema can lead to significantly elevated ICP and cause brain herniation and death. Moreover, sudden deterioration and death can occur from rupture of a brain abscess into the ventricular system[167] or through the cerebral cortex into the subarachnoid space.[170]

### Clinical Features

Children with intracranial infection often have a history of cerebral trauma, purulent nasal or aural discharge, fever, or headache. If there is suppuration within the epidural space, the child typically appears acutely ill with fever, headache, or earache at the time of the initial evaluation. If the epidural abscess is associated with a subperiosteal abscess, patients also commonly have a tender, fluctuant swelling in the scalp overlying the involved frontal sinus, mastoid air cells, or affected area of the diploic space (see Fig. 128-9). As infection spreads within the epidural space, the mass effect on the subjacent dura and brain increases and causes escalating headaches. Eventually, focal neurologic signs and a decreased level of consciousness develop as the abscess increases in size and brain herniation occurs.[160]

With spread of infection into the subdural space, rapid neurologic deterioration occurs as a result of cerebral edema, infarction, and herniation. Patients typically have signs and symptoms of a systemic febrile illness and raised ICP including malaise, fever, chills, meningismus, vomiting, headache, focal neurologic deficits, and altered mental status.[161] In addition, children with subdural empyema can have localized tenderness and swelling overlying the affected sinus or mastoid secondary to subperiosteal abscess formation (Pott puffy tumor; see Fig. 128-9), and focal seizures may be observed in 25% to 50% of patients.[158] Depending on the underlying cause, suppuration within the subdural space may be supratentorial or infratentorial, or both (Fig. 128-10). With subdural empyema in the posterior fossa, children typically have a systemic febrile illness, headaches, and a stiff neck, but focal neurologic signs and seizures are generally lacking.[171]

The clinical manifestations of a brain abscess are influenced by the size and location of the abscess, as well as the number of abscesses present, the virulence of the organism or organisms, and the patient's age and host defenses.[158] Children and adolescents with a brain abscess exhibit signs and symptoms of (1) systemic infection including malaise, fever, chills, and neck stiffness; (2) raised ICP as a result of the mass effect from the abscess and surrounding cerebral edema including headache, vomiting, and a declining level of consciousness; and (3) focal neurologic deficits reflecting the location of the abscess such as hemiparesis with an abscess in the posterior frontal region or as a consequence of uncal herniation, speech difficulty with an abscess in the dominant temporal lobe, a visual field deficit with a posterior temporal or occipital lobe abscess, and nystagmus, defective conjugate eye movements, ataxia, and hypotonia with a cerebellar abscess.[158] Infants with a brain abscess have signs and symptoms of increased ICP including irritability, lethargy, vomiting, a bulging anterior fontanelle, frontal bossing, and increasing head circumference. At least 25% to 50% of pediatric patients with a supratentorial brain abscess also manifest focal or generalized seizures during the course of their disease.[172]

### Diagnostic Studies

If intracranial infection is suspected, the patient should undergo a contrast-enhanced head CT or brain MRI study (or both). A head CT scan with contrast enhancement enables rapid diagnosis, whereas MRI provides accurate preoperative localization and is beneficial for monitoring resolution of

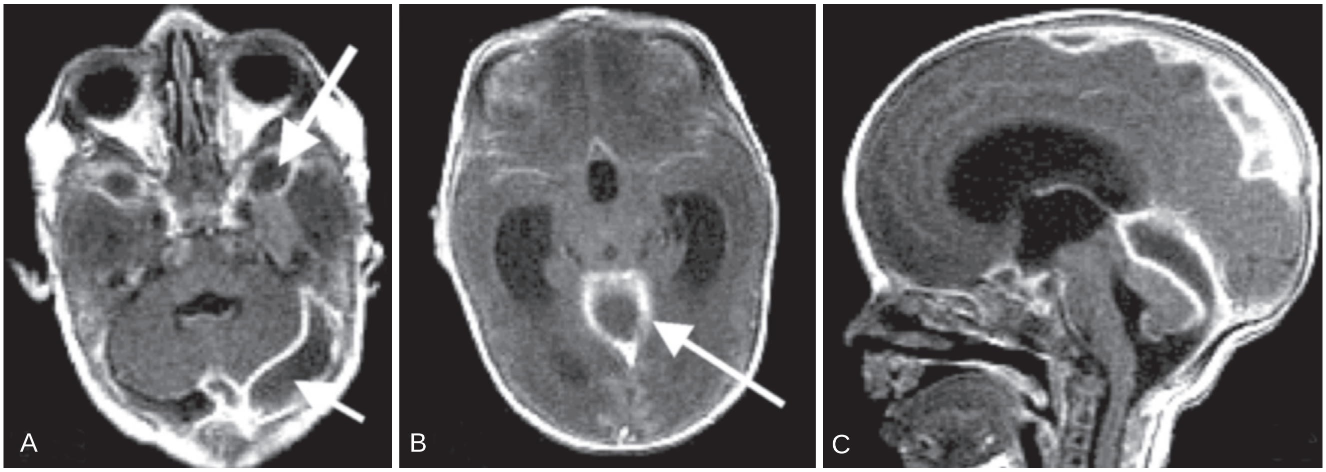


**FIGURE 128-10** Axial (**A** and **B**) and sagittal **(C)** brain magnetic resonance imaging (MRI) in a 35-week preterm male infant with a history of meningitis, organism unknown, who was on multiple antibiotics, but not metronidazole. He began having seizures and respiratory difficulty and required intubation. MRI showed extensive subdural empyema extending bilaterally, both above and below the tentorium (*arrows*). Cultures at the time of drainage grew *Bacteroides fragilis*. The infection eventually cleared with a prolonged course of antibiotics including metronidazole. He is now almost 4 years old, is no longer taking anticonvulsants, and has no neurologic sequelae.

infection. Depending on the type, extent, and stage of the intracranial infection, these studies may reveal dural enhancement, an empyema wall, an abscess capsule, and hypodense areas of cerebral edema, venous infarction, and early cerebritis. Sagittal and coronal views are also helpful for visualizing affected sinuses and suppurative collections at the vertex and skull base. In patients with a brain abscess, contrast-enhanced CT and MRI demonstrate a characteristic ring-enhancing lesion with surrounding edema. In particular, on MRI a brain abscess appears as an area of central hypointensity surrounded by a ring of enhancement after gadolinium administration on T1 weighting and as a hyperintense area of suppuration surrounded by a hypointense capsule and an outer layer of edema on T2 weighting.[173]

Laboratory studies helpful in the diagnosis of intracranial infection include a peripheral white blood cell count, erythrocyte sedimentation rate, and C-reactive protein, all of which may be mildly elevated.[172] Blood cultures may reveal the causative organism, especially in cases of epidural abscess and subdural empyema.[172] Because of the risk of herniation and the low diagnostic yield of CSF studies, a lumbar puncture should not be performed before neuroimaging, especially if a mass-occupying lesion is suspected. Identification of the causative organism(s) is accomplished by culturing purulent material obtained at the time of surgical drainage.[158] Such cultures determine the antibiotic sensitivity of the causative organism(s), which in turn guides antimicrobial therapy. Proper handling of specimens and appropriate aerobic and anaerobic culture techniques are required to achieve positive culture results.

## Treatment

A high index of suspicion is essential to ensure prompt diagnosis. Successful treatment requires surgical drainage, appropriate antimicrobial therapy, and close coordination of care between pediatric neurosurgeons and infectious disease specialists. Systemic antibiotics should be initiated as soon as the diagnosis is considered.[158] Although preoperative antibiotics may achieve some bone penetration, it is unlikely that they will interfere with culture results.

The initial choice of antibiotics is contingent on the microbial spectrum, which varies according to the primary site of infection.[158] Hence knowledge of the primary infection site can be used to guide antimicrobial therapy. For example, if frontal sinusitis is the primary site, the most likely infective agent is a streptococcal species and antibiotic coverage should include metronidazole and penicillin or a third-generation cephalosporin. If the primary site is unknown, the initial choice of antibiotics should include a penicillinase-resistant synthetic penicillin, a third-generation cephalosporin, and metronidazole to provide coverage of aerobic and anaerobic streptococci, other anaerobes, and staphylococci. Although the optimal duration of therapy remains unknown, intravenous antibiotics should be continued until systemic evidence of the infection has resolved and the intracranial infection appears to be diminishing in size.[160,163] An additional 2 to 3 months of oral antibiotics is recommended by some to prevent recurrence.[174]

Besides systemic antibiotics, children with intracranial infections may also require treatment with corticosteroids and anticonvulsants. Corticosteroids such as dexamethasone are effective in reducing the cerebral edema associated with intracranial infection and have not been shown to exacerbate the inflammatory response. Consequently, corticosteroids can be administered during the acute phase of the illness to reduce intracranial hypertension and prevent herniation. Because 25% to 50% of pediatric patients with intracranial infections exhibit seizures during the course of their illness, prophylactic anticonvulsants should also be started as soon as the diagnosis is made.

Besides enabling bacteriologic diagnosis and guiding antimicrobial therapy, surgical treatment permits evacuation of sizable collections of liquefied pus and reduces ICP.[158] If the primary site of infection is known and the patient's clinical condition permits, surgical intervention should also address the primary infection source. Surgical drainage of intracranial pus can be performed through a limited craniotomy, craniectomy, or burr hole. The bone removed should be just large enough to provide access to the abscess or empyema. If an epidural abscess occurs in the face of a previously devascularized bone flap, the devitalized bone is frequently left out and a delayed cranioplasty performed. However, if epidural infection complicates an extensive craniofacial reconstruction in which bone removal would probably generate irreparable defects, the bone is replaced after extensive irrigation of the epidural space with antibiotic solution and debridement, and systemic antibiotics are administered until the infection clears.[158] Follow-up neuroimaging studies are performed on all patients to monitor the progress of treatment.

For a subdural empyema, the subdural space is exposed by craniotomy, craniectomy, or a burr hole, often using stereotactic CT or MRI guidance to accurately localize the purulent fluid collection and keep the bone removal and dural opening to a minimum. Once the dura is opened, specimens are obtained for aerobic and anaerobic culture, the empyema is evacuated, and the subdural space is irrigated thoroughly with antibiotic solution. If a craniotomy has been performed and neither osteomyelitis nor epidural abscess is observed, the bone flap may be replaced. However, healing of the bone flap should be monitored closely because failure of healing can occur and result in reabsorption or sequestration of the bone flap.[175] Repeated drainage may also be necessary if the subdural empyema recurs. Infants in whom subdural fluid collections develop as a complication of *Haemophilus influenzae* meningitis typically do not require surgical intervention unless the fluid collection causes a mass effect and the patient becomes symptomatic from elevated ICP. If surgery is warranted, needle drainage through the lateral aspect of the anterior fontanelle or through a burr hole can be performed to remove the subdural fluid, which is typically sterile.[158]

Conservative management of brain abscesses with intravenous antibiotics, with or without neurosurgical intervention, has been reported. However, antibiotic treatment alone must be accompanied by frequent neuroradiographic follow-up to determine the effectiveness of the treatment. Careful monitoring of the patient's neurologic findings and level of consciousness is also essential. Immediate neurosurgical intervention is required if (1) the patient demonstrates any evidence of neurologic decline, (2) the abscess shows significant mass effect on CT or MRI, or (3) the abscess fails to respond to antibiotics within 2 weeks of the initiation of treatment.

Two surgical options are available to treat brain abscesses including needle aspiration, with or without catheter drainage, and excision. Ultrasound guidance or guidance with frameless or framed stereotaxy can be used to accurately localize an abscess and place a drainage needle or catheter within the abscess cavity. Ultrasound can also be used to visualize

decompression of the abscess cavity as the pus is aspirated. After gentle aspiration with a syringe and irrigation with normal saline, a catheter may be left in the abscess cavity for several days until drainage of purulent fluid ceases. If aspiration fails, as frequently occurs in the case of multiloculated abscesses, surgical excision may be required. To accomplish this, a limited craniotomy bone flap is turned, the dura is opened, a small corticectomy is generated in the closest noneloquent parenchymal area, and the abscess is excised en bloc while leaving the surrounding white matter intact. The craniotomy is closed in the usual fashion after thorough irrigation with saline, and the patient is treated with long-term antibiotics.

### Outcome

Outcome is determined by the rapidity of the diagnosis and initiation of treatment. Moreover, the prognosis for survival and neurologic recovery is contingent on the patient's level of consciousness at the time of diagnosis and institution of treatment. Consequently, early diagnosis and prompt aggressive therapy, with appropriate systemic antibiotics and surgical removal of suppurative collections, are paramount to minimizing the morbidity and mortality associated with suppurative intracranial infections. In support of this, the mortality associated with a brain abscess in older series approached 32% but has decreased to 10% in recent years as a consequence of more rapid diagnosis and treatment with appropriate antibiotics.[158] In contrast, the mortality rates associated with intraventricular rupture of a brain abscess remain high, ranging from 23.8% to 80%.[167,170] Long-term neurologic deficits occur in about 44% of patients who survive surgical treatment of brain abscess.[176] Moreover, children who survive are commonly left with learning disabilities[168] and seizures.[174]

## INTRASPINAL INFECTIONS

Spinal epidural abscess in children is a rare clinical entity[177] that often escapes diagnosis until significant neurologic deficits develop.[178] It is a rapidly progressive, compressive lesion of the SC that often requires rapid decompression to prevent permanent paraplegia. Hematogenous spread of bacteria from cutaneous or mucosal sources of infection such as furuncles, pharyngitis, and dental abscesses is the most commonly reported cause of spinal epidural abscess.[177,179,180] Other potential causes include direct extension from vertebral osteomyelitis, a paraspinal abscess, or a septic focus in the pelvis, retroperitoneum, or posterior mediastinum. Such extension can occur by way of veins passing through the intervertebral foramina or bacterial seeding of an epidural hematoma that forms as a result of blunt trauma.[177] The most common pathogen of a spinal epidural abscess in children is *S. aureus,* although anaerobic and gram-negative bacteria have also been isolated.

Spinal epidural abscesses occur posterior to the SC in about 80% of cases. Posteriorly, the dura is adherent to the posterior longitudinal ligament from C1 to S2. Consequently, pus that accumulates posterior or posterolateral to the dura can spread extensively rostrocaudally but is restricted dorsally by the laminae and ligamenta flava. Although epidural infection can occur anywhere along the spinal axis, lower thoracic and lumbar abscesses are most commonly reported in the literature.[180] Once infection is established in the epidural space, pus collects deep to the laminae and ligamenta flava and is surrounded by thrombosed veins and granulation tissue. The dura provides a formidable barrier to infection. Consequently, meningitis is uncommon unless a spinal tap is performed. However, the SC is defenseless against compression and may be injured as a result of vascular compromise from arterial or venous thrombosis.[180]

Children with spinal epidural abscess may have fever and malaise, and they typically complain of deep-seated back pain, spinal tenderness, or radicular pain. The back pain is usually midthoracic and radiates around the chest wall. The pain is constant and can be exacerbated by coughing or movement. Patients often exhibit nuchal rigidity and exquisite tenderness to percussion over the involved spinal segments. A primary source of infection may be evident. Symptomatic SC compression is manifested by rapidly progressive weakness and sensory loss in the legs and evidence of bladder or bowel dysfunction, or both.

If a child is suspected of having a spinal epidural abscess, a peripheral white blood cell count, erythrocyte sedimentation rate, and C-reactive protein level are obtained and are usually elevated. Moreover, blood cultures are performed because they may reveal the offending organism. A total spine MRI with and without gadolinium enhancement enables visualization of the extent and location of a spinal epidural abscess and is the diagnostic procedure of choice. A spinal tap should not be performed. If a myelogram must be performed as part of the diagnostic workup (e.g., if MRI is not available), the spinal puncture site should be placed as far away from the suspected position of the abscess as possible.

After the diagnosis of spinal epidural abscess is made, treatment must commence immediately to prevent long-term neurologic disability. Aggressive antimicrobial therapy is initiated with intravenous antibiotics that have good coverage against staphylococci, anaerobes, and gram-negative organisms. Parenteral antibiotics are continued for at least 4 to 8 weeks. Although there are a few reports in the literature of neurologically intact children being treated successfully with antibiotics alone,[179] in the majority of cases, successful treatment requires appropriate antibiotic therapy and emergency evacuation of the abscess with decompression of the SC and nerve roots, especially if the abscess is widespread. This is typically performed by means of a posterior decompressive laminectomy with drainage of the purulent material. A one- or two-level laminectomy at one or both ends of the abscess with catheter irrigation and drainage is usually sufficient. If a multilevel laminectomy is required for surgical decompression, the child must be monitored carefully postoperatively for kyphosis and spinal instability, which can occur as a complication of multiple-level laminectomies in children.[179]

The prognosis is related to the patient's preoperative neurologic condition.[181] If the infection is recognized early and the patient receives appropriate treatment, recovery is expected to be excellent. If mild motor weakness has been present for less than 36 hours, a good outcome is also possible.[182] However, once a child develops paraplegia, recovery is highly unlikely. Thus early diagnosis and appropriate treatment are paramount to achieving a good outcome in children with a spinal epidural abscess. Mortality from spinal epidural abscess, which is unquestionably related to a delay in instituting appropriate therapy, has remained stable over the past several decades at about 14%.[182]

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 129

# Major Congenital Orthopedic Deformities

Kosmas Kayes and William Didelot

## Developmental Dysplasia of the Hip

### TERMINOLOGY/INCIDENCE/ETIOLOGY

*Developmental dysplasia of the hip* (DDH) is a term used to describe a wide spectrum of pathology related to the hip joint. All cases involve some type of incongruity between the femoral head and acetabulum. This can vary from minimal acetabular dysplasia, in which the acetabulum has not developed fully (with a femoral head that may be normal in position or slightly subluxated), to complete dislocation of the femoral head, in which there is no contact with the acetabulum. Different findings will be present at different ages of the individual. In a newborn the changes vary from an unstable hip that is fully reduced within the acetabulum but can be gently subluxated or fully dislocated to a hip that is subluxated partially out of the acetabulum and may or may not dislocate to a hip that is dislocated completely and may be reducible or not.[1,2] Another variation of dislocation, called a *teratologic hip dislocation,* usually occurs with some type of neuromuscular problem such as myelomeningocele, arthrogryposis, or other type of syndrome. This type of dislocation is a rigid, fixed dislocation that occurs prenatally and will not respond to nonoperative methods of treatment as the more common types of hip dislocation usually will. Most cases of hip dysplasia are evident at birth by physical examination or ultrasound, but, rarely, instability may not develop until later in the first year of life and may have different findings. Still other types will not be identifiable until adolescence, when they are often manifested as pain without other physical examination findings. A change in terminology has occurred in the past 15 years from “congenital dislocation” to “developmental dysplasia” of the hip. This change reflects more accurate information about the less apparent types of dysplasia not identifiable at birth and the variations that are not always complete dislocations of the joint but rather abnormal development or “dysplasia.”[3,4]

Hip dysplasia is the most common hip disorder in children. One in 1000 newborns has a dislocated hip, and 10 in 1000 will have some form of subluxation or dysplasia. The majority of hips will tighten up on their own, usually within the first 2 weeks of life. Approximately 4 in 10,000 will eventually have problems of dislocation, subluxation, or acetabular dysplasia. Females have a higher incidence than males by a ratio of 4:1, which is thought to be due to sensitivity to the relaxin hormone produced by the mother during pregnancy; relaxin causes transient ligamentous laxity in females and not in males (because males are not sensitive to the hormone). The left hip is affected 60% of the time, probably because of pressure on the hip from the mother’s sacrum because most birth presentations are left occiput anterior.

The cause of hip dysplasia is multifactorial. Genetics, physiologic factors, and mechanical factors such as prenatal and postnatal positioning all play a role. Genetics is a factor because babies with a positive family history have a higher incidence of DDH, as do siblings and twins. Mechanical factors are also involved because any form of intrauterine crowding or abnormal positioning such as a first pregnancy, breech presentation, oligohydramnios, or multiple births puts the infant at higher risk. This is also true postnatally because cultures such as Native Americans that swaddle, strap, or papoose their babies have a higher incidence of DDH as well.[2,5–8]

### DIAGNOSIS

#### History and Screening

Early detection of DDH is crucial; the sooner treatment is initiated, the better the expected outcome. Classically, the pertinent history of the newborn consists of whether the newborn is the first child, the presentation in utero (breech), whether there is a family history of DDH, the presence of any associated orthopedic or genitourinary abnormalities, multiple births, and the presence of oligohydramnios. However, more evidence is showing that previous risk factors may no longer be completely accurate and the important risk factors are first born, family history, and oligohydramnios. Some studies show that breech position may not be a significant risk factor and that risk factors are different for early and late diagnosis.[9–11]

Most cases are detected early as a result of the screening protocol for pediatricians developed by the American Academy of Pediatrics; the protocol consists of serial physical examinations at birth, at 2 weeks, and then at every well-baby

follow-up visit at 1, 2, 4, 6, 9, and 12 months of age. New evidence suggests that risk factors alone are not enough to warrant ultrasound screening, so only a child with an abnormal physical examination should be imaged by ultrasound. Physical examination remains the gold standard for screening newborns, and ultrasound can be used after 4 weeks of life. Many hips are over-read on ultrasound as positive findings of dysplasia before 4 weeks in children who will otherwise spontaneously resolve their instability. Also, the accuracy of ultrasound is still operator dependent and variable.[12] A child at risk should have either an ultrasound before 4 months or radiographs of the hip taken after 4 months of age. Screening of the entire newborn population has not been necessary, although some cases of hip dislocation and dysplasia are not detected until later in life.[13–19] There is some thought that screening may even potentially cause harm because well over 90% of newborn hip instability will resolve spontaneously and many children may be overtreated. One meta-analysis showed that there was no clear evidence for or against ultrasound screening in DDH.[20–22]

## Physical Examination

Findings on physical examination vary with the age of the child. From birth to about 3 months of age, the most reliable findings are a positive Barlow or Ortolani maneuver. In the Barlow test the hip is held flexed 90 degrees with neutral adduction, and the knee is flexed 90 degrees. The first web space and the palm of the hand should cradle the knee and be outside the thigh with the long finger down the length of the thigh. The hand should gently push the thigh posteriorly while adducting the hip in an attempt to dislocate a reduced hip out the back of the socket. The Ortolani maneuver is the same, but instead of pushing posteriorly, the thigh is abducted with pressure on the femur toward the middle of the socket while pulling it up anteriorly and trying to reduce a dislocated hip. Symmetric abduction is also important during the evaluation. Any asymmetry of abduction on examination should be evaluated further. Asymmetric skinfolds have been shown to be a less reliable measure of hip dysplasia.

After 3 to 4 months of age, the hip is usually dislocated and no longer reducible. It may occasionally be reduced but is subluxable. The Barlow and Ortolani maneuvers will no longer be useful. Asymmetric abduction is the best indicator, as is leg-length inequality, or the Galeazzi sign, which is positive when both hips and both knees are flexed to 90 degrees and one knee is higher than the other, giving an apparent limb-length inequality. More accurately, the dislocated hip is more posterior in position, thus making it look like the leg is shorter. At walking age the most obvious findings are apparent leg-length inequality with pelvic obliquity and increased lumbar lordosis. The child will have a Trendelenburg gait from shortened (weak) abductors and hip flexion contracture. If the dislocation is bilateral, the child will have increased lumbar lordosis.

## Imaging

Ultrasound and plain radiographs are both useful tools for assessment of hip dysplasia, but their timing is different. Ultrasound is highly dependent on the technician performing the scan and the radiologist interpreting it. General screening of all newborns is not recommended in the United States. Ultrasound can assess the amount of subluxation by identifying the position of the cartilaginous femoral head, as well as evaluating acetabular development by measuring the alpha angle of the posterior wall in relation to the ilium (Fig. 129-1). It can also provide visualization of the labrum, capsule, iliopsoas, and femoral head ossific nucleus. An alpha angle greater than 60 degrees is considered normal.

Plain radiographs of the hip are not reliable before 3 to 4 months of age when the nucleus of the acetabulum is starting to ossify and becomes apparent radiographically. After this age, it is the standard means of diagnosis and the best way to monitor progression of a dysplastic hip.[23] An anteroposterior (AP) view and a “frog-leg” view are both required when ordering any hip radiographs on a child (referred to as “AP and frog pelvis”). Several important parameters should be measured on the AP film (Fig. 129-2). The Shenton line is the continuation of a semicircle drawn on the superior portion of the

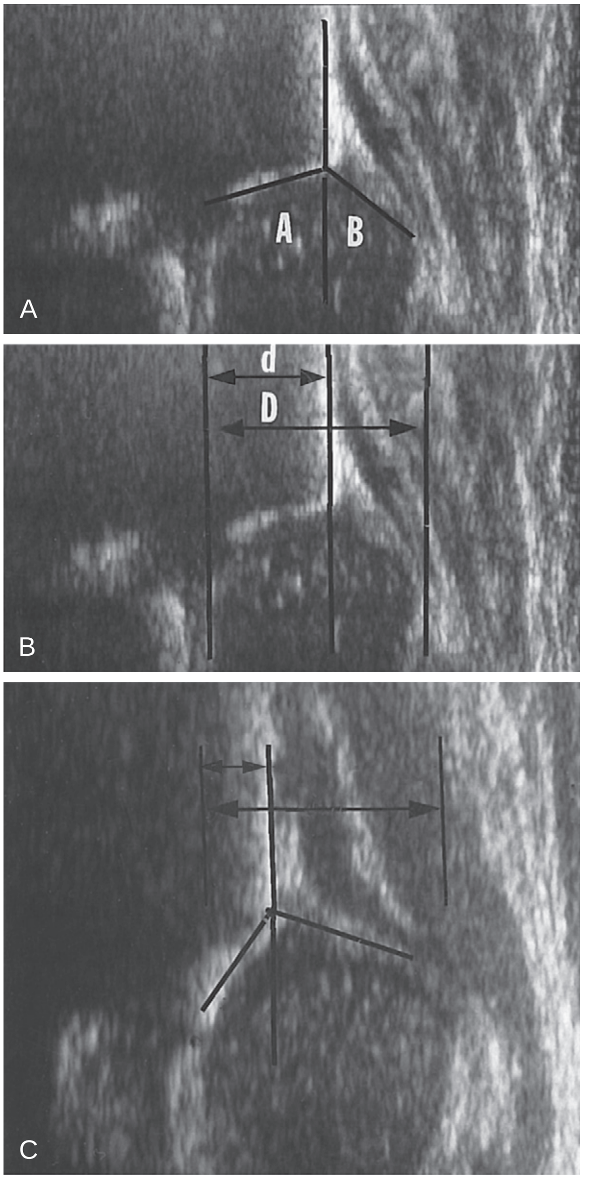


**FIGURE 129-1** **A,** Standard coronal plane ultrasonogram of a normal infant’s hip. The alpha angle *(A)* corresponds to the bony acetabular roof (normal, >60 degrees). The beta angle *(B)* represents the cartilaginous roof (normal, <50 degrees). **B,** Method for determining percent coverage of the femoral head: d/D × 100 (normal, ≥ 50%). **C,** Coronal plane ultrasonogram of a dysplastic hip. The alpha angle was 40 degrees; the femoral head was subluxated with only 25% coverage.

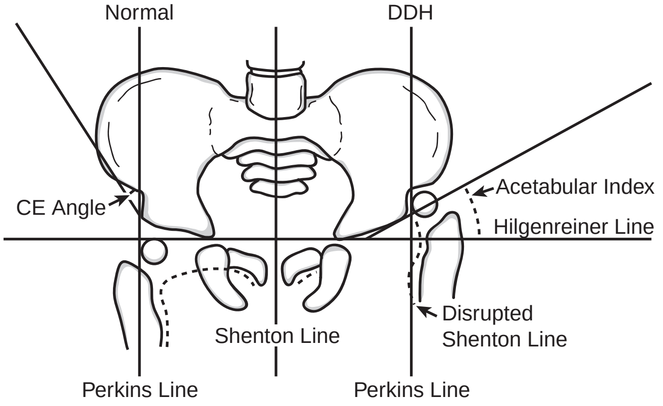


**FIGURE 129-2** Diagram of radiographic measurements. CE, center edge angle; DDH, developmental dysplasia of the hip.

obturator foramen and should be at the same level as the femoral neck. If the line is disrupted, the femur is too superior in the acetabulum. The Hilgenreiner line is a horizontal line drawn through the level of the triradiate cartilage on each side. A perpendicular line is then drawn at the lateral edge of the acetabulum and intersects the Hilgenreiner line to form four quadrants around the hip. The medial metaphyseal beak of the femur should be in the inferior/medial quadrant, or it is not in a reduced position. The acetabular index is the angle formed by the Hilgenreiner line and a line drawn from the triradiate cartilage to the lateral edge of the acetabulum. This angle should be less than 25 degrees by 1 year of age to indicate normal acetabular development. The higher the acetabular index is, the more dysplastic (more vertical) the acetabulum. This measurement has been shown to correlate with future hip osteoarthritis.

The most definitive way to assess a dysplastic hip is by injection of contrast material into the hip joint (hip arthrography); because this requires general anesthesia, it is usually performed at the time of operative reduction. Contrast outlines the cartilaginous femoral head and shows the exact relationship to the acetabulum. It can also show the position of the labrum and ligamentum teres and whether there is a pooling of dye in the medial joint space, which is indicative of laxity of the hip and a less than ideal reduction. Although ultrasound is helpful in assessing the position of the hip, arthrography can be performed if there is any question regarding stability and position of the hip. It is also extremely useful in assessing a closed reduction and in preoperative planning for any reconstructive surgery. Computed tomography (CT) is useful postoperatively to check the position of the hip in the cast after closed or open reduction with immediate casting. CTwith 3-D reconstructions can also be used preoperatively to assess the acetabulum. Magnetic resonance imaging (MRI) has had limited use in DDH, but recent studies show that it may be as useful as CT in postoperative assessment and without the radiation exposure.

## ANATOMY/PATHOANATOMY

Hip development starts with the femoral head and acetabulum being formed as a block of cartilaginous cells. At 7 to 8 weeks a cleft develops between the head and acetabulum and forms the joint. So the hip starts "reduced" in the socket, and other factors, previously discussed, contribute to the later instability.

The hip joint is completely developed by 11 weeks of gestation. The femoral head remains totally cartilaginous until 4 months of age, when the ossific nucleus starts to form bone. The hip is dependent on the femoral head and acetabulum, maintaining concentric reduction for continued normal development until growth ceases. A socket without a reduced femoral head will not form normally. If the hip stabilizes early, the joint will most likely remodel any dysplasia and form a normal joint. The longer the femoral head is not concentrically reduced, the less chance of the hip having normal anatomy at maturity. The acetabulum undergoes the most remodeling and development in the first year of life, but some remodeling continues until year 4 or 5, after which time there is minimal remodeling potential.

The anatomic structures involved in hip dysplasia (Table 129-1) contribute differently in each case. The adductor muscle becomes contracted. The iliopsoas muscle can be a major block to reduction of a completely dislocated hip. It becomes contracted and can exert a powerful obstacle to reduction by forming an hourglass-shaped constriction of the anterior medial capsule. The ligamentum teres connecting the fovea of the femoral head to deep inside the acetabulum can hypertrophy and pose a block to a good concentric reduction as well. The pulvinar is an accumulation of fat and fibrous tissue in the space next to the medial wall of the acetabulum, which can keep the femoral head lateralized during a reduction attempt. The labrum or cartilaginous rim of the acetabulum can become infolded and blunted and also block the femoral head. The anterior-medial joint capsule can become constricted. The transverse acetabular ligament spanning the inferior portion of the hip between the medial and posterior walls can also limit reduction inferiorly. All these problems may become more marked as the child gets older and pose more difficulty in achieving an adequate reduction.

## TREATMENT

There are two goals of treatment. The first is to reduce the hip and allow it to stabilize within the acetabulum. The second goal is to ensure remodeling of any acetabular dysplasia. If the first goal is met at a young age and concentric reduction is achieved, the acetabulum will be able to remodel with further growth. Because the remodeling potential of the acetabulum is greatest in the first year of life, it is important to begin treatment as soon as possible. Treatment protocols depend on the age of the child and the amount of dysplasia of the hip joint. Table 129-2 lists all possible methods to help achieve reduction and stability. Treatment is discussed as it relates to the age of the child. Some of the methods are useful only in certain age groups, whereas others span the entire age range.

**TABLE 129-1**

| Potential Blocks to Hip Reduction |
|---|
| Adductor tendon |
| Iliopsoas tendon |
| Medial capsule |
| Infolded labrum |
| Ligamentum teres |
| Pulvinar |
| Transverse acetabular ligament |

**TABLE 129-2**

**Available Treatments for Hip Dysplasia**

| |
|---|
| Pavlik harness |
| Closed reduction and casting |
| Open reduction and capsulorrhaphy |
| Femoral shortening osteotomy |
| Acetabular procedures |

## 0 to 6 Months

If a positive examination is recorded at birth (positive Barlow or Ortolani maneuver), immediate orthopedic referral is recommended. Evidence suggests that most hips will tighten up and stabilize within the first 2 weeks of life; therefore initiation of treatment before 2 weeks is controversial, and even how and when to screen is uncertain. Either way, close follow-up is mandatory. A Pavlik harness is the gold standard of treatment at this age and can often be used in children up to 6 months of age or less than 20 lb/9 kg (Fig. 129-3). When the hip is still dislocatable or reducible, the harness is the best choice. It is an active method of treatment that allows the baby to still have motion while encouraging the hip to remain in a position of stability. The harness maintains a hip flexion of 90 to 100 degrees (but should not be tightened any more than at 90 degrees to avoid hyperflexion) and abduction to keep the hip reduced in the most stable position. It is worn 24 hours a day, and correct placement and adjustments are crucial to help lower the incidence of complications. The harness can cause avascular necrosis (AVN; discussed later), which is thought to be due to hyperflexion of the hip or overtightening of the abduction straps. Once treatment is initiated, the harness should be checked 1 week later to ensure proper fit and use by the family. The length of treatment is generally twice as many weeks as the child's age at diagnosis, with some authors recommending a minimum of 3 months' treatment regardless of age at initiation of treatment. It can be weaned when the examination and imaging studies have normalized. It is effective in 90% or more children with Barlow-positive hips (reduced but dislocatable).[24–26] If the hip is Ortolani positive (dislocated but reducible), the harness may not be effective and should be discontinued after 3 weeks of treatment.

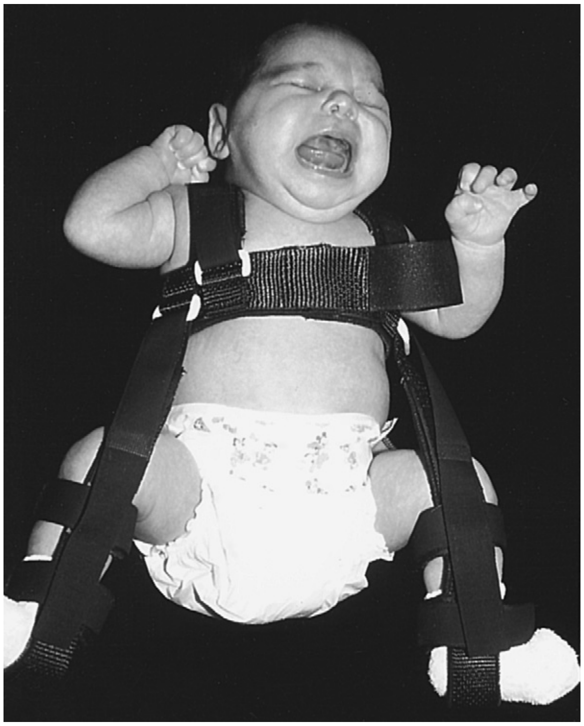

FIGURE 129-3 Infant being treated with a Pavlik harness. Hip flexion of approximately 100 degrees is maintained by anterior straps. Posterior straps (not seen) limit hip adduction.

Closed reduction may also be necessary in this age group if the hip will not easily reduce with gentle manipulation or does not respond to treatment in the Pavlik harness within 2 weeks. Arthrography is usually performed under general anesthesia, and the stability of the hip is checked. The child can then be placed in a hip spica cast if certain criteria are met during arthrography. The hip must be stable within the safe zone of 30 to 60 degrees of abduction and 90 degrees of hip flexion. If excessive abduction is required for stability, open reduction should be performed. The hip is at risk for AVN if extreme abduction is necessary to keep the hip reduced in the cast. There must also be only minimal (<3 to 5 mm) pooling of contrast in the medial aspect of the joint or the closed reduction will be less successful. Prereduction traction is controversial, with studies both supporting and refuting its use in reducing the incidence of AVN.[26–28]

After closed reduction, the child is placed in a hip spica cast in the human position for 6 to 8 weeks. A CT (or MRI) scan is usually checked postoperatively to ensure successful reduction. Another arthrogram is often obtained at the 6- to 8-week mark to assess progress of the hip. Casting may last 6 to 12 weeks, and then abduction bracing is used all day or nighttime only to encourage remodeling of the acetabulum. Some authors recommend some type of abduction bracing until radiographs have normalized.[29]

## 6 to 12 Months

As the child gets older, if the hip has not been reduced (Fig. 129-4), the compensatory changes become more severe and more invasive treatment is often necessary to overcome


FIGURE 129-4 Right hip dislocation. Left hip is normal.

the blocks to reduction. At this age a Pavlik harness is not indicated. Closed reduction is still the preferred method if a gentle, concentric, stable reduction can be obtained. If too aggressive abduction or pressure is necessary to keep the hip reduced easily in the cast, the chance of complications, mainly AVN, increases. At this point surgical open reduction should be considered. Some authors think that unless a closed reduction gives nearly perfect concentricity and is stable, care should proceed immediately to open reduction, which they believe is safer than a forced, incongruous closed reduction. This view may be changing somewhat as closed reduction is becoming more widely used. The goal of open reduction is the same as that of closed reduction, to achieve concentric stable reduction of the femoral head in the acetabulum. During open reduction, as many of the blocks to reduction as possible are corrected.

If the femoral head is superior to the acetabulum on radiographs and the soft tissue is significantly contracted, a femoral shortening osteotomy may be helpful to achieve a more stable reduction with less pressure on the femoral head. It helps decrease the possibility of AVN and improves the stability of the hip. If excessive coxa valga or femoral anteversion is present, the osteotomy can be readily modified to correct these deformities as well. The incision is made at the subtrochanteric level, and the bone is then fixed with a plate and screws to hold the alignment while bony union is achieved. Femoral shortening is almost always necessary in an older child of walking age.

### Walking Age, Older Than 12 Months

Once children have been bearing weight on the hip, adaptive changes occur and closed reduction becomes less successful. Closed reduction may be useful up to 18 months of age or more, but a larger percentage of these older hips will require open reduction and many will need femoral shortening osteotomy (Fig. 129-5).[30,31] The remodeling potential of the acetabulum decreases as the child gets older, and some children may need to undergo pelvic osteotomy to help gain coverage of the femoral head and provide a more stable reduction (see Fig. 129-5). A pelvic osteotomy can be performed in several ways, with most aimed at redirecting the socket to provide more anterior and lateral coverage of the femoral head. If more coverage is obtained and better congruency of the hip is achieved, there is more potential for the hip to form a more normal joint with time.[32,33] Evidence suggests that remodeling will occur until 2 years after surgery; then if it is not adequate, a secondary procedure may be necessary.

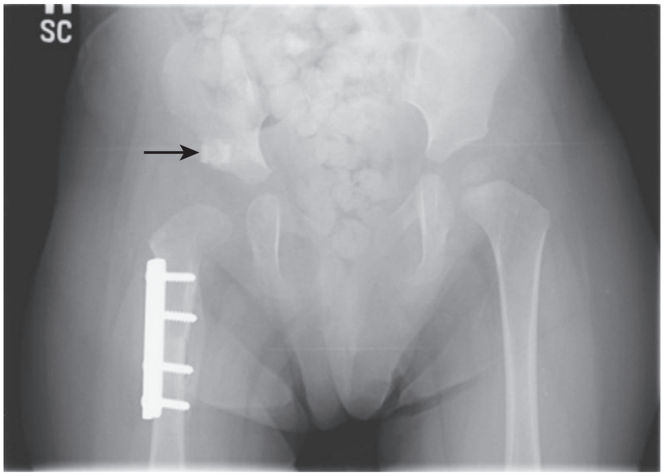


FIGURE 129-5 Femoral osteotomy fixed with plate and screws. Pelvic osteotomy *(arrow)*.

Some cases of hip dysplasia will go undetected until later in life. After 4 years of age, the risks of reducing a hip surgically increase. Some authors recommend attempting reduction up to the age of 8 years. If both hips are dislocated in older children, one must consider leaving them dislocated because they may do well for a long time before osteoarthritis develops. Other variations of DDH will be manifested in the early to late teens as hip pain, and acetabular dysplasia will be detected on radiographs. These hips are not dislocated, but the acetabulum is deficient in coverage of the femoral head and the femoral head may be subluxated to varying degrees. These children will benefit from redirectional acetabuloplasty of some type to provide a more congruous joint and better coverage. This is done in the hope of delaying further arthritic changes in the hip. Evidence supports the natural history of DDH in that any residual dysplasia of the joint will lead to osteoarthritis, which will eventually require total hip replacement. All treatment of DDH is directed at delaying this process for as long as possible.[29,32,33,34]

## COMPLICATIONS

### Avascular Necrosis

AVN of the femoral head can occur in up to 60% of treated hips if the long-term results are looked at critically. All forms of treatment put the blood supply at risk. The exact cause is unknown but is suspected to be a pressure phenomenon on the femoral head during closed reduction and injury to the medial circumflex vessels surgically. In younger children the cartilaginous femoral head is thought to be protective, and younger kids with AVN have a good chance of healing and doing well. AVN can cause growth arrest of the physis as well and give rise to shorter femoral necks or varus or valgus position of the neck at maturity. The final outcome, however, is unpredictable at any age.[34]

### Recurrent Dislocation

Some hips will not stabilize with conventional treatment whether it is the Pavlik harness or surgical intervention. Even after open reduction and bony procedures, the hip may again subluxate over time or even dislocate again. This will necessitate another surgical procedure, which increases the risk for AVN even more and also bodes for a poorer result in the long term.[34,35]

# Congenital Abnormalities of the Feet

## METATARSUS ADDUCTUS

### Terminology/Incidence/Etiology

Metatarsus adductus is a deformity in which an adducted forefoot gives the medial border of the foot a concave appearance and the lateral border looks convex (Fig. 129-6). The hindfoot is normal and has normal range of motion. It occurs in about 1 in 1000 births and has no gender predisposition.[36] The most

**FIGURE 129-6** Metatarsus adductus.

likely cause is intrauterine positioning. Although there was evidence of a positive association with hip dysplasia, this is no longer thought to be true.

### Diagnosis/imaging

The deformity is best identified with the child prone, and on examination the lateral border of the foot will deviate inward and look convex. Its severity is measured by a line called the *heel bisector,* which passes through the heel and is drawn out to the toes. Normally, this line bisects the second and third toe. In mild metatarsus adductus it bisects the third toe, and in severe forms it will bisect the fourth or fifth. The rest of the foot is normal. The hindfoot is normal, and there is normal ankle dorsiflexion. The abductor hallucis muscles may be overactive and pull the big toe into adduction as well (atavistic great toe). Radiographs may be obtained to assess the foot structurally but are not necessary unless there are other concerns.

### Treatment

The natural history is that most feet with metatarsus adductus will correct spontaneously if they are supple and correctable past neutral.[37] If the deformity is more severe and left untreated, it may cause problems with shoe wear later from a prominent base of the fifth metatarsal and medial deviation of the foot. It can also be a source of in-toeing in a child. Most deformities resolve without any treatment or with the parents manipulating the feet. If the deformity persists or the feet are stiff and not passively correctable, stretching casts may fix the deformity. If the problem persists past 5 years of age, consideration may be given to surgery. Correction at a young age by joint release may leave the foot stiff. In the past, metatarsal osteotomies were performed for correction and are still used at times. Waiting until after 5 years of age and then performing opening wedge cuneiform and closing wedge cuboid osteotomies is more reliable.[38–40]

## FLEXIBLE FLATFOOT

### Terminology/Incidence/Etiology

A flatfoot deformity occurs when the medial longitudinal arch is absent. This finding is common in younger children, especially when they first begin walking. Many of these children have ligamentous laxity that contributes to the arch being depressed because the ligaments that support the arch are also lax and unable to support the foot in the weight-bearing position. The posterior tibial tendon may be incompetent and contribute to the deformity.

### Diagnosis/Imaging

Diagnosis is by clinical examination. The medial arch is absent in the weight-bearing position and gives it the “flat-foot” appearance. The foot is flexible, and an arch will be reestablished when the foot is hanging free or the patient stands on tiptoes. As the patient goes up on toes, the heel will normally rotate into varus and the arch will become apparent. Radiographs will show a plantar-flexed talus that is not lined up with the first metatarsal on the lateral projection; however, radiographs are normally unnecessary unless other foot pathology is suspected.

### Treatment

No treatment is necessary if the foot is flexible. The parents need to be reassured that it does not need to be treated and an orthotic device will not help develop an arch—it will only support the arch. Many patients will tighten up over time as the ligamentous laxity improves and reestablish a medial arch as they get older. Arthroereisis or stabilization of the subtalar joint by an implant of some type (usually a Silastic or metal screw or staple) may be considered if the patient is symptomatic. An opening wedge osteotomy of the calcaneus or cuboid can be considered as well.[41–43] Fusion of the subtalar joint is reserved for patients with the most severe cases who continue to have pain despite other treatment options.

If the foot is not flexible and the arch does not reconstitute when the patient goes up on tiptoes (Root sign), it is considered a rigid flatfoot. This deformity may cause problems later in life, and surgery may be indicated in those with pain or significant deformity. Results are variable, and some patients may eventually undergo fusion of the subtalar joint for pain relief.

## CLUBFOOT

### Terminology/Incidence/Etiology

Clubfoot is a condition isolated to the foot and leg, in which the foot has varying degrees of the following deformities: metatarsus adductus, cavus, heel or hindfoot varus, and equinus (Fig. 129-7). Hence it is also called *talipes equinovarus.* It occurs in 1 in 1000 live births. The severity of the deformity is variable and ranges from a positional clubfoot that resolves with minimal stretching and casting to rigid deformities that are difficult to correct without surgery. The exact cause of clubfoot is unknown but multifactorial, and it is becoming more obvious that genetics plays a role.[44] Positioning problems can result from anything that decreases the in-utero space for the fetus (e.g., oligohydramnios, being the first baby, multiple births). Many of the rigid, resistant feet are associated with neuromuscular problems or syndromes such as spina bifida, diastrophic dysplasia, sacral agenesis, and arthrogryposis. Those that are not associated with one of these conditions are thought to result from a defect in formation. Classification was difficult, but recently methods by Dimeglio and Pirani have shown good correlation between the two systems.[45–49]

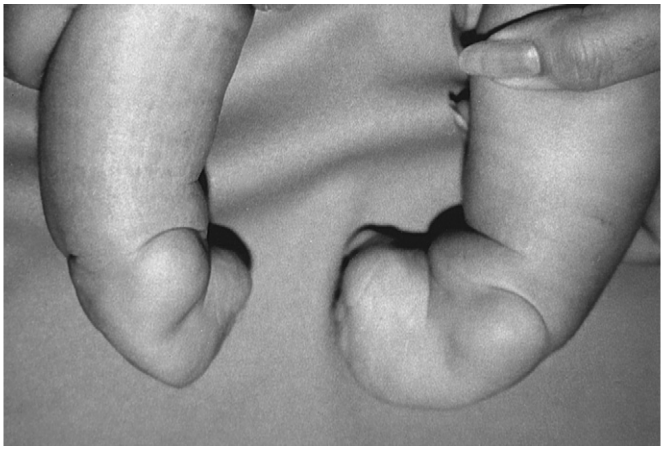

**FIGURE 129-7** An infant with bilateral clubfeet demonstrates the deformities that are part of clubfeet. The infant is prone, a position that reveals the varus deformity of the hindfeet. The crease in the arch shows that these feet have a cavus deformity. The feet are internally rotated and are in equinus.

### Diagnosis/Imaging

The diagnosis is usually apparent from the findings on physical examination discussed earlier. The forefoot is medially deviated as a result of the metatarsus adductus and supinated, which causes the forefoot to be almost touching the tibia. The calcaneus is rotated into varus and is high in the calf and not palpable in the heel pad. There is a medial crease of varying depth in the area of the medial arch. Finally, the Achilles tendon is tight, which causes the high-riding calcaneus. Occasionally, the diagnosis will be subtle if most of these deformities are mild, but such cases are rare. If the foot does not lack dorsiflexion and the heel is not in varus, it is probably not a true clubfoot.

Radiographs are not necessary at birth because most of the midtarsal bones are not yet ossified. Radiographs are helpful as the child gets older to monitor the progress of treatment.

### Anatomy/Pathoanatomy

The calcaneus and talus are normally divergent both in the axial and sagittal planes. In a clubfoot they are more parallel because of the varus deformity of the heel. This, along with the metatarsus adductus, is the major bony deformity. The first ray is also plantar-flexed, and the navicular is subluxated medially and dorsally on the talar head. The talus is often smaller and misshapen with a short neck. The soft tissue deformities consist of a severe contracture of the Achilles tendon, as well as contractures of the posterior tibial tendon, flexor hallucis longus, and flexor digitorum longus. Where these tendons cross in the medial aspect of the foot, they are occasionally confluent with abnormal slips of other tendons. These tendons are often entrapped in scar tissue and form what is called the *knot of Henry*. The plantar fascia is also tight.[50]

### Treatment

Treatment of a clubfoot usually requires some type of manipulation and casting and may require surgery. A technique of manipulation and casting advocated by Ponseti has been around for more than 40 years, but only in the past 10 to 12 years has it been gaining widespread popularity among pediatric orthopedists. There have been good short-term results, and now older patients are showing maintenance of the correction.[51–54] The process consists of the application of a series of four to five long leg casts with manipulation before each casting. The first step is to correct the plantar-flexed first ray and line it up with the other metatarsals in the foot. The next several casts bring the foot out of adduction and over into neutral alignment with the tibia and finally mild overcorrection into valgus. The last cast tries to improve the Achilles contracture by dorsiflexing the foot. Care should be taken to not dorsiflex the foot too quickly or before complete correction of the varus or a rocker-bottom foot deformity may be created. A tenotomy of the Achilles tendon is required in the majority of patients (>90%) to release the heel cord contracture, allow the calcaneus to come down into the heel pad, and permit the foot to dorsiflex. This can be done in the office under local anesthesia with or without sedation, and then a final long leg cast is applied with the foot slightly dorsiflexed and abducted 70 degrees. The cast is worn for 3 weeks, and then the patient goes into abduction bracing to keep the deformities from recurring. These shoes are worn until 4 years of age. Recurrence usually occurs after failure to fully correct the foot or inability to wear the abduction braces.

If supination persists or the heel cord contracture recurs, the patient may need to undergo posterior release with open heel cord lengthening and a transfer of all or half of the anterior tibialis tendon to the lateral side of the foot. This technique is usually successful in keeping the foot in a functional position. However, many centers favor manipulation for any deformity and any recurrence of deformity and avoid surgery if at all possible.

Correction can be achieved surgically, but overcorrection and undercorrection are both possible and over time recurrence or overcorrection of the foot may develop.[55–57] Many studies show deterioration of surgical results leading to arthritis and pain in the foot as the patient gets older.[58] The Ponseti method appears to produce a better foot clinically, both cosmetically and functionally.

In France, a technique developed by Dimeglio has produced good results. The feet are manipulated daily by the therapist and placed in a machine to give passive range of motion to the foot. It is labor intensive and has not been extremely practical in the United States. The Ponseti and Dimeglio techniques are considered to be the gold standards, with surgery having dropped out of favor.

## Congenital Dislocation of the Knee

Congenital knee dislocation covers a spectrum of deformity ranging from simple positional contractures that correct spontaneously to rigid dislocation of the knee joint requiring surgical intervention (Fig. 129-8). The problem often occurs in children with myelomeningocele, arthrogryposis, or other syndromes such as Larsen's. This deformity is frequently associated with DDH, clubfoot, and metatarsus adductus. It is extremely important to look for associated hip dysplasia when a knee dislocation is present. The deformity is recognized at birth in an infant with a knee that is hyperextended and a foot that is up by the infant's head because of a flexed hip. The pathology consists of one or all of the following: contracture of

**FIGURE 129-8** Congenital knee dislocation.

the quadriceps tendon, absent suprapatellar pouch, tight collateral ligaments, and anterior subluxation of the hamstring tendons.

If the problem has resulted from positioning in utero, the deformity is often mild and the knee is still fairly flexible. The knee will correct spontaneously within a few weeks or can be assisted by gentle range-of-motion exercises to accelerate correction. Serial casting may also be helpful, and if hip dysplasia is present, a Pavlik harness can be worn once knee range of motion increases enough to allow the harness to fit properly.

A more severe contracture or true dislocation will be apparent fairly early in the course of treatment because there will be minimal response to stretching and casting. It is usually evident within the first 3 months of treatment. If 30 degrees of knee flexion has not been gained by this time, surgery is indicated. Surgery may consist of one or more of the following procedures, depending on the severity of the condition. The first step is V-Y quadricepsplasty or Z-lengthening of the tendon, followed as needed by release of the anterior joint capsule, posterior transposition of the hamstring tendons, and mobilization of the collateral ligaments. Ninety degrees of knee flexion should be achieved, and then the knee is casted in 45 to 60 degrees of flexion for 3 to 4 weeks.

## Congenital Dislocation of the Patella

True congenital dislocation of the patella is rare. This entity must be distinguished from a recurrent dislocation that occurs later in life. In congenital dislocation of the patella, the patella is hypoplastic or absent and the femoral trochlea is often flattened. The lateral retinaculum is tight, and the patella is completely dislocated laterally. The patella is frequently adherent to the iliotibial band and is often irreducible over the condyle. Genu valgus is frequently present, as is a flexion contracture of the knee. Surgical intervention is required and involves extensive lateral retinacular release, often to the greater trochanter, medial plication, and either hamstring tenodesis or transfer of half of the patellar tendon.

## Congenital Deformities of the Spine

Congenital scoliosis is relatively uncommon. It is a malformation in vertebral column development, typically a failure of formation or a failure of segmentation.[59] Congenital implies that the deformity is present at birth. Even though the vertebral deformity is present at birth, the clinical deformity may not be recognized until years later, depending on the amount of growth imbalance that occurs. Isolated anomalies are usually sporadic, but multiple anomalies can be hereditary.[60] The true incidence is not known because some vertebral anomalies produce little deformity and go unrecognized.

Embryologic development of the spine occurs during the fourth to sixth weeks of gestation. By the sixth week the mesenchymal spinal anlage is complete. Defects in vertebral development occur at this time. They typically stem from failure of segmentation, failure of formation, or a mixed lesion. The resultant clinical deformity is determined by the type and location of vertebral deformity and the potential for asymmetric spinal growth.

Failure of segmentation most commonly occurs in the thoracic or thoracolumbar region. It can be unilateral or bilateral. Unilateral failure of segmentation, or a "bar," results in asymmetric growth of the spine (Fig. 129-9). It may not be evident on initial radiographs; however, there may be associated rib fusions that should raise suspicion. It is often rapidly progressive. The resultant deformity depends on the location of the bony tether. A lateral bar results in scoliosis, an anterior bar results in kyphosis, and a posterior bar results in lordosis. It can also occur in combination and result in kyphoscoliosis or lordoscoliosis. By far the most common is scoliosis, followed by kyphosis. Lordosis is quite rare. Bilateral involvement creates a block vertebra with minimal deformity.

Failure of formation can range from mild wedging to complete absence of half of the vertebra (hemivertebra) (Fig. 129-10). It can occur anywhere along the spinal axis. A hemivertebra is the most common. If present in the thoracic spine, there will be an associated extra rib. The extent of the clinical deformity depends on the location of the

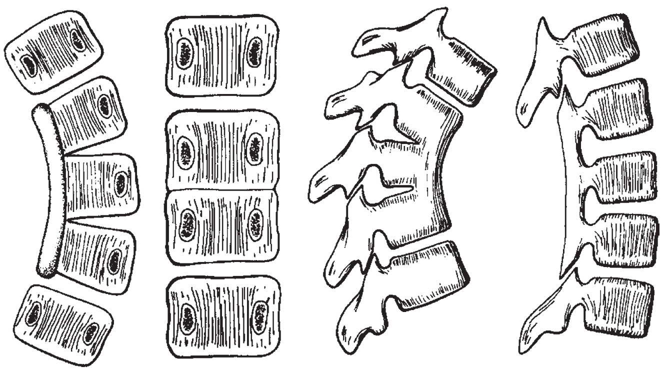


**FIGURE 129-9** Defects of segmentation. **A,** Unilateral unsegmented bar causing scoliosis, which is usually progressive. **B,** Block vertebra caused by bilateral failure of segmentation. **C,** Anterior segmentation defect causing kyphosis. **D,** Failure of segmentation posteriorly causing lordosis. (Modified with permission from Winter RB: Congenital Deformities of the Spine. New York, Thieme-Stratton, 1983.)

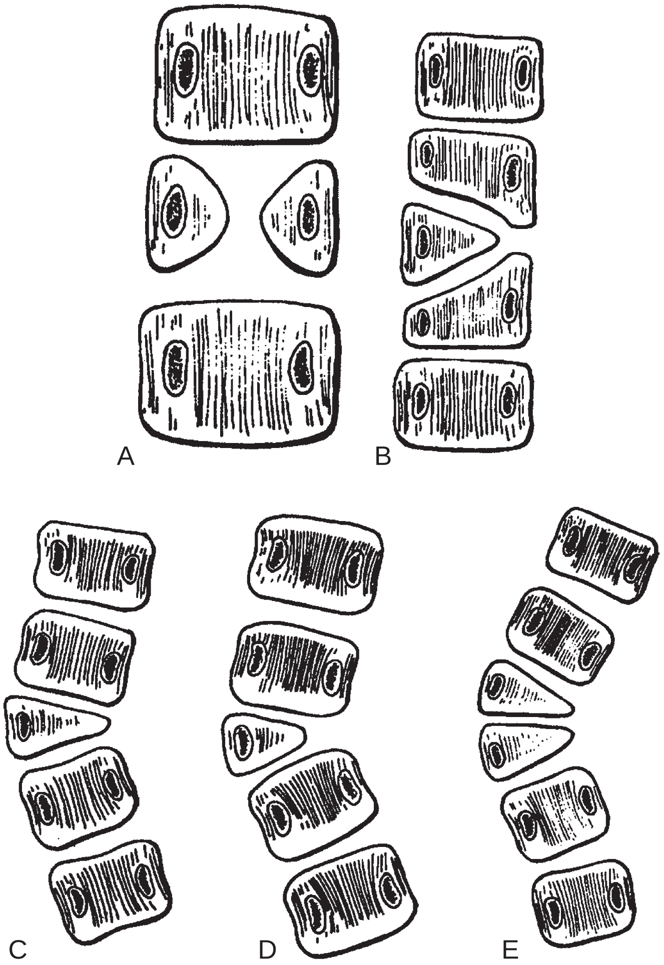


**FIGURE 129-10** Defects of formation. **A,** Anterior central defect ("butterfly vertebra"), usually nonprogressive. **B,** Incarcerated hemivertebra. Note the accommodation by adjacent vertebrae and minimal deformity. **C** to **E,** Wedge, free, and multiple hemivertebrae, respectively, demonstrating variation in the degree of vertebral wedging and increasing tendency for progression. (Modified with permission from Bradford DS, Hensinger RM: The Pediatric Spine. New York, Thieme, 1985.)

hemivertebra and on the potential for growth of the hemivertebra. A lateral hemivertebra will result in scoliosis, whereas a posterior hemivertebra will produce kyphosis.

The remaining deformities are either mixed or cannot be classified because of the extent of their pathology (Fig. 129-11). The amount of clinical deformity is variable, depending on the defect. The most progressive deformity, however, is a combination of a hemivertebra with a contralateral unsegmented bar.[61] Such deformities rapidly progress and will require intervention, usually at the time of diagnosis.

The neural axis forms in conjunction with the bony canal, and the frequency of intraspinal anomalies has been reported to be as high as 40%.[62,63] Abnormality of the overlying skin such as a dimple, lipoma, hairy patch, or nevus may be present 70% of the time. Diastematomyelia is believed to be the most common associated defect.[64] It is a sagittal split in the spinal cord or cauda equina by an osseous or fibrocartilaginous spur protruding posteriorly from the vertebral body. It should be removed if symptomatic or before any corrective spinal surgery. Other intraspinal anomalies include tethered cord, syringomyelia, epidermoid cyst, lipoma, and teratoma.

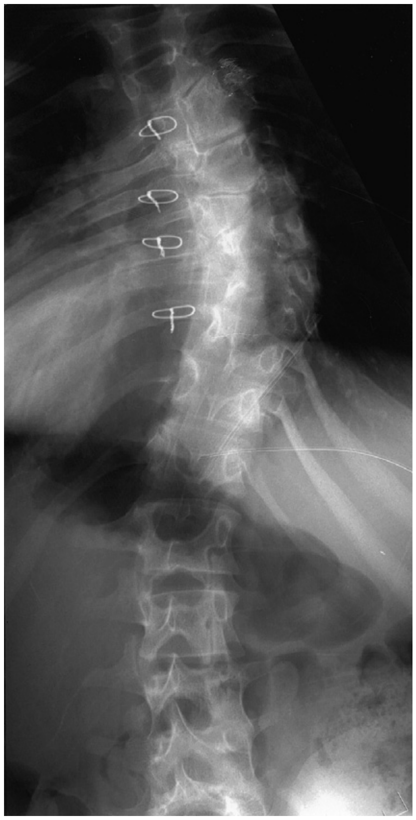

**FIGURE 129-11** Multiple anomalies with combined failure of formation and failure of segmentation. Note the fused ribs in a concavity suggestive of a "bar."

A thorough neurologic examination must be performed, and any clinical suspicion of neurologic abnormality requires imaging with MRI.

Associated anomalies occur in other systems up to 60% of the time[65] including genitourinary, 25%; Klippel-Feil syndrome (cervical spine fusions), 25%; and cardiac, 10%. Abnormalities of the gastrointestinal system can also be seen, as well as esophageal atresia and imperforate anus in connection with the VATER association (in addition to vertebral defects and radial and renal dysplasia).[66] Other musculoskeletal deformities such as Sprengel deformity (congenital elevated scapula), pectus abnormalities, and appendicular skeletal deficiencies are less common. All patients should undergo renal ultrasound screening to exclude underlying abnormalities because the genitourinary system is difficult to assess by physical examination alone.

An infant with congenital scoliosis may or may not have a spinal deformity at birth. If a deformity is present, it is typically a lateral deviation of the spine. It can be confused with congenital muscular torticollis (see Chapter 60) or infantile idiopathic scoliosis (thoracic spinal curvature). Both these conditions can cause clinical deformity at birth, but radiographs will fail to show vertebral anomalies. Most often, vertebral anomalies are incidental findings during the workup for other conditions (Fig. 129-12), and initial detection can occur at any age. The diagnosis is made with radiographs, but MRI or CT may be necessary to better delineate the pathology.

There is little nonoperative treatment to offer other than observation. Unlike other types of scoliosis that may respond to bracing, it is not routinely indicated for congenital scoliosis.

FIGURE 129-12 Incidental finding on a kidney-ureter-bladder radiographic workup for imperforate anus. Note the S1 hemivertebra.

The ideal therapeutic modality is surgical stabilization before spinal deterioration.

The surgical treatment of congenital scoliosis depends on the type of deformity present, the location of the deformity, and the amount of growth remaining. The goal of treatment is to halt progression and achieve spinal balance at maturity. The most rapid vertebral growth occurs up to the age of 2 years and again during adolescence. Thus clinical deformities can change rapidly during these times and require close monitoring. Surgical complications are increased in this population. This type of scoliosis carries the highest risk for neurologic complications with attempts at intraoperative correction. Ideally, patients who have deformities with a high probability of progression should undergo stabilization when their curves are small.[67] Other patients with a lower probability or an unknown probability of progression are managed by close follow-up with serial radiographs. Surgical intervention is delayed as long as the curve is not progressing and the spine remains in balance. Overall, 50% of curves will be stable, 25% will progress slowly, and 25% will have rapid progression.

Surgery is the definitive treatment of congenital scoliosis. It is indicated for rapidly progressive curves, deformities with a high propensity to progress, and deformities that cause spinal imbalance. Numerous surgical techniques are available, depending on the type and location of the deformity. Attempts at correction carry a high risk of neurologic impairment. Fusion in situ is considered the "gold standard"[68] and is indicated for curves that are progressive or prone to progress but still within a range where spinal balance can be maintained. In younger children, anterior and posterior fusion must be performed to balance the remaining growth. Posterior fusion alone is adequate for older children with little remaining spinal growth. Hemiepiphysiodesis is a variation of fusion in situ. It involves fusion of only the convex side of the curve, thus permitting the concave side to continue unopposed growth and allow correction to occur. Because the correction is gradual, the risk for neurologic impairment is decreased. Hemivertebra excision is typically reserved for deformities in the lumbar spine where spinal imbalance is more pronounced and the cauda equina is safer to retract (Fig. 129-13). Excision has been performed in the thoracic and thoracolumbar spine less often, but with favorable results.[69] An anterior and posterior approach is usually necessary. Spinal osteotomy or vertebrectomy is reserved for the most severe curves with imbalance that are not amenable to other more standard techniques. It carries the highest risk for neurologic injury because of the acute correction and is considered a "salvage" procedure by most.

Anterior approaches to the spine require the traditional thoracotomy or thoracoabdominal approaches. Postoperative morbidity can be significant in this population because of other coexisting abnormalities, and pulmonary function may be further diminished after these approaches. Video-assisted thoracoscopic surgery can be useful in some instances.[70] Visualization of the spine is adequate, and the instrumentation continues to improve to allow for more complete diskectomy and anterior fusion. Postoperative pulmonary morbidity should be lessened.

Congenital kyphosis is a variant of congenital scoliosis and usually occurs secondary to failure of formation of the anterior

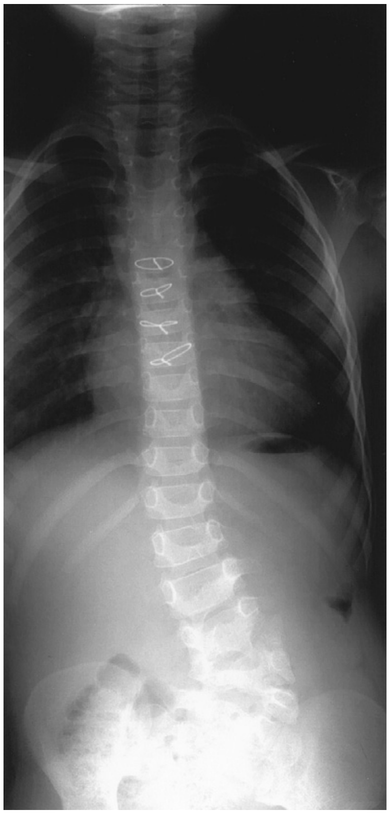

FIGURE 129-13 Left L5 hemivertebra causing spinal imbalance. This is the ideal location for hemivertebra excision.

**FIGURE 129-14** Posterior hemivertebra with anterior failure of formation resulting in kyphosis.

body (Fig. 129-14).[71] It can also result from failure of segmentation with an anterior or, more commonly, an anterolateral bar. This type of deformity has a poor prognosis for progression and neurologic involvement. If unrecognized, it can result in paraplegia. Congenital kyphosis requires surgical stabilization at the time of diagnosis to prevent further deterioration. Bracing is of no value. Because of the variability in deformity, no single surgical approach can be applied to all. Typically, if the patient is younger than 5 years and the kyphosis is less than 50 degrees, posterior fusion will suffice. If older than 5 years or more severe kyphosis exists, anterior and posterior fusion is required.[72]

Sacral agenesis, or complete or partial absence of the sacrum, is another type of congenital spinal anomaly. It has been associated with maternal insulin-dependent diabetes,[73] although this relationship has more recently been questioned.[74] It is often associated with gastrointestinal and genitourinary abnormalities. Neurologic involvement is variable and often results in hip, knee, and foot deformities. The prognosis and treatment depend on the degree of malformation, the stability of the spine, the level of neurologic involvement, and any other associated anomalies. Typically, only patients with stability of the spinal attachment to the pelvis are able to ambulate.[75] They may require surgical procedures to correct their lower extremity deformities. Most others with spinal instability at the spinal-pelvic junction will not ambulate functionally and require treatments aimed at improved sitting balance and positioning.

*The complete reference list is available online at www.expertconsult.com.*

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CHAPTER 130

# Congenital Defects of the Skin and Hands

Edward P. Miranda

The sequence of cellular proliferation, differentiation, and regression that is characteristic of human embryogenesis and subsequent development is complex and possesses little tolerance for error. Errors and injury during gestation do occur quite often as evidenced by spontaneous abortion rates of up to 26.9% when implantation is detected by measurement of human chorionic gonadotropin (HCG).[1] The "failure" of these gestations can also be viewed as "success" because embryos with errors incompatible with life (e.g., major chromosomal abnormalities) are culled out. This selection for major errors is not precise because many gestations continue with sublethal abnormalities.

## General Incidence and Risk

A major malformation has been defined as a structural anomaly with medical and social consequences. The incidence of major malformations has been estimated to be 2% to 3% of live births.[2–5] Minor malformations have been defined as structural alterations that pose no significant medical or social burden. At least one malformation is identifiable in about 15% of newborns. The distinction between major and minor is arbitrary because all human deformities exist on a continuum. However, even the most minor physical aberration can predispose the afflicted person to psychosocial isolation, justifying surgical therapy.

## SKIN AND SOFT TISSUES

### Embryology

The developmental origins of the skin, muscle, connective tissue, and tendons commence during the third week of embryonic life. During this period, a primitive streak appears and facilitates the formation of the trilaminar embryo (ectoderm, mesoderm, and endoderm), notochord, and somites.

### Development of the Epidermis

The skin is the largest organ in the body and is composed of two layers: the dermis and the epidermis. It serves a variety of functions beyond simply providing an interface between the body and the environment. The skin provides temperature regulation, sensory perception, and a barrier against water loss and microbial invasion and is a major neurally regulated immune organ.[6,7] The cutaneous system is also a medium for nonverbal communication, and the appearance of the skin contributes to interpersonal recognition and one's sense of self.

The epidermis originates from a monolayer of ectodermal cells forming the periderm at about 4 weeks of gestation. The early epidermis is a monolayer exposed to the amniotic fluid, with which it participates in significant salt and water exchange. By the third month the epidermis becomes three cell layers thick (basal, intermediate, and superficial layers). The epidermis continues to thicken, and by the sixth month differentiation has progressed far enough to achieve effective barrier function. Upon microscopy the skin is similar to newborn epidermis with several observable layers: the strata basale (inner layer), spinosum, granulosum, and corneum (outer layer). The stratum basale retains the keratinocyte stem cells that will repopulate the other layers over the lifetime of an individual. Keratinocytes over their lifetime progress from the stratum basale to ultimate sloughing from the stratum corneum. This migration is characterized by progressive differentiation and accumulation of keratin granules (in the stratum granulosum) and the intermediate filament filaggrin in the stratum corneum to maintain an effective barrier to the environment.

Several other cell types migrate into the epidermis to assist in its function. Melanocytes are neural crest–derived cells that first migrate into the dermis and then into the epidermis. These cells produce melanin pigment for defense against ultraviolet photoinjury. At approximately 3 months of gestation, Langerhans cells (LCs) are found in the epidermis. LCs are bone marrow derived, professional antigen-presenting cells that arrange themselves in the epidermis to form an immunologic net to detect and present foreign antigen to T cells.

### Development of the Dermis and Other Mesodermal Tissues

During the third week of embryogenesis a primitive knot appears at the cranial end of the primitive streak. Mesenchymal cells migrate cranially from the knot forming a midline cellular

cord known as the *notochordal process*. The process grows until it reaches the oropharyngeal membrane; at this point it can extend no farther because of the densely adherent ectoderm and endoderm. The notochord gives rise to the vertebral column and induces the overlying ectoderm to form the neural plate, the primordium of the nervous system.

As the notochord forms, the intraembryonic mesoderm thickens on each side of the notochord to form paired longitudinal columns of paraxial mesoderm. At the end of the third week, columns of paraxial mesoderm divide into paired cuboidal bodies called *somites*. Eventually, 42 to 44 pairs of somites develop in a craniocaudal sequence. Somites are the segmental precursors to most of the axial skeleton, musculature, and its associated dermis of the skin.

The emergence of mesenchyme at 3 weeks of embryonic life is essential to organogenesis. By 8 weeks of life, the face and hands are recognizably human. At 12 weeks of life, the palate has formed and the sex can be determined by visual inspection of the external genitalia. Interruptions in the development and differentiation of mesodermal events (mesenchymal migrations, notochord, somites) accurately reflect the wider diversity of congenital malformations found in the skin, connective tissues, muscles, and tendons. With such an expansive array of deformities, systematic analysis and anatomic regionalization of the defect are necessary to formulate an effective treatment plan.

## Analysis of Defects and Technical Aspects of Treatment

The structural aspect of any defect can be subdivided into malposition of otherwise normal structures, regional absence of normal tissue, and aberrations of tissue composition.

### MALPOSITIONING OF OTHERWISE NORMAL STRUCTURES

Congenital malpositioning of normal structures can occur from persistence of embryonic lines of fusion, displacement of anatomic landmarks from abnormal growth of adjacent tissues, or developmental malrotation. Visceral malpositioning may be entirely inconsequential to the affected individual. Dextrocardia with situs inversus is an incidental finding in asymptomatic patients. More commonly, malpositioning has more deleterious effects. The magnitude of the mishap depends on the cascade of events resulting from the derailment of normal development. Spina bifida and facial clefts are examples of defects resulting in severe functional and social consequences.[8–11]

### REGIONAL ABSENCE OF NORMAL TISSUE

Structural anomalies resulting from a deficiency or absence of tissue have taxed the ingenuity of plastic surgeons. Traditionally, alloplastic or autologous materials have been used in the reconstruction of congenital defects that are caused by deficient or absent tissues. Benefits of reconstruction with alloplastic materials include unlimited supply, no donor defect, and ease of use. However, reconstruction with autologous tissues is generally superior for congenital malformations because such tissues can fully integrate with living structures, maintain the potential for growth and wound healing, and resist infection after healing. Nevertheless, alloplastic surgical implants, judiciously placed during adolescence, remain an excellent reconstructive standard in special clinical circumstances such as congenital hypoplastic breast deformity.

A wide spectrum of surgical procedures has evolved to optimize the use of autologous tissues. Use of nonvascularized tissue grafts is a simple and effective way to replace skin, muscle, connective tissue, and tendons. This technique is justifiable only when the gain at the recipient site will compensate for the loss sustained at the donor site. Furthermore, a well-vascularized recipient bed is necessary to nourish the graft until neovascularization occurs. When the bed is not suitable for a graft or when specialized tissue is desired for the reconstruction, then en bloc (composite) flap transfer of specialized tissue with its own intrinsic vascular supply should be used. The method of tissue transfer depends on the proximity of the donor and recipient sites. Free microvascular flap transfer is an elegant method of moving tissue when the distance from donor to recipient site is too great for local rearrangement.

More recently, off-the-shelf biologic or combined biologic-synthetic materials have been used to reconstruct congenital and acquired defects of normal tissue. Recent improvements in acellular dermal matrices (ADMs) (e.g., Alloderm or Strattice) and bilayered dermal regeneration templates (combining an outer silicone film to recreate barrier function and a deeper synthetic layer of cross-linked collagen and cartilage, analogous to a synthetic extracellular matrix [ECM]) have bridged the divide between pure autologous tissue and alloplast-only reconstructions. ADMs have been used for reconstructions of the abdominal wall, diaphragmatic hernia, and other defects.[12,13] Postimplantation histologic analyses reveal that ADMs are incorporated by the body and used as a scaffold for the production of new fascia-like tissue with revascularization and ingrowth of fibroblasts.[14]

Bilayered dermal regeneration templates have been used as an intermediate step for reconstruction of full-thickness cutaneous defects followed by thin split-thickness skin grafting including those with limited exposure of tissues that have traditionally fared poorly with skin grafts alone (e.g., bone and tendon). These constructs limit the inflammatory response, decrease scar contracture, and allow for the formation of a neo-dermis via vascular and fibroblast ingrowth without the need for potentially morbid flap harvest (Fig. 130-1).[15]

Tissue expansion is an excellent way to create composite soft tissue for use with fewer donor-site demands. Hair-bearing replacement of deficient scalp in conditions such as aplasia cutis (see later) best illustrates the potential dividends gained from tissue expansion. Distraction osteogenesis is the analogous procedure for bone. The use of this powerful technique for bone lengthening, first described by Ilizarov for the lengthening of long bones, is now being used in the facial skeleton. Gradual facial-bone lengthening without donor deformity has been effective in treating mandibular hypoplasia, which is found in disorders such as hemifacial microsomia.

### ABERRATIONS OF TISSUE COMPOSITION

An imbalance in the relative cellular composition of a tissue may lead to significant malformation without a deficiency in tissue mass. Skin lesions such as congenital giant hairy nevus (see later) and port wine stains are anomalies that express an

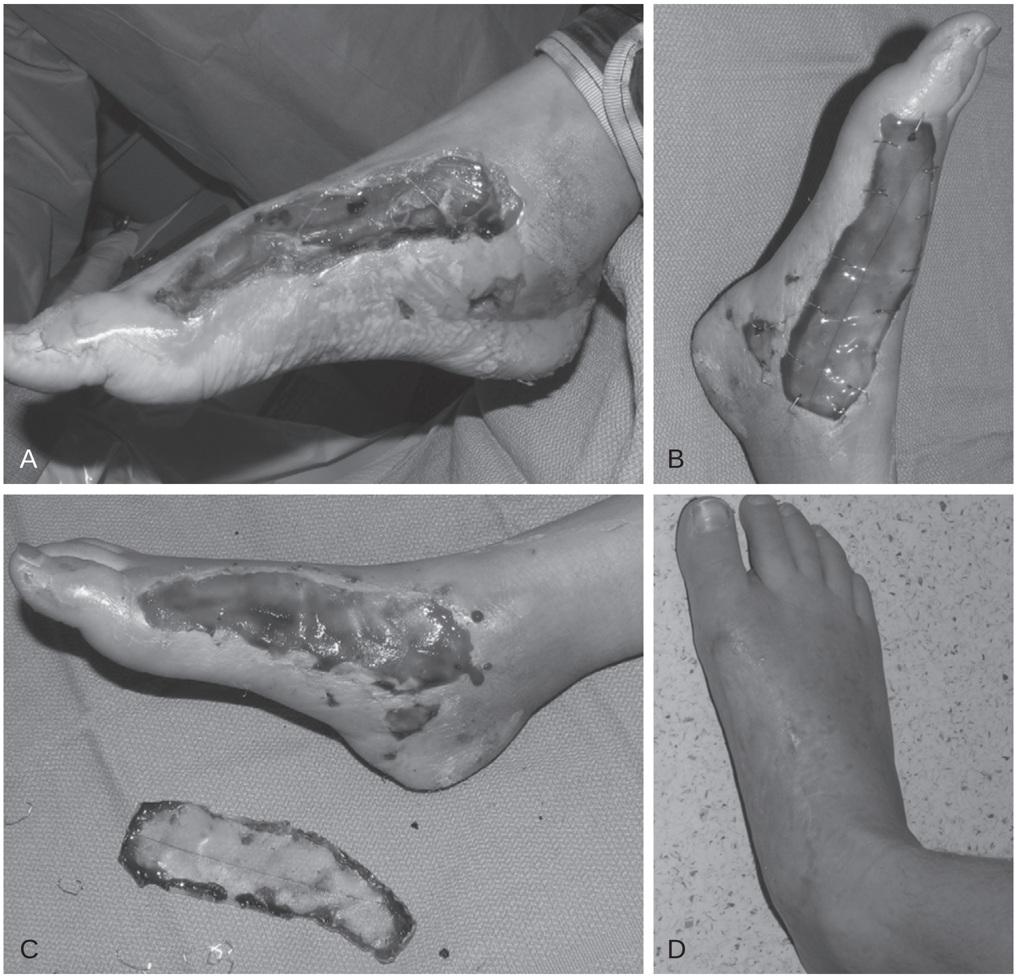



**FIGURE 130-1** Bilayered dermal regeneration matrix (Integra) for reconstruction of soft tissue defects. **A,** Preoperative appearance of a soft tissue defect in a 7-year-old girl with small amounts of exposed bone and tendon visible. **B,** Postoperative (2 weeks) after placement of bilayered dermal regeneration matrix (Integra). **C,** Postoperative (2 weeks) after removal of the silicone outer layer; note the vascularity of the neodermis. The tissue is ready for grafting. **D,** Postoperative appearance after skin grafting over the neodermis. An additional 2-mm dermis is present with decreased contracture and increased suppleness compared with traditional skin grafting. (Courtesy Edward P Miranda.)

excess of a specific cell or tissue type. In congenital giant hairy nevus, the melanocyte-related nevus cell has excessively proliferated in the dermis. After birth, these cells have an increased risk of degenerating into melanomas, leading to the rationale for surgical ablation.[16] Cutaneous capillary vascular malformations (port wine stains) result from an excessive developmental accumulation of abnormal microvascular tissue in the dermis. These lesions are not mitotically active and have no neoplastic potential. However, they are disfiguring and socially disturbing. Direct excision is generally undesirable due to subsequent scarring and deformity. Selective ablation of vascular tissue with laser light is an effective method for treating this disorder.[17]

Many localized congenital malformations are inconsequential and can be considered normal variants. For example, the congenital absence of the palmaris longus tendon has a prevalence of 15% to 20%.[18] Such anomalies require no treatment. However, when function or body image is threatened, a careful analysis of the magnitude of malpositioning of normal structure, degree of tissue deficiency, and composition of the aberrant tissue is essential in planning the reconstruction. Judicious timing of the operation can often interrupt a cascade of predictable secondary deformities.

# Specific Anatomic Regions

## SKIN

### Aplasia Cutis Congenita

Aplasia cutis congenita (ACC) is a rare congenital disorder characterized by full-thickness absence of the skin and underlying tissues over a section of the body. The scalp is involved in approximately 80% to 90% of cases with occasional loss of all cranial tissues including calvarium and dura (15% to 30%). The true incidence is unknown, and approximately 500 cases have been reported in the medical literature. The diagnosis of ACC is clinical and is generally discovered at birth, although diagnosis by prenatal ultrasound has been reported. The lesion generally presents as a thin, transparent membrane or as a dried cicatrix in place of normal skin; no hair follicles are present. The vertex of the scalp is the most common area involved. For small defects, the natural history is that of epithelialization from the lateral edges, but larger defects may not close and generally warrant treatment. The mortality for extensive scalp defects may be as high as 20% to 50%.[19]

The etiology of ACC is not well established. It has been reported to be associated with other defects including limb deformities, omphalocele, and clefts. Surgical treatment is generally indicated immediately for the larger defects and ones in which there is a bony defect. Bony involvement at the vertex of the scalp places the patient at risk for hemorrhage from the sagittal sinus and also mandates operative treatment. The defect is generally repaired with flaps and/or skin grafts. Recently ADM has been used for regeneration/reconstruction of the tissue defect.[20] Bony skull reconstruction is generally delayed until 2 years of age; occasionally the osteogenic dura may spontaneously generate new bone replacing the defect.[19] Reconstruction of a normal hair pattern is accomplished via tissue expansion of the scalp and subsequent coverage of the affected area with local flaps at about 5 to 7 years of age.[21]

### Congenital Melanocytic Nevus and Giant Hairy Nevus

Congenital nevi are composed of large clusters of pigment producing cells of melanocyte lineage that are clustered in the dermis and produce pigment at birth. When compared with the more common acquired nevi, congenital nevi are larger, have increased cellularity, and lie deeper in the dermis. The incidence of congenital nevi has been estimated to be 1 in 100 births for small lesions and 1 in 20,000 for large lesions. After birth it is difficult to distinguish congenital from acquired nevi even by histology. Congenital melanocytic nevi are classified according to size: small, less than 1.5 cm in diameter; medium, 1.5 to 19.9 cm; and large (giant), greater than 20 cm.[22,23]

The potential for congenital nevi to transform into melanoma is the prime reason that these lesions come to surgical attention. However, considerable uncertainty surrounds estimation of the true risk for malignant degeneration. Rates of 1% to 31% have been reported for giant congenital nevi (GCN), although these data may be even less reliable than the range suggests because the total number of patients with GCN is unknown. A metareview calculates an overall melanoma risk of 8.2% in GCN, which is high enough to make surgical ablation a priority. The risk for malignant melanoma is also immediate; 60% of observed GCN-related melanomas occurred in the first decade of life, with several studies suggesting that many malignancies occur by 3 years of age. Melanoma has also been reported in small congenital nevi, and melanoma rates of 2.6% to 4.9% have been estimated.[24]

Giant hairy nevi (GHN) are a special subset of congenital nevi. These melanocytic cutaneous lesions are extensive and encompass entire anatomic regions that may exceed 20% of the body surface area (Fig. 130-2). These nevi are often hairy with benign surface nodularity consisting of focal growths of neuroectodermal tissue.[25] When the head or upper part of the trunk is involved, neurologic abnormalities have been observed in up to 20% of patients. Neurologic findings of leptomeningeal melanosis, hydrocephalus, seizures, and myelopathy in association with GHN are consistent with the developmental origin of the neuroectoderm.[25]

GHN are disfiguring and easily identifiable at birth.[26] Parents of patients with GHN often seek treatment early. Some neonates with GHN have been found to have malignant melanoma shortly after birth, thus justifying early surgical ablation. Serial resection of GHN lesions with the use of subcutaneous tissue expanders is indicated to improve aesthetic appearance and diminish the risk for malignancy.[27] The increased compliance and elasticity of infant skin provide the first opportunity to debulk a large portion of the giant nevus in the first 6 months of life.[28] At this time areas of nodularity or increased pigment are resected. The timing of subsequent resections is based on changes in appearance of the nevus and the parents' decision to proceed with complete resection. Repeated excisions may expedite lesion removal with completion in early childhood. Complete excision of the nevus with skin grafts results in scar and contracture deformities both at the site of nevus resection and the skin graft donor site. The use of sequential excision with expansion of normal adjacent skin allows coverage of areas of nevus excision with normal skin and does not cause additional scarring.

### Nevus Sebaceous of Jadassohn

Sebaceous nevus (SN) is a solitary, well-circumscribed, alopecic plaque of epidermal origin. SN is commonly found on the scalp, temple, or preauricular region and is sometimes diagnosed at birth. Histologic analysis in children reveals epidermal hyperplasia and hypoplastic hair follicles and sebaceous glands. At puberty the sebaceous glands mature, and progression of the epithelial hyperplasia occurs. Progression to basal cell carcinoma (BCC) has been reported in up to 6% to 22% of adults.[29]

Controversy exists in the management of SN in children. Early reports of BCC formation in 10% to 15% of adolescents have been refuted by large retrospective studies that have shown a low incidence of benign epithelioid lesions and very low (0% to 0.8%) incidence of BCC in excised lesions from children up to 16 to 18 years of age.[29,30] However, there is still a well-documented incidence of NS-related BCC in adults. The management of choice remains excision, but delay until later in adolescence is reasonable.[29]

### Congenital Webs

Congenital webs (pterygia) are most commonly found in the neck (pterygium colli). In the neck, thick folds of skin and subcutaneous tissue extend from the mastoid process laterally to the acromion. The lesions are generally bilateral and can distort local structures including the posterior hairline, the border of which is often displaced laterally on the neck, causing a short-neck appearance. Webs have been identified similarly in the axillary folds and crural regions.

Congenital webbing may occur in isolation or in conjunction with other congenital deformities, however the etiology is unknown. Certain regional deformities such as Klippel-Feil syndrome can display this developmental lesion. Neck webbing is often a manifestation of Turner's syndrome. The webs can cause functional and/or aesthetic disabilities. Correction is by lengthening with multiple Z-plasties generally between ages 1 and 6 years.[31]

## CONGENITAL DEFORMITIES OF THE BREASTS

### Embryology

The breast develops in the fetus from ectodermal tissue during the fifth week of gestation. Bilateral *mammary ridges* extend from the axillae to the groins. During the seventh to eighth week of gestation, the mammary ridges undergo involution

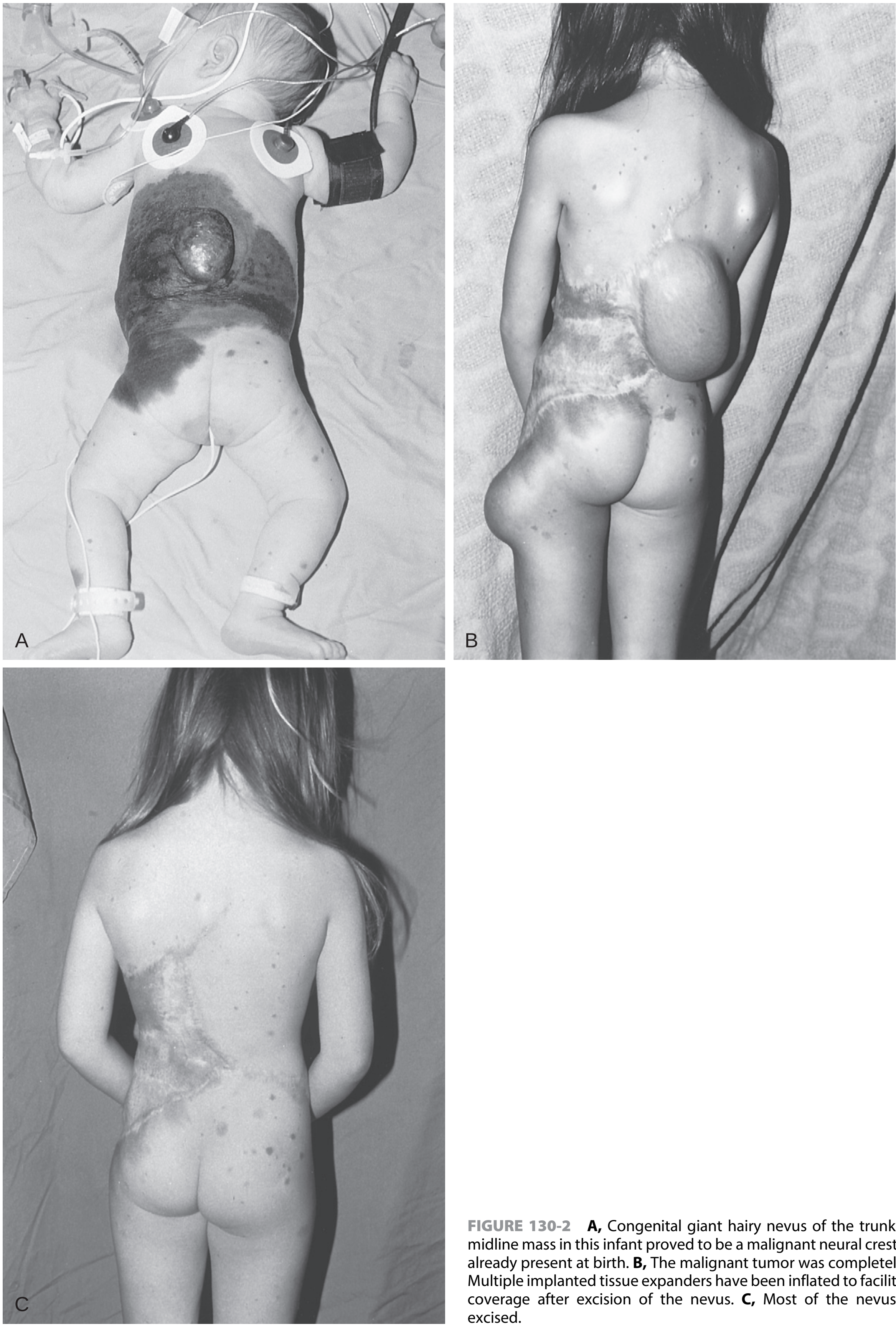



**FIGURE 130-2** **A,** Congenital giant hairy nevus of the trunk. The large midline mass in this infant proved to be a malignant neural crest cell tumor already present at birth. **B,** The malignant tumor was completely resected. Multiple implanted tissue expanders have been inflated to facilitate wound coverage after excision of the nevus. **C,** Most of the nevus has been excised.

in all areas except on the anterior thoracic wall and axillae. After 10 to 14 weeks of gestation, the primordial breast tissue penetrates the thoracic mesenchymal tissue and begins to form glands. The mesenchyme envelops the breast and forms layers in continuity with Camper fascia (outermost layer) and a second layer separating the breast from the underlying thoracic musculature. Camper fascia surrounds the anterior breast in all areas except just deep to the areola. A network of connective tissue runs through the mammary gland forming Cooper ligaments, which suspend the breast. Milk ducts begin to form at about 20 weeks of gestation, and the glandular tissue continues to develop until the end of puberty.[32,33]

### Polythelia and Polymastia

Supernumerary nipples *(polythelia)* and supernumerary breasts *(polymastia)* are relatively common congenital abnormalities with an incidence of approximately 0.2% to 2.5% (polythelia) and 0.1% to 1.0% (polymastia) (see also Chapter 61). Both of these deformities are observed to form along the milk lines that track from the axillae to the groins. Both supernumerary nipples and breasts form from a failure of normal apoptotic regression of the mammary ridges during gestation. Diagnosis of supernumerary nipples can often be made at birth. The most common site for polythelia is just inferior to a normal breast; the most common site for an accessory breast is in the axilla.[33]

Supernumerary nipples and breasts typically present as an aesthetic complaint but can also respond to hormonal changes similar to a normal breast including enlargement during puberty and milk production after pregnancy.[34] Treatment of these lesions is generally simple excision, but it is important to consider that diseases that afflict the normal breast can also affect supernumerary ones.[35] Breast masses must be excluded. Furthermore, several other anomalies have been associated with polythelia and polymastia including a higher rate of testicular tumors in boys.[36] Other more controversial associations include genitourinary tract abnormalities and renal cell carcinoma.[37,38]

### Congenital Absence of the Breast

Complete absence of one or both breasts is an extremely rare anomaly that can occur in isolation or with a variety of other developmental syndromes including Poland syndrome, Ullrich-Turner syndrome, and AREDYLD syndrome (acrorenal field defect, ectodermal dysplasia, lipatrophic diabetes) (Fig. 130-3). Bilateral congenital absence without other associated ectodermal defects is extremely rare, with few cases reported in the literature. Mendelian inheritance is possible but has not been definitively established; teratogen exposure has also been implicated. Due to the rarity of this condition, optimal treatment has not been established. Successful use of autogenous tissues including the use of abdominal or buttock free flaps for construction of a breast de novo has been reported.[38a] Tissue expansion and implant placement may also be reasonable options.[33,39]

### Tuberous Breast Disease

The breast anomaly known as the "tuberous breast" was initially described in 1976 by Rees and Aston for its likeness to a tuber root (Fig. 130-4).[40] Although there has been much confusion in the literature about both the nomenclature and the description of the tuberous breast and breast asymmetries in general, the following facts are known: 88% of women presenting for breast augmentation mammaplasty have breast asymmetry and 29% have breast base constriction.[41] However, the true tuberous breast is much less common and is defined not simply by asymmetry or constriction but also by the herniation of mammary tissue through a constricting fascial ring deep to the areola. The true incidence is uncertain, and there seems to be no heritable genetic component to the disorder.[33]

The presence of the tight fascial ring causes the breast to become asymmetric during pubertal development and ultimately herniate through it, causing areolar enlargement. This may be associated with hypoplasia of one or more quadrants, with the deficiency being most common in the inferior pole. The inferior mammary fold is often variably elevated.[42]

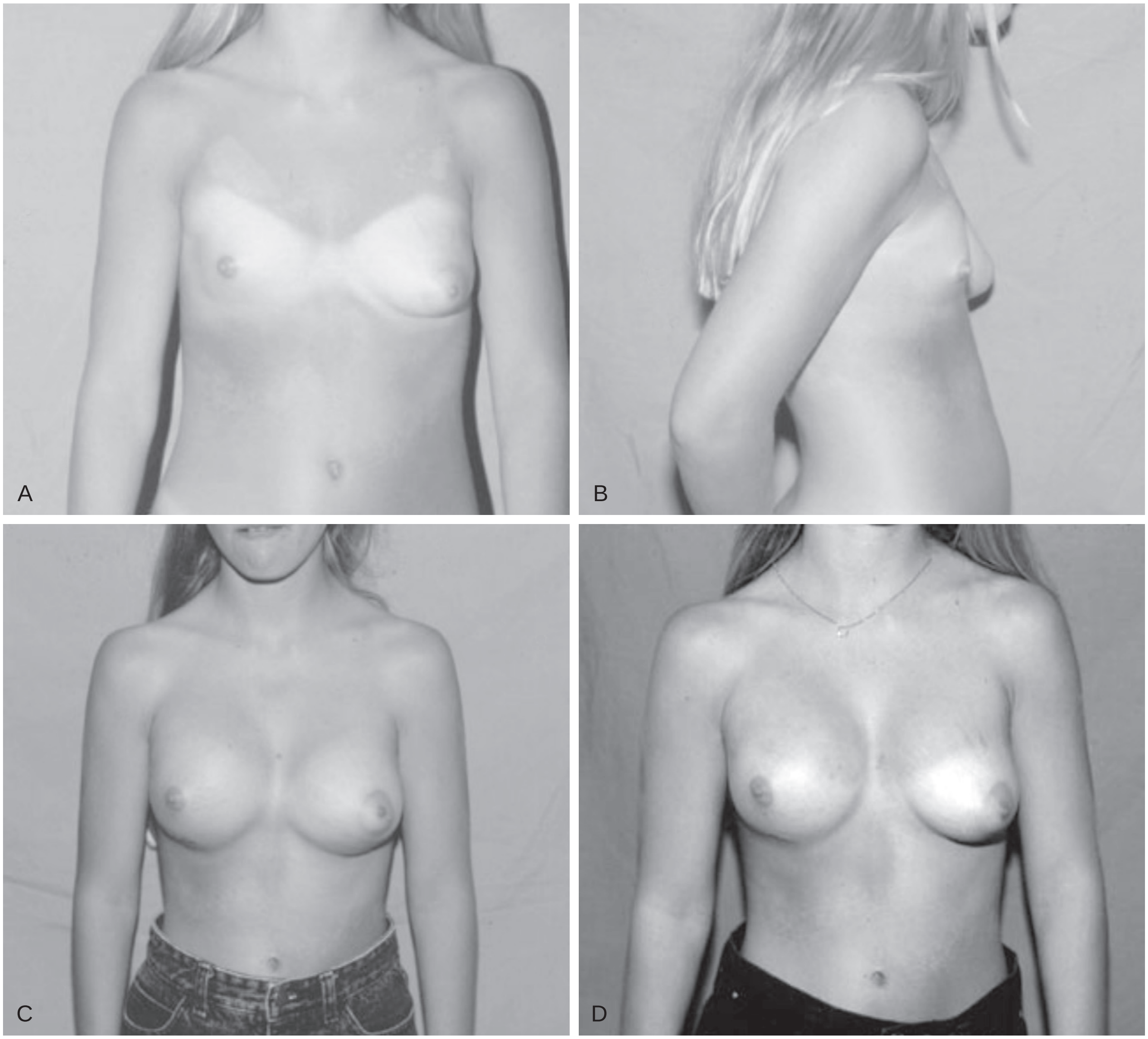
The tuberous breast often presents as an aesthetic concern in the early teen years. Differentiation of this disorder from more common asymmetries is essential because the treatment is generally different. Nearly 90% of cases are bilateral, and significant hypoplasia of the breast tissue is present in approximately one quarter of patients.[33]

Treatment for the tuberous breast is somewhat controversial, although several principles can be relied on. The patient should not be operated on until late in the second decade when breast development has finished. In nearly all cases, the herniated breast tissue causes enlargement of the areola, mandating a circum-areolar incision to reduce its size. This incision also allows for access to the fascial ring, which has constricting bands that must be released. Operative plans subsequent to these two steps are less definitive, although local tissue rearrangement is generally recommended with the establishment of a normal position of the inframammary fold and a natural inferior pole contour.[43] For hypoplastic or asymmetric breasts, tissue expansion and/or implant placement can be a useful adjunct to tissue rearrangement, but the use of an implant alone has been shown to be unsatisfactory with abnormalities of the inframammary crease being common.[33,44,45]

### Gynecomastia (Infantile and Adolescent)

Gynecomastia, or the abnormal presence of breast tissue in males, is a common but complex disorder with both congenital and acquired features (Fig. 130-5). The overall incidence has been reported to be 32% to 40% with a reported incidence of palpable breast tissue of 65% in adolescent boys.[46] Other studies have disputed these data; a cross-sectional study of 3082 healthy boys (aged 10 to 19 years) in Eastern Europe found a 3.93% prevalence of gynecomastia.[47] Variations in estimates are likely to be related to varying thresholds for diagnosis of overt gynecomastia (grade IIb/III gynecomastia) versus the presence of palpable breast tissue on the male chest (grade I/IIa gynecomastia).

Although numerous individual cases of gynecomastia have been identified, breast development in males generally occurs secondary to an excess of estrogens relative to testosterone because of an absolute estrogen excess, a testosterone deficiency, or receptor resistance. A full discussion of the causes of gynecomastia is beyond the scope of this section and is reviewed elsewhere.[48] Gynecomastia can be classified as congenital or acquired, as well as physiologic or pathologic. In boys, most cases are congenital and physiologic and occur in either the neonatal period or during adolescence. In utero, exposure to high maternal estrogen levels can cause the development



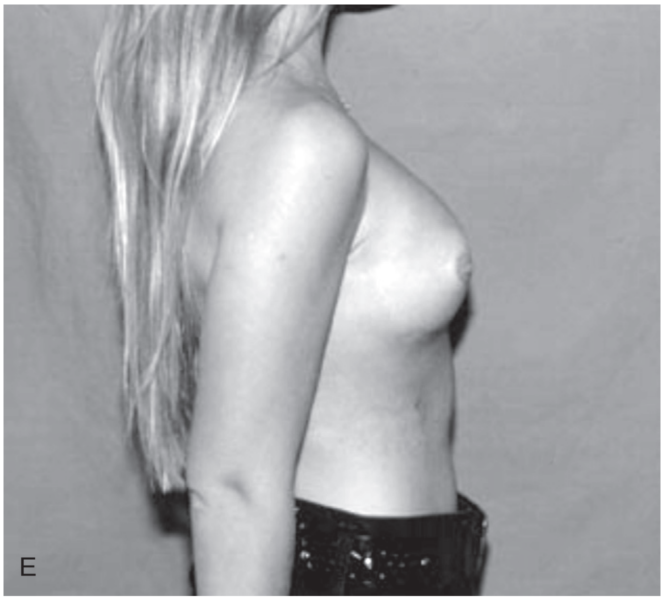




**FIGURE 130-3** Congenital absence of the breast. **A,** Anterior preoperative view of a patient with absence of natural breast volume on the right hemithorax. **B,** Lateral view. **C,** An expander has been inflated to establish an adequate skin envelope for breast mound reconstruction. **D,** Postoperative anterior view. The patient has a permanent saline implant in place to establish the right breast mound. **E,** Lateral view. Note that preexpansion of skin allows adequate projection and shape after the permanent implant is inserted.

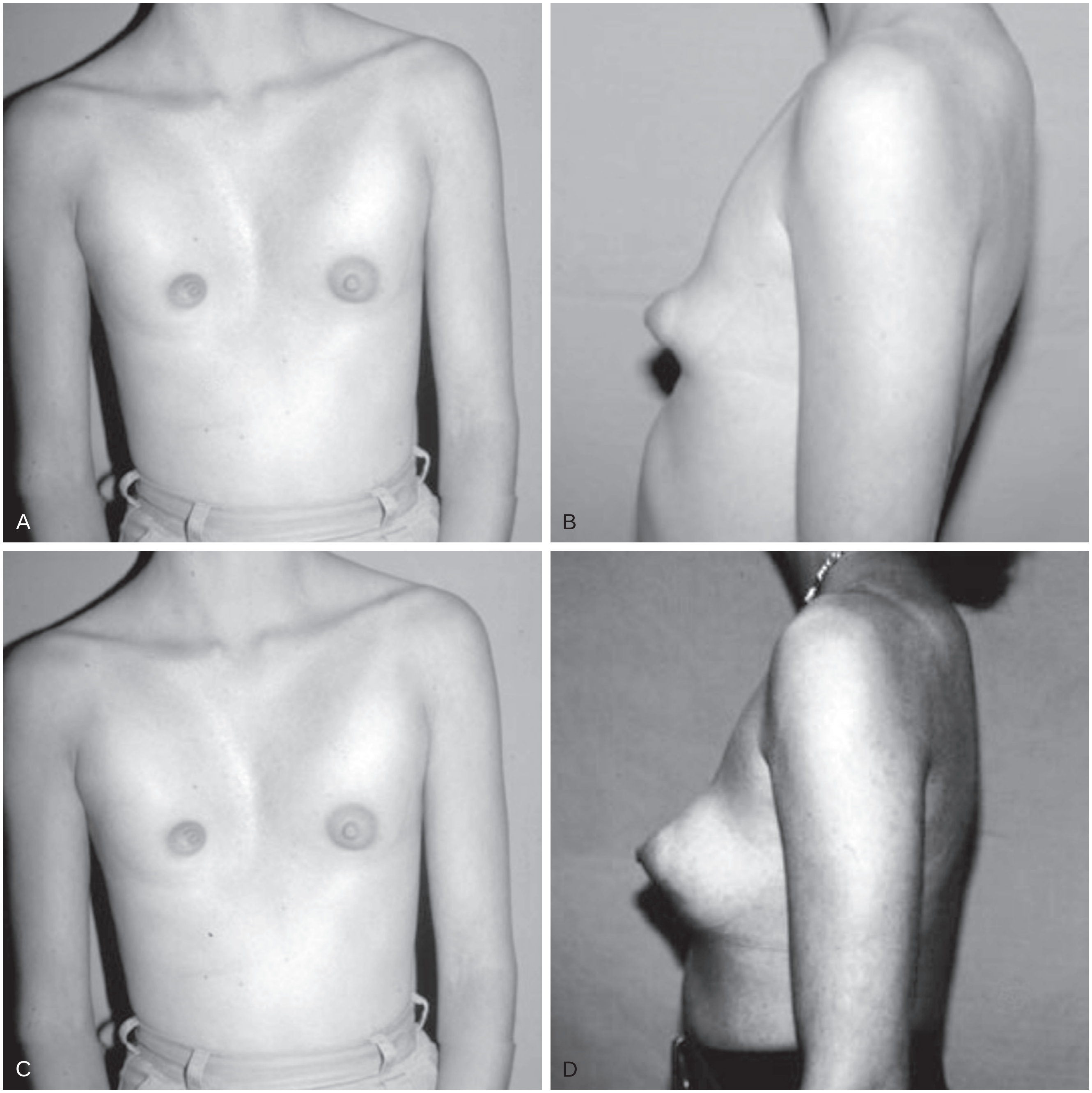


**FIGURE 130-4** Tuberous left breast with mild pectus excavatum. **A,** Preoperative anterior view of a congenital breast and central chest deformity. **B,** Lateral view. Note the tuberous breast deformity. **C,** Postoperative release of periareolar congenital constricting bands and the use of an implant to establish the breast mound. **D,** Postoperative lateral view.

of mammary tissue (neonatal gynecomastia), which regresses within a few weeks after birth. In adolescence, elevation of the estradiol-testosterone ratio causes detectable gynecomastia in up to 65% of boys. However, in most it is not noticeable without a focused examination and most noticeable cases occur during pubic Tanner stages 3 and 4.[47] Nearly all cases regress by the end of puberty.[33] Pathologic gynecomastia in children and adolescents is relatively rare but requires special attention, especially in the case of Klinefelter syndrome, which is associated with a 19.2- to 57.8-fold risk for breast cancer (unlike gynecomastia in general, which has no elevated risk).[49]

Although gynecomastia in adolescents is typically self-limited and resolves by the end of puberty, persistent gynecomastia (present for more than 1 year *and* beyond puberty) generally does not resolve without surgical treatment because the abnormal breast inevitably becomes fibrotic.[50] The gynecomastia for which a plastic surgeon is initially contacted is usually an aesthetic complaint; however, this does not obviate the need for a detailed history and physical examination. Although gynecomastia in the general population and even cases examined by a pediatrician are generally uncomplicated and benign, there is good evidence that gynecomastia needing

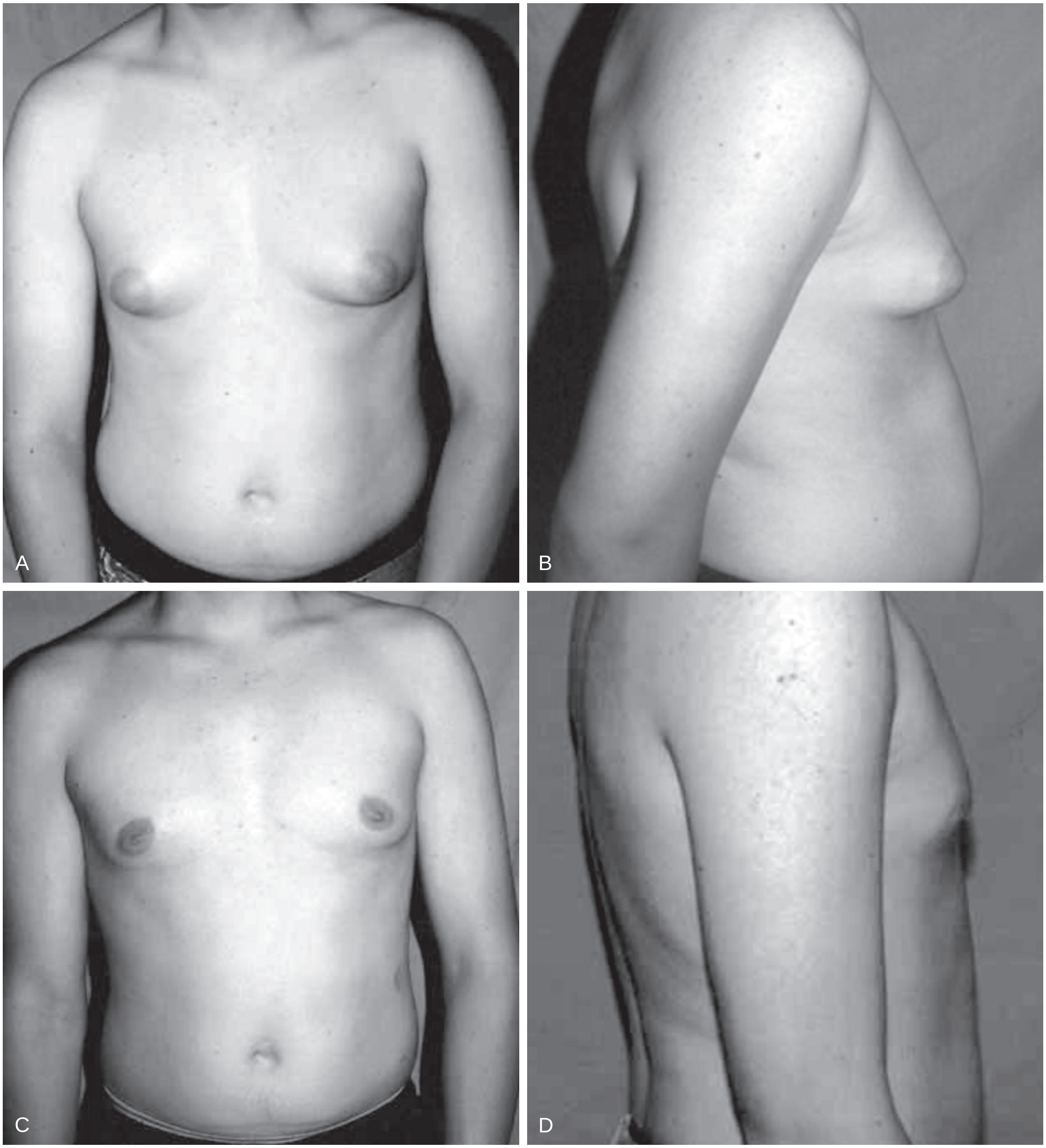



**FIGURE 130-5** Gynecomastia. **A,** Preoperative anterior view of an adolescent with abnormal breast development. **B,** Lateral view. Note the excessive breast tissue with the development of early breast ptosis. **C,** Postoperative view after the use of liposuction. **D,** Lateral view. A contour deformity caused by overresection was avoided by combining direct excision and liposuction.

surgical treatment is a more complicated subset of the disorder. In particular, several large studies have shown an increased incidence of testicular and nonmelanoma skin cancer in males with gynecomastia requiring operative treatment. The risk for testicular cancer is particularly elevated in young men and has a standardized incidence ratio reported at 5.82; 7% to 11% of patients with testicular cancer present to surgical evaluation for gynecomastia.[51,52] Examination of the testicles and skin, as well as education regarding skin cancer, is mandatory.

## Poland Syndrome

In 1841 Alfred Poland, a medical student, reported some unusual anatomic findings on a cadaver, describing unilateral hypoplasia of the pectoralis musculature, upper limb, and hand. The expression of the various components of this trait varies

widely. The incidence has been estimated to be 1:30,000 with a predilection in females of approximately 2-3:1.[53,54]

The etiology of Poland syndrome (PS) has been theorized to be due to obstruction of the subclavian blood supply during the sixth to seventh weeks of gestation. During this time, the ribs grow anterior and medially, depressing the subclavian artery into a U-shaped configuration. Tension on the arterial wall may cause kinking and obstruction. The site of diminished blood flow may determine the tissues involved in the defect, which may involve the thoracic wall, the pectoralis muscle, breast, upper extremity, and hand. Vascular studies have shown diminished blood flow in the subclavian artery on the affected side. More proximal vascular involvement of the subclavian or vertebral arterial systems has been shown to give rise to the bony cervical anomalies found in Klippel-Feil syndrome and the congenital palsies of cranial nerves VI and VII in Moebius syndrome. The synchronous presence of Poland, Klippel-Feil, and Moebius syndromes support a common embryologic event (i.e., vascular accident) in their genesis.[55–58]

The essential feature of PS is the absence of the sternal head of the pectoralis major muscle. Other features are hypoplasia or aplasia of the breast or nipple, deficiency of subcutaneous fat and hair across the chest and axilla, and abnormalities of the ipsilateral limb including shortening and brachysyndactyly. Other muscles may also be involved to variable degrees including absence of the pectoralis muscle (Fig. 130-6) and hypoplasia of the serratus anterior, supraspinatus, latissimus dorsi, and external oblique muscles. The thoracic cage itself may be involved with absence of the anterolateral ribs with possible lung herniation or symptomatic depressions in the chest wall. The hand deformities can be more involved with symphalangism occurring with syndactyly and hypoplasia or absence of the middle phalanges. Detection of syndactyly in a patient should make PS a consideration because 10% of all cases of syndactyly have been reported to have features of PS.[53,59,60]

Despite the hand deformities, the functional disability is generally mild and related to the presence of syndactyly. In milder forms of PS, treatment is primarily for aesthetic reasons. For more severe presentations, particularly in which the thoracic cage is involved, stabilization of the protective chest wall is warranted first because all other chest reconstructions will be placed on top of this foundation. Minor chest wall deformities are generally reconstructed with an ipsilateral latissimus dorsi muscle flap. Major chest wall deformities require better stabilization with either bone or prosthetic mesh. Split rib homografts and Marlex mesh have been used for moderate and severe defects and are covered with a latissimus dorsi muscle transfer. The transferred latissimus dorsi muscle replicates the missing anterior axillary fold of the pectoralis muscle and improves soft tissue coverage. Remaining major contour irregularities may be treated using a custom alloplastic implant.[53,61]

The reconstruction of the female breast in PS often presents a challenging problem. In severe cases the breast reconstruction generally occurs as a second-stage procedure late in adolescence, years after stabilization of the chest wall. The placement of an implant behind a latissimus dorsi muscle transposition has been effective. The successful use of free-tissue transfer has also been reported. In cases where the cutaneous envelope is hypoplastic, tissue expansion early in puberty will augment the soft tissues for later final repair and may guard against the psychologic distress of an absent breast.[62–65]

# HAND

## Embryology

Arm buds appear at 31 days, the fourteenth stage in embryonic development, coincident with the formation of the marginal vein beneath the surface ectoderm. The paddle-like hand segment forms on approximately day 33. Finger rays are evident at 41 days but do not begin to separate until day 47. Interdigital zones destined for apoptosis determine the separation of the fingers. The median artery supplying the embryonic hand is replaced by the radial and ulnar arteries between the fifth and sixth weeks. The reduced median artery maintains only the median nerve and interosseous blood supply. Dorsal and ventral blastemas differentiate into dorsal and volar forearm musculature, respectively, from the fifth to the eighth week, and are formed superficially and deeply. Intrinsic hand muscles arise from five embryonic layers; the deep hypothenar and thenar muscles in the seventh week are the last to separate. Condensation and then chondrification of the mesenchyme begins in the fifth week, ending with chondrification of the phalanges at week 6 and sesamoids at week 7. The eighth week marks the end of embryogenesis; much of the final form is in place. During weeks 4 to 8 of gestation, the embryo is at the highest risk of hand anomalies. Growth dominates the rest of fetal development, during which the fingernail fields develop and cartilaginous bones ossify.[66]

## Incidence

The estimated incidence of upper limb deformities has been studied in a longitudinal study of 261,914 live births in Sweden with a recorded incidence of 21.5 per 10,000 live births.[67] This result confirmed an earlier study from Western Australia, where an incidence of 19.8 per 10,000 was reported without an observed difference between Caucasian and non-Caucasian individuals.[68] The Centers for Disease Control and Prevention reported the following rates per 1000 live births: 0.8 for transverse deficiencies, 0.9 for syndactyly, 0.2 for polydactyly in Caucasians, and 0.12 for polydactyly in black persons.[69] In 40% to 50% of the cases, no clear cause can be determined. It is estimated that environmental factors account for 10% of limb anomalies. Rubella, cytomegalovirus (CMV), toxoplasma, and varicella in the first trimester have been linked to longitudinal deficiencies. Chemicals affecting limb development include thalidomide, ethanol, phenytoin, and warfarin. Many genetic syndromes (of Mendelian inheritance patterns or otherwise) have been associated with skeletal anomalies. Brachydactyly, clinodactyly, syndactyly, and polydactyly have been noted in trisomy 21; camptodactyly in trisomy 18; and polydactyly in trisomy 13.

## Congenital Hand Deformities: Classification and Treatment

The International Federation for Surgery of the Hand (IFSH) has established a seven-category classification system for hand deformities in 1976 (Table 130-1).[70]

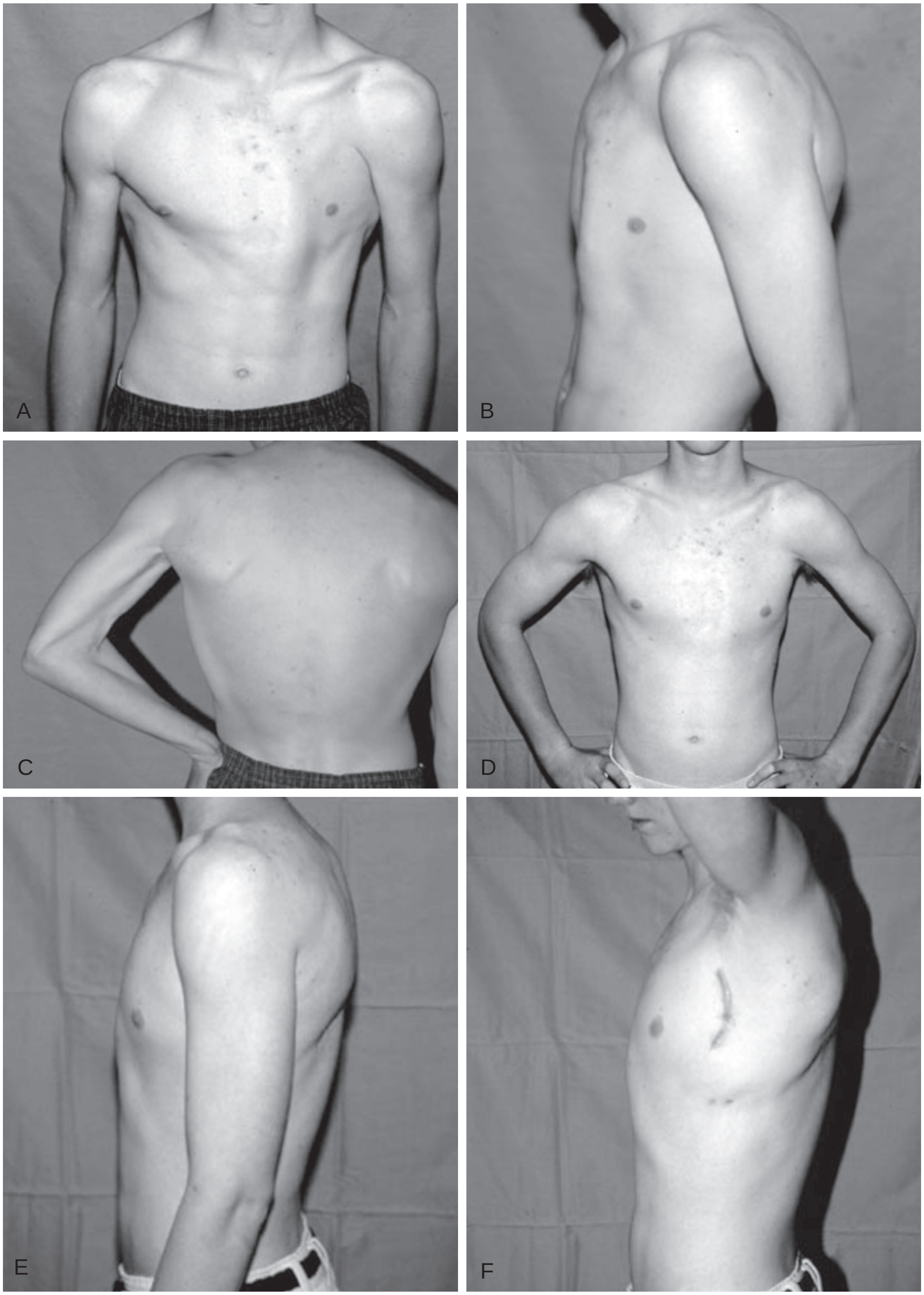



**FIGURE 130-6** Poland syndrome on the left side of the chest with an associated asymmetric pectus carinatum deformity. **A,** Preoperative anterior view. Note the absence of the left pectoralis muscle. **B,** Lateral view. **C,** Posterior view of the chest with the patient testing for the presence of the left latissimus dorsi muscle. Note the lateral edge of the muscle is visible with isotonic contraction. **D,** Postoperative anterior view. Note that functional transfer of the latissimus dorsi muscle to the anterior hemithorax provides contour correction and maintains latissimus dorsi function. **E,** Postoperative lateral view. The incision is concealed beneath the upper extremity. Note that the contour of the latissimus dorsi on the anterior aspect of the chest simulates the absent pectoralis muscle without contour deformity at the posterior chest donor site. **F,** A postoperative lateral view with the upper extremity abducted reveals the incision used for muscle harvest.

**TABLE 130-1**

**International Federation for Surgery of the Hand Classification System for Congenital Hand Anomalies**

1. Failure of formation
2. Failure of differentiation
3. Duplication
4. Overgrowth
5. Undergrowth
6. Congenital constriction band syndrome
7. Generalized skeletal abnormalities

***Failure of Formation*** Failure of formation is further divided into transverse and longitudinal arrest of development. Failure of formation has an incidence of 3.9 per 10,000 live births and contributes to 17.6% of all congenital hand anomalies.[67] Transverse deficiencies are congenital amputations, the most severe of which occur at the shoulder level and result in amelia. The short below-elbow defect, a common transverse deficiency, ends at the upper forearm. Prosthetic fitting should begin in infancy. Wrist disarticulation defects occur more often in girls than in boys. In this condition, the skeleton is absent beyond the distal radial and ulnar epiphyses, but pronation and supination abilities are generally maintained. In bilateral defects the Krukenberg procedure may be indicated on the dominant arm with a prosthesis worn only on the nondominant arm. The Krukenberg procedure separates the forearm bones into opposing prehensile forceps. Progressive length reduction defines longitudinal deficiencies, which may be preaxial (radial), postaxial (ulnar), central, or complete (phocomelia).[71]

**Radial Deficiencies** Radial deficiencies variably affect the radius, scaphoid, trapezius, trapezoid, and thumb, as well as associated musculotendinous, neural, and vascular structures. In the classic radial clubhand, the forearm is short, the hand is radially deviated, and the thumb is absent or floating. The defect begins in the first weeks of fetal life. Radial shaft development coincides with the development of the cardiac septum, which may explain the association of radial ray defects with the atrial septal defect found in Holt-Oram syndrome. Radial defects are also associated with vertebral defects, imperforate anus, esophageal atresia, radial and renal dysplasia syndrome (VATER or VACTERL), and blood dyscrasia such as Fanconi anemia and thrombocytopenia with absent radii (TAR) syndrome. Treatment begins shortly after birth; traditional methods stretch the hand (centralization) over the ulna by serial castings or distraction lengthening. Free fibula transfers have also been investigated.[71]

**Ulnar Defects** Ulnar ray deficiencies are rare and can be associated with defects of the fourth or fifth finger, elbow, humerus, or shoulder girdle (PS). Unlike the radius, which functions as a buttress for the wrist, the ulna may be deficient without any accompanying ulnar wrist deviation. Severity varies from hypoplasia to partial or total defects with or without humeroradial synostosis to ulnar deficiency with amputation at the level of the wrist. Prostheses such as an elbow disarticulation device can improve limb use. In selected patients, fusion of the ulnar remnant to the radius provides stability at the elbow.[71]

**Thumb Defects** The management of thumb defects depends on their severity. In total aplasia of the thumb, pollicization of the index finger is the most successful method of achieving functional opposition. Toe-to-thumb transfer is not successful because recipient nerve and tendon structures are absent and the brain lacks the motor and sensory homunculus for the thumb. Short thumbs can be lengthened by distraction osteogenesis. Widening of the first web space and tendon transfer to establish opposition may improve function. Floating thumbs are generally amputated and opposition is accomplished by pollicization of the index finger.[71]

**Central Longitudinal Deficiency** Central longitudinal deficiency, also known as *cleft hand* or *split hand,* applies to defects of the central (second, third, or fourth) rays. Typical deficiencies involve partial or complete loss of the central digit(s). Atypical deficiencies are syndactylous (the central finger remnants fuse to the second or fourth ray) or polydactylous. The polydactylous type contains supernumerary bony elements. Function determines treatment; appearance is a secondary consideration. Resection of the remnant third metacarpal assists closure of a deep cleft. Osteotomies correct rotatory deformities of the adjacent fingers. Thumb web space reconstruction is critical to overall hand function.[71]

***Failure of Differentiation*** Failure of differentiation includes soft tissue and skeletal failure of the separation of parts, as well as congenital tumors. Failure of differentiation is the most common congenital hand anomaly and has an incidence of 10.5 per 10,000 live births. It contributes to 47.2% of all congenital hand anomalies.[67]

**Syndactyly** Synostosis of the phalanges (symphalangism) is uncommon and usually occurs with syndactyly. Syndactyly itself is common and most often occurs between the middle and ring fingers. It has an estimated incidence of 5 per 10,000 live births.[72] True failure of differentiation is distinguished from the brachysyndactyly (short, webbed fingers) of PS and from acrosyndactyly with fusion of the distal digits secondary to a constriction band. Syndromes featuring syndactyly include Apert (acrocephalosyndactyly), Chotzen (cephalodactyly), Pfeiffer, and Golz; oculodentodigital; and trisomy 13.

Digits with acrosyndactyly should be separated before 1 year of age if the digits are of discrepant lengths or there is fusion of the phalangeal bones. In the absence of these features, separation can be performed at 2 to 3 years. The complexity of an Apert "mitten" hand presents a challenge to provide a functional hand with both prehensile function and fingertip sensation (Fig. 130-7). To this end, a three-finger hand is often preferable to four fingers and a thumb. The thumb and small fingers are released before 1 year of age. The remaining digits are separated within 6 to 9 months. Another feature of Apert syndrome is radioclinodactyly of the thumb (radial curvature of the thumb). Thumb osteotomy and bone graft are performed at 4 to 7 years of age, along with Z-plasty of the web space between the thumb and the index finger.[73]

**Congenital Flexion Deformities (Arthrogryposis)** Failure of soft tissue differentiation can lead to congenital flexion deformities. In the clasped thumb or thumb-in-palm contracture, the extensor pollicis longus, extensor pollicis brevis, and abductor pollicis longus muscle and tendon units are absent or attenuated. Splinting and manipulation begin in infancy, and surgical correction is delayed until 3 years of age. The clasped thumb must be differentiated from the trigger thumb, wherein a flexor pollicis longus nodule proximal to the A1 pulley interferes with interphalangeal and

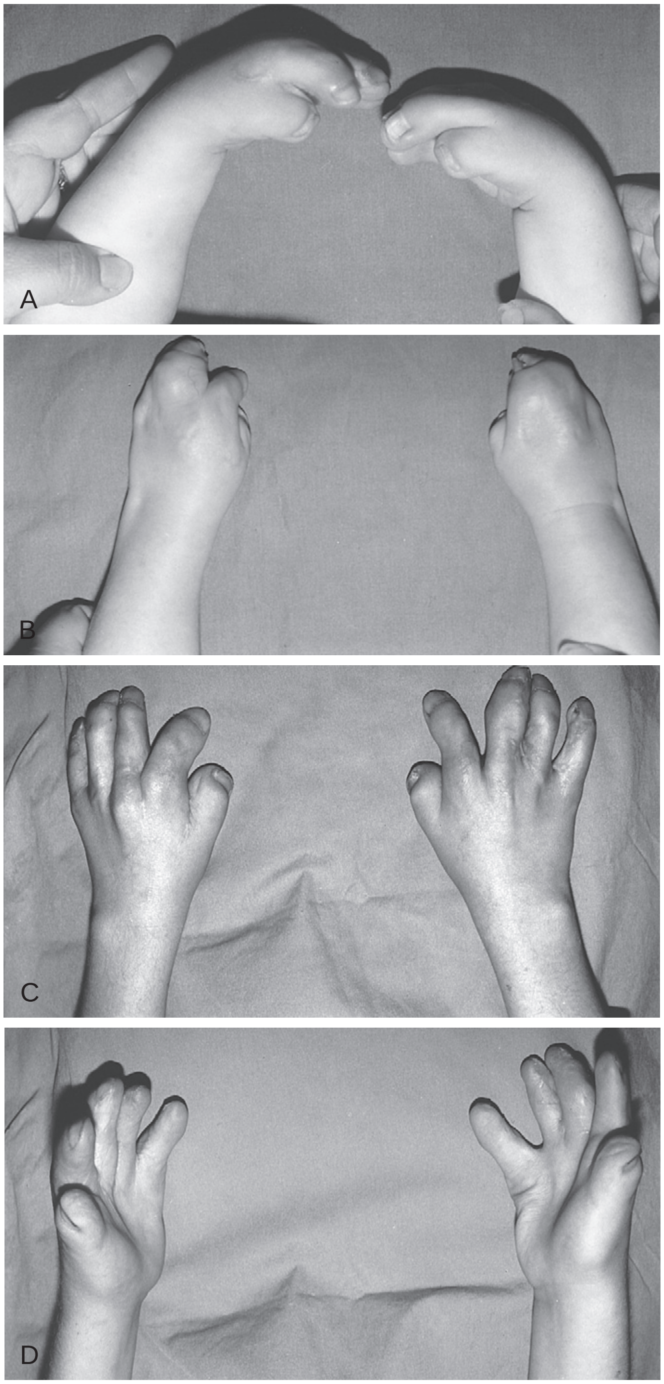



**FIGURE 130-7** **A,** Infant with Apert syndrome afflicted with the typical acrosyndactyly deformity of the hand. **B,** Complex bilateral acrosyndactyly. **C** and **D,** Postoperative appearance after release of syndactyly.

metacarpophalangeal extension. Because of a 30% spontaneous resolution rate, surgical trigger finger release is recommended for contractures that persist beyond 3 years of age.[74]

Clinodactyly most often affects the middle phalanx of the little finger and is seen in many syndromes (e.g., Treacher-Collins and Silver-Russell syndromes, orofaciodigital and oculodentodigital dysplasia). Camptodactyly refers to congenital proximal intraphalangeal flexion contracture, usually of the little finger, and is associated with such syndromes as Marfan, popliteal pterygium, and orofaciodigital and oculodentodigital dysplasia. Mild variants of camptodactyly can be found in up to 1% of the population.[75] If disabling or deforming, the contracture is released by dividing the flexor digitorum superficialis tendon and lengthening the volar skin with a full-thickness skin graft. In more severe cases arthroplasty or arthrodesis is performed. Arthrogryposis multiplex congenita features multiple congenital nonprogressive joint contractures and affects all extremities and the spine. In the upper extremity the shoulder may be flexed and internally rotated, the elbow flexed or extended, the wrist flexed and ulnarly deviated or extended and radially deviated, and the thumb and fingers flexed and ulnarly deviated.[74]

Arthrogryposis isolated to the hand manifests as the "windblown hand," with metacarpophalangeal flexion and ulnar deviation caused by malformation of the palmar fascia and retaining ligaments, with or without involvement of tendons and capsules. Thick, fibrous subcutaneous bands and shortened digitopalmar skin contribute to this malformation. Secondary metacarpal head deformation occurs with time. The thumb is flexed, and abduction is limited by a retracted volar carpal ligament and carpal skin.

Splinting and manipulation begins in infancy. If the deformity progresses, as often happens during the adolescent growth, operative intervention is indicated. Corrective procedures include release of the metacarpophalangeal joint capsule, ligament, and intrinsic tendon; relocation of the extrinsic tendon; metacarpal osteotomy; and division of palmar skin and fibrous bands followed by skin grafting for coverage.[74]

***Duplication of Parts*** Duplication of parts has an incidence of 5.9 per 10,000 live births and contributes to 26.5% of all congenital hand anomalies.[67] Duplication of parts occurs early in embryonic development. Polydactyly is a common hand malformation. Postaxial little finger duplication occurs more often than preaxial thumb duplication. Central duplications are rare. A flail, a poorly attached appendage, should be amputated early. Operative correction of preaxial polydactyly is sometimes delayed until 12 months of age, when functional evaluation is possible to identify the dominant (usually ulnar) thumb to be preserved. The collateral ligaments, even tendons and bony elements, of the ablated digit are salvaged for reconstruction of the retained digit. Alternatively, the Bilhaut-Cloquet procedure consisting of excising a central wedge from adjacent parts of both thumbs and then joining the remaining lateral portions can be performed. If the thumb resembles an index finger and cannot be opposed, treatment consists of rotational osteotomy, tendon transfer (e.g., Huber transfer of the abductor digiti minimi across the palm), and widening of the first web space.[76]

The mirror hand possesses seven or eight digits, one or two index with two ring and middle fingers, two ulnae, absent radius, absent thumb, and weak or absent extensor tendons. The hand loses its ability to pinch or grasp. An opposing digit needs to be constructed, and excess fingers should be discarded; the filleted skin is used to create a wide web space. Wrist arthrodesis may be required in early adolescence. Elbow motion may be improved by excising the olecranon off of one of the ulnae.[76]

***Overgrowth*** Congenital overgrowth anomalies are rare with an incidence of 0.4 per 10,000 live births and contribute to 1.7% of all congenital hand anomalies.[67] Digital gigantism

involves the overgrowth of bone and soft tissues. Classification has been difficult due to the wide range of etiologies for the overgrowth phenotypes and is beyond the scope of this chapter.[77] Classic type I macrodactyly is associated with lipofibromatous hamartoma of the median or (less frequently) the ulnar nerve. Phalangeal involvement is constant, and metacarpal involvement varies. Soft tissue overgrowth can affect skin and lymphatic or nerve structures, although flexor tendons and blood vessels may be spared. Gigantism of several adjacent digits is more prevalent than single-digit macrodactyly. Median nerve hamartoma can compress structures in the carpal tunnel. Type II macrodactyly is part of von Recklinghausen disease (neurofibromatosis). The distribution follows the path of a major peripheral nerve, most frequently the median nerve. Contrary to types I and II, type III macrodactyly (hyperostotic) is not associated with nerve enlargement but does follow the course of the sensory branches of the median nerve. Treatment has included epiphysiodesis, epiphyseal arrest, epiphyseal plate excision, multiple defatting procedures, longitudinal phalangeal osteotomies, soft tissue debulking, excision of distal nerves, and partial or ray amputation. Skin flap necrosis is not an uncommon complication after repair of macrodactyly.[78]

***Undergrowth*** Undergrowth malformations vary in the structures affected and the degree of the hypoplasia. Undergrowth anomalies have an incidence of 0.7 per 10,000 live births and contribute to 3.1% of all congenital hand anomalies.[67] Brachydactyly (shortened digits) is commonly seen in association with syndromic disorders, generally of autosomal dominant transmission. Ectrodactyly is the complete absence of phalanges or metacarpals. Short metacarpals are uncommon and often go unrecognized until the adolescent growth spurt; associated syndromes include pseudohyperparathyroidism, Turner, and cri-du-chat (chromosome 5p deletion). Treatment is usually unnecessary, but lengthening the affected ulnar metacarpals does increase palm size and improve grip. Lengthening procedures use either bone grafting or distraction osteogenesis.[79] Short phalanges are the major cause of brachydactyly. The middle phalanx of the little finger is the hand bone, the length of which varies the most, particularly in girls. Other than osteotomies to correct deviations, there is little role for operative intervention. Phalangeal lengthening procedures rarely improve function.[80]

***Constriction Band Deformities*** Constriction band deformities are rare (incidence of 0.3 per 10,000 live births, 1.7% of congenital hand anomalies) and occur during fetal rather than embryonic development.[67] The predominant theory is that amniotic bands wrapped around a limb cause local ischemia and necrosis. An alternate explanation proposes an intrinsic defect wherein hemorrhage or a local defect in the limb leads to necrosis of the superficial tissues. The necrotic area heals as a circumferential scar, and amniotic bands appear secondary to the limb injury. The distal regions of the extremities are more often affected than are proximal regions. Compression neuropathy distal to the constriction band scar has been reported. In the digits, acrosyndactyly results from tissue necrosis and fusion. Separations between the digits proximal to the fusion and distal transverse grooves or amputations characterize acrosyndactyly. For most constriction rings, simple or staged excision and Z-plasty suffice. Broad rings may require local flap coverage of large defects. Treatment of fused digits is individualized; separation may include cross-finger flaps, completion amputation, distraction lengthening, or free-toe transfer.[81]

## Summary

A wide spectrum of anomalies of varying severity can result from the congenital absence or alteration of tissues. Any anatomic region of the body can be affected. In determining the indications and timing for surgical correction, the severity of functional impairment, the degree of disfigurement, and the social pressures associated with the malformation must be considered. A sound plan of management relies on accurate diagnosis and analysis of the defect. Almost all defects can be systematically evaluated by the degree of malposition of normal structures, absence of tissues, and aberrations in tissue composition. Surgical correction can then be formulated to specifically address each component of the deformity. Using a systematic approach simplifies and optimizes a safe treatment plan for even the most complex malformations.

*The complete reference list is available online at www.expertconsult.com.*

CHAPTER 131

# Conjoined Twins

Lewis Spitz, Edward M. Kiely, and Agostino Pierro

Conjoined twins can be subdivided into (a) symmetric conjoined twins, which form the main bulk of this chapter, and (b) heteropagus or parasitic twins.

## Symmetrical Conjoined Twins

### HISTORY

Although there are numerous examples of figurines depicting conjoined twins dating back to classical times, particularly among Aztec art and ancient Turkish culture, it is doubtful whether these were factual representations.

The earliest example is a 17-cm marble statuette portraying parapagus twins, "the double goddess," dating from the sixth millennium BC. The statue of sisters of Catalhoyuk is housed in the Museum of Anatolian Civilization in Ankara, Turkey.[1] Another early example that appears more authentic is a stone carving of pygopagus twins dating back to 80 BC, discovered in Fiesole and kept in the San Marco Museum in Florence, Italy (Fig. 131-1).

The earliest attempt at separation of conjoined twins took place in Kapadokia, Armenia, around 945 AD. When one of the male ischiopagus twins died at the age of 30 years, an attempt was made to save the surviving twin by separating him from his dead brother, but he died 3 days later.[1]

The first well-documented case is that of the Biddenden maids born in Kent in 1100 AD and "joined at the hips and the shoulders"[2] (Fig. 131-2). They lived together for 34 years. When Mary became ill and died, Eliza was advised to be separated but absolutely refused, saying, "as we came together we will also go together." She died 6 hours later. They amassed a vast fortune and bequeathed to the parish of Biddenden 20 acres of land with the expressed wish that proceeds from rent should be spent on the distribution of cakes, bearing an impression of their images, to be given to the poor each Easter Sunday—a practice that endures to the present day. It is impossible that they were joined as depicted in numerous illustrations at the hips and shoulders. The more plausible explanation was that they were ischiopagus or parapagus twins.

The Scottish Brothers were born near Glasgow in 1490.[3] They were two complete individuals above the waist but the lower half of their bodies was fused—one set of genitalia and two legs. They were taken to the court of King James IV, who ordered that they be carefully brought up and educated at court. They learned to sing, one tenor and the other treble bass; played various musical instruments; and became fluent in several languages. They often differed in opinions and sometimes quarreled. They died in 1518, aged 28 years.

Geoffrey-Saint-Hilaire cited an example of twin girls, born in 1495, joined at the forehead, causing them to stand face to face: "When one walked forward, the other was compelled to walk backward." They lived to the age of 10 years, and when one died an unsuccessful attempt was made at separation.[4,5]

In the sixteenth century, Ambroise Paré collected examples of six sets of conjoined twins and was one of the first to classify the different varieties of conjoined twins.[6]

The Isle-Brewer xiphopagus twins, Priscilla and Aquila, were born in 1680 joined "from the navel up to a point just below the nipples."[7] The vicar at their christening believed that the monstrous birth was a sign of impending evil. They were visited daily by hundreds of people keen to view "the monstrous work of Nature and admire so great a piece of curiosity." They were abducted by Henry Walrond and displayed but died in 1683.

The first successful separation of conjoined twins took place in 1689. The surgeon, Johannes Fatio, separated omphalopagus twins in Basel, Switzerland, by "tracing the umbilical vessels to the navel, where he tied them separately. He then transfixed and tied the bridge between the two infants with a silken cord and cut the isthmus." The ligature fell off on the ninth postoperative day, and both children survived. Koenig,[8] an observer at the procedure, published the case as his own and to him is credited the first successful separation.[9,10]

Table 131-1 lists the early history of conjoined twins dating back from the mid nineteenth century.

The most celebrated pair of conjoined twins was Chang and Eng Bunker, born on a riverboat in Siam (Thailand) in 1911. They were joined at the xiphisternum by a short band that stretched so that they were eventually able to stand side by side (Fig. 131-3). Their father was a fisherman, and the family lived on a floating houseboat on the Mekong River. They became proficient swimmers, and their peculiar movement attracted the attention of Robert Hunter, a traveling Scottish merchant, who eventually persuaded their mother to permit him to take them to the United States, where they were exhibited by Captain Coffin and later by the showman Phineas Barnum. They married sisters, lived in separate houses in North Carolina spending 3 days in each house alternately,

FIGURE 131-1 Stone carving of pygopagus conjoined twins dating back to 80 BC.

ELISA & MARY CHULKHURST

A 34 Y IN 1100

BIDDENDEN.

A SHORT, but conciſe account of ELISABETH, and MARY CHULKHURST, who were born joined together by the Hips and Shoulders, in the Year of our Lord 1100, at BIDDENDEN, in the COUNTY of KENT;

COMMONLY CALLED THE

Biddenden Maids.

THE Reader will obſerve by the above Plate of them, that they lived together in the above ſtate, Thirty-four Years; at the expiration of which Time, one of them was taken Ill, and in a ſhort time died; the ſurviving one was adviſed to be ſeparated from the body of her deceaſed Siſter, by diſſection, but ſhe abſolutely refuſed the ſeparation by ſaying theſe words, as we came together, we will alſo go together, and in the ſpace of about ſix hours after her Siſter's deceaſe, She was taken Ill, and died alſo.

BY their WILL, they bequeathed to the *Churchwardens* of the Pariſh of BIDDENDEN, and their ſucceſſors *Churchwardens* for ever, certain pieces or parcels of Land in the Pariſh of *Biddenden*, containing twenty Acres, more or leſs, which now lets at £.31 10*s*. *per Annum*. There are uſually made in commemoration of theſe wonderful phænomena's of nature, about 1000 Rolls with their impreſſion printed on them, and given away to all Strangers, on *Eaſter Sunday*, after Divine Service in the Afternoon; alſo about 300 Quartern Loaves, and Cheeſe in proportion, to all the poor Inhabitants of the ſaid Pariſh.

BIDDENDEN: PRINTED AND SOLD BY R. WESTON

A

THE Reader will obſerve by the above Plate of them, that they lived together in the above ſtate, Thirty-four Years; at the expiration of which Time, one of them was taken Ill, and in a ſhort time died; the ſurviving one was adviſed to be ſeparated from the body of her deceaſed Siſter, by diſſection, but ſhe abſolutely refuſed the ſeparation by ſaying theſe words, as we came together, we will alſo go together, and in the ſpace of about ſix hours after her Siſter's deceaſe, She was taken Ill, and died alſo.

B

FIGURE 131-2 **A** and **B,** Broadsheet of Biddenden maids born in Kent in 1100 AD.

and had 21 children between them. Physiologically and psychologically they were totally different—Chang was smaller and more feeble; what Chang liked to eat, Eng detested; Eng was good-natured, Chang cross and irritable; Chang drank heavily, but Eng appeared unaffected by the alcohol. They wished to be separated but could not persuade surgeons to carry out the operation, which was considered to be too hazardous at the time. In retrospect, according to the autopsy findings, the procedure would have been quite straightforward because the connecting bridge between them contained only a small tongue of liver.[11–13] They lived together for 63 years and died in 1874.[14,15]

In 1840 an African village was raided, and many of the residents were sold to a slave trader and transported by ship to America. During the voyage, a woman gave birth to xiphopagus twins by cesarean section by the naval surgeon Brito y Boin, who surgically separated them. The mother died the next day, and one of the twins died 2 days later. Another slave woman took the surviving twin and raised him. He had keloid scars removed at age 8 years and was still reported as being alive at the age of 66 years at that time.[16]

In 1860 a physician separated his own omphalopagus twin daughters. The incision was closed with three through-and-through sutures. One twin died, but the other was well 5 years later.[17]

The "first successful separation of conjoined twins" was performed at The Military Families Hospital in Portsmouth, England, in 1912. One twin survived, but the other died of pneumonia at the age of 4 months.[18]

The Tocci Brothers, born in 1877, were extensively united parapagus conjoined twins. They also wished to be separated, but the extent of their union dictated that surgery at the time was clearly not feasible. They lived together for 63 years and died in 1940.[19,20] Other conjoined twins have declined any suggestion of separation. Lori and Reba Schappell, craniopagus twins, born in 1961, never wanted to be separated, stating "God made us this way and He had a purpose for us and you do not ruin what God has made."[15]

In 1990 Hoyle[21] reviewed all attempts at surgical separation of conjoined twins, performed successfully and unsuccessfully, through 1987. Of a total of more than 600 publications, separation was attempted in 167 cases. The survival rate increased dramatically in the most recent decade before 1987. He concluded that "the current excellent outcomes (for separation) suggest that separation should always be considered with rare exceptions."

## ETIOLOGY AND EMBRYOLOGY[22,23]

In the absence of an experimental model, the exact etiology of conjoined twins is unknown. The uncertainty between fission and fusion theories remains. Because it seems likely that fission of a single fertilized ovum occurs in the same manner each time, the wide variety of types of conjoined twinning make fusion the more likely mechanism. Unlike identical monovular twins, conjoined twins often have remarkably different personalities. This difference in personality is clear from the early months of life and remains unexplained. The inference may be drawn that these twins may not always result from monovular pregnancies. Regardless of the mechanism, twins are always joined homologously—chest to chest, pelvis to pelvis, etc.—and are always the same sex. Spencer has

**TABLE 131-1**

**History of Conjoined Twins to 1851**

| *Yr* | *Type* | *Sex* | *Details* | *Outcome* | *Origin* |
|---|---|---|---|---|---|
| 6500 BC | Dicephalic | Female | Marble statuette “Double goddess” | Unknown | Turkey[1] |
| 500-800 BC | Dicephalic | ? | Various clay figures Figure 131-1 | Unknown | Mexico[5] |
| 80 BC | Pygopagus | ? | Stone carving | Unknown | Fiesole, Florence, Italy |
| 375 | Dicephalus | Male | One twin ate and slept, but the other did neither | Died at age 2 | Castle of Emaus, England[19] |
| 945 | Thoracopagus | Male | Attempt at separation after one twin died aged 30 years | Died at age 30 | Kappadokia, Armenia[1] |
| 961 | Dicephalus | Female | When one laughed, ate and talked, the other wept, fasted, and was silent | Unknown—both died in the space of 2 days | Gascony, France[19] |
| 1100 | ? Ischiopagus | Female | Joined at hips and shoulders | Lived for 34 years—when one died, the survivor refused separation | Biddenden, Kent, England[2] |
| 1490 | Dicephalus | Male | Scottish brothers—brought up in the court of King James IV of Scotland | Musical and linguistic—lived to age 28 | Glasgow, Scotland[19] |
| 1495 | Craniopagus | Female | Joined at the foreheads—when one walked forward, the other walked backward | Lived to age 10—when one died, attempt at separation failed | Worms, Germany[5] |
| 1533 | Omphalopagus | Female | Umbilicus to stomach Liver | Died after 8 days | Hispaniola[57] |
| 1552 | Pygopagus | ? Male | Three lower limbs | ? | Middleton Stony, Oxon. England[58,59] |
| 1573 | Parapagus (1546)<br>Pygopagus (1475)<br>Ischiopagus (1570)<br>Thoracopagus (1572)<br>Craniopagus (1569) | Male<br>Female<br>?<br>Female<br>Female | Described by Ambroise Paré in 1573 | ? | Paris<br>Verona, Italy<br>Paris<br>Angers, France<br>Tours, France[6] |
| 1576 | Ischiopagus | Male | Born in the Jewish ghetto of Venice | Impossible to circumcise—threat of anti-Semitism Died soon after birth | Venice, Italy[5,60] |
| 1664 | Pygopagus | Female | Waterman—Martha and Mary | Lived for 2 days Normal female triplet | Somerset, England[61,15] |
| 1668 | Dicephalus | Female | “Fair maidens of Foscott” | Apparently lived to a “mature age” | Somerset, England[19] |
| 1670 | Thoracopagus | Female | One twin had esophageal atresia | Died at birth | Plymouth, England[62] |
| 1680 | Pygopagus | Female | “The Isle-Brewers Twins” | Died at age 3 | Somerset, England[7] |
| 1680 | Craniopagus | Female | Voyoen-Pieternella and Barbara | One slept while the other was awake, crying, and eating | Bruges, Belgium[5,63] |
| 1689 | Omphalopagus | Female | Connecting bridge ligated at 2 days old—both survived | Both survived Surgeon—Fatio Reported by Koenig | Basel, Switzerland[9] |
| 1701 | Pygopagus | Female | “Hungarian Sisters” Helen—active and intelligent Judith—hemiplegic | Lived to age 22 | Szony, Hungary[5] |
| 1706 | Parapagus | ? | Single trunk, 4 arms and legs | 30 minutes | Hitchin, England[58] |
| 1783 | Craniopagus | Male | “Two-Headed Boy of Bengal”—separate brains | Died after being bitten by a cobra at age 4 yr | India[64] |
| 1811 | Xiphi-omphalopagus | Male | Connecting bridge contained liver only Married sisters—had 21 children | Lived for 62 yr | Mekong, Siam (Thailand)[15,14] |
| 1829 | Parapagus | Female | Parodi—Ritta (weak, cyanotic) and Christina (healthy, voracious appetite) | Died at 8 months old Ritta—severely deformed heart—2 superior vena cavas | Sardinia, Italy[15] |
| 1848 | Ischiopagus | Female | “Martha and Maria” | Lived 10 days | Copenhagen, Denmark[15] |
| 1851 | Pygopagus | Female | “Millie and Christine” McKoy. Walked at 12 mo | Lived to age 61—died 1912 | North Carolina, USA[15] |

FIGURE 131-3 Portrait of Chang and Eng from the Royal College of Surgeons of England, London.

proposed that union occurs at sites where ectoderm is absent or programmed to disrupt or fuse. The fusion theory suggests that two separate embryonic discs from a monovular pregnancy lie on the surface of a single yolk sac. At around the third week of pregnancy, fusion occurs at sites where the ectoderm is not present or where it is disrupted. Ectoderm is absent over the precursors of the septum transversum and heart. Fusion at this level results in thoracopagus and omphalopagus twins. Ectoderm disrupts at the sites of the oropharyngeal and cloacal membranes and fuses at the edge of the embryonic disc. Union at these sites results in cephalopagus, ischiopagus, and parapagus twins. Dorsal union—craniopagus, rachipagus, pygopagus—results in each twin having its own umbilicus and separate abdomen. The other types of union are considered ventral and usually share a single cord and peritoneal cavity. These cords will frequently have more than three vessels. Associated anomalies are common and predominantly affect the structures that are joined. The patterns of abnormality encountered depend on the type of union, and each of the eight types of twinning has a range of associated anatomic defects.

These abnormalities may preclude extrauterine survival and may render separation impossible. According to Spencer, thoracopagus twins always have a single heart with multiple chambers and separation is rarely an option. Others have been less rigid in their definition of thoracopagus, and there have been well-documented cases in which separation of thoracopagus with separate hearts has been successful.

## INCIDENCE

The frequency of conjoined twins has been estimated at 1:50,000 pregnancies, but because up to 60% of these twins succumb in utero the true incidence is 1:250,000 live births. With the advent of routine prenatal ultrasound, the early diagnosis of the nature of the problem will become evident early in gestation and elective termination will be an option.

Female twins predominate in the ratio of 3:1.

## CLASSIFICATION[23–25]

Conjoined twins are classified on the basis of the union's site, with the suffix pagus meaning fixed or fastened. The twins can have four (tetrapus), three (tripus), or two (bipus) legs. The classification of conjoined twins, limited to eight types with approximate percentages of frequency, is summarized in Table 131-2.

1. *Thoracopagus:* The twins lie face to face and share the sternum, diaphragm, upper abdomen wall, and liver and have an exomphalos (Fig. 131-4). In the majority of cases they share the pericardium (90%) and heart (85%). They may have a common small intestine (50%), which joins at the duodenum and separates at the ileum; the biliary tree can be joined in 25% of patients. There may be associated

**TABLE 131-2**
**Characteristic Features of Different Conjoined Twins**

| *Type of Fusion* | *Incidence* | *Extent of Union* | *Shared Structures* |
|---|---|---|---|
| **Ventral (87%)** | | | |
| Cephalopagus | 11% | Top of head to umbilicus | |
| Thoracopagus | 19% | Thorax | Liver 100% |
| | | Upper abdomen | Pericardium 90% |
| | | Conjoined hearts 85% | Cardiac defects 75% |
| | | | Upper intestine 60% |
| | | | Biliary tree 17% |
| Omphalopagus | 18% | Upper abdomen | Liver 90% |
| | | Separate hearts | Upper foregut 16% |
| | | | Cardiac 25% |
| Ischiopagus | 11% | Cloacal membrane | Pelvic bones 100%<br>Lower gastrointestinal tract 70% |
| | | | Genitourinary 50% |
| Parapagus | 28% | Cloacal membrane | Cardiac 75%<br>Intestine 100% |
| | | | Liver 100% |
| | | | Genitourinary 100% |
| **Dorsal (13%)** | | | |
| Craniopagus | 5% | Cranial neuropore | Skull, venous sinus, and meninges 100% |
| | | | Cerebral cortex 37% |
| Rachipagus | 2% | Neural tube | Vertebral column |
| Pygopagus | 6% | Caudal neuropore | Sacrum and coccyx 100% |
| | | | Lower gastrointestinal tract 25% |
| | | | Genitourinary tract 15% |

**FIGURE 131-4** Thoracopagus conjoined twins sharing a heart.

**FIGURE 131-5** Omphalopagus.

cardiac anomalies such as ventricular septal defect, atrial septal defect, and tetralogy of Fallot.

2. *Omphalopagus:* The heart is never fused; the liver is joined in 80% of cases, and there is an exomphalos (Fig. 131-5). The stomach and proximal small bowel are usually separate, and each twin has a rectum. In up to one third of omphalopagus twins, the intestine usually joins at the Meckel diverticulum, the terminal ileum and colon are shared, and a dual blood supply may exist. There is usually no union of the genitourinary tract.
3. *Pygopagus:* The twins are joined dorsally, sharing the sacrococcygeal and perineal regions (Fig. 131-6). They face away from each other—share the sacrum, coccyx, and part of the pelvic bones. The spinal cords are usually separate.[26] Twenty-five percent share the lower gastrointestinal tract and have a single anus and one or two rectums. In 15% of cases there is a single bladder. There is an increased incidence of vertebral anomalies including hemivertebrae, hemisacral agenesis, and thoracic anomalies.[27] Although the pelvic conjunction is fundamentally different than in ischiopagus twinning, the types are similar insofar as numerous other associated orthopaedic anomalies have been reported in association with pelvic conjunction such as hip subluxation or dislocation, congenital vertical talus, talipes equinovarus, Sprengel shoulder, and scoliosis. There can also be a variable degree of spinal and cord fusion. Although there may be only one anus and rectum, the remainder of the intestines are usually separate. The upper bodies are not fused, and there are four arms and four legs.
4. *Ischiopagus:* The twins may lie face to face or end to end (Fig. 131-7). They have two sacra or two symphysis pubis. They may share the lower gastrointestinal tract (70%) and/or the genitourinary tract (50%) and may have crossing

**FIGURE 131-6** Pygopagus.

**FIGURE 131-7** Ischiopagus.

ureters. The twins can be tetrapus, tripus, or bipus, although the most common arrangement is the presence of four legs. Pelvic conjunction leads to complex urogenital and orthopedic anatomy. The kidneys usually function normally but are often malrotated or ectopic in location. When two bladders are present, they lie side by side in a collateral position or they may lie in a sagittal midline location with one bladder draining into the other. The ureters frequently cross over and insert into a contralateral bladder such that they will need to be rerouted during separation. Partial urethral duplication is possible, but a single urethral orifice is typical. The distal gastrointestinal tract is often shared, with anorectal agenesis and rectovesical fistula. Contrast studies are necessary to delineate distal bowel anatomy. Urogenital sinus or cloaca may be present. In boys there is an increased incidence of undescended testes.

5. *Craniopagus:* The conjoined twins share the skull, meninges, and venous sinuses (Fig. 131-8). The brains are usually separate, although some cortical fusion can occur in 33% of cases.
6. *Cephalopagus:* The twins often have a fused thorax in addition to a fused head. The single fused head may have two faces (janiceps) facing away from each other; one face may be rudimentary. These twins are terminated or die in utero. They are nonviable.

**FIGURE 131-8** Craniopagus.

7. *Rachipagus:* The twins generally have vertebral anomalies and neural tube defects.
8. *Parapagus:* This is a relatively new term denoting extensive side-to-side fusion (Fig. 131-9). The twins share the umbilicus, lower abdomen, pelvis (single symphysis pubis), and the genitourinary tract. They can have anorectal anomaly and colovesical fistula and may be at risk of anencephaly.

## DIAGNOSIS

### Antenatal Diagnosis and Imaging

Fetal ultrasound can detect the presence of conjoined twins in almost all cases. Accurate antenatal assessment allows the parents to be counseled about the probable outcome of the pregnancy and the likelihood of successful postnatal separation. Prenatal diagnosis of conjoined twins is important for optimum obstetric management including decisions regarding termination of pregnancy and the timing and method of delivery to minimize maternal and fetal mortality.

***Fetal Ultrasound*** Prenatal ultrasonography (US) is capable of diagnosing conjoined twin pregnancies as early as 12 weeks' gestation.[28–30] Transvaginal US may also aid early diagnosis.[31] Diagnosis of conjoined twins may be straightforward when fusion of fetal parts is obvious (Fig. 131-10). In addition, the possibility of conjoined twins should be suspected in a twin

**FIGURE 131-9** Parapagus. (From Spitz L, Stringer MD, Kiely EM, et al: Separation of brachio-thoraco-omphalo-ischiopagus bipus conjoined twins. J Pediatr Surg 1994;29:477-481.)


**FIGURE 131-10** Prenatal ultrasound of conjoined twins.

pregnancy with a single placenta and no visible separating amniotic membrane. Conversely, observation of two placentas or an amniotic membrane excludes conjoining.[32] The sonographic findings in conjoined twins include inseparable fetal bodies and skin contours, an unchanged relative position of the fetuses, both fetal heads persistently at the same level, bibreech or bicephalic presentations, fewer limbs than expected, and a single umbilical cord with more than three vessels.[32] Most conjoined twins face each other and are fused ventrally, resulting in hyperextension of their cervical spines. Polyhydramnios occurs in up to 50% of conjoined twin pregnancies compared with 10% of normal twins and 2% of singleton pregnancies. Detailed US assessment at around 20 weeks' gestation should be able to define the site and extent of the conjoined area and provide a reasonable evaluation of which viscera are, and are not, shared.

Fetal echocardiographic assessment needs to be detailed because there is an increased incidence of congenital heart disease in conjoined twins overall, particularly thoracopagus twins.[33] A shared heart is seldom compatible with life and usually an indication for termination of the pregnancy. Hearts can be confirmed as separate when they are seen to be anatomically separate or when the heart rates are different. It has been the experience of many authors that fetal echocardiography underestimates the severity of cardiac anomalies.[32]

The thoracopagus heart typically has six chambers. Due to the abnormal cardiac anatomy and function, an increased nuchal translucency and subcutaneous edema have been noted in thoracopagus twins in particular.[29] Communications at the atrial and ventricular levels can often be well defined with US. However, the great vessel relationships and atrial morphology are often difficult to determine. Prenatal US does, nevertheless, provide an opportunity to accurately define the morphologic connections among the various chambers of the hearts. That is important because the state of the cardiac conjunction is the fundamental pointer to eventual outcome. Prenatal echo is made easier by amniotic fluid, particularly polyhydramnios in later pregnancy, acting as an acoustic window, and the lack of lung aeration permits US evaluation from different approaches. Prenatal diagnosis can be technically easier for the operator because it avoids the anatomic constraints of scanning fused chests postnatally, and fetal fluid-filled lungs may allow better images.[35]

Recently three-dimensional (3D) US imaging has been advocated as a new tool to demonstrate the extent of fusion in conjoined twins. 3D US may add anatomic information and thus improve the accuracy of classification of individual twins.[33,35] In some cases the category of conjoined twins is suspected by two-dimensional scanning but can be better appreciated on 3D US. It would seem sensible, however, to postpone attempts at detailed 3D US until after 14 weeks' gestation, when better views of the anatomy can be obtained.[30] Although 3D US may add more information regarding the extent of the union in utero, it is questionable whether these findings affect management prenatally.[33]

***Magnetic Resonance Imaging*** Magnetic resonance imaging (MRI) can be superior to US for overall fetal assessment. MRI, with its ability to differentiate soft tissues, provides an excellent alternative technique.[33] Ultrafast T2-weighted (T2-W) sequences of short duration such as the single-shot fast spin-echo sequence allow minimal image degradation by fetal motion and high-quality images of fetal organs without the need for fetal or maternal sedation.[36] The larger field of view of MRI permits better evaluation of the spatial relationships of anatomic anomalies or between normal structures (Fig. 131-11). Additional 3D MRI models may be useful in specific circumstances.[37]

### Postnatal Imaging

The choice of imaging study will depend to some degree on the site of fusion. All conjoined twins should have chest and abdominal radiography for an overall general assessment, as well as to help health professionals understand the extent of the conjoined area. Unexpected diaphragmatic hernia or vertebral anomalies can thus be detected early.

***Ultrasound*** All neonates should have routine cerebral US and, when indicated, a spinal US as baseline investigations.[33] In addition, abdominal US to assess the liver and to document the presence of two spleens, gallbladders, biliary systems, bladders, and four kidneys is necessary. Detailed Doppler studies to evaluate the great vessels in the abdomen and hepatic venous drainage should also be performed, but midline abdominal conjunction may make accurate Doppler assessment unreliable. Meticulous labeling of the images ensures the correct twin is consistently noted to be on the same side.

***Echocardiography*** Echocardiography (ECHO) is mandatory for every twin due to the high frequency of congenital heart disease. 3D ECHO has been advocated postnatally to make it easier to understand the cardiac connections and help plan treatment.[35] Andrews and colleagues[35] analyzed 23 sets of conjoined twins and classified twins according to the degree of cardiac fusion as follows: separate hearts and pericardium (group A, $n = 5$), separate hearts and common pericardium (group B, $n = 7$), fused atria and separate ventricles (group C, $n = 2$), and fused atria and ventricles (group D, $n = 9$). The degree of cardiac fusion was correctly diagnosed in all but one set. The intracardiac anatomy was correctly diagnosed in all cases, although the antenatal diagnosis was revised postnatally in three cases. Abnormal intracardiac anatomy was found in one twin only in two group A pairs, one group B pair, and both group C pairs. All group D twins had abnormal anatomy. Ventricular function was good in all twins scanned prenatally, and postnatally function correlated well with clinical condition. None of the twins from groups C or D survived

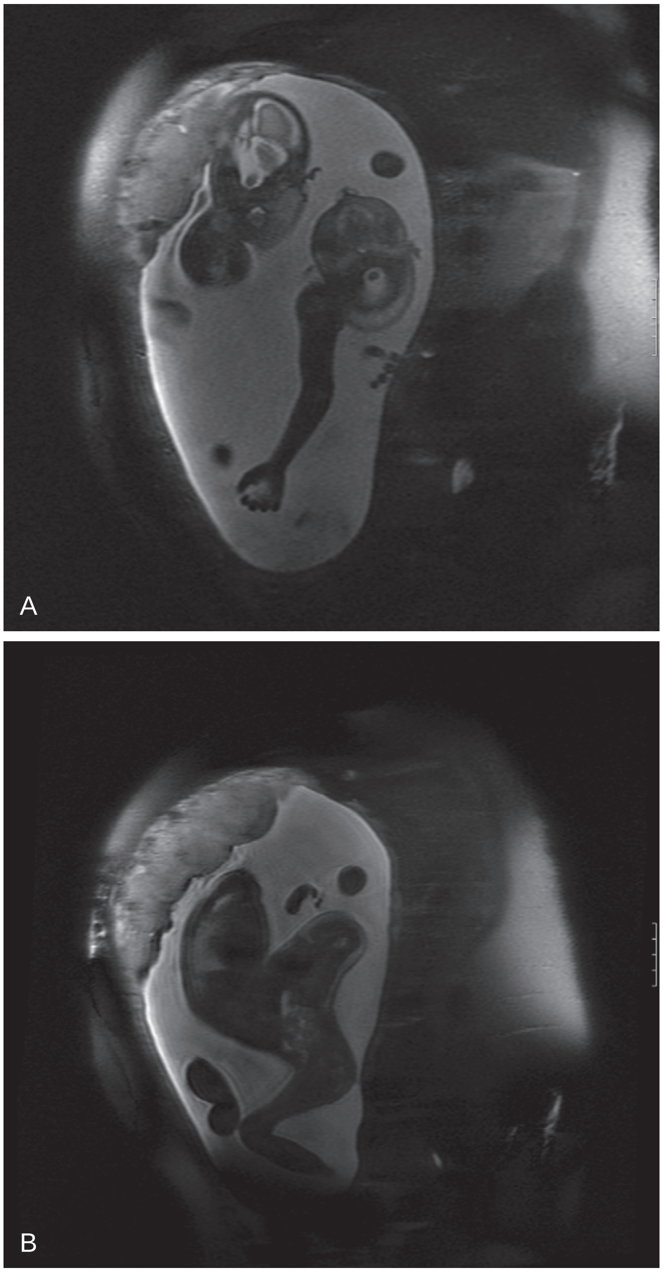



**FIGURE 131-11** **A,** Prenatal magnetic resonance imaging of conjoined twins. **B,** Scan of twins showing abdominal conjunction.

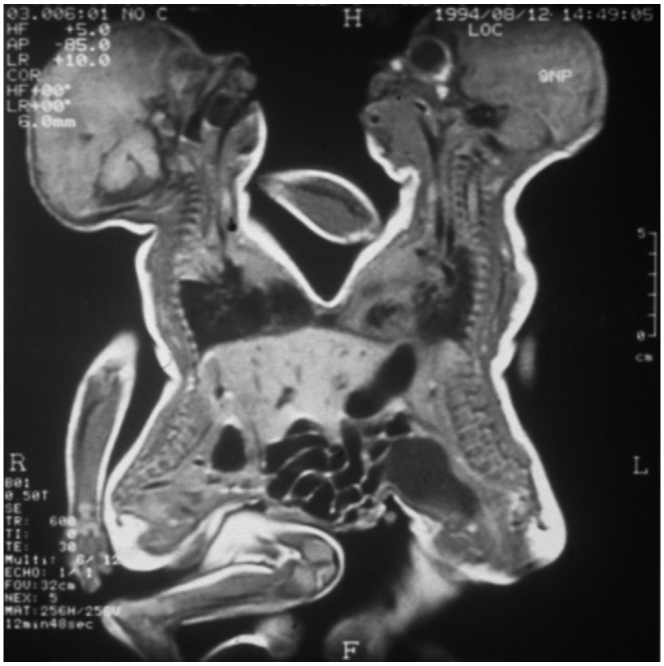



**FIGURE 131-12** Computed tomography scan of thoracopagus conjoined twins.

**FIGURE 131-13** Contrast-enhanced computed tomography showing conjoined liver and large arterial connection.

demonstrating that the outcome in twins with fused hearts remains dismal.

***Computed Tomography*** Radiologists avoid CT where possible in infancy due to the high radiation burden. Conjoined twins, even when stable and asymptomatic, are a well-justified exception. Due to the high spatial resolution and speed in particular of multidetector CT (MDCT), it is the best overall modality for evaluating conjoined twins in the postnatal setting (Fig. 131-12).

Contrast enhancement is mandatory to assess the vascular anatomy and so prior cannulation to minimize the stress of the procedure is advisable. Intravenous contrast agents (Fig. 131-13) for CT are given[33]; this can demonstrate the shared liver and vascular connections. Delayed images give very useful information on excretion by both twins' kidneys, the ureteric anatomy, and the location and number of bladders. Separate studies examining each twin's vascular anatomy on different days are recommended.[33]

***MRI*** MRI has an increasing role in the postnatal evaluation of conjoined twins, particularly those joined at the head or thorax (Fig. 131-14). MRI has the capability of producing 3D-reconstructed images in any direction with much better resolution and tissue characterization than 3D US. MRI is the optimum examination to assess for any cortical fusion in craniopagus twins. Although the ultrafast sequences such

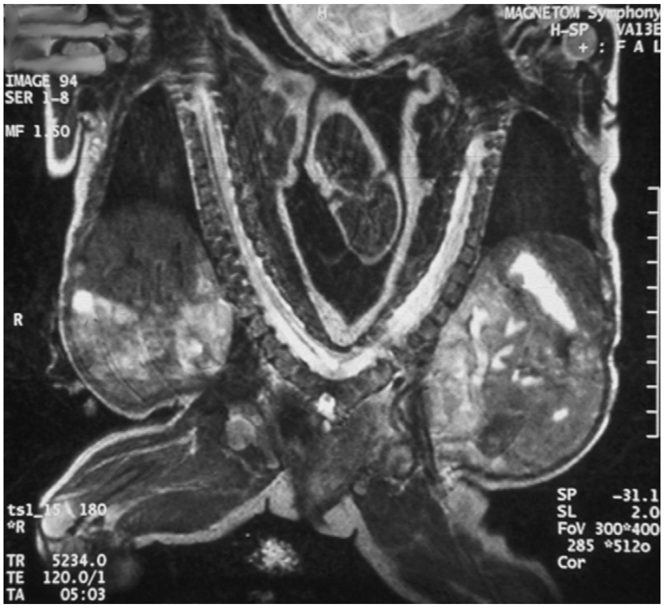


FIGURE 131-14 Postnatal magnetic resonance imaging: coronal T1 image after contrast administration to the right twin showing enhancement of that twin's liver parenchyma.

as single-shot T2-W images have advantages in the constantly moving fetus, more conventional T1-W, T2-W, and T1-W images after IV gadolinium administration are used in the postnatal imaging of conjoined twins. Intracardiac anatomy, great vessel anatomy and blood flow, and ventricular wall motion can all be accurately assessed in thoracopagus cases. Many complex fusions will inevitably get both MRI and MDCT. These modalities are often complementary with MRI showing soft tissue anatomy to best effect and CT detailing complex bony anatomy in pelvic conjunction. MRI with magnetic resonance cholangiopancreatography (MRCP) is likely to offer the best hope of assessing the biliary anatomy. Liver anatomy can be best appreciated after intravenous contrast enhancement, either via CT or MRI. Additional coronal or 3D reconstructions will provide further information. Demonstration of separate hepatic venous drainage into the inferior vena cava and right atrium of each twin is essential to plan separation as absent or severely anomalous hepatic venous drainage in one twin is incompatible with survival after surgery.

It is not unusual to find large-caliber vessels crossing the area of fusion. It is important to visualize these vessels by CT or MRI before separation to minimize blood loss and mortality during separation. It is rarely necessary to perform an angiogram before separation to clarify the vascular anatomy.

***Contrast Studies of the Gastrointestinal and Genitourinary Tracts*** Abdominal conjunction often involves fusion of parts of the intestine. In addition, there is always a common peritoneal cavity. Even in the absence of fused bowel, when contrast medium is given to one twin the bowel loops may be freely mobile across the "midline" and be seen to project into the peritoneal cavity of the other twin during fluoroscopy.[33] Pelvic conjunction leads to complex fusion and anomalies in the anorectal region. These require an individual approach with contrast studies (enemas, loopograms, and cystograms) of the distal bowel and bladder. Although performed in many cases, in practice, contrast studies provide limited information and often, particularly due to overlapping bowel loops, the anatomy can only be revealed at the time of separation.[38]

Urologic abnormalities are confined to those in whom the pelvis is joined: ischiopagus, parapagus, or pygopagus twins. Most twins share four kidneys and two bladders, occasionally with one ureter crossing from the contralateral twin to the other. The bladders are usually side by side, but they may be sagittally placed, which presents a reconstructive challenge.[39] CT scanning usually provides sufficient information regarding the upper renal tracts and bladders. Detailed urethral anatomy and possible fistulas require retrograde contrast medium examinations.

***Nuclear Medicine*** The kidneys, albeit ectopic or too few in number, usually function normally in conjoined twins.[33] Cross-sectional imaging can usually clarify the genitourinary anatomy without the need for isotope renography studies. There is an increased frequency of pelviureteric or ureterovesical obstruction in these twins, but this is seldom of major importance before separation.

Although hepatobiliary agents have been used to demonstrate separate biliary drainage, these are seldom necessary in practice. It is important to demonstrate the presence of two separate gallbladders. When two gallbladders are definitely seen in thoracopagus or omphalopagus twins, the likelihood of separate biliary systems is high.[40] When twins share the liver or have shared hepatic veins or other large shunts, then mixing of blood precludes the use of a hepatobiliary radiopharmaceutical. Despite detailed preoperative imaging, complex biliary anatomy may only become apparent at the time of surgery. MRCP may have a particular role to play in this area in the future. Individual twins raise unique individual dilemmas, and nuclear medicine studies may nevertheless be useful in specific circumstances.

## Obstetric Management

Delivery should take place at, or close to, the surgical unit where separation will be performed. Delivery must always be by classical cesarean section at 36 to 38 weeks' gestation.

## Anesthetic Management

Anesthesia involves two completely separate teams with all members being clearly aware for which twin they are responsible.[41] All drugs and intravenous fluids administered are calculated on a total weight basis with half being delivered to each twin. Because of the cross-circulation, drugs given intravenously may have an unpredictable effect and particular care must be taken to administer such drugs incrementally. Endotracheal intubation should be via the nasal passage for added security during repositioning, especially once separation has been achieved and the infants are moved into separate operating rooms or onto separate operating tables, as well as for continuing respiratory support postoperatively. Full arterial and central venous monitoring is essential and, in addition, ECG, pulse oximetry, capnography, and urine output must be carefully monitored. All lines and monitoring cables must be color coded for the individual twin to avoid confusion during repositioning. Adequate venous access is essential because brisk hemorrhage may be encountered, necessitating

rapid large-volume transfusion. Cardiovascular monitoring is particularly important because, with relative changes in position of the two infants, significant shifts in blood volume may occur.

### Separation Procedure

The key to a successful outcome is thorough preoperative planning. From the imaging, the extent of major organ union will be apparent, and the details of each phase of the procedure are planned in advance. The order in which these phases of separation will be performed is best decided during the operation itself because operative findings will often dictate a different sequence of events to what was originally envisaged.

Many anatomic variants exist for each of the different types of union. For instance, although the liver is joined in 100% of thoracopagus twins, in 50% there is intestinal union in addition. The surgeon will need to have planned for each possibility—such as what to do if there is a single duodenum or a single common bile duct.

In the most extensive forms of ischiopagus or parapagus union, the terminal ileum and the large bowel are single. Allocation of these structures cannot be planned in detail because the mesenteric blood supply is abnormal and unpredictable. As a general rule, these children have two bladders, which may lie side by side or anteriorly and posteriorly. Plans must be in place to deal with either eventuality, together with plans for dealing with crossed or uncrossed ureters. Finally, there may be a single urethra, although more commonly there are two urethras. Finally, with extensive union, there will be a substantial body wall defect after separation. The management of this problem also needs to be planned in advance. We have used tissue expanders in the past and found them to be troublesome and unhelpful in providing substantial extra tissue. With the sole exception of craniopagus twins, we would not recommend their use. We use polypropylene mesh over a plastic liner to close the defect and plicate this, as one would with any other abdominal wall defect. Even with the largest of defects, the body wall can be closed within 2 weeks.

Initially, one surgical team comprising both lead surgeons is sufficient to commence the procedure. Our preference is to start the operation posteriorly. The skin and soft tissue are divided down to muscle and fascia. The wound is then sutured closed, and the babies are turned around. We have done this with the more extensive unions; otherwise, it is difficult to allocate body wall equally and one may easily leave one with significantly less. Although this sounds cumbersome, we have never regretted taking the time for this maneuver. Once this incision has been made, it is easy to complete the separation at the final stage of the operation.

If a vestigial limb is present posteriorly, it may be bivalved and divided and the bones filleted out. This provides vascularized healthy tissue to assist in closure. Allocation of this extra tissue is decided at the time of surgery.

On opening the chest and abdomen anteriorly, it is usually best to divide the conjoined sternum to improve access. The lobar anatomy of conjoined livers is not readily discerned, and in any case it is not necessary to be precise about this. A point is chosen, midway between the gallbladders and the porta hepatis on either side, and the liver is divided in the usual manner. The use of an ultrasonic dissector combined with one of the high-energy sealing devices results in virtually bloodless conditions.

Once the liver is divided, the remainder of the gastrointestinal anatomy is easier to manage. The urologic aspects are dealt with before the decision about allocating the rectum.[39] Usually each twin has a bladder and at least a posterior urethra. Occasionally, two bladders lying fore and after are divided and the two halves are united on either side. If the bladders are side by side, the division takes place between them. In ischiopagus and parapagus twins the ureters may cross into the opposite twin's bladder. Our experience suggests that in almost all cases, it is possible to preserve at least one corpus of the penis for each twin. Occasionally, there are three or more corpora cavernosa in which case a more normal penis will result.

Once the urologic aspect has been completed, a decision is made on allocation of the rectum and anus. This will depend on the blood supply that is available. It has been our practice to leave the terminal ileum and colon with one twin while leaving the rectum with the other when conditions permit.

Once the pelvic viscera have been allocated, the posterior part of the pelvic ring is divided. Preoperative imaging will have revealed if there are substantial vessels crossing at this level. Finally, the previously sutured skin wound is opened and separation is complete.

Closure of a large body wall defect is straightforward. If the sternum is short and the heart or pericardium is exposed, a polypropylene patch is sutured to the chest wall laterally and superiorly and to the diaphragm inferiorly. This patch is left permanently in situ. The abdomen is closed by suturing two flaps of polypropylene mesh to the muscle on either side and covering the viscera with a plastic liner such as an intestinal bag.

Usually there is sufficient skin to cover the chest wall defect. The skin over the abdomen is tacked to the mesh to cover the area where the mesh is sutured to muscle (Fig. 131-15). This allows tissue to grow from the fascia through the mesh to the overlying subcutaneous fat and ensures a strong attachment of mesh to muscle.[42–46]

### Postoperative Management

Almost all these patients are electively ventilated after surgery with the usual monitoring that is used after major surgery. There are, however, two problems that are not common in other children—fluid loss and cardiac performance.

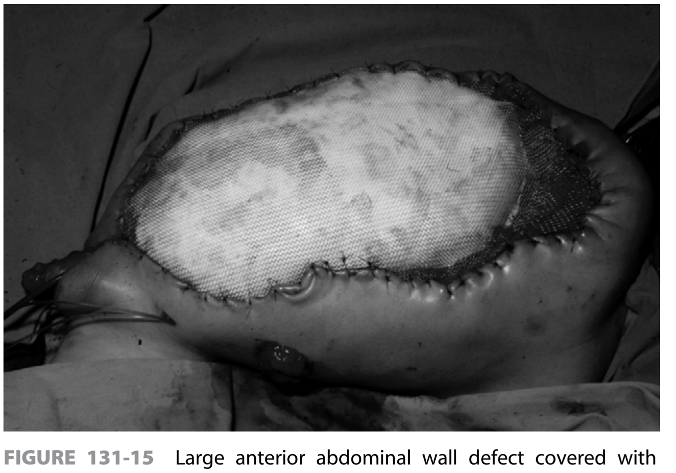


**FIGURE 131-15** Large anterior abdominal wall defect covered with polypropylene (Prolene) mesh after separation.

If the abdomen has been closed with a mesh, there will be substantial fluid losses for the first few days.

We estimate the losses by use of absorbent gauze dressings, which are weighed on an hourly basis. The fluid is then replaced milliliter for milliliter with human albumin solution. The mesh is tightened, commencing on the day after operation, although for the first few days, the degree of tension applied is limited. However, after the first 4 days, increasing tension can be applied to the mesh because it is tightened and the abdominal wall stretches and grows in an impressive fashion. It is usual to achieve abdominal wall closure within 2 weeks.

The other aspect in which conjoined twins differ is in cardiac performance. It is a feature of those who have extensive union that one circulation supports the other. In general, the thinner and more active twin has a heart that is more robust and supports the other twin's circulation. This difference in cardiac performance is not evident on echocardiography.

However, once the circulations are separated, the more dependent twin may have a compromised circulation. It is of critical importance that the lowest filling pressure possible is used and that the afterload is also reduced. We try to maintain as low a central venous pressure as possible, together with as low a blood pressure as possible, commensurate with an adequate urine output. This phase of compromised cardiac performance lasts a number of days but is usually resolved by 7 days postoperation.

The timing of enteral feeding is variable but should not necessarily await body wall closure. In the majority, complete removal of the mesh is achieved when the abdomen is closed. On occasion, it is necessary to leave some mesh, and this has not been a particular problem over the following years.

The management after birth can take one of three courses (Table 131-3):

1. **Nonoperative management** is indicated when there is complex cardiac union without the possibility of reconstructing even a single functioning heart or where there is extensive cerebral fusion. Parents faced with the prospect of a surviving twin having severe deformities may refuse consent for separation. In eight of nine cases in our series there was cardiac fusion, while in one with extensive parapagus fusion (a normal triplet survived) parents refused surgery. All nine sets died within a short period.
2. **Emergency separation** is required when one twin is dead or dying and threatening the survival of its sibling, where there is a correctable congenital anomaly incompatible with survival if left untreated such as esophageal or intestinal atresia, or where serious damage has occurred to the connecting bridge or area of fusion (ruptured omphalocele).

   Emergency separation was necessary in eight of our cases. One had a rupture of the shared omphalocele resulting in tearing of the united liver with exsanguinating hemorrhage resulting in the death of one twin. Emergency separation was undertaken in an attempt to salvage the surviving twin who unfortunately died at the end of the procedure. In three sets of thoracopagus twins, cardiac instability prompted emergency separation. Only one of these infants survived. Prenatal volvulus with necrosis and perforation occurred in a set of omphalopagus twins, necessitating emergency separation. Both twins had intestinal atresia that was repaired, but both had short bowel syndrome that required many months for adaptation to occur. They survived and eventually thrived. Another set of omphalopagus twins was transferred soon after birth because one had severe pulmonary hypoplasia needing mechanical ventilation. This twin died in the ambulance during transfer. The transport team was instructed to digitally compress the area of union to prevent exsanguination into the surviving twin and avoid applying a clamp because prior experience showed that much of the surviving twin's intestine may reside in the peritoneal cavity of its sibling. This twin did survive.

   The survival rate for emergency separation was 4 out of a possible 16 infants—25%. In retrospect, survival was not possible in six of these cases.
3. **Planned separation—**if the twins are stable and healthy at birth, they should be allowed to feed normally and thrive with the intention to separate at around 2 to 3 months. This allows time to carry out investigations to define as accurately as possible the nature and extent of shared organs. The operative procedure can then be planned with involvement of all the relevant staff.

Fourteen sets underwent planned separation, of whom three died (two at home 6 months after successful separation) and 25 survived (89%) (Table 131-4).

## Follow-up

The extent of the union will determine whether the infants will have minor or major residual problems. One or both twins may have congenital cardiac abnormalities that may require surgical correction. Residual scars or contractures may require plastic surgical correction. Short bowel syndrome occurs when each twin is allocated 50% of the shared intestine. There will be a need for parenteral nutrition and meticulous dietary support for a period of time pending intestinal adaptation, which generally occurs. Intestinal stomas may be temporary or permanent and will require the input of a stoma therapist. Imperforate anus will need reconstruction if possible. Prolonged urinary follow-up is essential, particularly in the cases of ischiopagus and pygopagus twins. Shared bladder, cross ureters, vesicoureteric reflux, and renal abnormalities will require regular monitoring to prevent further damage and to diagnose early and treat urinary calculi. Lifelong orthopedic follow-up will be necessary for limb deformities, deletion of lower limbs, and scoliosis and chest wall deformities.

Psychologic support should commence preoperatively when separation is undertaken at a later age and is essential following separation, especially when one twin dies. When the separation has involved prolonged periods of hospitalization (some of our twins have been discharged within 2 weeks of separation), there may be developmental and behavioral problems that require attention.

## Ethics

If separation is possible with the expected survival of both twins, we strongly recommend that the surgical procedure be performed. If the hearts of the twins are fused, the chances of survival of one or both twins is so remote that surgery should be declined and nature allowed to take its course.

If one twin has a lethal abnormality and cannot survive independently from his or her "normal" twin, and without separation both twins would die, then separation should proceed, even though it is at the expense of the abnormal twin.

**TABLE 131-3**

**Outcome of Cases**

**Separation Not Attempted**

| *Type (-pagus)* | *Sex* | *Age at Operation* | *Shared Organs* | *Associated Anomalies* | *Outcome* |
|---|---|---|---|---|---|
| Thoraco | F | | Cardiac fusion | Pulmonary atresia, esophageal atresia | Died |
| Thoraco | F | | Cardiac fusion | Exomphalos | Died |
| Thoraco | F | | Cardiac fusion | | Died |
| Para | F | | Extensive union | (Surviving triplet) | Died |
| Thoraco | F | | Cardiac fusion | | Died |
| Thoraco | F | | Cardiac fusion | | Died |
| Thoraco | F | | Cardiac fusion | | Died |
| Thoraco | F | | Cardiac fusion | | Died |
| Thoraco | F | | Cardiac fusion | | Died |

**Treated by Emergency Separation**

| *Type (-pagus)* | *Sex* | *Age at Operation* | *Shared Organs* | *Associated Anomalies* | *Outcome* |
|---|---|---|---|---|---|
| Thoraco | F | 3d | Pericardium, diaphragm, liver, CBD, small bowel | Pulmonary atresia | 1 died of pulmonary atresia<br>1 **alive** |
| Omphalo | F | 1d | Liver, small bowel | Exomphalos (ruptured), lacerated liver, cloacal anomaly | 1 died before admission<br>1 died postoperation |
| Thoraco | M | 8d | Cardiac-atrial communication, liver | Unilocular heart<br>One absent hepatic veins | 1 early death,<br>1 died 6 after wk of SIDS |
| Thoraco | F | 1d | heart, liver | Unilocular heart, CDH | Both died |
| Omphalo | F | 2d | Liver, midgut | Exomphalos, volvulus, bowel atresia | Both **alive** |
| Omphalo | M | 1d | Bowel, bladder | Imperforate anus, hypoplastic lungs | 1 died during transfer—pulmonary hypoplasia<br>1 **alive** |
| Para | F | 1d | Lungs, diaphragm, aorta, liver, bowel | AV canal defect, PPH | Both died |
| Thoraco | F | 5d | Pericardium, liver | Cardiac, Porencephalic cyst | One died immediately (PPH)<br>The other died after 2 wk |

**Treated by Planned Separation**

| *Type (-pagus)* | *Sex* | *Age at Operation* | *Shared Organs* | *Associated Anomalies* | *Outcome* |
|---|---|---|---|---|---|
| Cranio | F | 2m | Sagittal sinus | | 1 alive<br>1 died 6m |
| Cranio | | | Sagittal sinus | | Both alive |
| Ischio | M | 8m | Liver, distal gut, genitalia | ARA<br>Tripus | Both alive |
| Para | F | 3y | Pericardium, diaphragm, liver, distal gut, genito-urinary | Renal agenesis | 1 alive<br>1 died 6m |
| Para | M | 10m | Pericardium, liver, distal gut, genito-urinary | ARA | 1 alive<br>1 died 6m |
| Thoraco | F | 3m | Pericardium, liver, biliary atresia, small bowel atresia | Exomphalos | Both alive |
| Omphalo | F | 3m | Liver | | Both alive |
| Pygo | F | 2m | Spinal cord | ARA | Both alive |
| Ischio | F | 2m | Pelvis | Bladder exstrophy<br>ARA | Both alive |
| Omphalo | F | 6w | Liver | | Both alive |
| Omphalo | F | 8m | Liver | | Both alive |
| Pygo | F | 3m | Sacrum<br>Spinal cord | | Both alive |
| Ischio | M | 9m | Liver, colon | Tripus | Both alive |
| Ischio | M | 5m | Sternum, pericardium, liver, distal ileum and colon, anorectum, penis | | Both alive |

d, days; w, weeks; m, months; y, years; AV, atrioventricular; CBD, common bile duct; CDH, congenital diaphragmatic hernia; SIDS, sudden infant death syndrome; PPH, persistent pulmonary hypertension; ARA, anorectal anomaly.

**TABLE 131-4**
**Outcome of Management of Conjoined Twins in the Major Series**

| *Authors* | *Yr* | *No.* | *No Operation* | *Emergency Separation Survivors (%)* | *Planned Separation Survived (%)* |
|---|---|---|---|---|---|
| O'Neill (USA)[65] | 1988 | 18 | 5 | 5 sets<br>1 (10%) survived | 8 sets<br>13 survived (81%) |
| Cywes/Rode (South Africa)[66,67] | 2006 | 33 | 16 | None | 17 sets<br>22 survived (65%) |
| Al Rabeeah (Saudi Arabia)[68] | 2006 | 29 | 19 (1 abandoned operation) | None | 10 sets<br>19 survived (95%) |
| Saguil (Philippines)[69] | 2009 | 22 | 6 | 6 sets<br>1 (8%) survived | 9 sets<br>15 survived (83%) |
| Spitz/Kiely/Pierro (UK) | 2010 | 31 | 9 | 8 sets<br>4 (25%) survived | 14 sets<br>25 survived (89%) |

Yet twins can survive joined together for many years. Alice D. Dreger, PhD, a professor in medical humanities and bioethics, contends that "when it comes to cases in which one twin must be 'sacrificed,' it is ethically wrong to take one life so another may live."[46a] She further states that "not in a single case has the twin chosen to survive ever actually survived to go home." This is clearly incorrect as borne out in our and other series.

# Heteropagus (Parasitic) Twins

Heteropagus or parasitic twin is a grossly defective fetus, or fetal parts, attached externally, with or without internal connections, to a relatively normal twin (the autosite) in one of the same eight areas in which symmetrical twins are united.[23] They are usually composed of externally attached supernumerary limbs but may also contain viscera or visceral parts and only rarely a beating heart or intact brain.

Fetus in fetu is a fetiform mass enclosed within the body of the autosite, usually the abdominal cavity, rarely within the brain, with grossly recognizable fetal parts including an axial skeleton, attached to the autosite by a pedicle containing a few large blood vessels. Its growth rate is similar to the host within which it is discovered.

## INCIDENCE

The estimated incidence of heteropagus twins is much less than for symmetrical twins—1 per 1 million births or less. The female preponderance seen in symmetrical twins is not evident in heteropagus twins where there is an equal distribution of the sexes.

## EMBRYOLOGIC CONSIDERATIONS

The most plausible theory for the occurrence of heteropagus twins was proposed by Dönitz in 1866.[47] He postulated that heteropagus twins originated from symmetrical twins, one of which suffered secondary damage as a consequence of vascular compromise. The affected "twin" would then have to rely on collateral blood supply from the autosite while ischemic damage occurred in various parts of the affected "twin." In support of this theory, hypoplastic umbilical vessels have been found in the heteropagus twin and vascular connections from the autosite to the heteropagus twin may be found during surgical separation. Others have disputed this theory because it cannot account for all the abnormalities found in these twins and particularly cannot explain the acephalic occurrence. It is generally accepted that the heteropagus twin is genetically identical to the autosite, and this has been substantiated by DNA analyses.

## ANATOMIC TYPES

Reports of 157 cases of heteropagus twins have appeared in the literature until 2003. Recently, Sharma and colleagues[48] reviewed 39 cases reported in 23 publications since 2003. In six cases the specific variety was not defined.

Table 131-5 provides a breakdown of these cases:

*Dipygus* or *caudal duplication* (Fig. 131-16)[49] is a rare abnormality comprising two sets of accessory lower limbs sited between the autosite's limbs and including accessory external genitalia.

*Omphalopagus* (Fig. 131-17) or *epigastric heteropagus* accounts for the majority of cases—more prevalent in recent series, in which almost 60% of cases were in this region.[50–52]

*Fetus in fetu*[53–55] occurs most commonly within the abdominal cavity with 57 reported cases with only 9 having a brain and 6 a heart, both always small and rudimentary. In most cases a pedicle of vessels arises from the retroperitoneal region and attaches to the umbilical area of the parasite. In the cranial region the majority of fetuses in fetu are epignathi attaching to the posterior pharynx near the Rathke pouch. Only seven cases of intracranial fetuses in fetu have been reported.

Sacral parasite is a rare variety of heteropagus twin and needs to be differentiated from sacrococcygeal teratoma.[56] Some authors consider fetus in fetu and fetiform teratomas within the spectrum of teratomas, but this remains controversial.

**TABLE 131-5**
**Types of Heteropagus Twins Reported**

| | |
|---|---|
| Thoracopagus | 1 |
| Cephalopagus | 6 |
| Parapagus | 3 |
| Omphalopagus | 71 |
| Ischiopagus | 32 |
| Pygopagus | 46 |
| Craniopagus | 11 |
| Rachipagus | 28 |

FIGURE 131-16 Dipygus with prolapsed intestine.

FIGURE 131-17 Parasitic omphalopagus twins.

## DIAGNOSIS

Prenatal identification of heteropagus twins has been documented on at least seven occasions at gestational ages ranging from 9 to 28 weeks. The importance of recognition of the nature of the abnormality is evident in that the condition is entirely benign and compatible with normal development. The diagnosis in utero should not be considered an indication for termination of the pregnancy provided that it is not causing gross deformity of adjacent structures.

## OBSTETRIC CARE

Depending on the size and extent of the parasitic twin, delivery can be by normal vaginal route. If there is a suspicion of expected obstructive delivery, then cesarean section at around 38 weeks of gestation would be indicated.

## INVESTIGATION

Sharing of organs and vascular connections are infrequent in heteropagus twins. As a result, preoperative imaging has usually been restricted to CT, ultrasound, and MRI scans, which reveal bony and soft tissue structures. Occasionally angiography has been undertaken to show vascular communications, but in recent years magnetic resonance angiography, which is safer and noninvasive, has replaced the invasive conventional angiography. Echocardiography of the autosite is mandatory in thoracopagus parasitic twins because more than 25% have congenital cardiac defects.

## SURGERY

Separation of the parasite from the autosite is generally undertaken in early infancy. As mentioned earlier, sharing of organs and major vascular connections is unusual in heteropagus twins. Therefore the surgical procedure is generally straightforward and uncomplicated. The initial skin incision should be carefully planned to take sufficient skin and subcutaneous tissue from the parasite to ensure tension-free closure of the wound following separation. One of the common complications following separation is wound breakdown or infection, and this can be avoided by careful planning and meticulous closure of the incision. A thorough search of the autosite at the site of attachment must be carried out to exclude any retained abnormal or extraneous tissue and to correct possible anomalies in the autosite such as associated congenital intestinal abnormalities.

## OUTCOME

The prognosis for the autosite is generally excellent except for cases with severe cardiorespiratory problems. Wound complications can be avoided by careful preoperative planning and meticulous attention to detail in the operative procedure.

### *Acknowledgments*

Special thanks to Dr. Simon Eaton for collating the references and organizing the illustrations.

*The complete reference list is available online at www.expertconsult.com.*

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